



**COMPARATIVE LOGARITHMIC PARTITION COEFFICIENT COMPARISON STUDY
OF SYNTHESIZED HYDRAZINE AND PHENYL HYDRAZINE SERIES OF UREA,
THIOUREA AND GUANIDINE TO FORM AMIDE AND LACTAM UNITS**

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ABSTRACT

Partition coefficient of any compound shows the solubility profile of the compound in protic or aprotic solvent. In chemistry, a protic solvent is a solvent that has a hydrogen atom bound to oxygen (as in a hydroxyl group) or nitrogen (as in an amine group). In general terms, any solvent that contains a labile H^+ is called a protic solvent. The molecules of such solvents readily donate protons (H^+) to reagents. Conversely, aprotic solvents cannot donate hydrogen. Polar protic solvents are often used to dissolve salts. In general, these solvents have high dielectric constants and high polarity. Common characteristics of protic solvents: solvents display hydrogen bonding, solvents have acidic hydrogen (although they may be very weak acids such as ethanol), solvents dissolve salts, cations by unshared free electron pairs, anions by hydrogen bonding. Examples include water, most alcohols, formic acid, hydrogen fluoride, and ammonia. Polar protic solvents are favorable for SN_1 reactions, while polar aprotic solvents are favorable for SN_2 reactions. Polar aprotic solvents are solvents that lack acidic hydrogen. Consequently, they are not hydrogen bond donors. These solvents generally have intermediate dielectric constants and polarity. Although discouraging use of the term "polar aprotic", IUPAC describes such solvents as having both high dielectric constants and high dipole moments, an example being acetonitrile. Other solvents meeting IUPAC's criteria include DMF, HMPA, and DMSO. Common characteristics of aprotic solvents: solvents that can accept hydrogen bonds, solvents do not have acidic hydrogen, solvents dissolve salts. The criteria are relative and very qualitative. A range of acidities are recognized for aprotic solvents. Their ability to dissolve salts depends strongly on the nature of the salt. Polar aprotic solvents are generally incompatible with strong bases, such as Grignard reagents or n-butyllithium. These reagents require ethers, not nitriles, amides, sulfoxides, etc. In this project water (dielectric constant: 78.7F/m) and ethanol (dielectric constant: 24.3F/m) were taken as solvents for investigation of solubility during crystallization. Since water is more polar than ethanol so polar compounds dissolve faster in water than ethanol which gave a good result during purification of all compounds.

KEYWORDS: Ethyl acetoacetate, Hydrazine, Phenyl hydrazine, Hydrogen peroxide, Potassium hydroxide, Potassium permanganate, Thionyl chloride, Urea, Thiourea, Guanidine.

INTRODUCTION

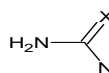
Partition coefficient is the ratio of solute in immiscible organic solvent and water. In the physical sciences, a partition-coefficient (P) or distribution-coefficient (D) is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium. This ratio is therefore a measure of the difference in solubility of the compound in these two phases. The partition-coefficient generally refers to the concentration ratio of un-ionized species of compound whereas the distribution-coefficient refers to the concentration ratio of all species of the compound (ionized plus un-ionized). In the chemical and pharmaceutical sciences, both phases usually are solvents. Most commonly, one of the solvents is water while the second is hydrophobic such as 1-octanol.

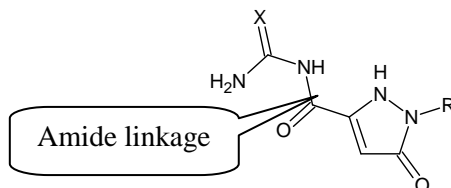
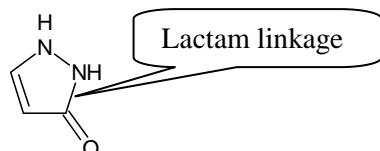
Hence the partition coefficient measures how hydrophilic ("water-loving") or hydrophobic ("water-fearing") a chemical substance is. LogP is a component of Lipinski's Rule of 5 a rule of thumb to predict drug-likeness. The most commonly used measure of lipophilicity is logP; this is the partition coefficient of a molecule between an aqueous and lipophilic phase, usually octanol and water.^[1]

Chemistry

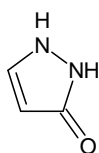
Electronegativity as well as lone pair of electrons present in the molecule shows a remarkable focus on the logP profile of compounds. Generally polarity of a molecule depends on the molecular structure of chemicals if there any electronegative atoms are present or not. In this

project three variables have been taken for preparing desired molecules:

