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COMPARATIVE LOGARITHMIC PARTITION COEFFICIENT STUDY OF SYNTHESIZED FIVE MEMBERED LACTAM DERIVATIVES FOR LIPOPHILICITY

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ABSTRACT

Five membered heterocyclic moiety (pyrazolone) has been synthesized by reacting between phenyl hydrazine and hydrazine with β-keto ester (ethyl acetoacetate) by condensation reaction to get the desired moiety which on alkaline permanganate oxidation gives the corresponding carboxylic acid derivatives in two series. The four compounds (I & II) of 1st series and (II & IV) of 2nd series were characterized for structural framework. The ***logP*** *profile of all four compounds is as follows:*

Reagents: *[Highest] Phenyl hydrazine > Ethyl acetoacetate > Hydrazine hydrate [Lowest].*

Compounds: *[Highest] I (5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one) > II (5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylic acid) > III (5-methyl-1,2-dihydro-3H-pyrazol-3-one) > IV (5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylic acid) > [Lowest].*

This logarithm of partition coefficient of all the said items is totally dependent on the polarity and solubility of the matters. The hydrophobicity and hydrophilicity of all synthesized four compounds depend on logP values due to the substituted functional groups of pyrazolone ring. Phenyl/Methyl/Carboxylic acid the three main chromophore groups change their logP parameters as well as surface tension.

logP profile:
I (5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one)>II (5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylic acid).

III (5-methyl-1,2-dihydro-3H-pyrazol-3-one)>IV (5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylic acid)

Surface tension profile:
I (5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one)<II (5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylic acid).

III (5-methyl-1,2-dihydro-3H-pyrazol-3-one)<IV (5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylic acid)

Lipophilicity and hydrophilicity of all compounds depend on the substitutions. Phenyl group is more lipophilic than methyl and carboxylic acid group is more hydrophilic so IV becomes liquid but II becomes solid due to the presence of phenyl ring but I is more lipophilic than III due to the presence of phenyl ring in I and III is more hydrophilic due to the presence of methyl group. Main ring pyrazolone is common in all I-IV: I (phenyl+methyl), II (phenyl+carboxylic acid), III (methyl), IV (carboxylic acid). I & III produce white compounds and II & IV are orange compounds in which IV is found liquid and rest all are solids which have been characterized by UV spectra and obeys wavelength of UV & Visible spectra.

KEYWORDS: Pyrazolone, Pyrazolone carboxylic acid, logP, $KMnO_4$/KOH oxidation, H_2O_2 oxidation, Polarity, Partition coefficient, Surface tension.

INTRODUCTION

Pyrazolone is five membered cyclic amide which is also called as lactam. This lactam ring is present in barbiturates, benzodiazepines as CNS depressants and opened chain amide in carbamates and in CNS stimulants and in β-lactam antibiotics. The carboxylic chain which is the main precursor of cyclooxgenase enzyme inhibitor present in all COX-1 inhibitors as anti-inflammatory drugs. This idea has been implemented to design such kind of synthetic entity which can possess these multi action pharmacological responses along with antioxidant property.[1-4]

