Calculation of Properties of Phenobarbital an Antiepileptic Drug Using Chemcalise Software

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Abstract: Medications of barbiturate class are used in the treatment of certain types of diseases like insomnia (difficulty sleeping), and for controlling certain seizures. One such type of medicinally important compound is Phenobarbital. It is also known for its activities .as anticonvulsant, antidepressant and antihypnotic. In view of medicinal importance of Phenobarbital its structure and properties were studied by using chemcalise software of Chemaxon and data obtained is interpreted.

Keywords: Phenobarbital, Properties, pka, Isoelectric Point, logP, logD, Solubility, Geometry, HNMR

I. INTRODUCTION

A compound Phenobarbital is well known medications of barbiturate class which is used in treating insomnia (difficulty sleeping). It is also used for controlling seizures caused due to Epilepsy [1-3].

By the use of Chemaxon's cutting edge technology , a powerful online facility of chemcalize was developed. In this it is possible to peform the chemical calculations , name-structure conversion , search etc. We can draw the chemical structure as an input and the calculation view gives the structure, structure-based calculations , its 3D view , the molar and exact mass. Structural properties (like atom count, Hydrogen bond acceptor count , polar surface area, polarizability are given by the calculation view. pKa, isoelectric point ,logP, logD ,solubility,H-NMR spectral data were also obtained in the chemcalise software.

In the present paper the structure of chemical compound Phenobarbital is drawn by using the chemicalise software and all the results obtained were presented in detail. The particulars of basic properties, structural properties, names and identifiers like IUPAC name, Traditional name, Common names, SMILES, InChI, CAS Registry numbers of Phenobarbital are provided in this paper. pKa,isoelectric point, logP. logD, Solubility, Geometry and ^{1}HNMR spectrum of Phenobarbital were analysed in detail as given in this manuscript.

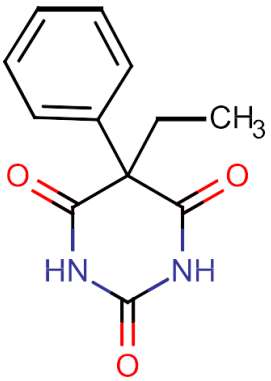


Fig 1. Structure of Phenobarbital

Basic properties of Phenobarbital

The structure of Phenobarbital is drawn as the input and from the data[4,5] given **(Table 1)** it is clearly evident that the formula of phenobarbital is $C_{12}H_{12}N_2O_3$ and its composition is C=69.06 % ,H=5.21 %,N=12.06 %, O=20.67% .The molar mass of Phenobarbital is 239.239 g/mol and its exact mass is 232.084792254 Da.

Table 1. Data of mass and composition of Phenobarbital

Input	Phenobarbital
Molar mass	239.239 g/mol
Exact mass	232.084792254 Da
Formula	$C_{12}H_{12}N_2O_3$
Composition	C=69.06 % H=5.21 % N=12.06 % O= 20.67%

II. STRUCTURAL PROPERTIES OF PHENOBARBITAL

Data of structural properties of Phenobarbital were presented in Table.2. The atom count of 29 of Phenobarbital is in agreement with the number of atoms as given in chemical formula of $C_{12}H_{12}N_2O_3$. In this there are 12 carbons , 2 nitrogens and 3 oxygens which are the heavy atoms and the sum of these is in agreement with the total heavy atom count of 17 atoms. There is no asymmetric atom and Phenobarbital has two rotatable bonds [6-8]. It has two rings among which one is aromatic ring and one is hetero ring. It has two H bond donor(two –NH sites) and 3 H bond acceptors(three =O sites) as evident from the structure of Phenobarbital [9-10] (fig 1). The topological polar surface area[11] is Phenobarbital is75.27 A^2. Molar refractivity of Phenobarbital is indicated to be 59.75 cm^3/mol.