 $\text{H}_2\text{N}-\text{C}(=\text{X})-\text{NH}_2$ X=O for Urea, X=S for Thiourea, X=NH for Guanidine. All these have amide linkages $[-\text{CO}-\text{NH}-]$ in

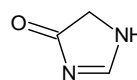


1,2-dihydro-3H-pyrazol-3-one: Amide $[-\text{CO}-\text{NH}-]$ in cyclic form [Lactam] and Amide $[-\text{CO}-\text{NH}-]$ in side



1,2-dihydro-3H-pyrazol-3-one

chain. (R=H for hydrazine series and R=Aromatic ring for phenyl hydrazine series) [logP: -0.39]



1,5-dihydro-4H-imidazol-4-one

1,5-dihydro-4H-imidazol-4-one: This 5 membered ring [logP: -0.97] is isomer of **1,2-dihydro-3H-pyrazol-3-one** (both have same molecular formula= $\text{C}_3\text{H}_4\text{N}_2\text{O}$ & molecular weight: 84) but [logP: -0.39] is different

because in imidazole ring two nitrogen atoms are linked by one carbon atom where as in pyrazole ring same two nitrogen atoms are adjacent to each other which effects on logP of both.

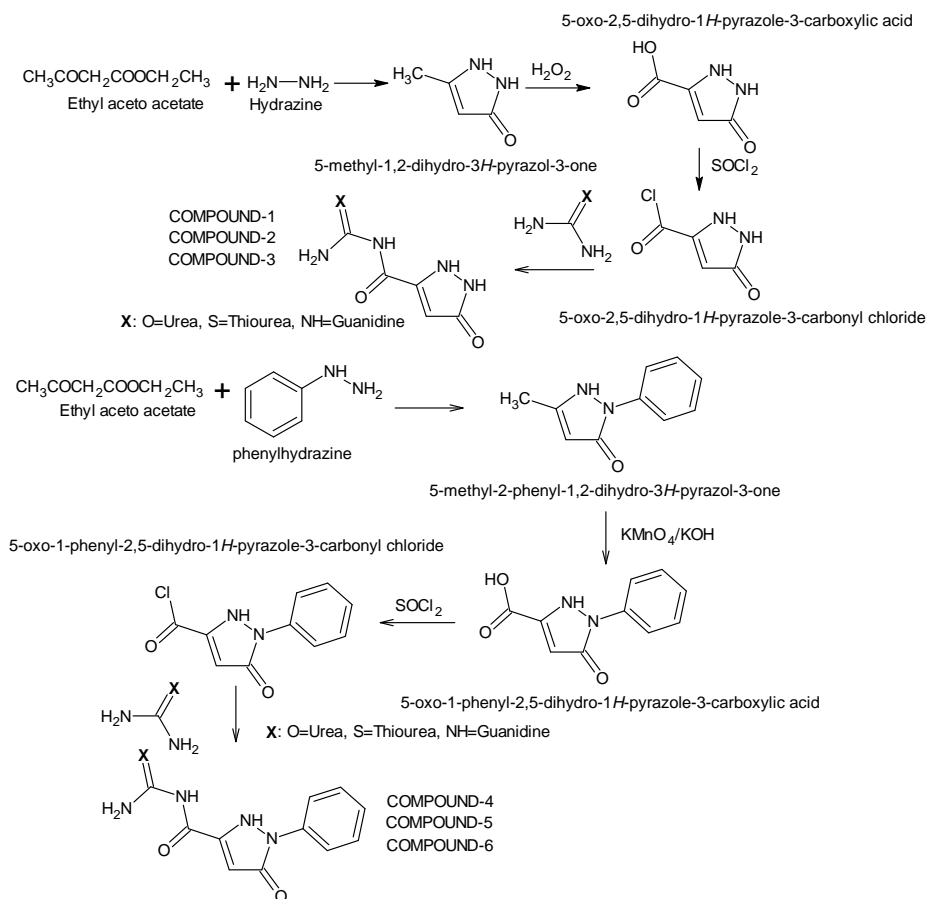


Figure-1: Scheme.

