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Research Article

MOLECULAR P PREDICTION, DOCKING STUDIES AND SYNTHESIS OF 5-BENZIMIDAZOLE-1-YL-METHYL –[1,3,4] OXADIAZOLE-2-THIOL AND THEIR DERIVATIVES

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ABSTRACT

Molecular property is a complex balance of various structural features which determine whether a particular molecule is similar to the known drugs.These properties mainly hydrophobicity, molecular size,flexibility and presence of various pharmacophoric features influence the behavior of molecules in a living organism, including oral bioavailability. This investigation deals with the design and calculation of molecular properties, drug likeness, lipophilicity and solubility parameters of 5-Benzimidazole-1-yl-methyl-[1, 3, 4] oxadiazole-2-thiol and their derivatives using Osiris, mol inspiration ,Mol soft software's, and ALOPGPS 2.1 program. The compounds followed the Lipinski 'Rule of five' for better bioavailability, were synthesized and characterized by IR, NMR, and mass spectral analysis. Furthermore, the binding conformations of these compounds for anti inflammatory activities were determined in silico docking. This is an energy optimization process concerned with the search of the lowest free energy binding mode of a ligand within a protein binding site and estimates the forces involved in the protein-ligand recognition, carried out in Mastro V 2011 in the active site of the cyclooxygenase-2 (COX-2) enzyme.

Keywords: Benzimidazole, oxadiazole, Molecular properties, docking studies.

INTRODUCTION

Molecular properties are fast and reliable estimating which are very crucial in the process of drug discovery and development. Drug likeness is a qualitative concept, used to design a drug. It plays a vital role in the screening of molecules. In the development of drugs intended for oral use, good drug absorption and appropriate drug delivery are fundamental. Because of poor pharmacokinetics and Tox liabilities, drugs fail in the process of development. Therefore the bioavailability related properties and Toxicity reports are important before actual synthesis to reduce the chemical expenses and valuable time. An *in Silico* model for predicting oral bioavailability is very essential prior to synthesis.

The molecular properties of oxadiazole analogues were calculated using Mol inspiration, Osiris, and Mol Soft Softwares. Lipophilicity and solubility parameters were calculated using ALOGPS 2.1 program to filter the compounds for further synthesis. [1, 2, 3]

Benzimidazole and its derivatives are an important class of bioactive molecules. Their importance is due to their versatile application in the field of drugs and pharmaceuticals.[4] Benzimidazole structures are associated with a wide range of activities including anti-cancer, antiviral, anti-inflammatory, anti-microbial, anti-oxidant and proton pump inhibitor, anticoagulant properties.[5]

1, 3, 4-Oxadiazoles are a significant class of heterocycles which has attracted significant interest in medicinal chemistry in a number of biological targets including, anti-inflammatory and anticonvulsant, antimicrobial, anti tubercular, activities. An Azole group of heterocyclic compounds possesses significant pharmacokinetic property, lipophilicity that influences the ability of the drug to reach the target by transmembrane diffusion and show promising activity [6-9]. 1, 3, 4-oxadiazole derivatives were synthesized by the treatment of acid hydrazide with carbondisulphide in the presence of potassium hydroxide leading to the formation of oxdiazole moiety [10-13].

In the present study, we synthesized title compounds which have both the advantages of benzimidazole and oxadiazole molecule in the single molecule. The title compound was subjected to molecular properties prediction and Toxicity report by Mol inspiration and Mol Soft, Osiris Software's. The ALOGPS method is part of the ALOGPS 2.1 program used to predict lipophilicity and aqueous solubility of compounds. The log KOW (KOW-WIN) program estimates the log octanol/water partition coefficient.XLOGP2 is an atom additive method applying corrections. Docking studies were carried out to understand binding interactions of the title compounds with the inflammatory target COX-2.