Table 2. Data of structural properties of Phenobarbital

Atom count	29
Heavy Atom count	17
Asymmetric Atom count	0
Rotatable bond count	2
Ring count	2
Aromatic Ring count	1
Hetero Ring count	1
FSP3	0.25
Hydrogen bond donor count	2
Hydrogen bond acceptor count	3
Formal charge	0
Topological polar surface area	75.27 A^2
Polarizability	23.18 A^3
Molar Refractivity	59.75 cm^3/mol

Names and Identifiers of Phenobarbital

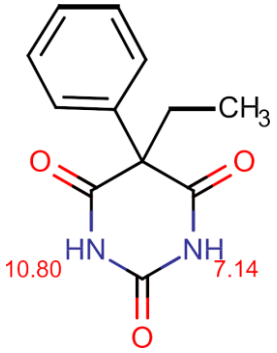
The following names of Phenobarbital were given by the chemcalise software.other details like SMILES, InChI, InChIKey ,CAS Registry numbers of Phenobarbital were also obtained(Table 3)

Table 3. Names and Identifiers of Phenobarbital

IUPAC name	5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione
Traditional name	Phenobarbital

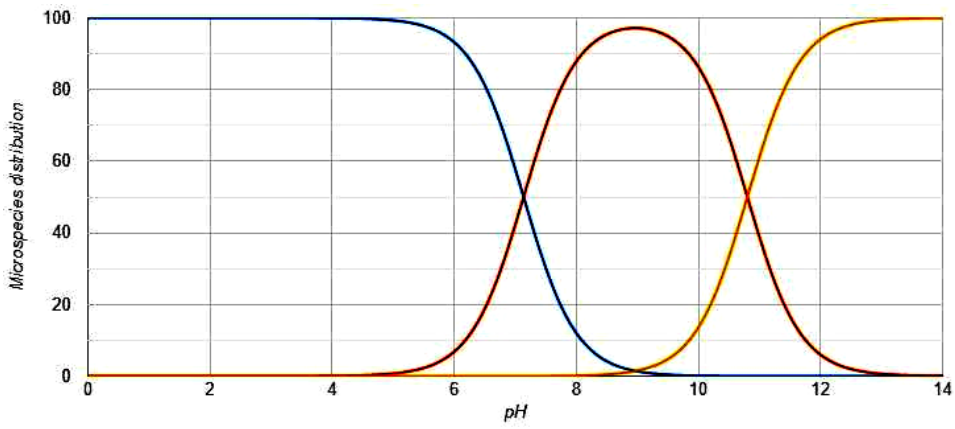
Common names	fenobarbital; luminal; Phenobarbital; Phenobarbitol; phenobarbitone; phenobarbituric acid; phenylethylbarbitursaeure; phenyalethyl barbiturate; phenylethyl barbituricacid; phenylethylbarbitursaeure; phenylethylmalonylurea
SMILES	CCC1(C(=O)NC(=O)NC1=O)C1=CC=CC=C1
InChI	InChI =1S/C12H12N2O3/c1-2-12(8-6-4-3-5-7-8)9(15)13-11(17)14-10(12)16/h3-7H,2H2,1H3,(H2,13,14,15,16,17)
InChIKey	DDBREPKUVSBGFI-UHFFFAOYSA-N
CAS Registry numbers	11097-06-6,46755-67-3,50-06-6

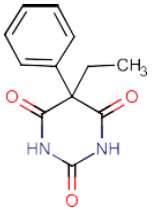
Fig 2. Structure of Phenobarbital with pKa values of 7.14 and 10.80 **indicating strongest acidic nature**

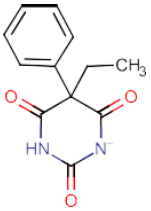


pKa is the measure of the acid dissociation constant given as pKa = - log $_{10}$ (K) and it is a measure of the strength of an acid in solution quantitatively[12-15]. In chemcalise the pKa values of Phenobarbital is found to be 7.14 and 10.80 thereby indicating its strong acidic nature(Fig 2.). This is attributed to the dissociation of protons of amide group (-NH).

The following graph(Fig 3.) shows the distribution of pH for the different microspecies of Phenobarbital







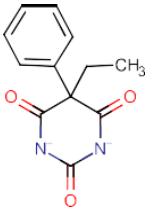


Fig 3. Distribution of pH for the different microspecies of Phenobarbital

Isoelectric Point of Phenobarbital

Isoelectric point is defined as the pH of a solution at which the molecules of a substance remain electrically neutral and do not migrate in an electric field. It is the point at which positively and negatively charged groups are in equal numbers. At this point the substance is neutral and has zero electric potential.

