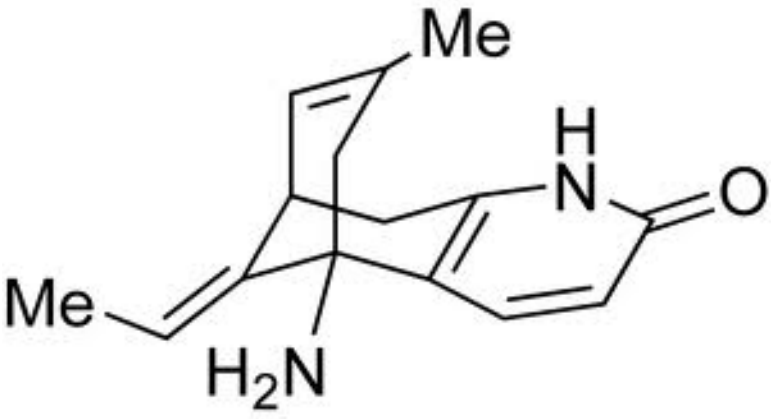
Modulation of the aqueous solubility and dissolution rate of Huperzine A

through pharmaceutical co-crystals



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"Huperzine A is a naturally occurring alkaloid extracted from Chinese club moss, Huperzia serrata, or from any other Huperzia species, and is used in clinical trials to possible treat Alzheimer's Disease because of its effects as an Acetyl cholinesterase Inhibitor (AChEI), which therefore leads to an improvement im memory function, thinking capabilities and thinking processes. Huperzine A is poorly soluble in water and thus the major goal from this proposed research is to modulate the aqueous solunility and dissolution rate of Huperzine A."

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INTRODUCTION

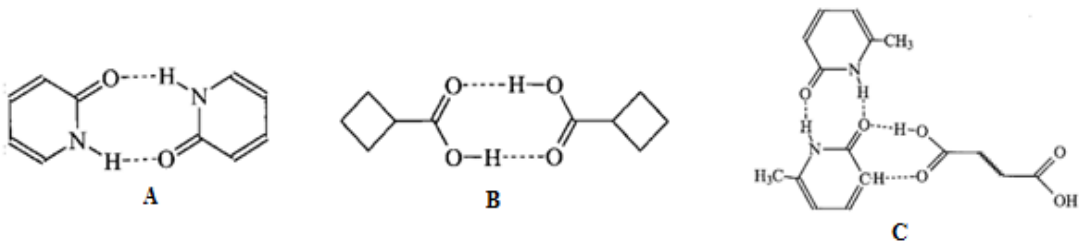
Huperzine A is a highly purified drug extracted from the Chinese club moss, Huperzia serrata, or from any other Huperzia species and is a naturally occurring alkaloid. Huperzine A is a powerful acetyl cholinesterase inhibitor, as acetyl cholinesterase is a neurotransmitter which enables communication between nerve cells released at the neuronal synapses which are responsible for breaking down acetylcholine which interprets thinking, learning and memory. Huperzine A inhibits the activity of acetyl cholinesterase that breaks down acetylcholine which results in an increase in memory, learning and thinking capability and it is upon this principle that this drug is being used to treat neurological disorders such as Alzheimer's Disease and nerve gases and senile and multi-infract Dementia. The dosage of Huperzine A usually varies depending on the clinical condition but is recommended to take one tablet of the oral drug (Huperzine A 50 mcg) d day with doctor supervision as the amounts of Huperzine A can accumulate within the body causing serious side effects.

Huperzine A does not readily dissolved in water or in other words its dissolution rate is poor. This property is essential in the effectiveness of the drug to treat Alzheimer's disease as it must cross the blood-brain barrier for it to have its effect in inhibiting acetyl cholinesterase in nerve synapses. As a result of Huperzine A's poor solubility property, the major goal of this research is to address this problem, hence the effort to modulate the aqueous solubility and dissolution rate of Huperzine A by co-crystal formation.

Compared to using salt formations, to be able to modulate aqueous solubility and dissolution rate a broader range of solid forms, such as the engineering of co-crystals will give one more optimization to choose and API (Active pharmaceutical ingredient) and tamper with

the crystal's physiochemical properties without changing the structure of the molecule itself. Co-crystallization engineering results from the combination of two or more molecular compounds within the same crystalline lattices in specific stoichiometric ratios, without making or breaking covalent bonds. As a result, the crystal structure determines the resulting physiochemical characteristics of the compound. Forming co-crystals without creating or breaking new bonds makes it possible to tamper with the compound's physical properties. Modulation of aqueous solubility and dissolution rate of an API can be rationalized upon this same principle that the physiochemical propertied of the co-crystals is determined from the aqueous solubility of that of the carboxylic acids used relation to the API itself. From this relationship, systematic changes to the co-crystallization agent's molecular nature and its crystalline lattice make it possible to establish predictable physiochemical properties.

Huperzine A compound have on it the presence of a functional 2-pyridone group which makes it an appealing compound for co-crystallization preferences. This 2-pyridone moiety (Scheme 1-A) as well as the head to head dimerization of carboxylic acids (Scheme 1-B) are well known to form predictable catemer rigid dimmers (recurring patterns forming infinite chains) in the solid state and are utilized extensively for co-crystal engineering. In each case to co-crystal structure results from the planar dimerization of 2-pyridone (from Huperzine A) N - H ··· O hydrogen bonds is bridged or linked by adjacent head to head dimerization from the carboxyllic acid through the combination C-H ··· O and O-H··· O hydrogen bonds to generate infinite homomeric 1-D ribbons of dimer ··· acid ··· dimer ··· acid chains (Scheme 1-C) oriented by changes in the molecular shape and conformational flexibility of the carboxylic acids.



Scheme 1: **(A)** Hydrogen-bonding motifs for 2-pyridone dimers and dicarboxylic acids; **(B)** Head-to-head dimer of two carboxylic acid moieties; **(C)** Hydrogen-bonding motifs for 2-pyridone dimers and dicarboxylic acids.

GOALS & OBJECTIVES

The aim(s) of this proposed research are to:

1. Perform co-crystallization experiments between Huperzine A and carboxylic acids using various techniques such as Grinding techniques, melt techniques and slow evaporation techniques.
2. Analyze prepared samples through TLC, melting point and IR as a means of screening potential for co-crystal formation.
3. Perform experiments to test and modulate the aqueous solubility and dissolution rate Huperzine A co-crystals.

PROCEDURES

3.1 Grinding Experiments

1 a. Benzoic acid (0.0252g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

1 b. Benzoic acid (0.0252g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

1c. Benzoic acid (0.0252g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the

sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

2 a. Trans-3,4-dihydroxy cinnamic acid (0.0372g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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3 a. Sorbic Acid (0.0231g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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4 a. Glycolic Acid (0.0157g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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5a Gallic Acid (0.0351g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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6a. DL-Malic Acid (0.0227g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

6b. DL-Malic Acid (0.0227g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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7a. Maleic Acid (0.0239g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

7b. Maleic Acid (0.0239g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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8a. Ibuprofen (0.0426g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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9a. Acetylsalicylic Acid (0.3720g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

9b. Acetylsalicylic Acid (0.3720g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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10a. Citric Acid (0.0396g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

10b. Citric Acid (0.0396g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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11a. Adipic Acid (0.0302g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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12a. Succinic Acid (0.0244g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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13a. Hippuric Acid (0.0370g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

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14a. DL-Tartic Acid (0.0310g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

14b. DL-Tartic Acid (0.0310g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

14c. DL-Tartic Acid (0.0310g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

15a. Salicylic Acid (0.0285g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

15b. Salicylic Acid (0.0285g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

15c. Salicylic Acid (0.0285g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

16a. Fumaric Acid (0.0239g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

16b. Fumaric Acid (0.0239g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

16c. Fumaric Acid (0.0239g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

17a. Malonic Acid (0.0215g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

17b. Malonic Acid (0.0215g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

17c. Malonic Acid (0.0215g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

18a. Terephthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

18b. Terephthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

18c. Terephthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

19a. Orotic Acid (0.0322g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

19b. Orotic Acid (0.0322g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

19c. Orotic Acid (0.0322g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes

until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

20a. Isophthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. This powder was transferred into a glass vial and labeled dry accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

20b. Isophthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 1 drop of ethanol was added and the mixture and the grinding process continued for another five to ten minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled one drop of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

20c. Isophthalic Acid (0.0240g) and Huperzine A (0.050g) were weighed respectively and placed into a mortar. The mixture was then grinded using a glass pestle for about five to ten minutes until a uniform homogenous powder was formed. To this, 2 drop of ethanol was added and the mixture and the grinding process continued for another five to ten

minutes until a homogenous powder resulted. This powder was transferred into a glass vial and labeled two drops of ethanol accordingly by the name of the acid used. A little of the sample was then taken into a blind ended capillary tube and its melting point was then taken as the sample in the capillary tube was placed in the melting point apparatus. The temperature at which the powder melted was then recorded in a table.

3.2 Slow Evaporation 1:1 (50mg Huperzine A)

A. Initially, a stock solution of 20mL Huperzine A was made by weighing one gram (1g) of Huperzine A solid and placing it in a conical flask, to which 20mL of methanol was added to dissolve the Huperzine A. Little heat along with swirling action was required to fully dissolve the solution.
B. Sodium Hydroxide (9.3035g) was weighed and dissolved in 50mL distilled water to produce a 6M concentration solution.

1. Benzoic Acid (0.0252g) was dissolved in 1mL ethanol. To it was added Huperzine A (0.050g), 1mL from the stock solution and the beaker was covered with parafilm. Initially white crystals were afforded and when re-dissolved in 1mL isopropanol afforded white crystals. M.p. 195^{o}C and 193 ^{o}C respectively.
2. Trans-3,4-dihydroxy cinnamic Acid (0.0372g) was dissolved in 1mL ethanol. To this solution was added 1mL of the Huperzine A (0.050g) solution in methanol. Initially yellow solids were obtained and when re-dissolved in isopropanol afforded the same results. M.p. 179 ^{o}C and 188 ^{o}C respectively.
3. Sorbic Acid (0.0231g) was dissolved in 1mL ethanol. To this solution was added 1mL of methanol solution containing Huperzine A (0.050g) from the stock solution. Initially dark red/brown solid was obtained and when re-dissolved in 1mL isopropanol afforded the same results. M.p. 131 ^{o}C and 140 ^{o}C respectively.

4. DL-Tartic acid (0.0310g) was dissolved in 1mL ethanol. To this solution was added 1mL of the Huperzine A(0.050g) solution in methanol. Initially nothing resulted as everything seem to have dissolved but when re-dissolved in 1mL isopropanol, clear solid, yet gel like was obtained. M.p. 185-189 ^{o}C.
5. Gallic Acid (0.0351g) was dissolved in 1mL ethanol. To this solution was added 1mL of Huperzine A solution (0.050g) in methanol. Initially everything seemed to have evaporated, and when re-dissolved in 1mL isopropanol yellow solids were obtained. M.p. 196 ^{o}C.
6. Glycolic Acid (0.0157g) was dissolved in 1mL of ethanol. To this solution was added 1mL of Huperzine A (0.050g) solution in methanol from the stock. Initally everything seemed to have evaporated but when redissolved in 1mL isopropanol afforded clear solids. M.p. 145 ^{o}C.
7. DL-Malic acid (0.0227g) was dissolved in 1mL of ethanol. To this was added 1mL of the Huperzine A (0.050g) stock solution that was dissolved in methanol. Initially everything seemed to have evaporated, but when re-dissolved in 1mL isopropanol afforded clear gel. M.p. 175 ^{o}C.
8. Maleic Acid (0.0239g) was dissolved in 1mL ethanol. To this was added 1mL Huperzine A (0.050g) in methanol. Initially, everything seemed to have evaporated likewise after it had been re-dissolved in 1mL isopropanol.
9. Ibuprofen (0.0426g) was dissolved in 1mL ethanol. To this solution was added 1mL of the Huperzine A (0.050g) solution in methanol. Initially white crystalline clear formed and after it was re-dissolved on 1mL isopropanol. White crystalline solids were afforded. M.p. 110 ^{o}C and 113 ^{o}C respectively.

10. Isophthalic Acid (0.0240g) was dissolved in 1mL ethanol. To this solution was added 1mL of the methanol solution containing Huperzine A (0.050g). Initially clear crystalline solids resulted, and after redissolved in 1mL isopropanol, white solids were afforded. M.p. 119 ^{o}C and 197 ^{o}C respectively.

