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# SYNTHESIS, CHARACTERIZATION AND LIPOPHILICITY STUDIES OF BENZOTHIAZOLE DERIVATIVES

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## ABSTRACT

Benzothiazole is a heterocyclic chemical compound. The aim is to synthesize title compounds by facile synthesis procedure starting from p- substituted aniline & potassium thiocyanate to give 6-substituted 2-amino benzothiazole. Subsequently added substituted benzaldehyde, in chlorine, O-NO2, M-NO2, P-NO2, and OCH3 to give these compounds' lipophilicity is determined. Our experiment is to determine lipophilicity as it has become a critical parameter in the pharmaceutical industry. This indicates the relationship of a drug with its biological pharmacokinetic and metabolic properties lipophilicity can be measured by the distribution of a drug between the organic phase which is generally n-octanol pre-saturated with water and the aqueous phase as the water it can be experimentally determined by using various methods like shake flask method, potentiometric, and chromatographic methods. The structure of the synthesized compound was confirmed on the basis of spectral studies (U.V, I.R, H.NMR). The lipophilicity parameter of (4-substituted benzylidene -6- substituted benzo[d] thiazol – 2 amine) was determined by using solvents such as n-octanol and benzene, following the shake flask method and titration method. Which was found that the product is distributed greater in the organic phase than in the aqueous phase, which is lipophilic in nature.

**KEYWORDS:** Lipophilicity, Synthesis of benzothiazol derivatives, Characterization.

## INTRODUCTION

The objective isto improve the knowledge base required for the synthesis, isolation, purification, and characterization of various pharmaceuticals. Heterocyclic chemistry plays a very important role in medicinal chemistry as well as inorganic chemistry. Most ofthe drug molecules formed and possess therapeutic activity due to the heterocyclic scaffold.[6-12] A slight change in heterocyclic moiety leads to a major therapeutic change in the drug molecule. Benzothiazole can serve as a unique and versatile moiety for experimental drug design. Benzothiazole and its derivatives are essentially chemical compounds with tremendous application in the research area as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. Heterocyclic analogs and their derivatives have attracted strong interest in medicinal chemistry due to their biological and pharmacological properties.[12-15]

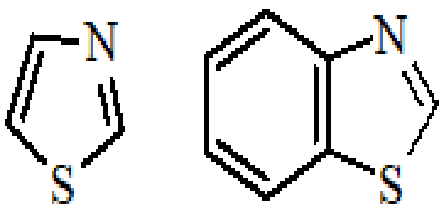



**Fig. 1: Structure of benzthaizole derivatives.[29]**

### Lipophilicity

Lipophilicity is defined as the affinity of a molecule or moiety to a lipophilic environment. It is an important parameter described by the partition coefficient (*P*). It describes the partition of the compound between aquatic and nonpolar solvents. It is commonly assessed by the distribution in a liquid-liquid system (withthe shake-flask method) or liquid-solid (using chromatographic techniques). Lipophilicity is a complex effect of molecular interactions both between solute and solvent as well as interactions between solvent molecules in each phase. The substance, when dissolved in the solvent, disrupts its structure, which causes the breakdown of intermolecular bonds. The substance must create a free space in a given volume of solvent.[15-23] It requires a certain amount of energy and results in a clear correlation of the lipophilicity with the volume or surface of the dissolved molecule.