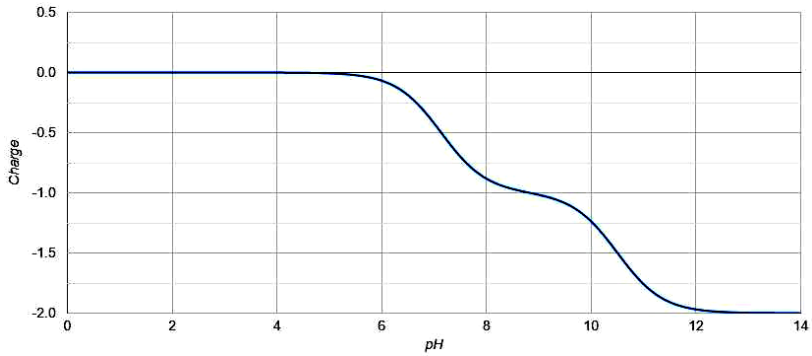


Fig.4 Distribution of charge with pH of Phenobarbital

Table 5. Data of distribution of charge with pH of Phenobarbital

pH	charge
1.7	0.00
4.6	0.00
6.5	-0.19
7.4	-0.65
8	-0.88

The distribution of charge with pH of Phenobarbital is graphically depicted in the fig 4 and the coressponding data is given in the table 5 . From the above graph it is evident that phenobarbital is electrically neutral with zeo electric charge within the pH range of 1.7 to 4.6 indicating the isoelecrtric point.

log P and log D of Phenobarbital

logP is the octanol-water partition for the neutral (un-ionized) form of the compound. logP value of Phenobarbital [16-18] is found to be 1.41

log D is a log of partition of a chemical compound between the lipid and aqueous phases.The following figure shows the variation of the log D value of Phenobarbital [16-18] with pH. It is observed that the log D value is same being 1.41 within the pH range of 1.7 to 4.6 and further log D value decreases as the pH increases.(Fig 5 &Table 6) . The column and the line graph showing variation of log D with pH is given in the figures 6 & 7 respectively

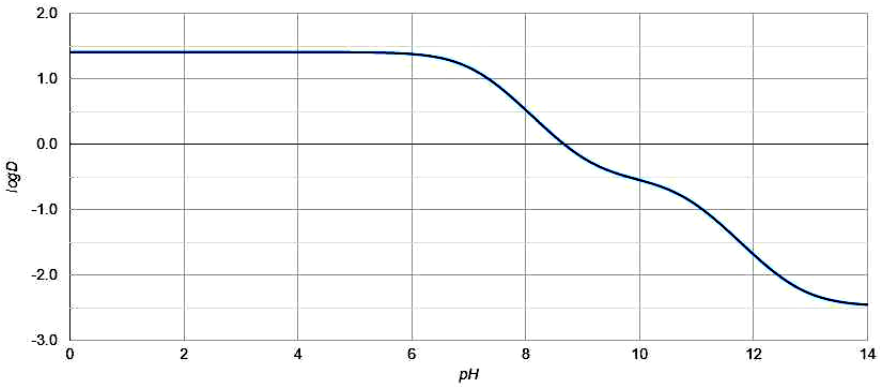
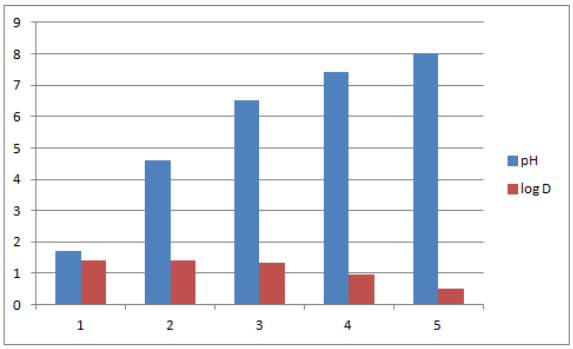