11. Acetylsalicylic Acid (0.0372g) was dissolved in 1mL ethanol. To this solution was added 1mL of the methanol containing Huperzine A (0.050g) stock solution. Initially, clear crystal solids were formed, and when re-dissolved in 1mL of isopropanol clear get resulted. M.p. 175 ^{o}C and 266 ^{o}C respectively.

12. Citric Acid (0.0396g) was dissolved in 1mL ethanol. To this solution was added 1mL of the Huperzine A (0.050g) containing solution in methanol. Initially, nothing afforded as everything seemed to have evaporated and when re-dissolved in isopropanol resulted in the formation of a clear gel. M.p. 206 ^{o}C.

13. Adipic Acid (0.0302g) was dissolved in 1mL of ethanol. To this was added 1mL of the methanol solution containing Huperzine A (0.050g). Initially, nothing resulted but when re-dissolved in 1mL ethanol clear crystalline solids resulted. M.p. 181 ^{o}C.

14. Succinic Acid (0.0244g) was dissolved in 1mL ethanol. To this solution was added1mL Huperzine A (0.050g) in methanol. Initially, nothing resulted but when re-dissolved in 1mL isopropanol afforded a yellowish gel. M.p. 126 ^{o}C.

15. Hippuric Acid (0.0370g) was dissolved in 1mL ethanol. To this solution was added 1mL Huperzine A solution (0.050g). Initially, nothing resulted but when re-dissolved in 1mL isopropanol afforded clear solids. M.p. 154 ^{o}C.

16. Salicylic Acid (0.0285g) was dissolved in 1mL ethanol. To this solution was added 1mL Huperzine A solution (0.050g). Initially, clear crystalline solids were afforded, and when re-dissolved in 1mL of isopropanol clear gel resulted. M.p. 219 ^{o}C and 221 ^{o}C respectively.

17. Fumaric Acid (0.0239g) was dissolved in 1ml ethanol. To this solution was added 1ml of Huperzine A (0.050g) in methanol. Both initially and when re-dissolved in 1mL of isopropanol white solids were afforded. M.p. 244 ^{o}C and 234 ^{o}C respectively.

18. Malonic Acid (0.0215g) was dissolved in 1mL ethanol. To this solution was added 1mL of Huperzine A (0.050g) in methanol. Initially, noting resulted and after re-dissolved in 1mL isopropanol clear solid resulted. M.p. 217 ^{o}C.

19. Terephthalic Acid (0.0240g) was dissolved in 1mL 6M Sodium Hydroxide solution (NAOH). To this solution was added 1mL of the methanol solution containing Huperzine A (0.050g). Nothing resulted as all efforts to initially dissolve Terephthalic Acid failed.

3.3 IR SPECTROSCOPY of Grinding Experiments

1. A small quantity of each Carboxylic Acid grounded with Huperzine A (0.050g) was used to obtain the Infrared (IR) spectrum.

2. The IR was recorded by passing IR radiation at frequency ranges 500-4000cm^{-1}; at resolution 4cm^{-1}; and at scanning speed at 32mm/s through the sample.

3. The IR spectrum obtained was compared with the standard spectrum of each functional group to determine each ground experiment molecular structure.

4. These procedures above were repeated over for all grounded experiments (dry, with one drop of ethanol and two drops of ethanol).

3.4 Melt Experiments

1. In a 1:1 mole ratio, both Huperzine A and a ditopic nitrogenous base were placed in a glass vial.

2. The mixture was then directly heated using the heat gun until both components melted into a homogenous molten sample which was quickly formed into a solid product.

3. The procedures above were then repeated using the same Huperzine A mole ration combined with the mole ratios of the other ditopic nitrogenous bases again in a 1:1 molar ratio.

3.5 IR SPECTROSCOPY of the Melt Experiments

1. A small quantity of a melted sample (Huperzine A along with a ditopic nitrogenous base) used to obtain the Infrared (IR) spectrum.

2. The IR was recorded by passing IR radiation at frequency ranges 500-4000cm^{-1}; at resolution 4cm^{-1}; and at scanning speed at 32mm/s through the sample.

3. The IR spectrum obtained was compared with the standard spectrum of each functional group to determine each melted experiment's molecular structure.

4. These procedures above were repeated over for all other melt experiments (with all the other remaining ditopic nitrogenous bases).

RESULTS / OBSERVATIONS

TABLE 4.1 - A

Experiment #	Carboxylic Acid (°C)	Melting Point of Carboxylic Acid (°C)	Description	Melting Point of Crystal formation (°C)	Melting Point of Crystal formation re-dissolved in 1ml Isopropanol (°C)
1.	Benzoic Acid	122.38	White crystal formed	195*	193*
2.	Trans-3,4-dihydroxycinnamic acid	194-198	Yellow solid formed	179	188
3.	Sorbic acid	135	Brown/orange crystalline solid formed around edge of beaker	131	140
4.	DL-Tartic Acid	206	N/A everything evaporated	-	185-189
5.	Gallic Acid	250	Yellow powder/solids formed		196
6.	Glycolic Acid	75	N/A everything evaporated	-	145*
7.	DL-Malic Acid	130	N/A everything evaporated	-	175*
8.	Maleic Acid	135	N/A everything evaporated	-	-
9.	Ibuprofen	76	Clear crystalline solids formed around edge of beaker	110*	113*
10.	Isophthalic Acid	347	Clear crystalline solids formed	199*	197*
11.	Acetylsalicylic Acid	135	Clear crystalline solids formed	174*	266
12.	Citric Acid	153	Clear gel formed around d edge of beaker	-	206*
13.	Adipic Acid	152.1	Clear gel formed around d edge of beaker	-	181*
14.	Succinic Acid	184	N/A everything evaporated	-	126
15.	Hippuric Acid	187-188	N/A everything evaporated	-	154
16.	Salicylic Acid	159	Clear crystalline solids	219**	221**
17.	Fumaric Acid	287	White crystalline solids	244*	234*
18.	Malonic Acid	135-136	N/A everything evaporated	-	217**
19.	Terephthalic Acid	300	White suspension	X	X

TABLE OF RESULTS FROM THE SLOW EVAPOATION EXPERIMENTS 1:1 50mg MOLE RATIO

**Note

(*) – Presence of Co-crystal
(**) – Presence of Huperzine A
(-) – N/A everything evaporated; no sample present to test Melting Point
(X)- Sample failed to dissolve; experiment was canceled

TABLE 4.1 - B

Experiment #	Carboxylic Acid	Melting Point of Carboxylic Acid (°C)	Melting Point of Sample (°C)		
			Pure	One Drop	Two drops
1.	Benzoic Acid	122.38	116-118	116	191
2.	Trans-3,4-dihydroxycinnnamic acid	194-198	203	203	175
3.	Sorbic acid	135	95-97	74-78	112
4.	DL-Tartic Acid	206	195	115	115
5.	Gallic Acid	250	182	191	186
6.	Glycolic Acid	75	136	131	-
7.	DL-Malic Acid	130	-	116-118	-
8.	Maleic Acid	135	119	190	180
9.	Ibuprofen	76	98-99	91	109
10.	Isophthalic Acid	347	201-204	196-200	207
11.	Acetylsalicylic Acid	135	106-107	114	130
12.	Citric Acid	153	250	225-230	230
13.	Adipic Acid	152.1	180-182	182	179-183
14.	Succinic Acid	184	149-150	108-110	-
15.	Hippuric Acid	187-188	154-157	110-111	111
16.	Salicylic Acid	159	218	138	129
17.	Fumaric Acid	287	188-190	108-110	117
18.	Malonic Acid	135-136	178	178	-
19.	Terephthalic Acid	300	212	196	245
20.	Orotic Acid	345	273	266	263

TABLE OF RESULTS FROM GRINDING EXPERIMENTS IN 1:1 50mg MOLAR RATIO

****Note**

Pure – means Pure Carboxylic Acid + Huperzine A
One Drop – means Pure Carboxylic Acid + Huperzine A + 1 drop of Ethanol
Two Drops - means Pure Carboxylic Acid + Huperzine A + 2 drop of Ethanol
(-) - means sample was too little or pasty to test Melting Point

TABLE 4.2

Experiment #	Carboxylic Acid	Description	IR of Carboxylate Frequencies
1.	Benzoic Acid	Dry	1537.66 ; 1373.66
		1 drop	-
		2 drops	1535.90 ; 1372.36
2.	Trans-3,4-dihydroxy Cinnamic Acid	Dry	1548.79 ; 1376.73
		1 drop	1376.83 ; 1376.95
		2 drops	1509.01 ; 1306.10
3.	Sorbic Acid	Dry	1574.51 ; 1376.08
		1 drop	1547.66 ; 1369.79
		2 drops	1547.08 ; 1368.71
4.	Gallic Acid	Dry	1541.42 ; 1385.14
		1 drop	1540.60 ; 1383.92
		2 drops	1443.28 ; 1306.10
5.	Glycolic Acid	Dry	1548.42 ; 1360.75
		1 drop	1548.36 ; 1377.43
		2 drops	-
6.	DL-Malic Acid	Dry	1545.14 ; 1359.55
		1 drop	1414.69 ; 11359.33
		2 drops	1547.25 ; 1359.93
7.	Ibuprofen	Dry	1548.52 ; 1360.75
		1 drop	1548.03 ; 1360.75
		2 drops	1546.31 ; 1359.54
8.	Ispohthalic Acid	Dry	1547.97 ; 1352.42
		1 drop	1597.90 ; 1355.77
		2 drops	1545.69 ; 1360.93
9.	Acetylsalicylic Acid	Dry	1548.04 ; 1376.62
		1 drop	1547.49 ; 1378.98
		2 drops	1551.92 ; 1380.47
10.	Citric Acid	Dry	1550.25 ; 1359.86
		1 drop	1549.41 ; 1305.42
		2 drops	1454.44 ; 1358.31
11.	Succinic Acid	Dry	1546.87 ; 1304.83
		1 drop	1538.07 ; 1359.81
		2 drops	1583.54 ; 1305.31
12.	Hippuric Acid	Dry	1555.44 ; 1351.90
		1 drop	1545.58 ; 1390.76
		2 drops	1607.21; 1379. 79
13.	Fumaric Acid	Dry	1547.73 ; 1352.38
		1 drop	1546.73 ; 1376.43
		2 drops	1536.95 ; 1360.46
14.	Malonic Acid	Dry	1554.25 ; 1395.71
		1 drop	1544.48 ; 1359.48
		2 drops	-
15.	Terephthalic Acid	Dry	1548.21 ; 1352.71
		1 drop	1547.04 ; 1365.54
		2 drops	1597.08 ; 1364.71

TABLE OF IR SPECTROSCOPY OF CARBOCYLATE SALT SAMPLES

TABLE 4.3		
	IR SPECTROSCOPY OF MELT SAMPLES cm^{-1}	
Melt Sample	**2-pyridone**	**NH_2**
HupA-1,4bis5,6dimethylbenzimidazol-1-ylmethylbenzene	1650.98	3362.87 , 3276.84
HupA-4,4dipyridyl	1663.89	3370.68 , 3284.69
HupA-1,2bis4pyridylethane	1650.18	3354.17 , 3273.34
HupA-4,4trimethylenedipyridine	1650.01	3355.07 , 3268.78
HupA-4phenylpyridine	1649.96	3355.96 , 3270.69
HupA-trans1,2bis4pyridylethylene	1644.44	3421.66 , 3351.14

TABLE OF IR FREQUENCIES FROM THE IR SPECTROSCOPY OF THE MELT SAMPLES

ANALYSIS / DISCUSSION

Huperzine A has an appealing functionality because of the presence of the 2-pyridone group on its structure. This structure or motif readily forms a predictable dimer with the functionality of Carboxylic Acids by forming a chain by hydrogen bonds between dimer ··· acid ··· dimer ··· acid. This dimerization is important in studying the physiochemical properties especially to modulate the aqueous solubility and dissolution rate of co-crystals formed between Huperzine A and carboxylic acids as Huperzine A is not highly soluble in water.