Methyl group oxidation of 5-methyl-1,2-dihydro-3H-pyrazol-3-one by hydrogen peroxide:

Two molecules of hydrogen peroxide decompose to produce two molecules of water and one molecule of oxygen gas *in-situ*. Oxygen molecule is attached by double bond which decomposes by sharing of one lone pair of single oxygen atom to another lone pair of

oxygen atom and charge of one oxygen atom gets cation (\oplus) and another oxygen atom gets anion (\ominus). This now reacts with methyl group (CH_3-) and all three hydrogen atoms ($\text{H}-$) get oxidized into ($\text{OH}-$) but since any carbon atom is unable to hold same functional groups so one water (H_2O) molecule is eliminated and produce carboxylic ($-\text{COOH}$) group.^[2]

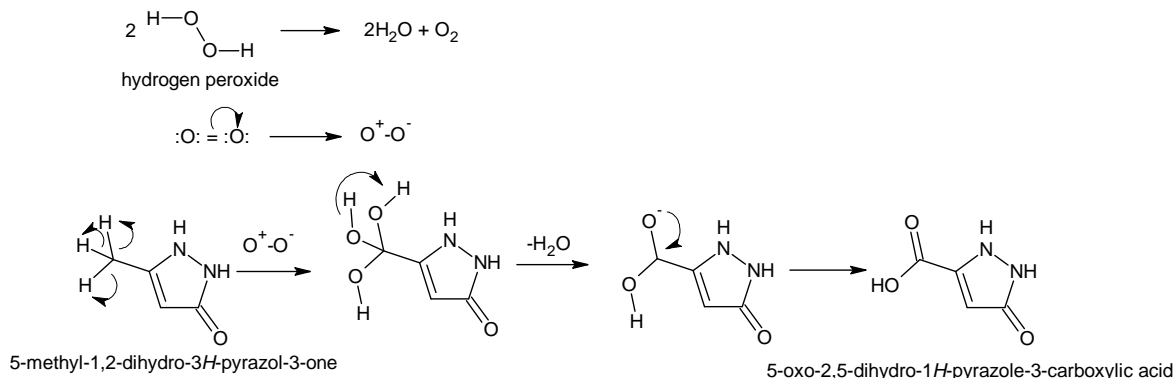


Figure 2: Methyl group oxidation of 5-methyl-1,2-dihydro-3H-pyrazol-3-one by hydrogen peroxide.

Methyl group oxidation of 5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one by alkaline potassium permanganate:

$\text{MnO}_4^- + 4\text{OH}^- + 3\text{e}^- = \text{MnO}_2 + 2\text{H}_2\text{O} + 2\text{O}_2$. Alkaline potassium permanganate oxidation in potassium hydroxide medium consumes three electrons to produce two oxygen molecules *in-situ*. So here one equivalent weight of potassium permanganate is molecular weight/3 [158/3=52.66]. $\text{KMnO}_4 \equiv \text{KOH} \equiv \text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$. $\text{KMnO}_4/3$ (158/3=52.66) $\equiv \text{KOH}/3$ (56/3=18.66) $\equiv \text{C}_{10}\text{H}_{10}\text{N}_2\text{O}/3$

(174.2/3=58). Hence alkaline KMnO_4 oxidation process 1Eq.wt of KMnO_4 (52.66gm):1Eq.wt of KOH (18.66gm):1Eq.wt of 5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (58gm) has been taken for proper oxidation. The byproduct of manganese dioxide precipitate was removed by filtration and acidification of filtrate produced desired compound 5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylic acid.

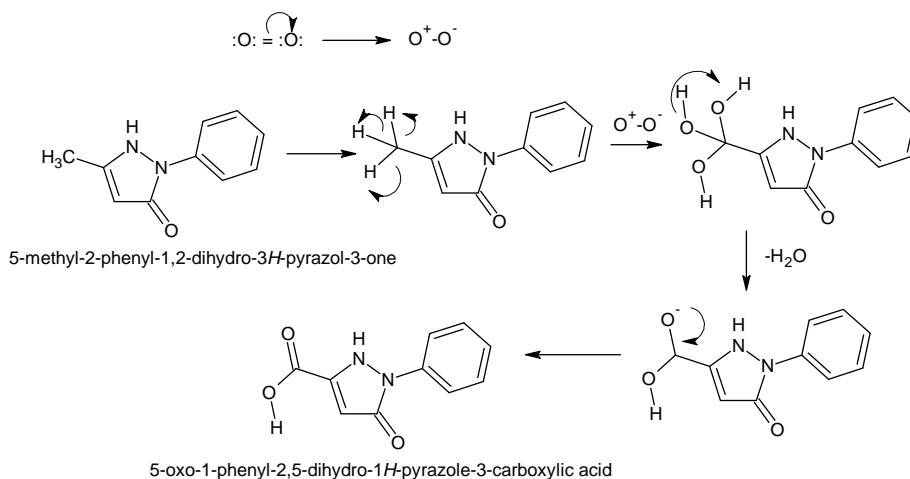


Figure-3: Methyl group oxidation of 5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one by alkaline potassium permanganate.