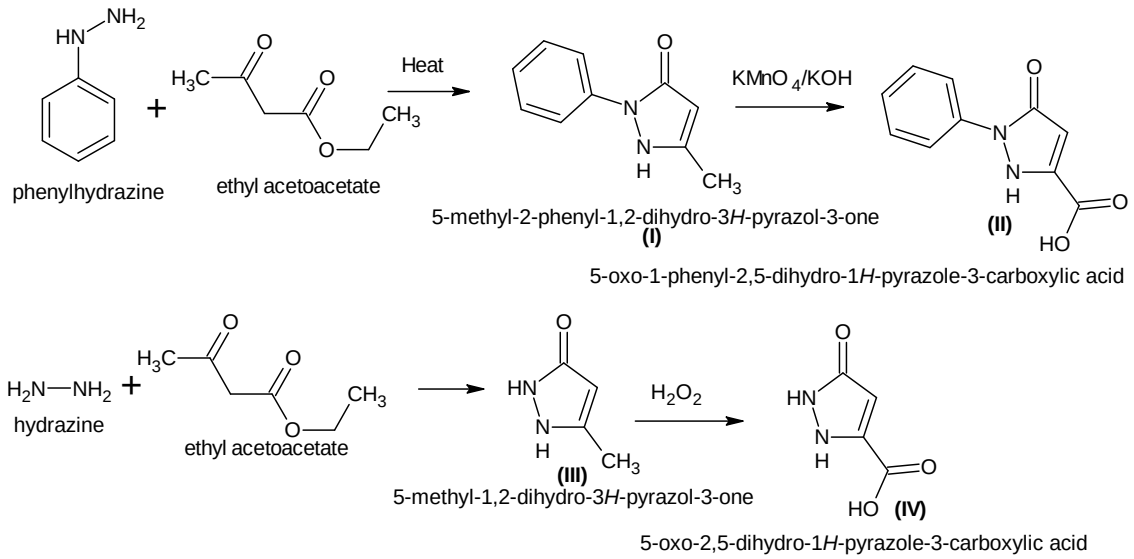
EXPERIMENTAL PART

Two series of pyrazolone derivatives have been synthesized by reacting between phenyl hydrazine with ethyl acetoacetate and 1st series and hydrazine hydrate with ethyl acetoacetate in 2nd series. 1st series gives the product (II) after heating with both for 2h and then boiling with water & cooling to get the product after 2 days where as in 2nd series gives the product (III) all at a time. This condensation reaction of 1st series is slower than 2nd series due to the presence of unreactive phenyl group. Compound (I) undergoes alkaline potassium permanganate oxidation ($KMnO_4$/KOH) to give Compound (II) and Compound (III) undergoes hydrogen peroxide oxidation to produce Compound (IV). Compound (II) and

Compound (IV) both have carboxylic acid group (-COOH) obtained by oxidation of methyl group of I & III.[5,6]

13g (0.1M) of ethyl acetoacetate has been reacted with 10.8g (0.1M) of phenyl hydrazine (1:1molar ratio) for 1st series and 10g (0.1M) of 80% hydrazine hydrate for 2nd series on water bath to get the solid product of I & III. Both have been crystallized by aqueous ethanol to get the pure product. Both have been subjected to oxidize by $KMnO_4$:KOH ratio (5.26g:5.26g). The reaction has been occurred in alkaline $KMnO_4$ oxidation so equivalent weight of $KMnO_4$ is calculated as:

Molecular Weight of $KMnO_4$ = 39+55+16×4 = 158g and Equivalent Weight of $KMnO_4$ in alkaline medium is 158/3=52.6g.