**Bioavailability and Lipophilicity**

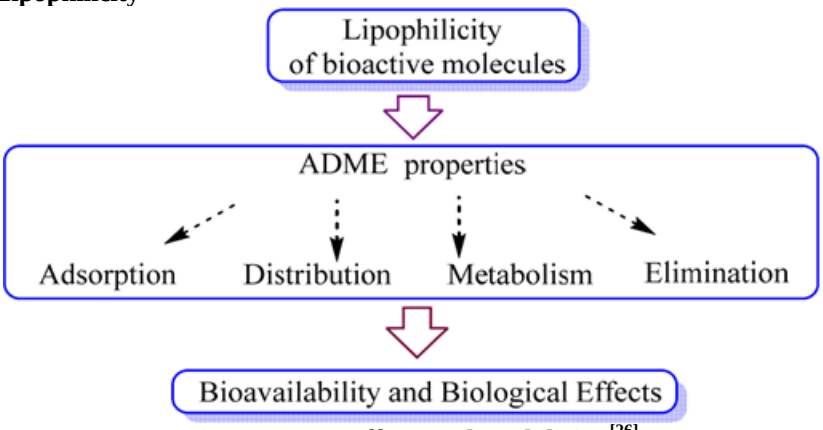



**Fig. 2: ADME effects on lipophilicity.[26]**

Bioavailability is a parameter that is highly dependent on solubility, permeability, and clearance; moreover, all three parameters, in turn, depend on lipophilicity. Studies report that the optimum range of lipophilicity to achieve good availability is log P (logarithm of the partition coefficient) between zero and three. Also, parameters, such as rotatable bonds and ionization state are also good predictors of bioavailability as these also have an effect on parameters, including hydrogen bonding, lipophilicity, molecular volume, and ionizability. Thus, there has been an increase in the drive to control properties, such as solubility and lipophilicity, in order to improve the quality and likelihood of therapeutic success of drug compounds compounds.[30-35]

**FORMULA**

$$\text{Partition coefficient(p)} = \frac{\text{conc. of Drug in org. phase.}}{\text{conc. of Drug in aq. Phase.}}$$

## MATERIALS AND METHODS

Precoated silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds: n-octanol:benzene(1:2),IR spectrometer (model Shimadzu)in the range of 666-4000cm$^{-1}$ and spectra were interpreted. FTIR spectrometer(model 8400 S) showing different vibration levels by using KBR pellet in the region 3433cm$^{-1}$,NMR spectra the samples are analysed on advance 300MH$_2$ and spectra were interpretned.Melting point of the organic compounds were determined by capillary tube method.

### Experimental Section

**First step: General synthesis of 2-amino-6-fluoro-7-chloro-benzothiazole**

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was cooled in a water bath and mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added, from a dropping funnel at such a rate that the temperature never rise beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and the slurry was heated at 85$^0$c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85$^0$c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to p$^H$ 6 A dark yellow precipitate was collected. Recrystallized from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino- 6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in an oven at 80$^0$C, the dry material (1gm51.02%) melted at 210-212$^0$c.[41-45]

**Second step: Synthesis of 4-substituted benzylidene)-6-substituted benzo[d] thiazol-2amine**

A mixture of compound (I) in step 1 (0.01M) and substituted benzaldehyde (0.02M) and 2-3 drops of glacial acid in methanol (20ml) was refluxed in a water bath for 5 hours. The solid was separated and recrystallized from ethanol.[45-47]

**Structure (plan of work)**

**Identification and characterization:** Melting point, Solubility, thin layer chromatography,UV-spectroscopy, infrared spectroscopy, nuclear magnatic resonance spectroscopy.

### Spectral Studies

**Ultra Violet Spectra**

Molecular absorption in the UV region of the spectrum is characteristic of the structures of the molecules. The UV scanning of the compounds was carried and 3-chloro-4-fluoroaniline exhibited $\lambda_{max}$ at 265nm (Spectrum No.1).

The UVspectra of 2-amino-6-fluoro- 7-chloro benzothiazole exhibited $\lambda_{max}$ 303 and 288nm (Spectrum No.2). This clearly indicates the bathochromic shift of the compounds.

**IR Spectra**

The peaks in the IR spectrum give an idea about the

probable structure of the compound IR region ranging between 4000-666 $cm^{-1}$. Quanta of radiation from this region of the spectrum corresponds to energy differences between different vibrational levels of molecules.The compounds were recorded on a SHIMADZU FTIR-8400S spectrophotometer showing different vibration levels of molecules by using the KBr pellet technique. The IR spectrum of 3-chloro-4-fluoro aniline exhibited an absorption band in the region of 3433 $Cm^{-1}$ due to Ar NH2 stretching vibrations, a band at 1622 $Cm^{-1}$ due to NH bending, banded 1494 $Cm^{-1}$ due to Ar C=C stretching, a band at 1200 due to Ar C-F stretching, a band at 762 $Cm^{-1}$ Ar C-Cl stretching (Spectrum No.3).