Materials and methods

Materials were obtained from commercial suppliers and used without purification. All the melting points were determined on a Melter FP-51 melting point apparatus and are uncorrected. Analytical TLC was performed on Merck pre-coated silica gel-60 F_{254} plates. Visualization was done by exposing to iodine vapor, UV light. IR spectra (KBr pellet) are recorded on a Perkin Elmer model 283B and Nicolet-740 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varion Gemini 200, Varian unity-400 and avance MHZ, BrukerUx-NMR spectrometer. Chemical shift values are given in ppm (δ) with tetra methyl silane as an internal standard. Mass spectra are recorded on VG micro mass 7070 H (EI and CI) VG auto spec (FAB) using CS^+ ion gun.

Molecular properties prediction

Molecules which contain functional groups have properties; these are constant with most of the known drugs with the intention to achieve good oral drugs [14]. Molecular properties are fast and reliable estimation and very important process of drug discovery and development. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility of various pharmacophoric features which influence the behavior of molecules in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability, LogP and molecular volume . Molecular properties were calculated using Mol inspiration–cheminformatics, Mol soft and Osiris online service.

Molecular Polar surface area (PSA) was determined by the fragment-based method. PSA is the sum of the surfaces of polar atoms (O, N, and attached Hydrogen) in a molecule. Hydrogen bonding capacity is an important parameter for describing drug permeability. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, and blood–brain barrier penetration. Number of rotatable bonds are important for conformational changes of molecules; LogP is useful in rational drug design as a measurement of molecular hydrophobicity, and used in QSAR studies. Hydrophobicity affects drug absorption, bioavailability, metabolism of molecules, toxicity, hydrophobic drug receptor interactions. Molecular volume is also used in QSAR studies to determine transport characteristics of molecules such as intestinal absorption or blood-brain barrier penetration [15-20].

Besides the above properties, Balance between solubility and partitioning properties are essential for good bioavailability. The ALOGPS 2.1 program used to predict lipophilicity calculations and aqueous solubility of compounds. The logKow (Kow-WIN) program estimates the log octanol/water partition coefficient (LogP) of organic chemicals and drugs using an atom/fragment contribution method. The XLOGP2 is an atom-additive applying corrections. Both the XLOGP2 method and the logKow (Kow-WIN) are the best supported for the most of the compounds on the basis of lipophilicity (≤5) to consider an oral drug /lead .Partition coefficient, Solubility and Drug likeness model score of the synthesized compounds are tabulated in Table 3.

High oral bioavailability is an important factor for the development of bioactive molecules as therapeutic agents. Molecular properties such as membrane permeability and

bioavailability are always associated with some basic molecular descriptors such as LogP value, molecular weight, hydrogen bond acceptors and donors in a molecule. Lipinski 'Rule five' states that most molecules with good membrane permeability have LogP ≤5, molecular weight ≤500, number of hydrogen bond acceptors≤10, and number of hydrogen bond donars≤5. This rule is widely used as a filter for drug-like properties.[1, 2] Pharmacokinetic parameters, physicochemical properties are tabulated in Table 2, 4.

After successful prediction of molecular properties title compounds were selected for the next steps of synthesis.

Preparation of 1H-benzo[d]imidazole (2a)

The o-phenylenediamine **1a** (2.8 g, 18 mmol) was refluxed with formic acid (1.65 g, 25 mmol) for 3 h. After the completion of the reaction, the mixture was allowed to cool at room temperature and made alkaline with 10% aq. NaOH, a solid appeared this was recrystalized from water to obtain the desired compound as a white solid, yield 73.5%, m.p.172-177°C (Lit^{R}., 172-174 °C). IR (KBr): υ 3114 (NH), 1584 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 7.15-7.25 (m, 2H, Ar-H), 7.50-7.70 (m, 2H, Ar-H), 8.02 (s, 1H, N=CH), 12.20(s, 1H, NH). EI-MS: m/z = 118 $[M]^+$

Preparation of 5-Nitro-1H-benzimidazole (2b)

As a brown solid, yield 76.7%, m.p.155-160 °C. IR (KBr): υ 3062 (NH), 1586 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 7.69 (d, 1H, Ar-H), 8.11 (d, 1H, Ar-H), 8.32 (s, 1H, N=CH), 8.52 (s, 1H, Ar-H). EI-MS: m/z =164 $[M]^+$.