Three major processes or techniques were used to produce or synthesize co-crystals for the purpose of this paper. The first technique used was a slow evaporation technique where all twenty of the carboxylic acids were dissolved respectively in 1mL of ethanol by their respective molar ratio in relation to the molarity and stoichiometry of Huperzine A (1:1 ratio of 50mg) which the total mass was dissolved in 1mL of methanol per mg of Huperzine A in a stock solution. From the stock solution, 1mL of the solution and that of the carboxylic acid was placed in a beaker and covered with parafilm. The mixture was left to evaporate slowly over time while facilitation the dimerization to synthesize the co-crystal. The second technique used was the Grinding technique where a mass of each carboxylic acid in relation to the mole ratio of that of Huperzine A (1:1 ratio of 50mg) and Huperzine A was grounded in a pestle where kinetic energy for the dimerization for co-crystal formation would have been provided by the grinding action in itself. Also, drop(s) of ethanol was added to the grounded homogenous powder as a catalyst in an effort to speed up the resulting co-crystallization formation reaction. The results showed a slight decrease in the melting point of the pure, dry sample compared to that when one drop of ethanol was added compared to when two drops of ethanol were added to the sample. The third technique the melt will be explained later.

The melting point of co-crystals is used as a screening method to indicate its formation. Its melting point tends to fall between the range of components (i.e. the respective co-crystal and Huperzine A) and from the result obtained for co-crystal formation from the slow evaporation technique some samples were considered to be co-crystals based upon this theory. However, from their Infrared spectroscopy, specific functionalities based upon IR frequency shifts indicated that the "possible" co-crystals synthesized were actually salts. The same principle of melting point as a screening method for co-crystallization formation was used to indicate possible co-crystals from the grinding experiments (1:1 50mg Huperzine A). Again, based upon IR spectroscopy, specific functionalities based of their respective IR frequencies indicated that the possible co-crystals formed were actually salts.

From the Infrared Spectroscopy of the grounded samples, fifteen (15) of the Huperzine A - carboxylic acid samples were determined to be salts rather than co-crystals and the other five (5) samples are unknown or unidentified. Typical IR stretching frequencies of carboxylates would typically lie around 1650-1550 cm^{-1} frequencies which indicates salt formations which resulted from the protonation of the hydrogen atom on the carboxylic acid functional group. This deprotonation caused the deprotonated carboxylic acid to form an ionic bond to the protonated NH_3^+ group on the 2-pyridone functionality on Huperzine A. Co-crystals tend to have a shift in the frequencies for typical carboxylates (C=O) as well as that for the typical frequency, 1643.37 cm^{-1} , for the 2-pyridone group present on Huperzine A. take for example, there was no prominent shift within the frequencies for typical carboxylates on the IR spectrum for the dry pure sample of Benzoic Acid. Its carboxylate frequency lies at 1537.83 cm-1 and 1373.66 cm-1 indicating that the sample is a salt rather than co-crystals. The IR spectroscopy for the other fifteen known salts, their carboxylate frequencies lies within the range for typical carboxylates. (Refer to Table 4.2 for all determined salts and their respective frequencies).

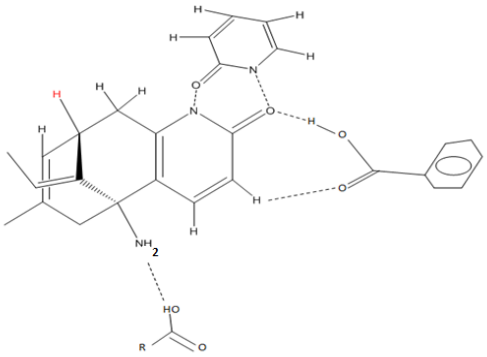


Figure 1 Showing the deprotonated carboxylic acid forming an ionic bond to the protonate NH3+ group of the Huperzine A.

From the grinding results, there is a decrease in temperature as you add one drop of ethanol versus two drops of ethanol when compared to the pure dry sample of the grounded homogenous powder of the Huperzine A and a respective carboxylic acid. The trending decrease in temperature was initially thought to result from co-crystallization formation occurring quicker and more readily with one drop of ethanol and even more readily with two drops of ethanol, having the ethanol being a co-catalyst for crystal formation. However, based upon the IR spectrum of the fifteen identified salt, rather than co-crystallization formation, the difference in temperature with respect to ethanol indicates the formation of more salt products with more drops of ethanol compared to the salt products in the pure and dry samples. From the IR spectrum, looking as specifically Benzoic acid for example, the carboxylate frequencies tend to decrease with the additional drops of ethanol indicating more salt formation occurring more readily. The carboxylate frequency of the pure, dry sample of Benzoic acid and Huperzine A lies at 1537.83 cm-1 and 1373.66cm-1 compared to this same sample with two drops of ethanol (1535.90 cm-1 and 1372.36 cm-1).

The third technique used was the Melt method, where Huperzine A was added to ditopic nitrogenous bases (ofcourse in a 1:1 mole ratio). The mixture was heated using the heat gun to a homogenous molten sample that quickly solidified. The heat gun was use to provide sufficient energy for co-crystal formation which seem to have resulted based on their respective IR spectroscopy. There were small shifts, yet prominent in the IR frequencies of the free NH2 group and on the of the

2-pyridone group itself. The shifts in the frequency`s in the melt samples compared to that of Huperzine A suggests that no deprotonation occurred as a result of hydrogen bonds formed between the partial positive hydrogen of the amide group (NH2) bonded to partial negative lone pairs on the free Nitrogens the ditopic nitrogenous base.

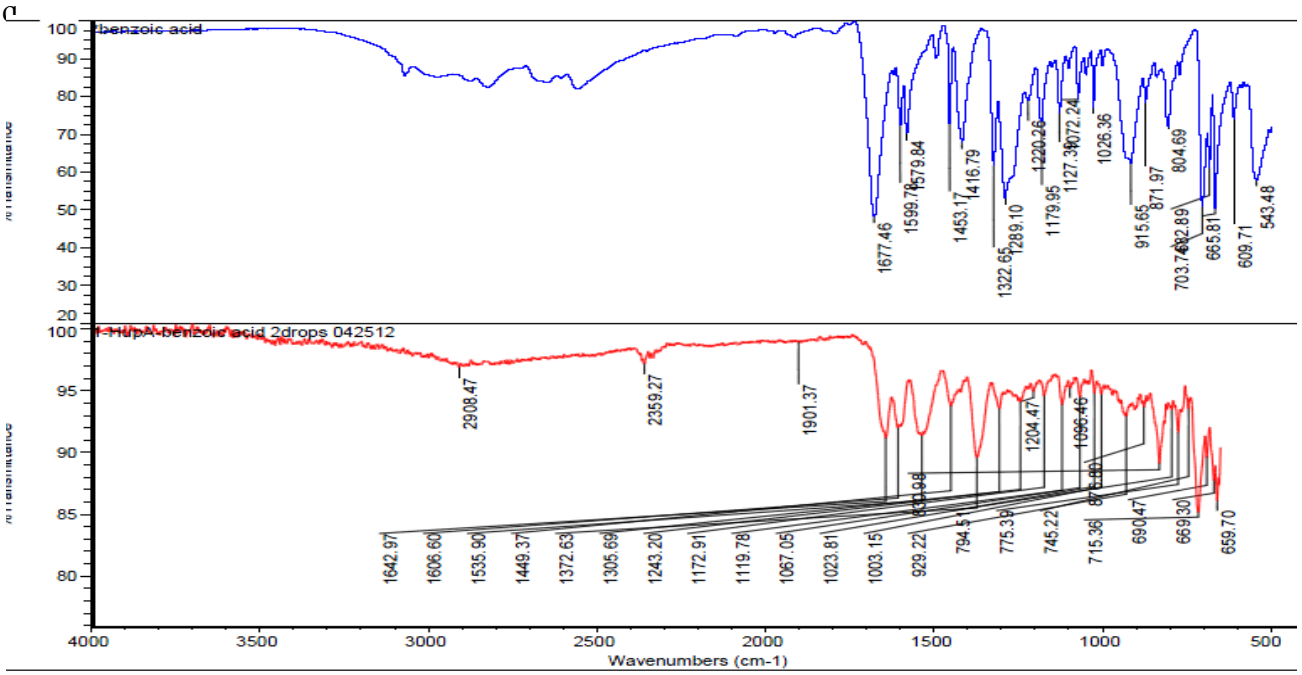
The actual process to synthesize single, solid co-crystals is still ongoing. Presently, experiments involving these ditopic nitrogenous bases along with Huperzine A show prominent results for co-crystallization synthesis, and slow evaporation experiments have already been established and now the actual process of slowly evaporation is occurring to actually afford these co- crystals as they precipitate out of solution. The major goal for this research is to actually set up experiments to modulate the aqueous solubility and dissolution rate of these co-crystals, such experiments are pending on the results of the previously mentioned slow evaporation experiments, involving Huperzrine A and the ditopic nitrogenous bases, from which our aim is to obtain single solid co-crystals. In reinstating the problem proposed of this research, Huperzine A is poorly soluble in water; so for it to be an effective drug as an acetylcholine esterase inhibitor (AChEI) it must readily pass the blood brain barrier for it to have its effect in neural synapses. Actual experiments to modulate this physiochemical property of Huperzine A via co-crystallization to effectively treat Alzheimer's disease are still not completed. The final objective of this research will be completed and documented with efforts that are presently underway as well to those of future.

CONCLUSION

The results initially taught to be co-crystals from slow evaporation experiments as well as from grinding experiment were actually determined to be carboxylate salts when Infrared spectroscopy of these samples were taken. From the grinding experiments, the samples had peaks within the normal carboxylate typical frequency range of $1600cm^{-1}$ – $1550\ cm^{-1}$; and at $1400cm^{-1}$. Also peaks for the 2-pyridone functionality from Huperzine A were also found at its typical frequency in each of the samples from the grinding experiments, $1643.37\ cm^{-1}$.The salt formation resulted from Hydrogen atoms on the carboxylic becoming deprtotnated by free amide (NH_2) groups on Huperzine A forming an ionic bond with the protonated NH_3^+ group on the Huperzine A molecule. Infrared spectroscopy of the melt samples indicated to us that protonation by free hydrogen on the NH_2 group on the Huperzine A molecules did not occur which resulted from hydrogen bonds being formed between these same Hydrogen atoms to the free lone pairs (that are partial negative) on the Nitrogen atoms present on the ditopic nitrogenous bases. From this result, we speculate that possible co-crystals have been formed from these melt experiments, as there were significant shifts in the IR frequency peaks of the 2-pyrodone group and the free NH_2 groups in the molten samples compared to the pure sample of the ditopic nitrogenous bases. Future work still continues as efforts have been carried out to actually obtain these solid co-crystals from slow evaporation experiments, of Huperzine A and the ditopic nitrogenous bases, to be used in actual experiments to modulate the aqueous solubility and dissolution rate of the active pharmaceutical ingredient (API) Huperzine A through co-crystallization.