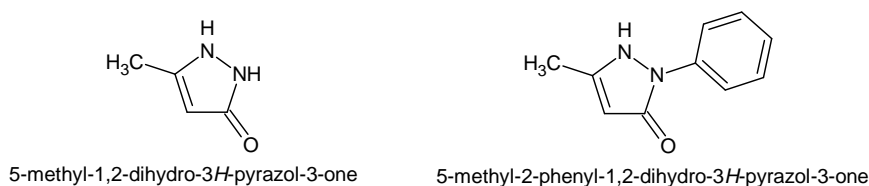


Figure-4: 5-methyl-1,2-dihydro-3H-pyrazol-3-one & 5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one.

5-methyl-1,2-dihydro-3H-pyrazol-3-one: In this molecule methyl group shows positive inductive effect because hydrogen bond is active in lactam nitrogen so here methyl group oxidation is possible by hydrogen peroxide.

5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one: In this molecule methyl group shows negative inductive effect because one inactive group phenyl is attached by lactam nitrogen which withdraws electrons by resonance action so here methyl group oxidation is possible by alkaline potassium permanganate.^[3]

Chemicals

Ethyl acetoacetate (Loba Chemie), Hydrazine (Finar), Phenyl hydrazine (Loba Chemie), Hydrogen peroxide (Finar), Potassium hydroxide (Finar), Potassium permanganate (Finar), Thionyl chloride (Finar), Urea (Finar), Thiourea (Finar), Guanidine (Finar)

Instrument

Beckman DU640 UV/Vis spectrophotometer.

Procedure

Hydrazine series: Ethyl acetoacetate (0.1m) was reacted with hydrazine (0.1m) and were mixed well in ice bath to get white crystals which was recrystallized by hot water with activated charcoal to get purified product [5-methyl-1,2-dihydro-3H-pyrazol-3-one] (m.p. 128-130°C; yield 36%). This was reacted with hydrogen peroxide to oxidize methyl substituent into free carboxylic acid [5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylic acid] (m.p. 100-102°C; 74% yield). This compound was reacted with thionyl chloride to convert free carboxylic acid into acid chloride [5-oxo-2,5-dihydro-1H-pyrazole-3-carbonyl chloride] and finally this has been reacted with urea/thiourea/guanidine to get three products.^[4]

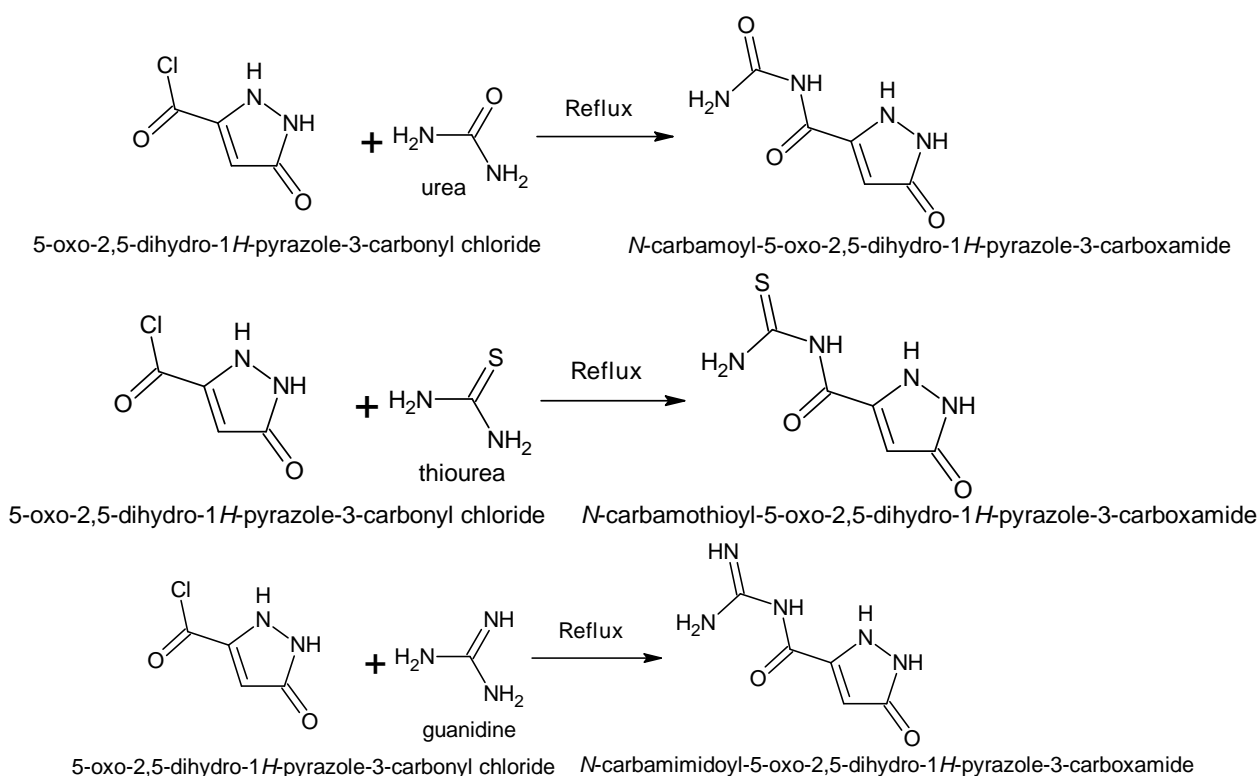
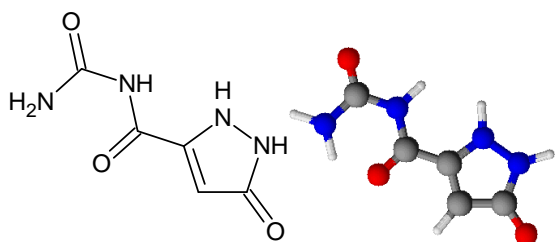
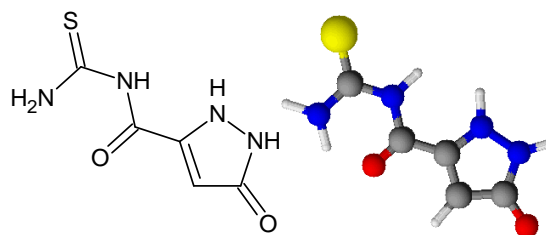