Fig 5. Distribution of log D with pH of Phenobarbital

Table. 6 Data of Distribution of log D with pH of Phenobarbital

pH	log D
1.7	1.41
4.6	1.41
6.5	1.32
7.4	0.96
8	0.52



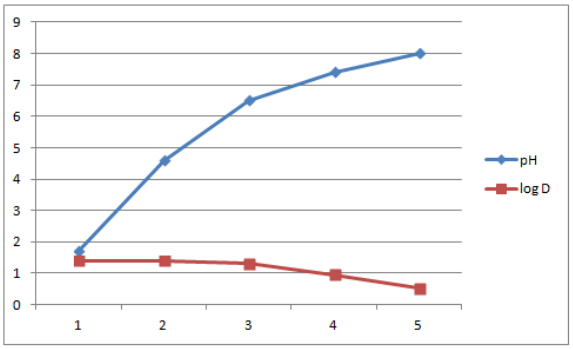


Fig. 6 Column graph of Distribution of log D with pH

Fig.7 Line graph of Distribution of log D with pH

Solubility of Phenobarbital (log S)

Log S is the unit of expressing solubility and it is the 10 based logarithm of the solubility . It is expressed in three units as log S,mol/l and mg/ml.The following graph shows the distribution of log S with pH (Fig.8) and the data (Table. 7) indicates that Phenobarbital[19-20] is of High solubility category with Intrinsic solubility of -2.23. The column and the line graph showing variation of Solubility of Phenobarbital (log S) with pH is given in the figures 9 &10

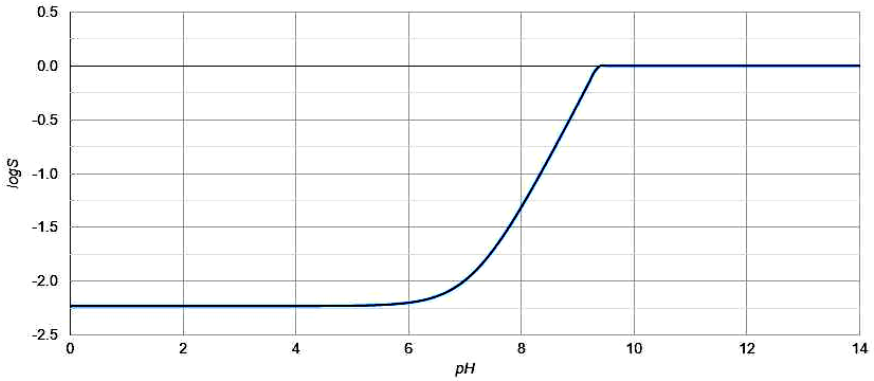
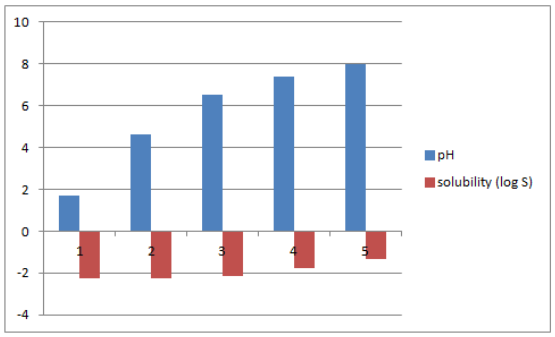


Fig.8 Distribution of log S with pH of Phenobarbital

Table. 7 Data of Distribution of solubility (log S) with pH of Phenobarbital

pH	solubility (log S)
1.7	-2.23
4.6	-2.23
6.5	-2.14
7.4	-1.78
8.0	-1.31



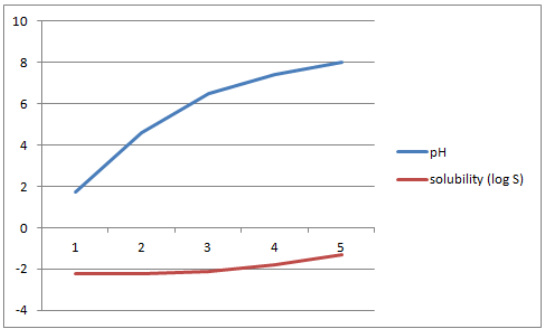


Fig.9 Column graph of Distribution of log D with pH

Fig.10 Line graph of Distribution of log D with pH

Solubility of Phenobarbital in mg/L

Solubility of an organic compound is affected by the pH of the solution. with the change in the pH there will be change in the charge state of the organic compound.At low pH the molecule carries neutral electric charge due to which the solubility of the compound is minimum and precipitate is formed as the compound comes out of the solution. Table 8 below shows that Phenobarbital[19-20] has low solubility of 1.36 mg/l at pH of 1.7 and can be precipiotated at this pH. with the increase in the pH of the solution, the solubility of Phenobarbital increases to maximum value of 11.32 mg/l at pH of 8 as evident from the following table and graphs. A graph showing the increase in solubility of Phenobarbital with pH is given as following figure 11 .The column and the line graph showing variation of Solubility of Phenobarbital in mg/L with pH is given in the figures 12&13