APPENDIX

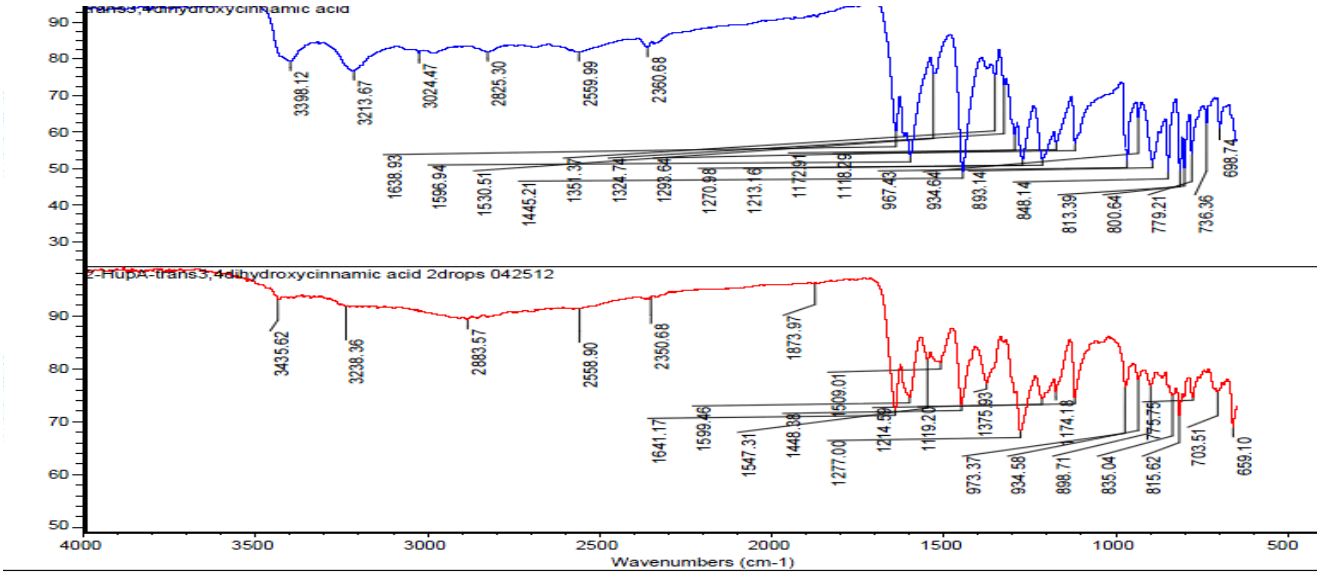
c



Date: Wed Apr 25 15:17:42 2012 (GMT-05:00)1-HupA-benzoic acid 2drops 042512

Scans: 32 -8.218686e-005

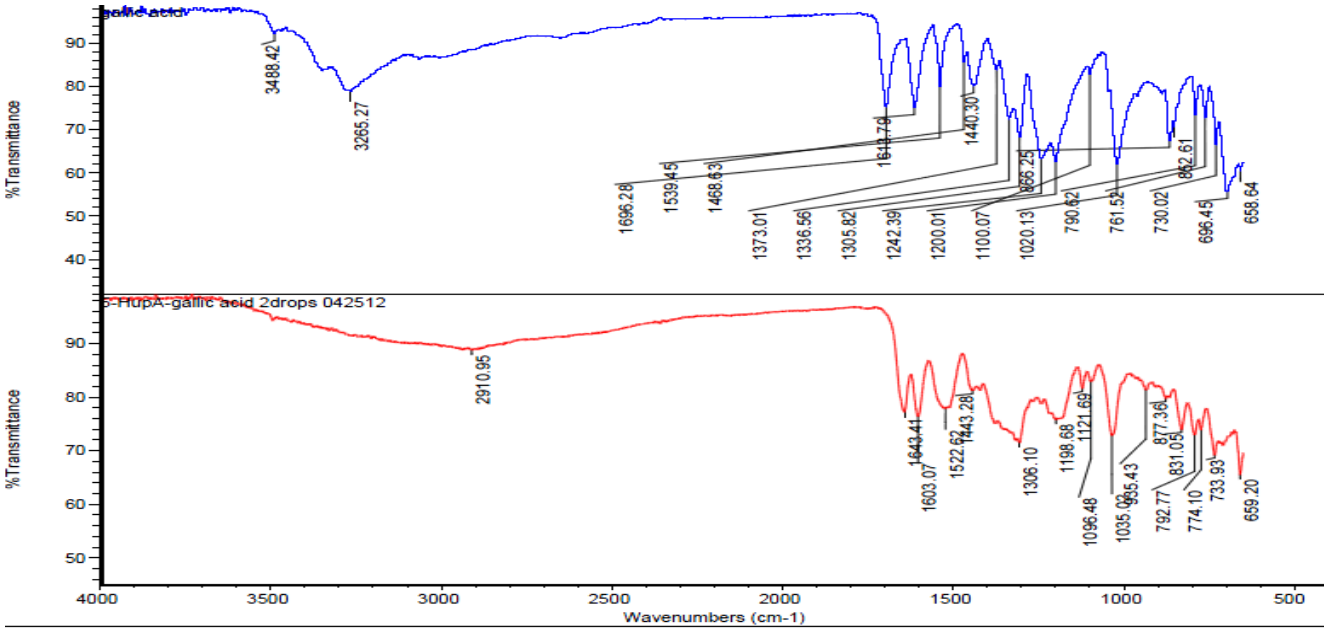
Resolution: 4.000 -8.338456e-005



Date: Wed Apr 25 15:47:52 2012 (GMT-05:00)2-HupA-trans3,4dihydroxycinnamic acid 2drops 042512