Figure 5: Hydrazine series synthesis.



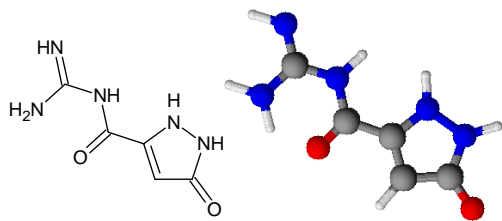
COMPOUND-1:

N-carbamoyl-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxamide [logP: -1.92].



COMPOUND-2:

N-carbamothioyl-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxamide [logP: -1.31]



COMPOUND-3: *N*-carbamimidoyl-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxamide [logP: -2.15]

All three compounds [COMPOUND-1, COMPOUND-2 & COMPOUND-3] have been crystallized and recorded their melting points and % yields.

Phenyl Hydrazine series: Ethyl acetoacetate (0.1m) was reacted with phenyl hydrazine (0.1m) and were mixed well in ice bath to get white crystals which was recrystallized by hot aqueous alcohol with activated charcoal to get purified product [5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one] (m.p. 134-136°C; yield 48%). This was reacted with alkaline potassium permanganate to oxidize methyl substituent into free carboxylic acid [5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid] (m.p. 142-144°C; 66% yield). This compound was reacted with thionyl chloride to convert free carboxylic acid into acid chloride [5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxyl chloride] and finally this has been reacted with urea/thiourea/guanidine to get three products:^[5]