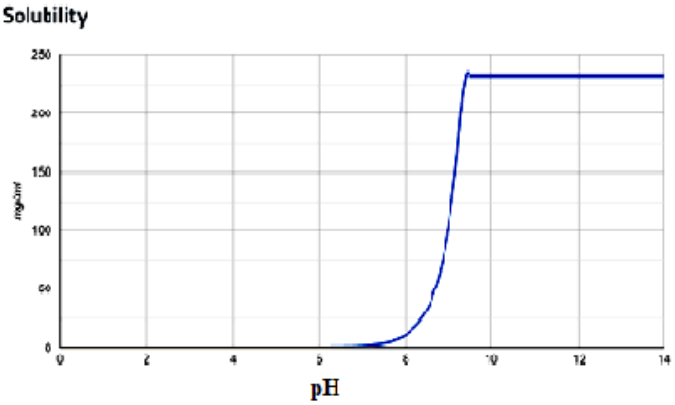


Fig. 11 Distribution Solubility in mg/L of with pH of Phenobarbital

Table. 8 Data of Distribution of solubility in mg/L with pH of Phenobarbital

pH	solubility mg/l
1.7	1.36
4.6	1.37
6.5	1.68
7.4	3.86
8.0	11.32

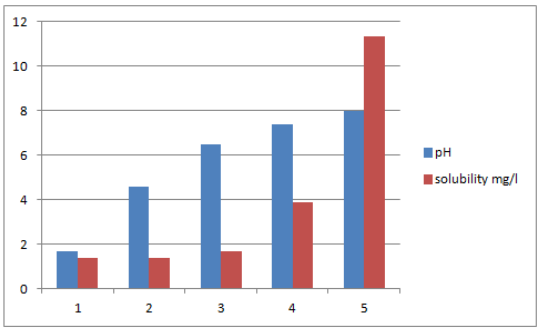


Fig.12 Column graph for Distribution of Solubility in with pH of Phenobarbital

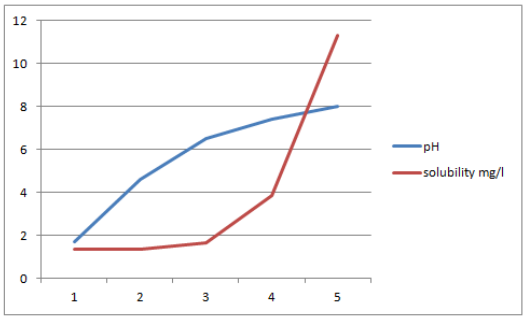
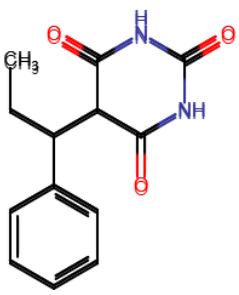


Fig. 13 Line graph for Distribution of solubility in mg/L mg/L with pH of Phenobarbital

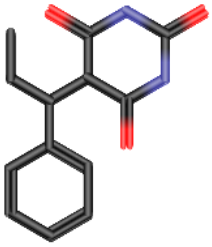
Various forms of Structure of Phenobarbital

The following figures 14a to 14e shows the various forms of structure of Phenobarbital like wire frame model, ball & stick form, stick form, space fill model and structure with with explicit hydrogens added as indicated by the chemcalise software.