Preparation of Ethyl 2-(1H benzo[d] imidazole-1-yl) (3a)

The Ethyl 2-(1*H* benzo[*d*] imidazole-1-yl) **2a** (7.00 g, 59 mmol) was refluxed with an equivalent amount of sodium in absolute ethanol for 2 h. Then ethyl bromo acetate (10.63 g, 65 mmol) was added and the mixture was refluxed for additional 7 h. After concentrating the reaction mixture a semisolid mass appeared which was coloumn chromatographed over silica gel (60-120 mesh) using hexane: ethyl acetate, (4: 6) to obtain the desired compound as syrup, yield 53.68%. IR (KBr): υ 1774 (ester C=O), 1489 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.25 (t, 3H, CH_3), 4.19 (q, 2H, OCH_2), 4.82 (s, 2H, NCH_2), 7.25 (s, 3H, Ar-H), 7.78 (m, 1H, Ar-H), 7.88 (s, 1H, N=CH). EI-MS: m/z = 204 $[M]^+$.

Preparation of (5-Nitro-benzimidazole-1yl)-acetic acid ethyl ester (3b)

As a brown solid, yield 52.08%, m.p.140-145 °C. IR (KBr): υ 1739 (ester C=O), 1595 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.30 (t, 3H, CH_3), 4.23 (q, 2H, OCH_2), 5.23 (s, 2H, NCH_2), 7.23 (d, 1H, Ar-H), 8.11 (d, 1H, Ar-H), 8.35 (s, 1H, N=CH), 8.56 (s, 1H, Ar-H). ESI-MS: m/z = 249 $[M+H]^+$.

Preparation of 2-(1H benzo[d] imidazole-1-yl) acetohydrazide (4a)

A solution of Ethyl 2-(1*H* benzo[*d*] imidazole-1-yl) **3a** (2.8 g, 13 mmol) in ethanol was refluxed with hydrazine hydrate (1.72 g, 34 mmol) for 4 h. After evaporating the solvent under reduced pressure, a solid appeared. This was recrystallized from ethyl acetate to obtain the desired compound as a white crystalline solid, yield 72.8%. M.p.178-183 °C. IR (KBr): υ 3313 (NH), 1660 (hydrazide C=O) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 4.81 (s, 2H, CH_2), 7.14-7.26 (m, 2H, Ar-H), 7.46-7.50 (m, 1H, Ar-H), 7.61-7.67 (m, 1H, Ar-H), 8.04 (s, 1H, N=CH), 9.54 (brs, 1H, NH). ESI-MS: m/z = 191 $[M+H]^+$.

Preparation of (5-Nitro-benzimidazole-1yl)-acetic acid hydrazide (4b)

As a yellow solid, yield 81.49%, m.p. 180-185 °C. IR (KBr): υ 3382 (NH), 1663 (hydrazide C=O), 1501 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 4.91 (s, 2H, CH_2), 7.65 (d, 1H, Ar-H), 8.09 (d, 1H, Ar-H), 8.36 (s, 1H, N=CH), 8.58 (s, 1H, Ar-H), 9.62 (s, 1H, NH). ESI-MS: m/z = 235 $[M]^+$.

Preparation of 5-Benzimidazole-1-ylmethyl-[1, 3, 4] oxadiazole-2-thiol (5a)