Scans: 32 -5.963871e-005

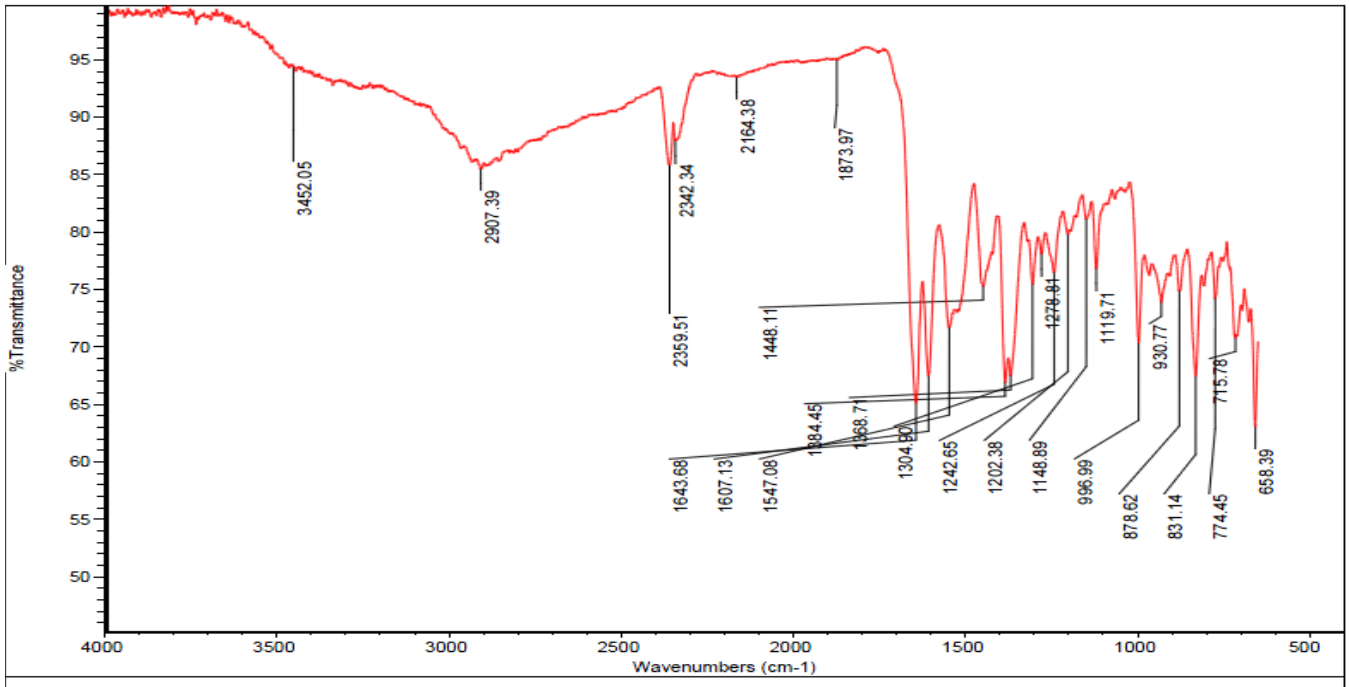
Resolution: 4.000 -8.161755e-005



Date: Wed Apr 25 18:48:13 2012 (GMT-05:00)5-HupA-gallic acid 2drops 042512

Scans: 32 -5.742033e-005

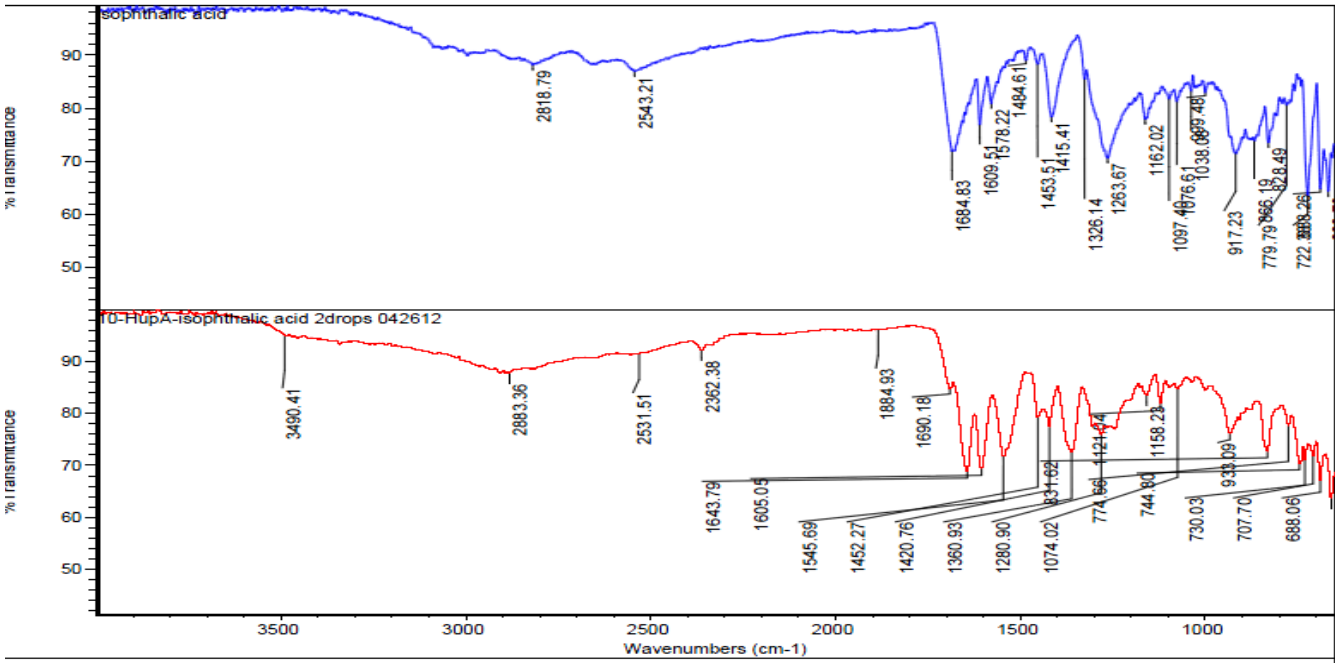
Resolution: 4.000 -7.991064e-005

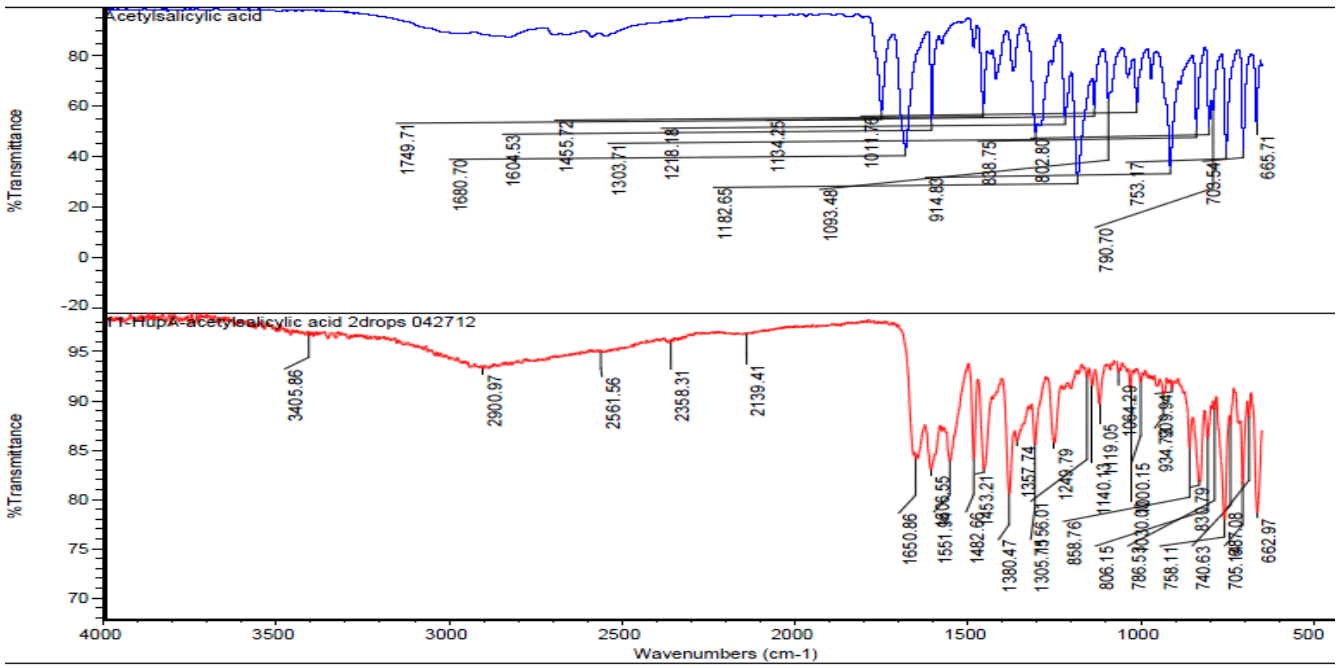


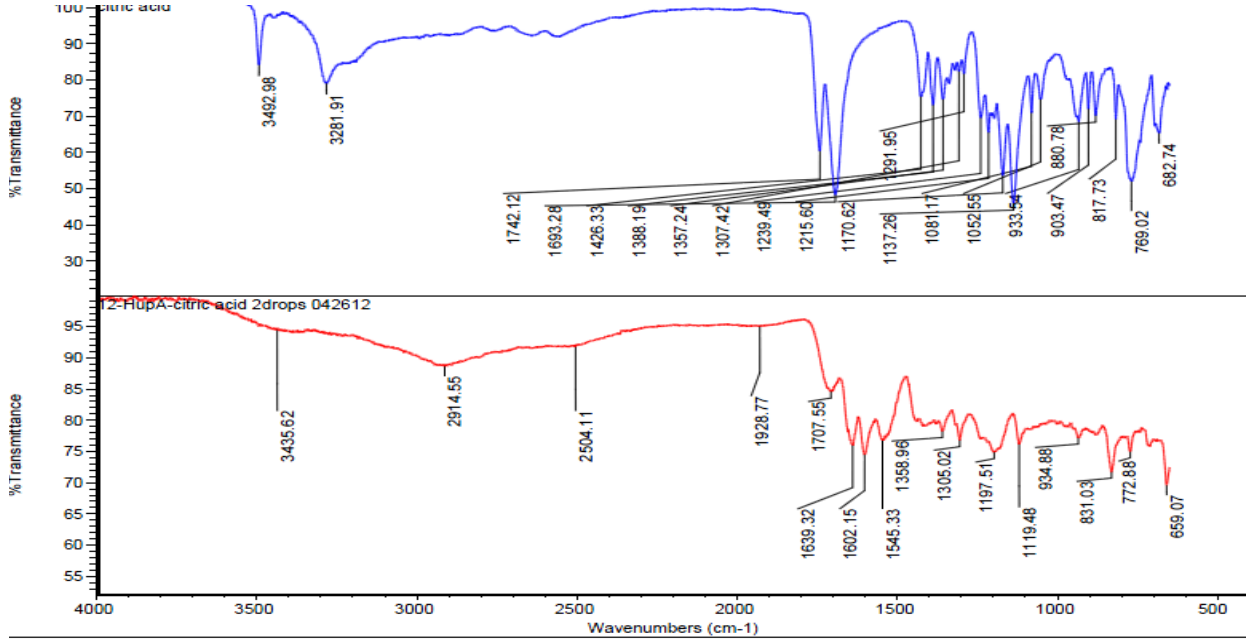
Date: Wed Apr 25 16:12:14 2012 (GMT-05:00)3-HupA-sorbic acid 2drops 042512

Scans: 32 -7.845727e-005

Resolution: 4.000 -8.482764e-005


Isophthalic acid
2818.79
2543.21
1684.83
1609.51
1578.22
1484.61
1453.51
1415.41
1326.14
1263.67
1162.02
1097.40
1038.08
917.23
779.79
722.26
10-HupA-isophthalic acid 2drops 042612
3490.41
2883.36
2531.51
2362.38
1884.93
1690.18
1643.79
1605.05
1545.69
1452.27
1420.76
1360.93
1280.90
1074.02
1158.29
744.80
730.03
707.70
688.06
% Transmittance
Wavenumbers (cm-1)
Date: Thu Apr 26 09:41:39 2012 (GMT-05:00) 10-HupA-isophthalic acid 2drops 042612
Scans: 32
-8.389039e-005
Resolution: 4.000
-8.922123e-005


Acetylsalicylic acid
1749.71
1680.70
1604.53
1455.72
1303.71
1218.18
1134.25
1182.65
1093.48
914.89
838.75
802.80
753.17
709.54
790.70
665.71
11-HupA-acetylsalicylic acid 2drops 042712
3405.86
2900.97
2561.56
2358.31
2139.41
1650.86
1551.94
1482.66
1453.21
1380.47
1357.74
1305.70
1249.79
1140.13
1119.05
1064.29
1000.15
934.79
858.76
806.15
786.53
758.11
740.63
705.08
662.97
% Transmittance
Wavenumbers (cm-1)
Date: Fri Apr 27 09:50:50 2012 (GMT-05:00) 11-HupA-acetylsalicylic acid 2drops 042712
Scans: 32
-7.997166e-005
Resolution: 4.000
-8.157935e-005

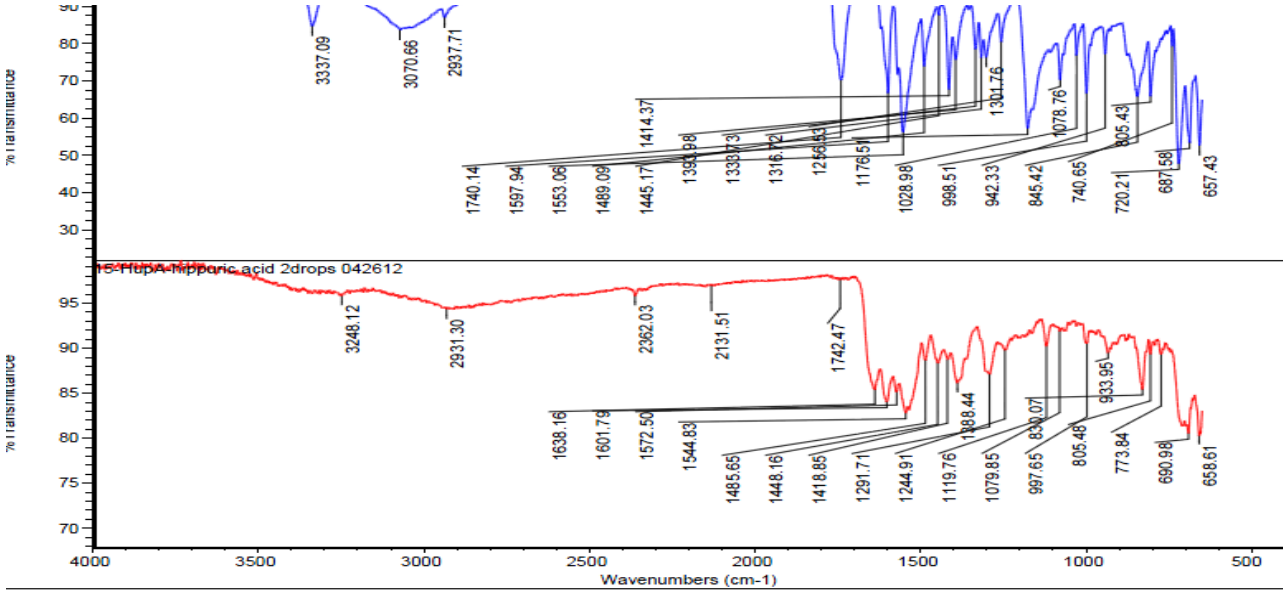


Date: Thu Apr 26 19:25:21 2012 (GMT-05:00) 12-HupA-citric acid 2drops 042612

Scans: 32 -7.003442e-005

Resolution: 4.000 -7.992132e-005

IR Spectrum 7: Huperzine A and Citric Acid – two drops of Ethanol

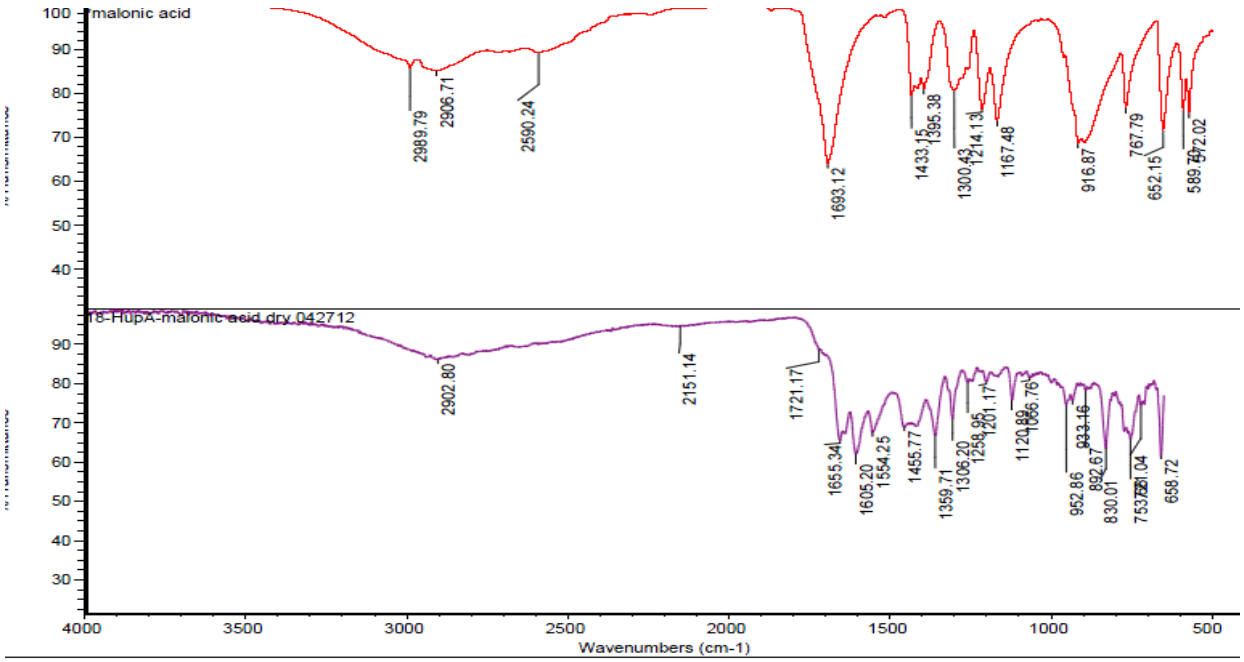


Date: Thu Apr 26 11:45:37 2012 (GMT-05:00) 15-HupA-hippuric acid 2drops 042612

Scans: 32 -8.355147e-005

Resolution: 4.000 -7.826983e-005

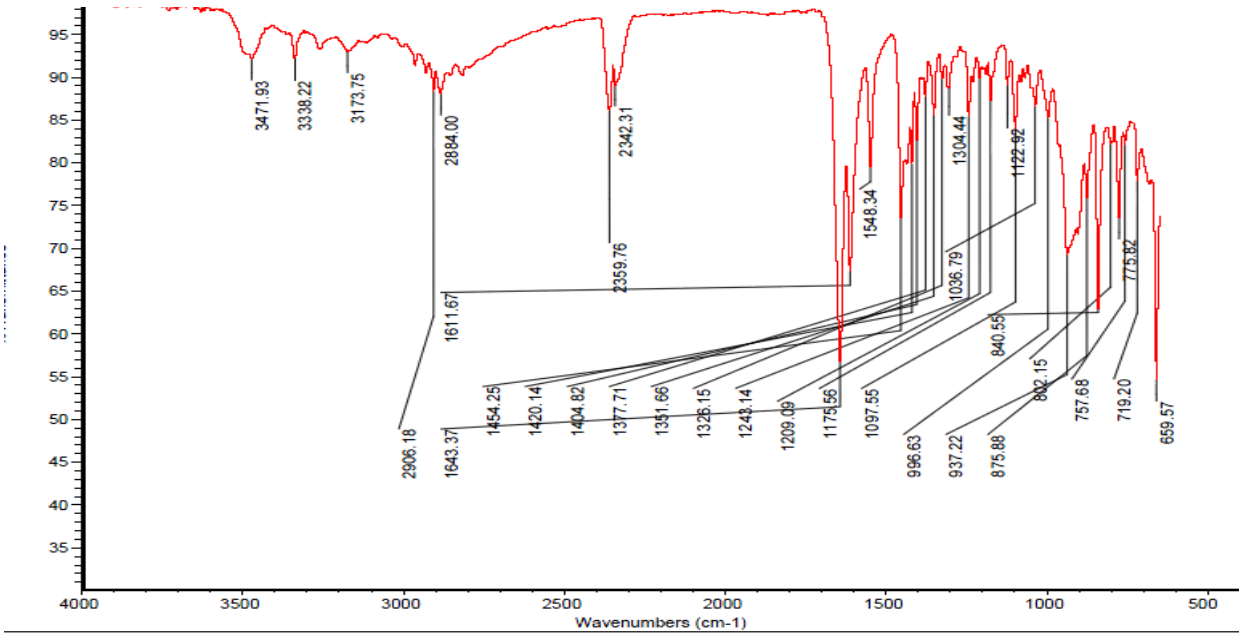
IR Spectrum 8: Huperzine A and Hippuric Acid – two drops of Ethanol