**NMR Spectra**

NMR spectroscopy enables us to record differences in magnetic properties of the various magnetic nuclei present and to deduce in a large measure the position of these nuclei are withinthe molecule We can deduce how many different kinds of the environment are there in the molecules and also which atoms are present in neighboring groups. The proton NMR spectra enable us to know different chemical and magnetic environments corresponding to protons in a molecule. The samples are analyzed on Avance 300 MHz spectrometer.

**Determination of partition co efficient**

**Procedure**

Take thoroughly cleaned and well dried separating funnel and label it Take 100ml of benzene,100ml of distilled water, and 100mg of derivative of benzothiazole in the separating funnelShake the above solution mixtureAllow the solution to stand for 30 minutes for separating the aqueous and organiclayersAfter 30 minutes aqueous and organic layers are separated out in different beakersAfter separating out the aqueous and organic layers in different beakers label thebeakersTake 10ml of organic solution in a conical flask and titrate against 0.2N NaOH usinga phenolphthalein indicator observe the burette readings until the color changes to pink note down the value of burette readings Follow the same above procedure for an aqueous solution and note down the burette readings. After finding out the values substitute the values in the formula.[35-37]

**$N_1V_1 = N_2V_2$**

$N_1$=normality of NaoH

V1= Volume of NaOH Burette Readings

N2 = Normality of organic /aqueous solution

$V_2$= Volumeof organic / aqueous solution

**Partition co efficient $K = C_{aq}/C_{org/1/n}$**

## RESULTS AND DISCUSSION

**Organic Layer**

**Table 1: Partition coefficient results on organic layer.**

| SNO | VOLUME OF ORGANICLAYER SOLUTION | BURETTE READINGS | AVERAGE |
|---|---|---|---|
| 1. | 10ml | 0.4 | |
| 2. | 10ml | 0.3 | 0.4 |
| 3. | 10ml | 0.5 | |

**$N_1V_1 = N_2V_2$**

COrganic = 1.44

**Aqeous Layer**

**Table 2: Partition coefficient results on aqueous layer.**

| S.NO | VOLUME OF AQUEOUS LAYER | BURETTEREADING | AVERAGE |
|---|---|---|---|
| 1. | 10ml | 0.4 | |
| 2. | 10ml | 0.2 | 0.3 |
| 3. | 10ml | 0.3 | |

**$N_1V_1 = N_2V_2$**

$C_{aq}$ = 1.08

**Partition co efficient=** $K = \sqrt{C_{org}/C_{aq}}$

$K = \sqrt{1.44/1.08}$

K = 1.1

**Result:** As the partition coefficient value is greater than 1. the drug is more soluble in the organic phase than aqueous phase.

**Table 3: Physical data compounds structure.**

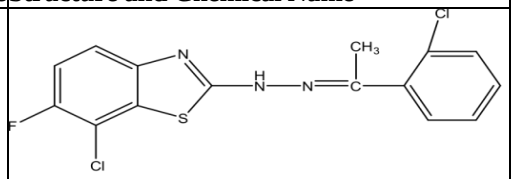
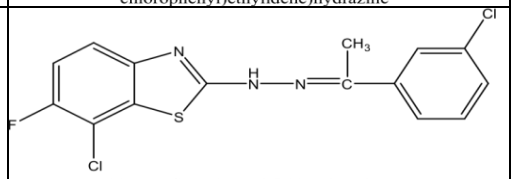
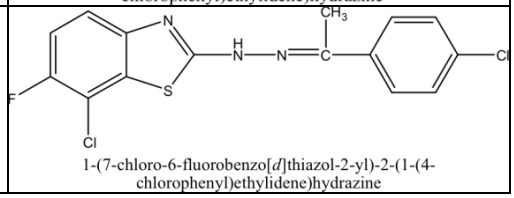
| Sl. No. | Compound Code | Structure and Chemical Name |
|---|---|---|
| 1 | V D1 |  1-(7-chloro-6-fluorobenzo[*d*]thiazol-2-yl)-2-(1-(2-chlorophenyl)ethylidene)hydrazine |
| 2 | V D2 |  1-(7-chloro-6-fluorobenzo[*d*]thiazol-2-yl)-2-(1-(3-chlorophenyl)ethylidene)hydrazine |
| 3 | V D3 |  1-(7-chloro-6-fluorobenzo[*d*]thiazol-2-yl)-2-(1-(4-chlorophenyl)ethylidene)hydrazine |