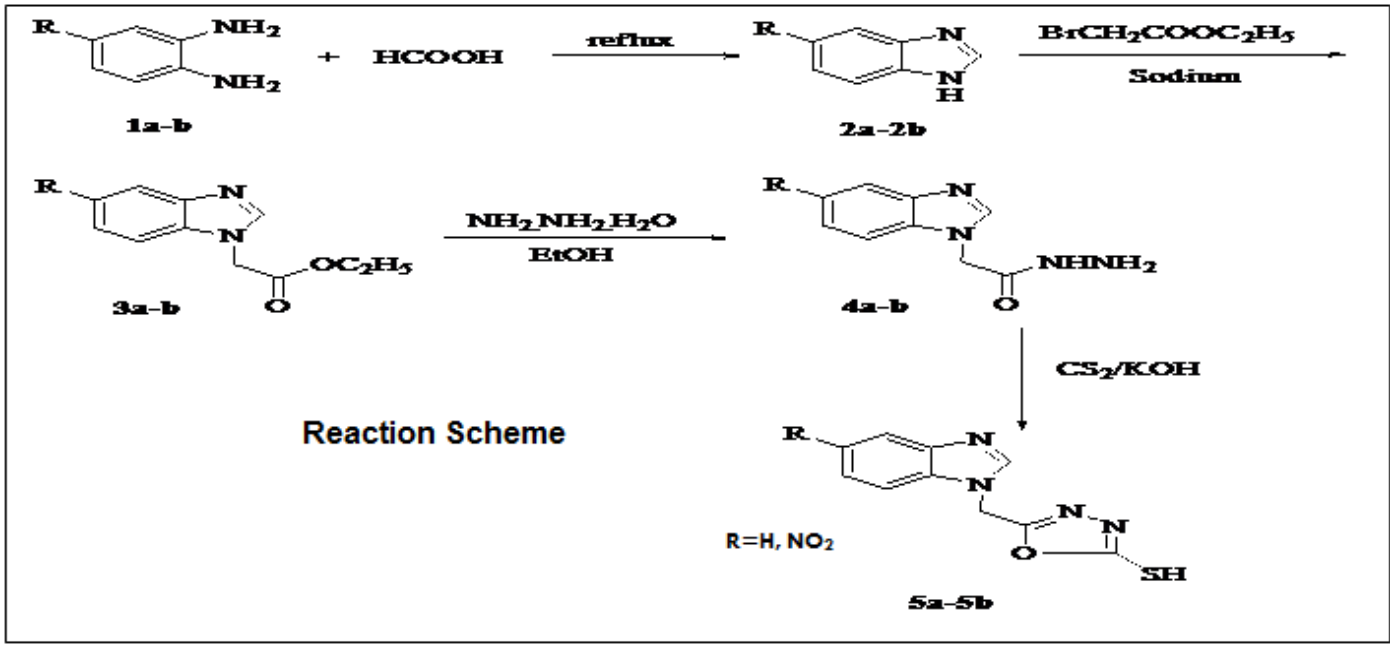
A mixture of 2-(1*H* benzo[*d*] imidazole-1-yl) Acetohydrazide **4a** (0.2 g, 1 mmol), potassium hydroxide (0.05 g, 1 mmol) in ethanol was refluxed with carbondisulphide (1 mL) at 60 °C. The solution thus resulted was concentrated, cooled and acidified with 5% aq. HCl. The precipitated product was filtered, washed with water and dried to obtain desired compound as a yellow solid, yield 94.69%, m.p. 235-240 °C. IR (KBr): υ 1520 (C=N), 1149 (C=S) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 5.92 (s, 2H, CH_2), 7.45-7.52 (m, 2H, Ar-H), 7.74-7.90 (m, 2H, Ar-H), 9.31 (s, 1H, N=CH). ESI-MS: m/z = 233 $[M+H]^+$.

Preparation of 5-(5-Nitro-benzimidazole-1-ylmethyl-[1, 3, 4] oxadiazole-2-thiol (5b)

As a brown solid, yield 88.95%, m.p. 248-253 °C. IR (KBr): υ 1519 (C=N), 1149 (C=S) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 5.74 (s, 2H, CH_2), 7.70 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H). 8.46 (s, 1H, N=CH), 8.51 (s, 1H, Ar-H). ESI-MS: m/z = 277 $[M+H]^+$.