Date: Sat Sep 12 13:22:20 2009 (GMT-05:00) *malonic acid

Scans: 32 -8.967242e-006

Resolution: 4.000 -3.941365e-006

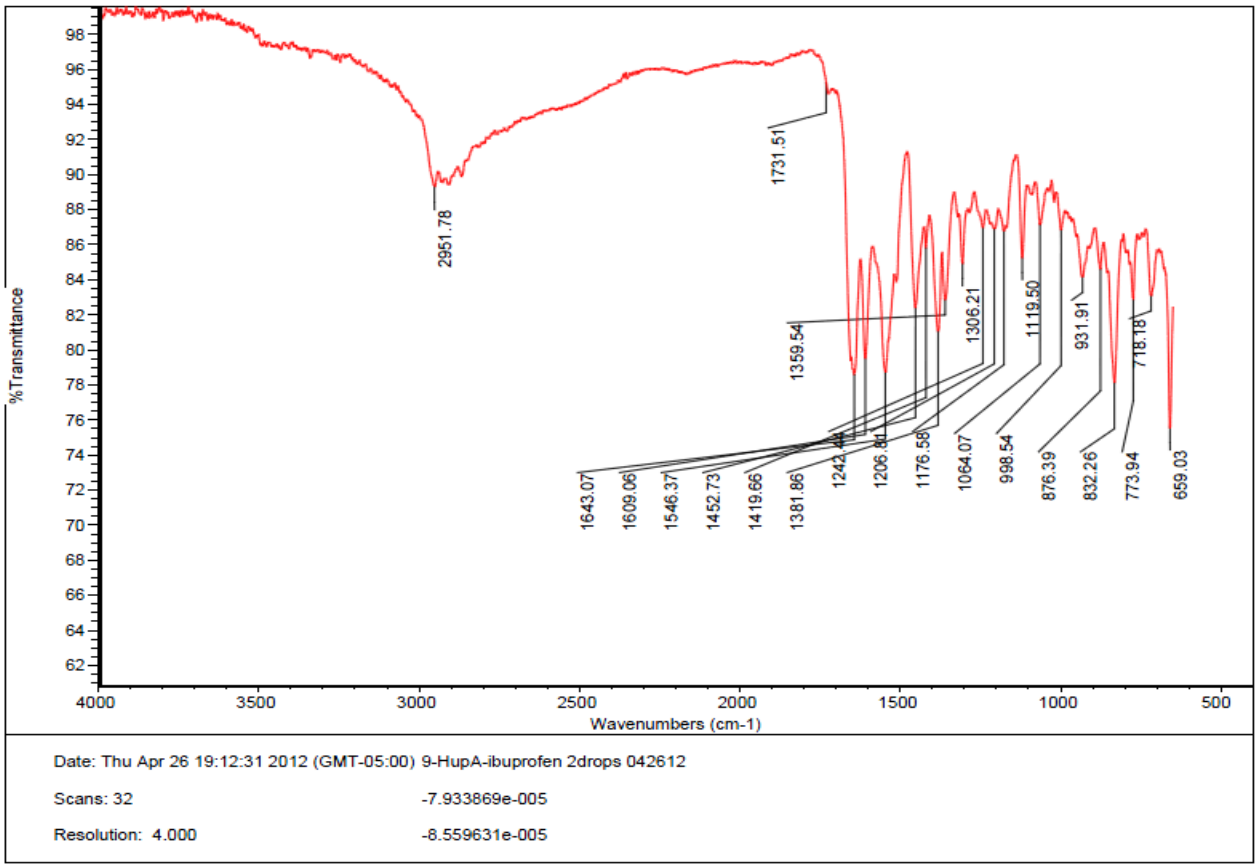


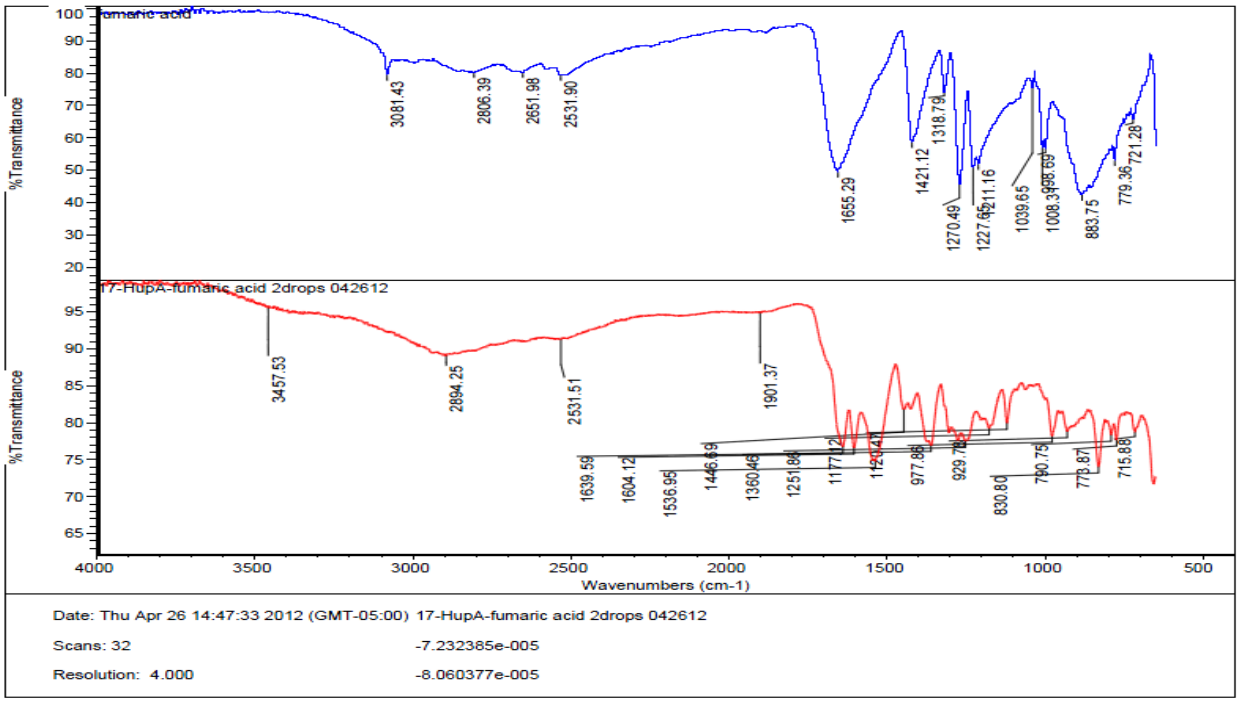
Date: Wed Apr 25 14:52:26 2012 (GMT-05:00)HupA 042512

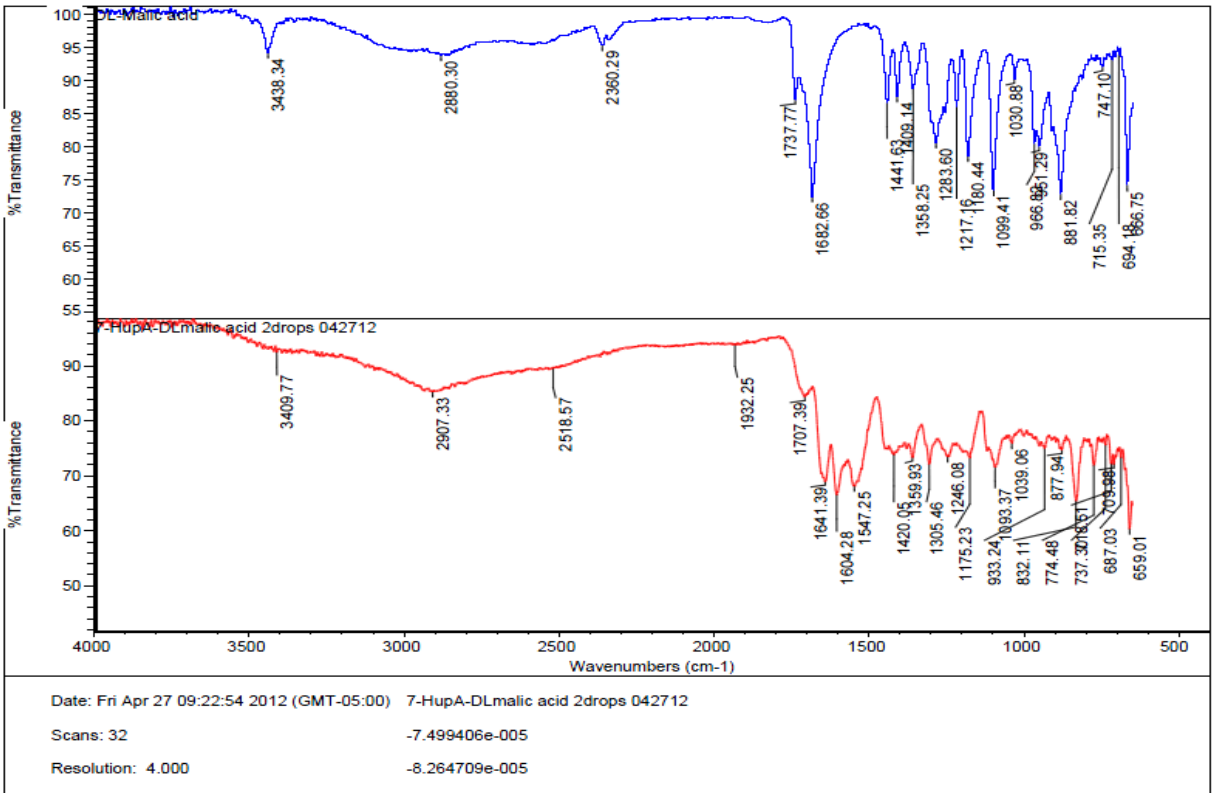
Scans: 32 -9.437108e-005

Resolution: 4.000 -8.784446e-005

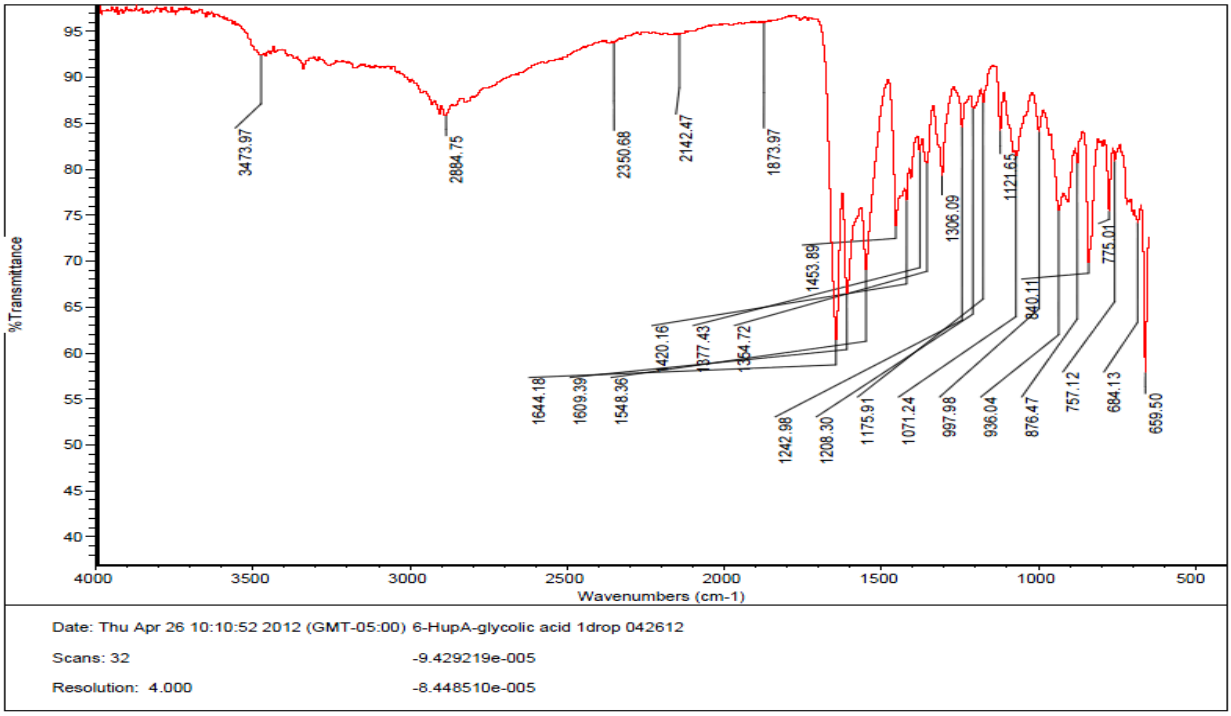
IR Spectrum 10: Huperzine A


%Transmittance
Wavenumbers (cm-1)
2951.78
1731.51
1359.54
1306.21
1119.50
931.91
718.18
1643.07
1609.06
1546.37
1452.73
1419.66
1381.86
1242.48
1206.80
1176.58
1064.07
998.54
876.39
832.26
773.94
659.03
Date: Thu Apr 26 19:12:31 2012 (GMT-05:00) 9-HupA-ibuprofen 2drops 042612
Scans: 32
-7.933869e-005
Resolution: 4.000
-8.559631e-005