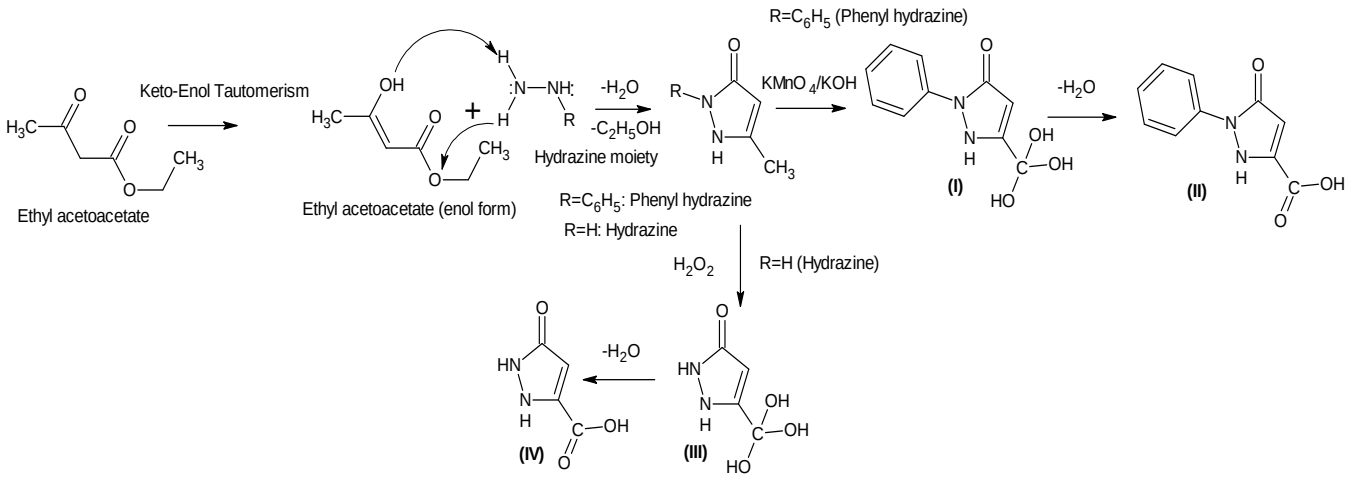
Scheme

Since the entire process has been done by taking 0.1M of all components so 5.26g of $KMnO_4$ has been dissolved in 50ml water in hot condition and 5.26g of both solid I & III have been added in this solution with stirring on water bath until all the effervescence stops and precipitate of MnO_2 appears. The reaction medium has been made alkaline by solution of 5.26g of KOH in 50ml water. The reaction contents were cooled in ice and filtered well to remove MnO_2 precipitate and washed thoroughly with water and collected all the filtrate which on acidification by conc.HCl produced the desired carboxylic acids of compounds II & IV. All the products were purified by aqueous ethanol by charcoal and recorded the %yield and MP/BP.

*Modification: In the case of oxidation of I to II it is convenient in alkaline oxidation and solid product can be easily isolated because logP of I is **1.72** and for II it is **0.91** but in case of alkaline oxidation of III to IV it is quite difficult to isolate because potassium salts are also incorporated with it is it has been done by hydrogen peroxide oxidation and liquid product IV is obtained from III because logP of III is **0.2** and for IV it is **-0.61**.*

Mechanism: Ethyl acetoacetate when reacts with hydrazine/phenyl hydrazine then it undergoes keto-enol tautomerism and then it reacts with two amino parts of hydrazine/phenyl hydrazine to eliminate one mole of water and one mole of ethyl alcohol to cyclize the methyl substituted pyrazolone moiety by condensation reaction in heated condition and these on reaction with alkaline potassium permanganate in heated condition then the methyl group is oxidized into free carboxylic moiety. In oxidation process the methyl ($-CH_3$) group takes up oxygen and becomes trihydroxy moiety but one carbon cannot hold same three functional groups so one mole of H_2O is eliminated to produce –COOH functional group and gives precipitate of MnO_2.

Each oxygen molecule is attached by one double bond and each oxygen atom has two lone pair of electrons which undergoes mesomeric effect to form +/− charges on oxygen linkage which directly reacts with hydrogen atoms of methyl group to form trihydroxy moiety which is then further liberates one mole of water to produce carboxylic group.



Mechanism

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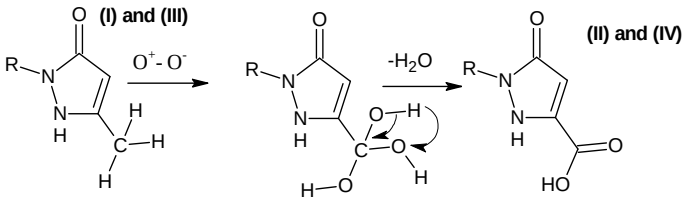
incorporated with it is it has been done by hydrogen peroxide oxidation and liquid product IV is obtained from III because logP of III is **0.2** and for IV it is **-0.61**.