Ligand preparation

All the ligands were drawn in Maestro and converted to 3D conformations using Ligand prep. All the possible tautomers and stereo isomers were generated using EPIK. The geometry optimization for all the molecules was carried out using the OPLS-2005 force field with Steepest Descent followed by



Molecular docking

Docking in a true sense is the formation of non- covalent protein-ligand complexes in silico. Given the structure of a protein and a ligand, the task is a predict the structure of the complex. A docking method estimates the forces involved in the protein-ligand recognition viz.electrostatic, van der walls and hydrogen bonding and place the ligand appropriately in the active site [21].

Nonsteroidal anti–inflammatory drugs (NSAIDs) are used as therapeutic agents for the treatment of pain and inflammation. The pharmacological target of NSAIDs is cyclooxygenase (COX) or prostaglandin H_2 synthase (PGHS). Three isoforms of COX have been identified; COX -1, COX -2 and COX -3. COX-2, which is induced by cytokines, nitrogen's and endotoxins in inflammatory cells [22, 23].

All the computational studies were carried out using Maestro V 2011 (Schrodinger, LLC, and Newyork, USA) installed in an Intel core 2 Duo processor with 2 GB RAM and 160 GB hard disk with Windows 7 operating system.

truncated Newton conjugated gradient minimization methods. Partial atomic charges were computed using OPLS-2005 force field.

Protein Preparation

The crystal structure of COX-2 (pdb code: 4COX) with 2.9 Å resolution was used in the study. Amino acid residues within 10 A radius of the ligand, Indomethacin were considered as Active site residues. All the crystallographic waters outside

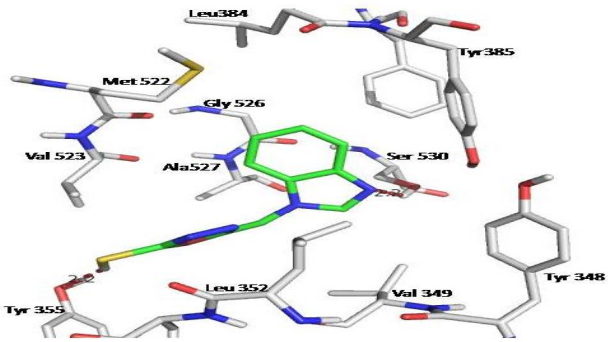


Fig. The active site of COX-2 with Molecule 5a docked into it. H-bonds are seen as dotted lines.

Table-1. Chemical data of the synthesized compounds

Compound no	R	IUPAC name
5a	H	5-((1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol
5b	NO_2	5-((5-nitro-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol

Table-2. Physical constants of the synthesized compounds

Compound code	R	Molecular formula	Molecular weight	MP °C	% Yield
5a	H	$C_{10}H_8N_4OS$	232	235-240	94.69
5b	NO_2	$C_{10}H_7N_5O_3S$	277	248-253	88.95

Table-3. Characterization of title compounds for Mass, NMR, and IR spectral studies

Compound no	Mass(m/e)	IR(cm^{-1})	H^1 NMR (ppm)
5a	233	IR (KBr): υ 1520 (C=N), 1149 (C=S) cm^{-1}	δ 5.92 (s, 2H, CH_2), 7.45-7.52 (m, 2H, Ar-H), 7.74-7.90 (m, 2H, Ar-H), 9.31 (s, 1H, N=CH
5b	277	υ 1519 (C=N), 1149 (C=S) cm^{-1}.	δ 5.74 (s, 2H, CH_2), 7.70 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H). 8.46 (s, 1H, N=CH), 8.51 (s, 1H, Ar-H).

Table-4. Pharmacokinetic parameters

Compound	Volume(A3)	TPSA(A2)	RB	HBA	HBD	Log*P*	MW	N atoms	Lipinski's violation
Rule		≤140Å^2	10	<10	<5	≤ 5	<500		≤ 1
5a	188.372	56.75	2	5	0	1.113	232.26	16	0
5b	211.706	102.57	3	8	0	1.048	277.26	19	0
IND	303.24	68.53	4	5	1	3.986	357.79	25	0

TPSA: Total polar surface area; RB= Rotatable bonds; HBA=Hydrogen bond acceptors; HBD=Hydrogen bond donors; MW=Molecular weight; IND=Indomethacin