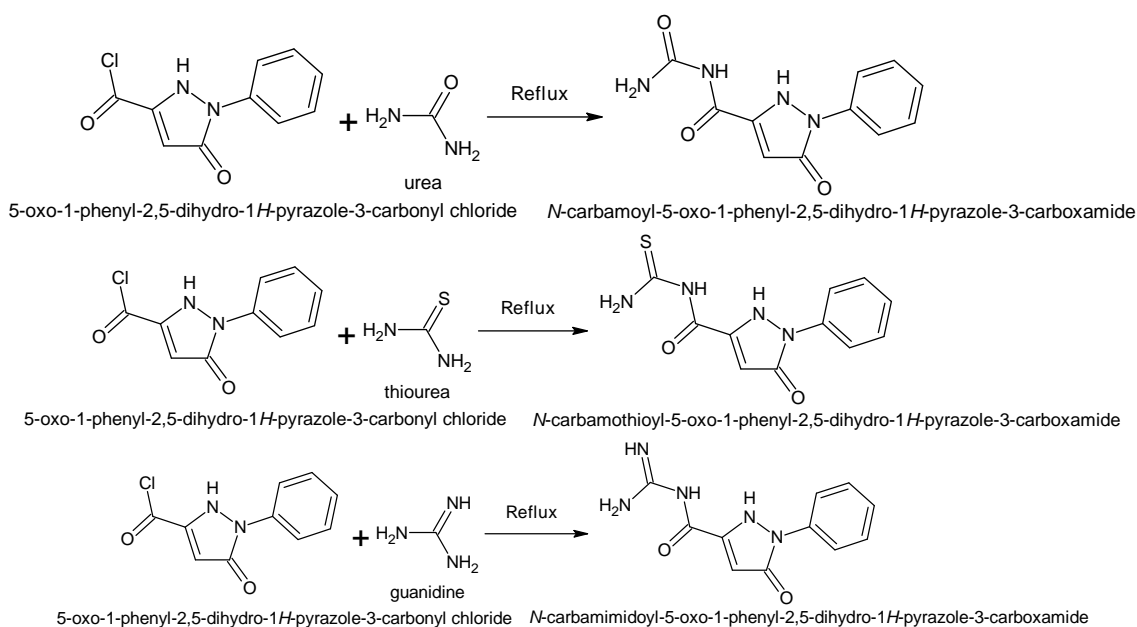
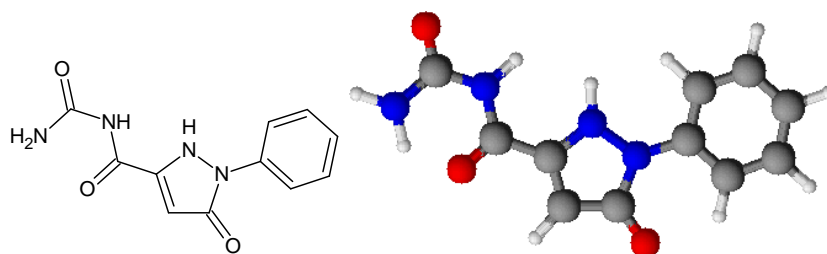
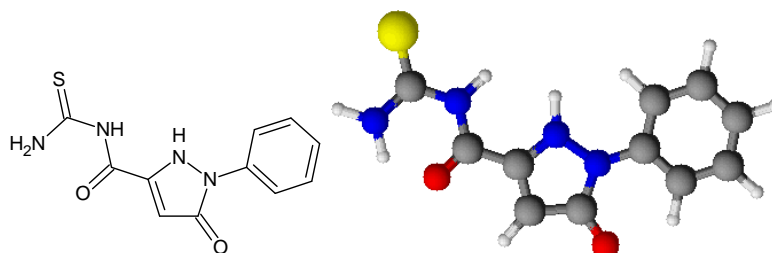


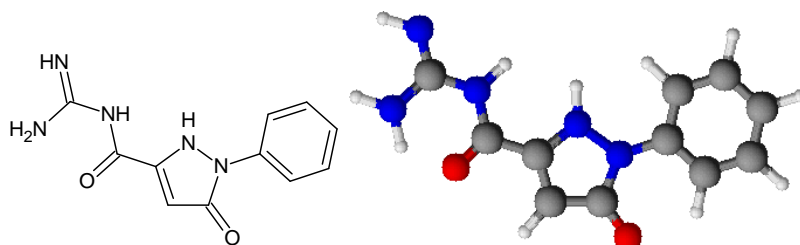
Figure 6: Phenyl Hydrazine series synthesis.



COMPOUND-4: *N*-carbamoyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxamide [logP: -0.4].



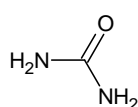
COMPOUND-5: *N*-carbamothioyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxamide [logP: 0.2].



COMPOUND-6: *N*-carbamimidoyl-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxamide [logP: -0.64]

All three compounds [COMPOUND-3, COMPOUND-4 & COMPOUND-5] have been crystallized and recorded their melting points and % yields.^[6]

Polarity index: COMPOUND-3 (-2.15)>COMPOUND-1 (-1.92)>COMPOUND-2 (-1.31)>COMPOUND-6 (-0.64)>COMPOUND-4 (-0.4)>COMPOUND-5 (0.2).



Open chain amide (N-C-N linkage):
Solubility of open chain amide is high [logP: -2.11].

Closed amide (N-C-N linkage) (lactam):
Solubility of closed ring of amide (lactam) is less [logP: -0.95].