$$2MnO_4^- + 4OH^- + 3e^- = 2MnO_2\downarrow + 2H_2O + 2O_2\uparrow$$

$$2H_2O_2 = 2H_2O + O_2\uparrow$$

$$O_2 \rightarrow :O:=:O: \rightarrow O^+–O^-$$



Mechanism of oxidation

Table-1: logP profile

Compounds	logP
Phenyl hydrazine	1.25
Ethyl acetoacetate	0.72
Hydrazine hydrate	-1.19
I	1.72
III	0.20
II	0.91
IV	-0.61

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. These coefficients are a measure of the difference in solubility of the compound in these two phases. The partition coefficient is a ratio of concentrations of un-ionized compound between the two liquid phases. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P: When one of the solvents is water and the other is a non-polar solvent, then the log P value is also known as a measure of lipophilicity. For example, in an octanol-water system:

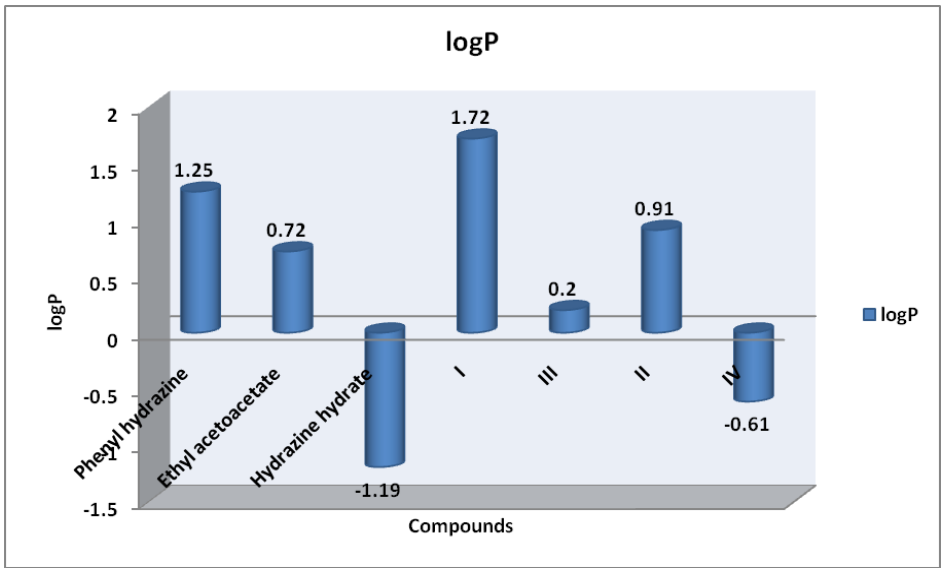
$$\log\ P_{\mathrm{oct/wat}} = \log\left(\frac{[\mathrm{solute}]^{\mathrm{un-ionized}}_{\mathrm{octanol}}}{[\mathrm{solute}]^{\mathrm{un-ionized}}_{\mathrm{water}}}\right)$$

Logarithmic calculation of partition coefficient

Table-2: Physicochemical parameter

Compounds	Chemical Name	Molecular Formula	Yield %	M.P.°C	Solubility
I	5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	$C_{10}H_{10}N_2O$	54	126-128	Soluble in alcohol
III	5-methyl-1,2-dihydro-3*H*-pyrazol-3-one	$C_4H_6N_2O$	52	132-134	Soluble in hot water
II	5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid	$C_{10}H_8N_2O_3$	22	192-194	Soluble in hot water
IV	5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid	$C_4H_4N_2O_3$	45	B.P.°C =140-142	Soluble in water

In the first approximation, the non-polar phase is usually dominated by the electrically neutral un-ionized form of the solute. This may not be true for the aqueous phase. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is also un-ionized.