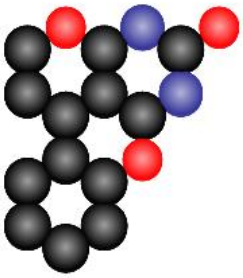


(a) wire frame form

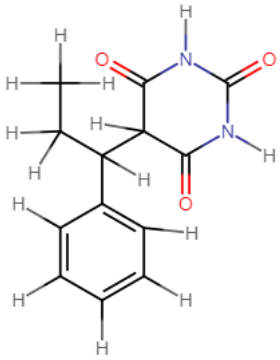
(b) ball & stick form



(c) stick form



(d) spacefill model



(e) with explicit hydrogens added

Fig.14 various forms of structure of Phenobarbital

Geometry of Phenobarbital

By using the chemcalise software the following information of vanderwaals volume, surface area ,projection area projection radius were obtained.(Table. 9)

Table. 9 Data of of volume, surface area , Projection area and Projection radius of Phenobarbital

Vanderwaals volume	**202.91A^3**
Vanderwaals surface area	**322.18 A^2**
Solvent accessible surface area	**358.58 A^2**
Topological polar surface area	**75.27 A^2**
Minimum Projection area	**41.97 A^2**
Maximum Projection area	**60.57 A^2**
Minimum Projection radius	**4.34 A**
Maximum Projection radius	**5.48 A**

^{1}H-NMR spectrum of Phenobarbital

The NMR Predictor in ChemAxon is able to predict NMR spectra for standard organic molecules containing most frequent atoms.(molecules with H,C,N,O,F,Cl,Br,I,P,S,Si, Se,B, Sn,Ge,Te andAs atoms). The chemical shifts are estimated by a mixed HOSE and linear model based on topological description scheme and are in relation to the chemical shift of tetra methylsilane (TMS = 0ppm).H Chemical shift training data were retrived for training from the NMR Shift Database. H-NMR spectrum of Phenobarbital[21] is given in the figure 15.

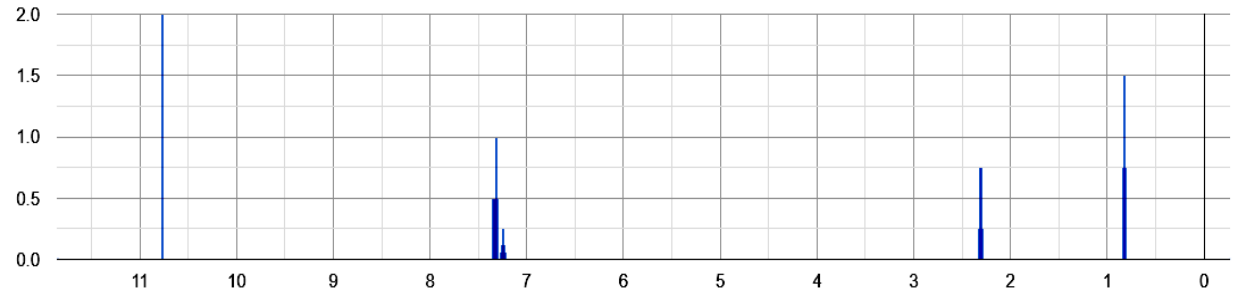
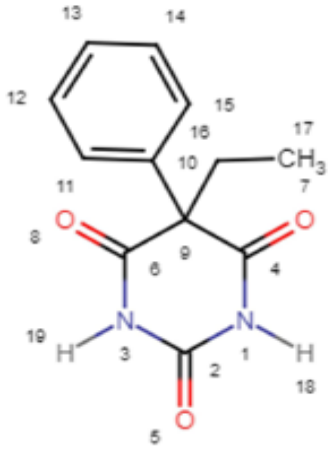


Fig.15 [1]HNMR spectrum of Phenobarbital

Table 10. shifts caused by the protons of Phenobarbital and the intensity and quality for each shift and corresponding protons are shown in the figure



Atoms	shift		Intensity	multiplet	Quality
17,17,17	0.83 ppm	Methyl protons	3	t	good
16,16	2.308 ppm	Aromatic protons	2	q	medium
13	7.248 ppm	Aromatic protons	1	n	good
12,14	7.320 ppm	Aromatic protons	2	t	good
11,15	7.340 ppm	Aromatic protons	2	q	good
18,19	10.772 ppm	-NH	2	s	rough

The above table 10 shows the shifts caused by the protons of Phenobarbital and it also indicates the intensity and quality for each shift. A multiplet observed at 10.772 ppm corresponds to protons of -CONH(amide groups). Multiplets observed in the range of 2.308 ppm to 7.340 ppm indicates the aromatic protons and the shift at 0.83 ppm coressponds to protons of methyl group.