Table-5. Partition coefficient, Solubility and Drug likeness model score of the synthesized compounds

Compound	R	Mol. formula	ALOGPS	KoW-WIN	XLOGP2	Drug-likeness model score
5a	H	$C_{10}H_8N_4OS$	-3.35 (0.10g/l)	1.12	2.65	0.4
5b	NO_2	$C_{10}H_7N_5O_3S$	-3.35 (0.12g/l)	0.94	2.54	-0.24
IND		$C_{18}H_{14}ClNO_4$	4.87(4.68mg/l)	3.68	3.95	0.57

the active site were removed and the protein was prepared for docking using the protein preparation tool implemented in the Schrodinger suite 2011 (Schrodinger LLC). The resulted structure was minimized using the OPLS-2005 force field with normal Batch Min cutoffs - 7.0 Å van der Waals [VDW]; 12.0 Å electrostatic [ELE]. The Generalized Born/Solvent Accessible (GB/SA) water salvation model was used in the minimization.The Docking studies were carried out using the Glide docking program in Schrodinger suite. The Docking grid was generated using the co-ordinates of the X-ray ligand (Indomethacin) with the standard settings. The molecular recognition of Indomethacin with active site residues of COX2 includes several hydrophobic and hydrophilic interactions. The side chain carboxylic acid group of indomethacin forms hydrogen bonds with Tyr355 and Arg 120 residues. While the indole moiety along with the side

Table-6. Osiris calculations

Compd	R	CLP	Toxicity Risks			
			MUT	TUM	IRRI	REP
5a	H	1.51				
5b	NO_2	1.51				
IND		3.83				

CLP: clogP, MET: Mutagenic, TUM: Tumorogenic, IRRI: Irritant, REP:Reproductive effect.
Green color indicates no toxicity risk, and red color indicating a moderate mutagenic effect.

chain phenyl ring forms weak hydrophobic interactions with the active site residues Val 349, Ala 527, Leu352, Val 523 and Ser 353.

drug /lead. The title compounds were synthesized on the basis of molecular properties, and subjected to docking studies, The compound **5a** show good interactions with Tyr 355 and Arg 120 similar to the side chain carboxylate group of indomethacin in the crystal structure (4COX). The side chain Sulfahydryl group mediates the hydrogen bond with Tyr 355. Additionally it is observed that the ring nitrogen of Benzimidazole ring forms hydrogen bond with Ser 530. Apart from these interactions, van der Waal's (vdw) or hydrophobic interactions are seen Ala527, Tyr 385 and Val 523. Hence the interactions of indomethacin with the COX-2 active site residues are similar to the interaction of the synthesized compounds, this confirm the anti inflammatory activity.

Table - 7 Molecular bioactivity of the synthesized compounds

Compound	GPCR ligand	Ionchannel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
5a	-0.95	-1.14	-0.51	-1.36	-0.7	-0.27
5b	-0.86	-0.99	-0.43	-1.08	-0.65	-0.3
IND	0.24	-0.31	-0.11	0.42	-0.11	0.30

Docking studies of molecule **5a** shows interactions with the COX-2 active site residues. Figure **of 5a** shows the interactions of molecule **5a** with the active site residues. The side chain Sulfhydryl group mediates the hydrogen bond with Tyr 355. Additionally it is observed that the ring nitrogen of Benzimidazole ring forms hydrogen bonds with Ser 530. Apart from these interactions, van der Waal's (vdw) or hydrophobic interactions are seen Ala527, Tyr 385 and Val 523. Compound 5a showed the interactions of indomethacin with the COX-2 active site residues. This explains the anti inflammatory activity of **5a**.

Results and discussion

After successful prediction of molecular properties, values are within the limit, following Lipinski rule, fulfill the requirements of solubility, low polar surface area, total hydrogen bond count are important predictors of good oral bioavailability. Both XLOGP2 and KoW-WIN are the best supporters on the basis of lipophilicity to consider as oral

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