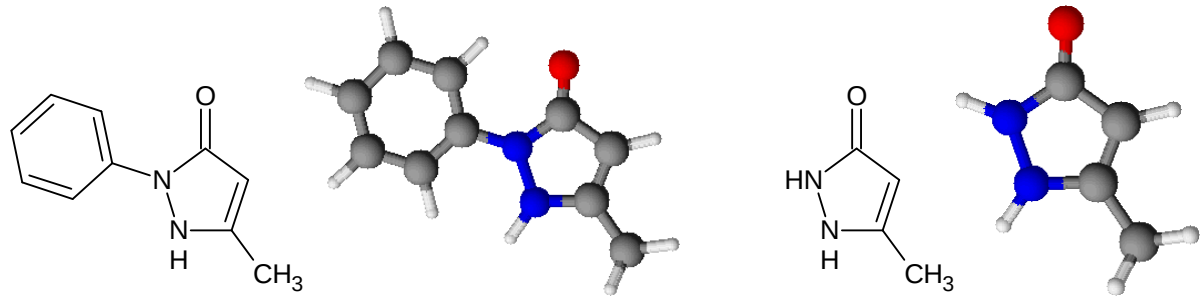
LogP profile of compounds according to partition coefficient.

LogP profile of compounds according to partition coefficient:

Phenyl hydrazine (1.25) is less polar than hydrazine **(-1.19)** because of phenyl group which has resonance property and pulls in the electrons towards the benzene ring.

Compound (I) is less polar **(1.72)** than **Compound (III) (0.20)** due to presence of phenyl ring.

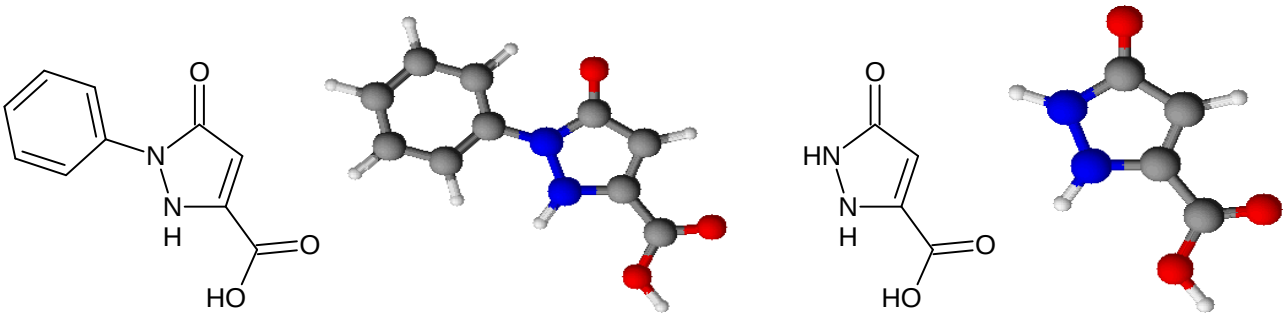
Compound (II) is less polar **(0.91)** than **Compound (IV) (-0.61)** due to presence of phenyl ring.



3D structure comparison of I & III

Table-3: Physical properties of I & III

Compound	Molecular Formula	Formula Weight	Composition	Surface Tension
I	$C_{10}H_{10}N_2O$	174.19	C (68.95%), H (5.79%), N (16.08%), O (9.18%)	42.8 dyne/cm
III	$C_4H_6N_2O$	98.10	C (48.97%), H (6.16%) N (28.56%), O (16.31%)	29.3 dyne/cm



3D structure comparison of II & IV

Table-4: Physical properties of II & IV

Compound	Molecular Formula	Formula Weight	Composition	Surface Tension
II	$C_{10}H_8N_2O_3$	204.18	C (58.82%), H (3.95%), N (13.72%), O (23.51%)	66 dyne/cm
IV	$C_4H_4N_2O_3$	128.08	C (37.51%), H (3.15%), N (21.87%), O (37.47%)	63.6 dyne/cm