CONCLUSIONS

From the chemcalise software data of pKa values and [1]HNMR spectral data it is clear that Phenobarbital is a strongly acidic compound with two dissociable protons. Distribution of log D, log S, solubility in mg/L with pH of Phenobarbital were intrepreted graphically and were studied in detail. The structure of Pheniobarbital in various forms is also representated and this enabled the proper intrepretation of structural features. As indicated by the geometry all the features like vanderwaals area,vanderwaals volume, projection area projection radius were obtained.

REFERENCES

1. Ilangaratne, NB; Mannakkara, NN; Bell, GS; Sander, JW (Dec 1, 2012). "Phenobarbital: missing in action." *Bulletin of the World Health Organization* 90(12): 871–871A. doi:10.2471/BLT.12.113183. PMID 23284189.

2. Brodie, MJ; Kwan, P (December 2012). "Current position of phenobarbital in epilepsy and its future". *Epilepsia.* 53 Suppl 8: 40–6. doi:10.1111/epi.12027. PMID 23205961.

3. "The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care NICE guidelines [CG137]". *National Institute for Health and Care Excellence*. January 2012.

4. G. Audi, A.H.Wapstra, The 1995 update to the atomic mass evaluation, *Nuclear Physics A*, Vol. 595, Issue 4, pp. 409-480, 1995.
5. E. A. Hill, On A System Of Indexing Chemical Literature; Adopted By The Classification Division Of The U. S. Patent Office., *J. Am. Chem. Soc.*, 22(8), pp. 478-494, 1900.
6. ChemAxon article: Molecules from the Minkowski space: an approach to building 3D molecular structures
7. ChemAxon poster: 3D structure prediction and conformational analysis
8. ChemAxon poster: Advanced automatic generation of 3D molecular structures
9. Ferrara P,. Apostolakis J., Caflisch A., *Proteins* **2002 ,** 46, 24-33; DOI: https://doi.org/10.1002/prot.10001
10. Hasel W., Hendrickson T., Still W., *Tetrahedron Computer Methodology*, **1988**, Vol. 1, Issue 2, 103-116, DOI: https://doi.org/10.1016/0898-5529(88)90015-2
11. Ertl, P., Rohde, B., Selzer, P., *J. Med. Chem.*, **2000,** *43*, pp. 3714-3717; DOI: https://doi.org/10.1021/jm000942e
12. Prediction of dissociation constants using microconstants, J.Szegezdi and F.Csizmadia.27th ACS National Meeting,Anaheim, California, March 28- April 1, 2004.
13. Calculating pKa values of small and large molecules, J.Szegezdi and F.Csizmadia , American Chemical Society Spring meeting ,March 25-29th,2007
14. Clark F.H, Cahoon,N.M., *J.Pharm Sci*., 1987,76,8, 611-620
15. Dixon .S.L ; Jurs,P.C., *J.Comp.Chem*.,1993,14,12,1460-1467
16. Viswanadhan, V. N.; Ghose, A. K.; Revankar, G. R.; Robins, R. K., *J. Chem. Inf. Comput. Sci.*, **1989**, *29*, 163-172; DOI: https://doi.org/10.1021/ci00063a006
17. Klopman, G.; Li, Ju-Yun.; Wang, S.; Dimayuga, M.: *J.Chem.Inf.Comput.Sci.*, **1994**, *34*,
18. 752; DOI: https://doi.org/10.1021/ci00020a009
19. Csizmadia, F; Tsantili-Kakoulidou, A.; Pander, I.; Darvas, F., *J. Pharm. Sci.*, **1997**, *86*, 865-871; DOI: https://doi.org/10.1021/js960177k
20. Hou, T. J.; Xia, K.; Zhang, W.; Xu, X. J. ADME Evaluation in Drug Discovery. 4. Prediction of Aqueous Solubility Based on Atom Contribuition Approach. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 266-275
21. Shoghi, E.; Fuguet, E.; Bosch, E.; Rafols, C. Solubility-pH profiles of some acidic, basic and amphoteric drugs *European Journal of Pharmaceutical Sciences* **2013**, *48*, 291-300.
22. Gottlieb, H.E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.*, **1997**, *62*, 7612-7515; DOI: 10.1021/om100106e