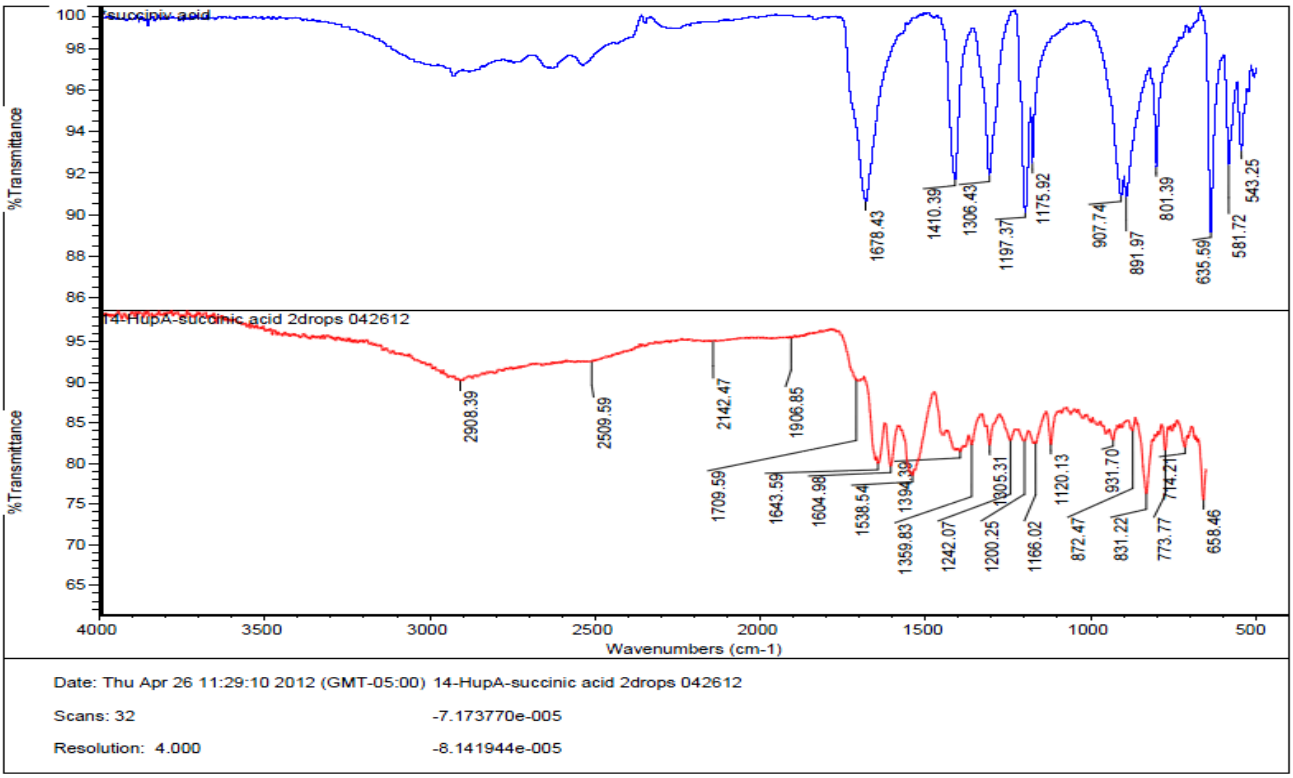

%Transmittance
fumaric acid
3081.43
2806.39
2651.98
2531.90
1655.29
1421.12
1318.79
1270.49
1227.65
1211.16
1039.65
1008.39
998.69
883.75
779.36
721.28
17-HupA-fumaric acid 2drops 042612
3457.53
2894.25
2531.51
1901.37
1639.59
1604.12
1536.95
1446.69
1360.46
1251.86
1177.12
1124.41
977.86
929.78
830.80
790.75
778.87
715.88
Wavenumbers (cm-1)
Date: Thu Apr 26 14:47:33 2012 (GMT-05:00) 17-HupA-fumaric acid 2drops 042612
Scans: 32
-7.232385e-005
Resolution: 4.000
-8.060377e-005



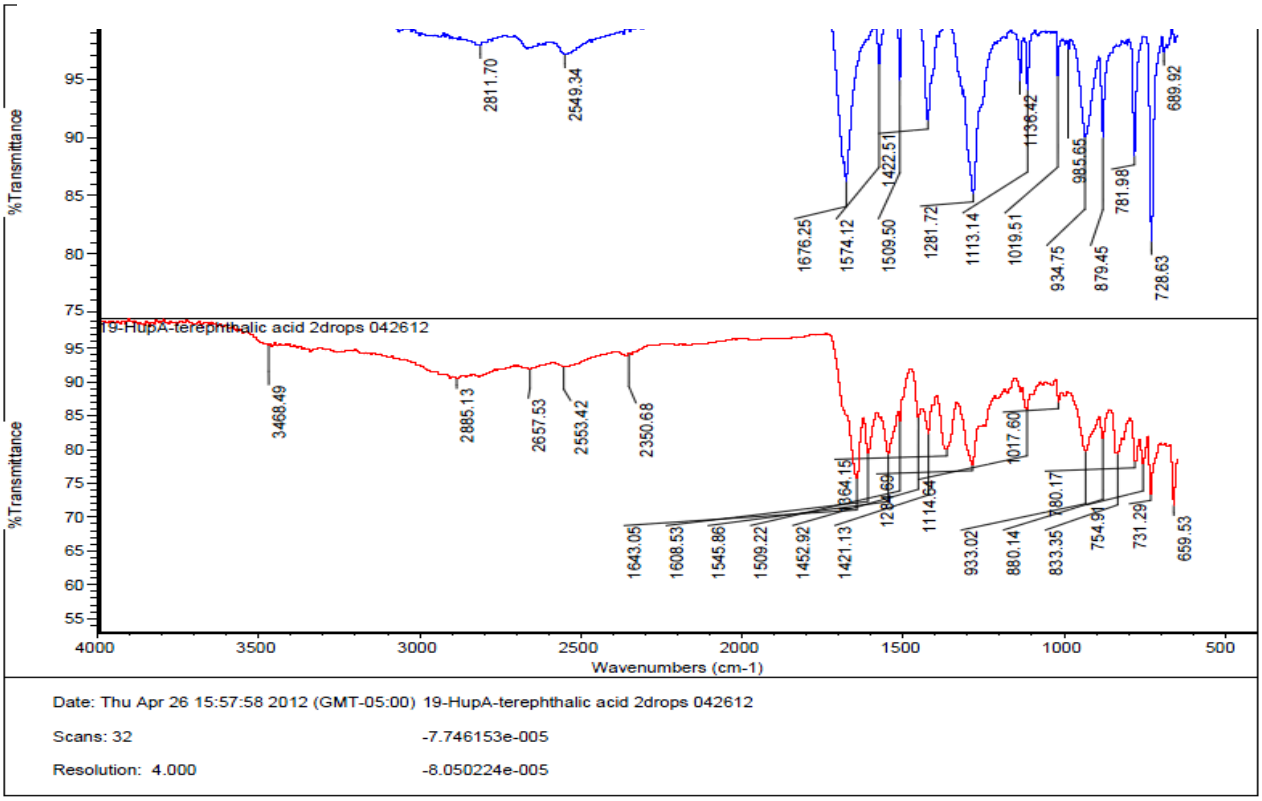
IR Spectrum 13: Huperzine A Malic Acid – two drops of Ethanol



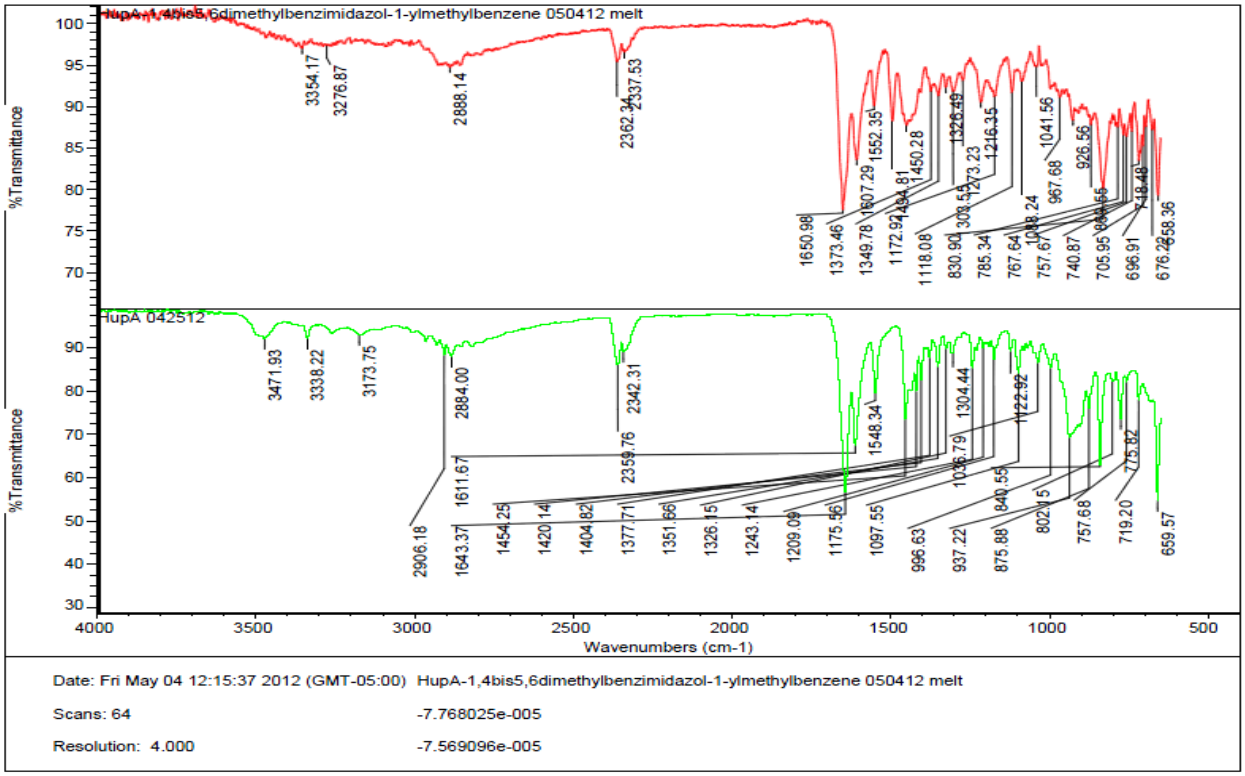
IR Spectrum 14: Huperzine A and Glycolic Acid – two drops of Ethanol