Spectroscopic analysis

UV Spectra: λ_{max} (nm)

I: 5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one: 275nm (white product)

II: 5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid: 630nm (orange product)

Orange Standard Wave length=590-630nm

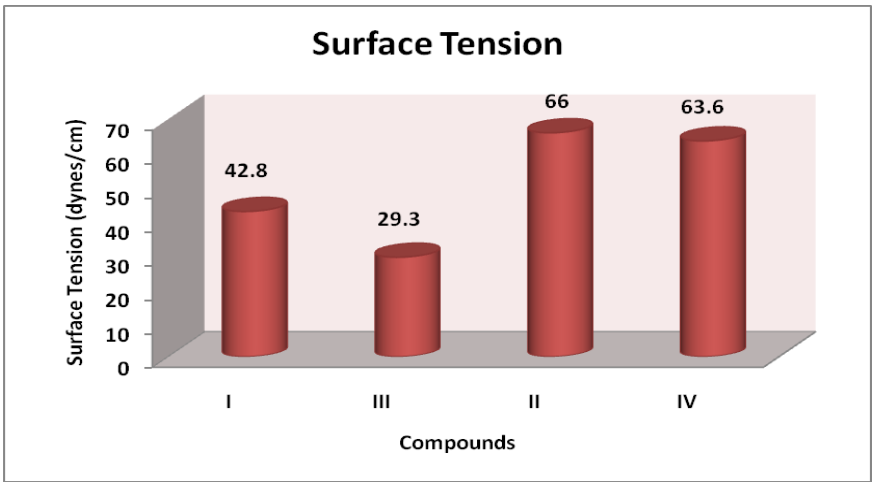
III: 5-methyl-1,2-dihydro-3*H*-pyrazol-3-one: 374nm (white product)

IV: 5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid: 620nm (orange liquid)

Orange Standard Wave length=590-630nm.

Table-5: Surface Tension

Compounds	Surface Tension
I	42.8 dyne/cm
III	29.3 dyne/cm
II	66 dyne/cm
IV	63.6 dyne/cm



Surface tension profile

RESULT AND DISCUSSION

The hydrophobicity and hydrophilicity of all synthesized four compounds depend on logP values due to the substituted functional groups of pyrazolone ring. Phenyl/Methyl/Carboxylic acid the three main chromophore groups change their logP parameters as well as surface tension.

logP profile:

I (5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one)>II (5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid).

III (5-methyl-1,2-dihydro-3*H*-pyrazol-3-one)>IV (5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid).

Surface tension profile:

I (5-methyl-2-phenyl-1, 2-dihydro-3*H*-pyrazol-3-one)<II (5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid)

III (5-methyl-1,2-dihydro-3*H*-pyrazol-3-one)<IV (5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid).

I & III produce white compounds and II & IV are orange compounds in which IV is found liquid and rest all are solids which have been characterized by UV spectra and obeys wavelength of UV & Visible spectra.

CONCLUSION

In the case of oxidation of I to II it is convenient in alkaline oxidation and solid product can be easily isolated because logP of I is 1.72 and for II it is 0.91 but in case of alkaline oxidation of III to IV it is quite difficult to isolate because potassium salts are also incorporated with it is it has been done by hydrogen peroxide oxidation and liquid product IV is obtained from III because logP of III is 0.2 and for IV it is -0.61. Lipophilicity and hydrophilicity of all compounds depend on the substitutions. Phenyl group is more lipophilic than methyl and carboxylic acid group is more hydrophilic so IV becomes liquid but II becomes solid due to the presence of phenyl ring but I is more lipophilic than III due to the presence of phenyl ring in I and III is more hydrophilic due to the presence of methyl group. Main ring pyrazolone is common in all I-IV: I (phenyl+methyl), II (phenyl+carboxylic acid), III (methyl), IV (carboxylic acid).

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