N-C-N linkage is present in amide and same is present in lactam. Here open chain amide is made of urea (X: O), thiourea (X: S) and guanidine (X: NH).^[7]

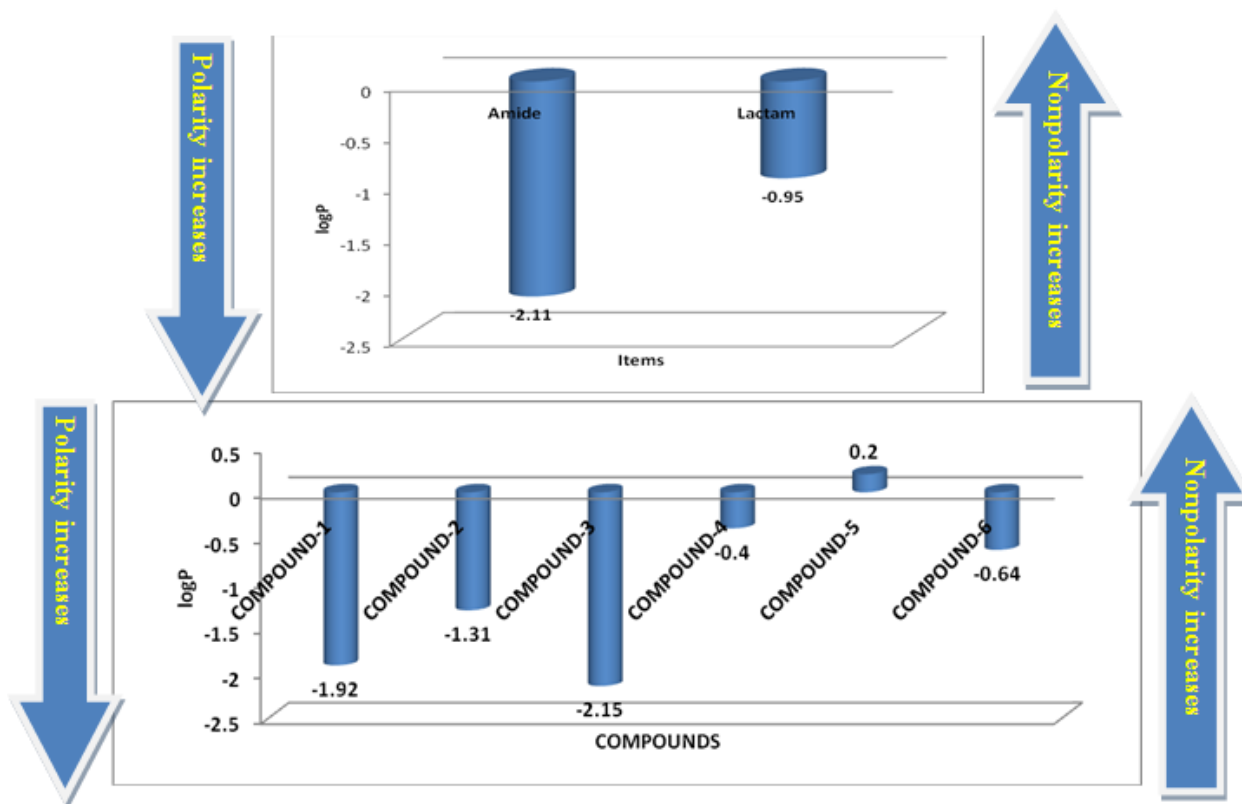


Figure-7: Histogram.

Oxygen has electronegativity 3.44 having two lone pair of electrons. Sulfur has electronegativity 2.58 having two lone pair of electrons. Nitrogen has electronegativity 3.04 having one lone pair of electrons. So the logP profile of six synthesized compounds show the solubility parameters in **hydrazine series**: COMPOUND-3 (Nitrogen derivative of guanidine=-2.15)>COMPOUND-1 (Oxygen derivative of urea=-

-1.92)>COMPOUND-2 (Sulfur derivative of thiourea=-1.31).

In **phenyl hydrazine series**: COMPOUND-6 (Nitrogen derivative of guanidine=-0.64)>COMPOUND-4 (Oxygen derivative of urea=-0.4)>COMPOUND-5 (Sulfur derivative of thiourea=0.2).