**Table 4: Solubility results.[48]**

| Sl.No. | CompoundCode | Soluble in | Insoluble in |
|---|---|---|---|
| 1 | V D1 | DMF, DMSO, Ether, benzene, AcetoneChloroform, Methanol, Ethanol | Water |
| 2 | V D2 | DMF, DMSO, Ether, benzene, AcetoneChloroform, Methanol, Ethanol | Water |
| 3 | V D3 | DMF, DMSO, Ether, benzene, AcetoneChloroform, Methanol, Ethanol | Water |

**Table 5: Physical data of Thin layer chromatography results.**

| Sl.No | CompoundCode | M.P/ B.PC | % Yield | MOL. FORM | M.Wt. | C% | H% | N% |
|---|---|---|---|---|---|---|---|---|
| 1 | V D1 | 71-72 | 80% | C15H10S1N3F1Cl2 | 354 | 50.84 | 2.82 | 11.86 |
| 2 | V D2 | 80-82 | 82% | C15H10S1N3F1Cl2 | 354 | 50.84 | 2.82 | 11.86 |
| 3 | V D3 | 83-85 | 65% | C15H10S1N3F1Cl2 | 354 | 50.84 | 2.82 | 11.86 |

**Table 6: Analytical data results.**

| Sl.No | CompoundCode | Solvent system for developing | Proportion ofComponents | Rf Value |
|---|---|---|---|---|
| 1 | V D1 | Butanol Ethyl acetate Chloroform | 1:2:1 | 0.73 |
| 2 | V D2 | Butanol Ethyl acetate Chloroform | 1:2:1 | 0.76 |
| 3 | V D3 | Butanol Ethyl acetate Chloroform | 1:2:1 | 0.72 |

**Table 7: Physical data of IR spectra results.**

| Sl. No. | Spec No. | Compound code | Ar- NH2 $cm^{-1}$ | ArC=C $cm^{-1}$ | CyclicC=N $cm^{-1}$ | C-F $cm^{-1}$ | C-Cl $cm^{-1}$ | NO2 $cm^{-1}$ | CH3 $cm^{-1}$ | C-N $cm^{-1}$ | C-O-C $cm^{-1}$ | Benzo-thiazole $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 3 | CFA | 3433 | 1494 | - | 1259 | 762 | - | - | - | - | - |
| 2 | 04 | 2AB | 3479 | 1460 | 1646 | 1193 | 685 | - | - | - | - | 1390 |
| 3 | 05 | 2HB | 3476 | 1450 | 1632 | 1194 | 688 | - | - | - | - | 1390 |
| 4 | 06 | V D1 | 3350 | 1375 | 1620 | 1190 | - | 740 | 1175 | 1635 | 1075 | 1350 |
| 5 | 07 | V D2 | 3425 | 1380 | 1625 | 1200 | - | 740 | 1175 | 1610 | 1075 | 1350 |
| 6 | 08 | V D3 | 3360 | 1360 | 1600 | 1200 | - | 725 | 1175 | 1630 | 1075 | 1350 |

**Table 8: NMR Spectral Data of Compounds $VD_1$.[49]**

| Sl. No. | SpectraNo. | CompoundCode | Hydrogen | (ppm) | Multiplity | Solvent |
|---|---|---|---|---|---|---|
| 1 | | VD1 | -7H-Ar-H | 6.6-7.8 | Multiplet | CDCl3 |
| | | | -1H-NH | 4.2 | Singlet | |
| | | | -3H-CH3 | 2.85 | Singlet | |

## CONCLUSION

Synthesis characterization and lipophilicity in the present work, fluoro chloro aniline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino- 6- fluoro-7-acid and ammonia to get 2-amino-6-fluoro-7-chloro (1,3)-benzothiazole, which was condensed with hydrazine hydrate and aldehyde in presence of con Hcl to get (4- substituted benzylidene -6-substituted benzo[d] thiazol – 2 amine). And the structure of the synthesized compounds was confirmed on the basis of spectral studies (UV, IR, NMR). And lipophilicity parameter of (4-substituted benzylidene -6-substituted benzo[d] thiazol – 2 amine)was determined by using solvents n-octanol and benzene, following the Shake flask method and titration method. Which was found that the product is distributed greater in the organic phase than in the aqueous phase, which is lipophilic in nature.

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