Any organic compound made up of carbon, hydrogen, oxygen, nitrogen, sulfur shows different solubility due to the presence of elements according to their position in

the structure and due to this factor the logP profile of all compounds become different from one another.^[8]

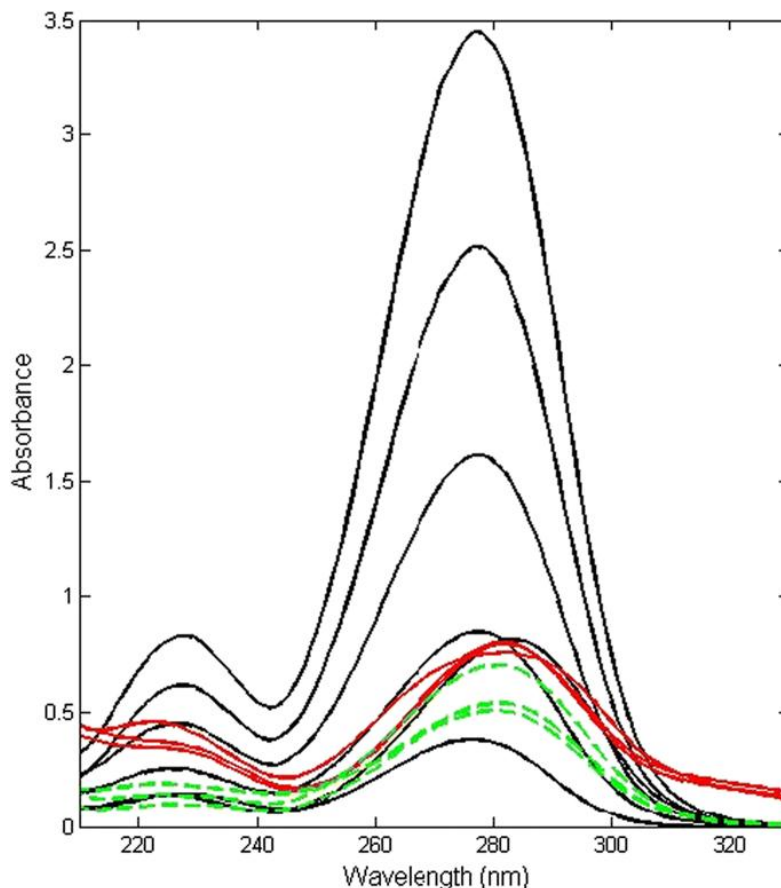


Figure-8: UV absorption spectra.

λ_{\max} of the six samples were determined by making solution of samples in methanol (1 μ g/ml) and data were recorded.

Table 1: Physicochemical parameters.

Compounds	Molecular Weight	Molecular Formula	Melting Point	% yield	λ_{\max}
COMPOUND-1	170g	C ₅ H ₆ N ₄ O ₃	88-90°C	54%	232nm, 276nm
COMPOUND-2	186g	C ₅ H ₆ N ₄ O ₂ S	100-102°C	62%	236nm, 274nm
COMPOUND-3	169g	C ₅ H ₇ N ₅ O ₂	122-124°C	64%	234nm, 276nm
COMPOUND-4	246g	C ₁₁ H ₁₀ N ₄ O ₃	168-170°C	70%	232nm, 278nm
COMPOUND-5	262g	C ₁₁ H ₁₀ N ₄ O ₂ S	178-180°C	56%	226nm, 275nm
COMPOUND-6	245g	C ₁₁ H ₁₁ N ₅ O ₂	188-190°C	68%	230nm, 274nm

CONCLUSION

Hydrazine is more polar than phenyl hydrazine because hydrazine has two free amino groups where as phenyl hydrazine has one non polar group attached at one extremity. So, the polarity of hydrazine series compounds [Compound-1 to Compound-3] are higher than phenyl hydrazine series. Polarity index: COMPOUND-3 (-2.15) > COMPOUND-1 (-1.92) > COMPOUND-2 (-1.31) > COMPOUND-6 (-0.64) > COMPOUND-4 (-0.4) > COMPOUND-5 (0.2). The logP values of all synthesized compounds follow the electronegativity if variable hetero atoms (Oxygen=3.44, Sulfur=2.58 Nitrogen=3.04) along with the amide as well

as lactam (cyclic amide) present in all six compounds because logP of amide is lower than lactam as polarity of amide is higher than lactam because in amide the N-C-N linkage is present in open chain where as in lactam N-C-N linkage is present as closed form. Hence the Solubility of open chain amide is high [logP: -2.11] and Closed amide (N-C-N linkage) (lactam): Solubility of closed ring of amide (lactam) is less [logP: -0.95].

The UV spectra of six sample showed the two λ_{\max} within the range 220-280nm due to the presence of two amide linkage (open chain and closed chain). The lower absorbance is due to open chain and higher absorbance is due to lactam ring.

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