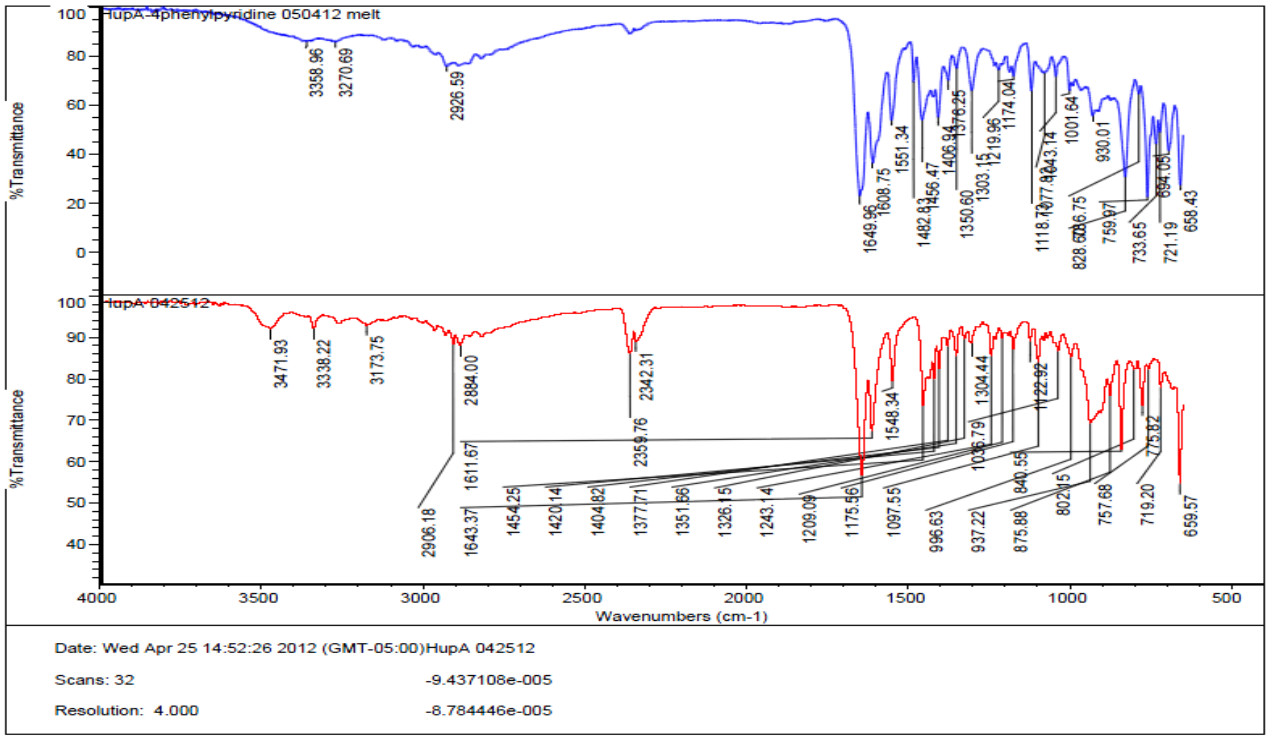
IR Spectrum 15: Huperzine A and Succinic Acid – two drops of Ethanol



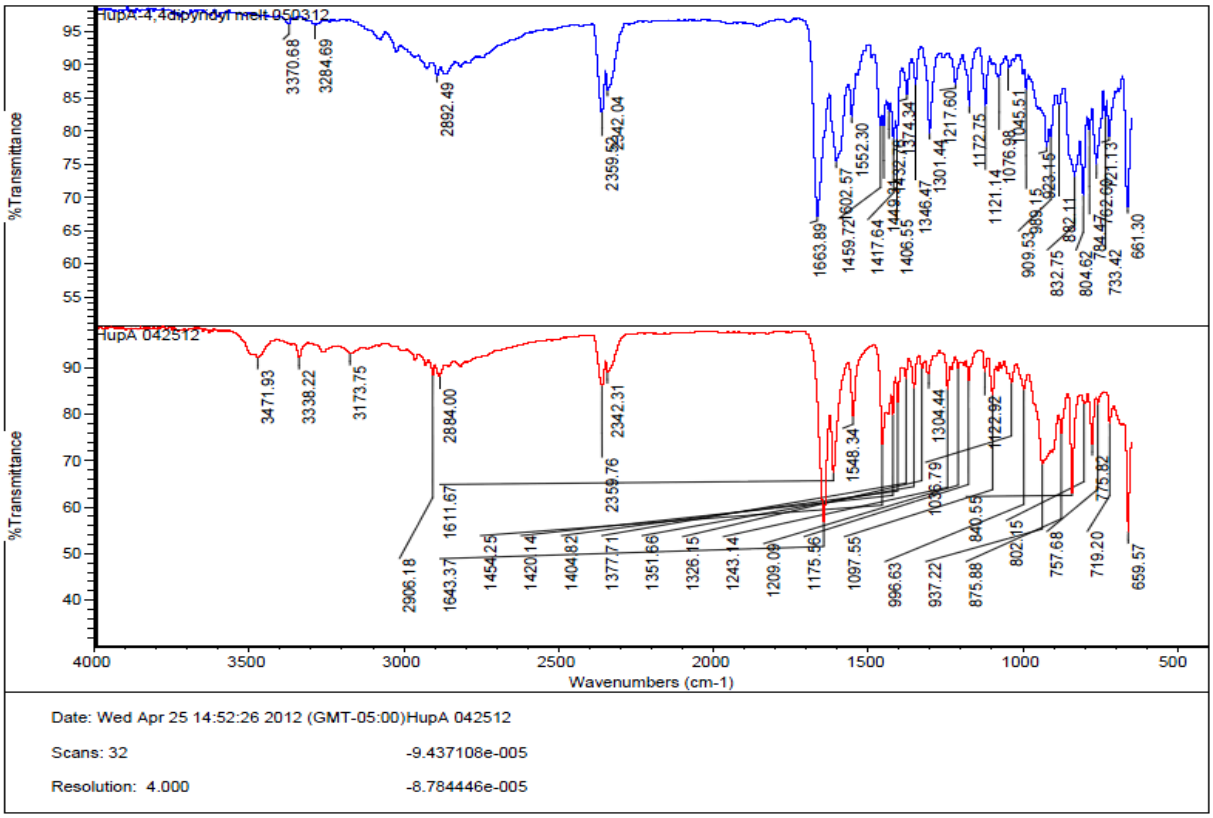
IR Spectrum 16: Huperzine A and Terephthalic Acid – two drops of Ethanol



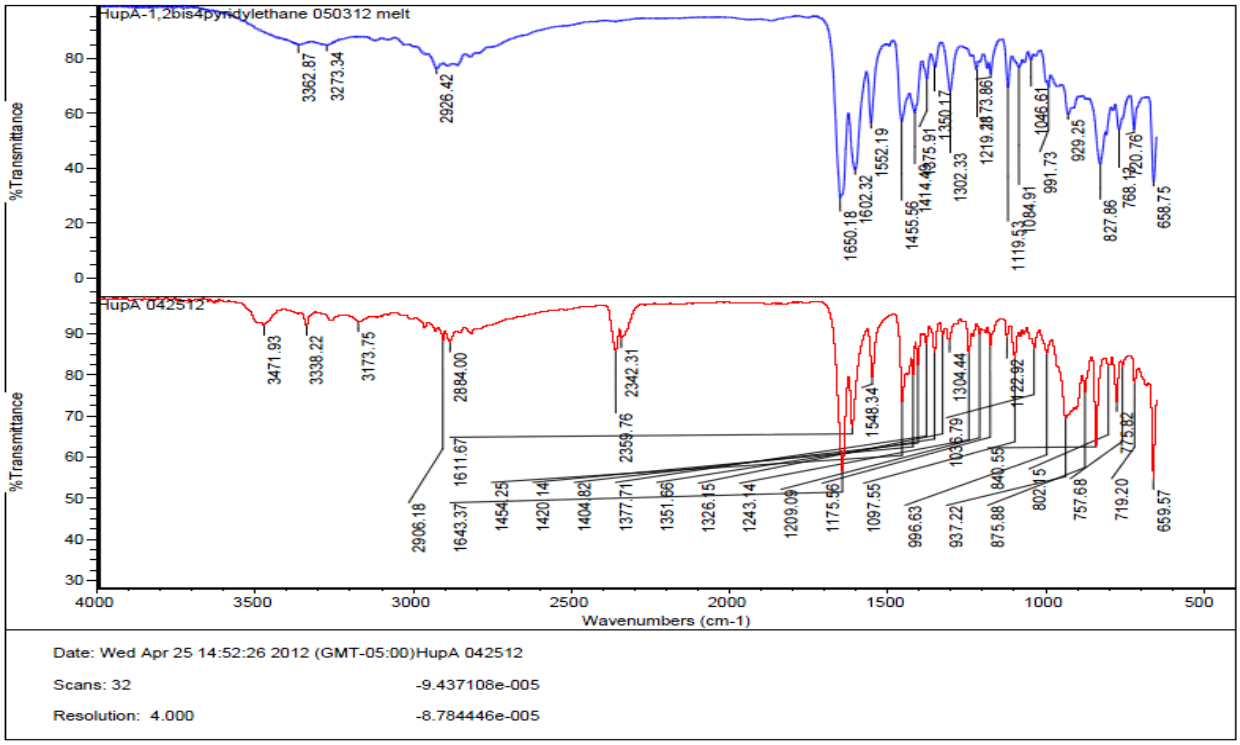
IR Spectrum 17: Huperzine A and 1,4bis5,6dimethylbenzimidazol-1-ylmethylbenzene Melt Sample



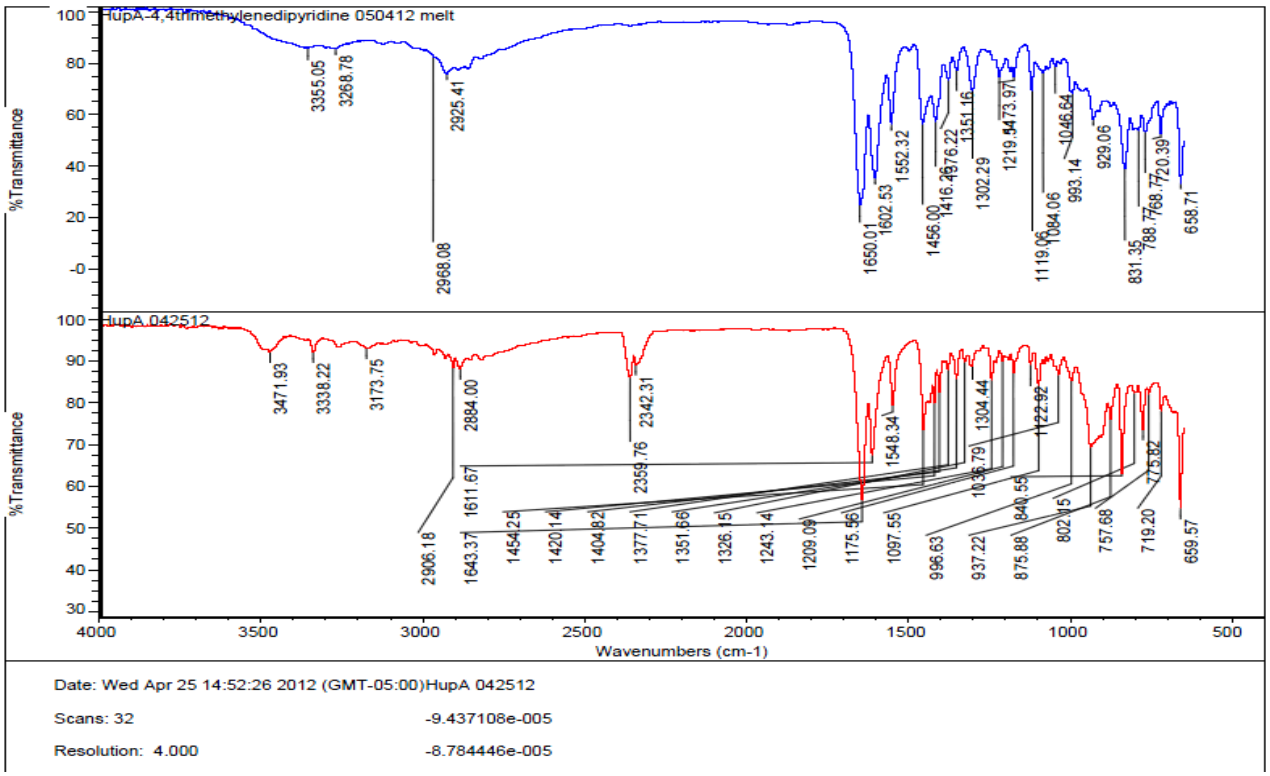
IR Spectrum 18:Huperzine A and 4phenylpyridine Melt Sample



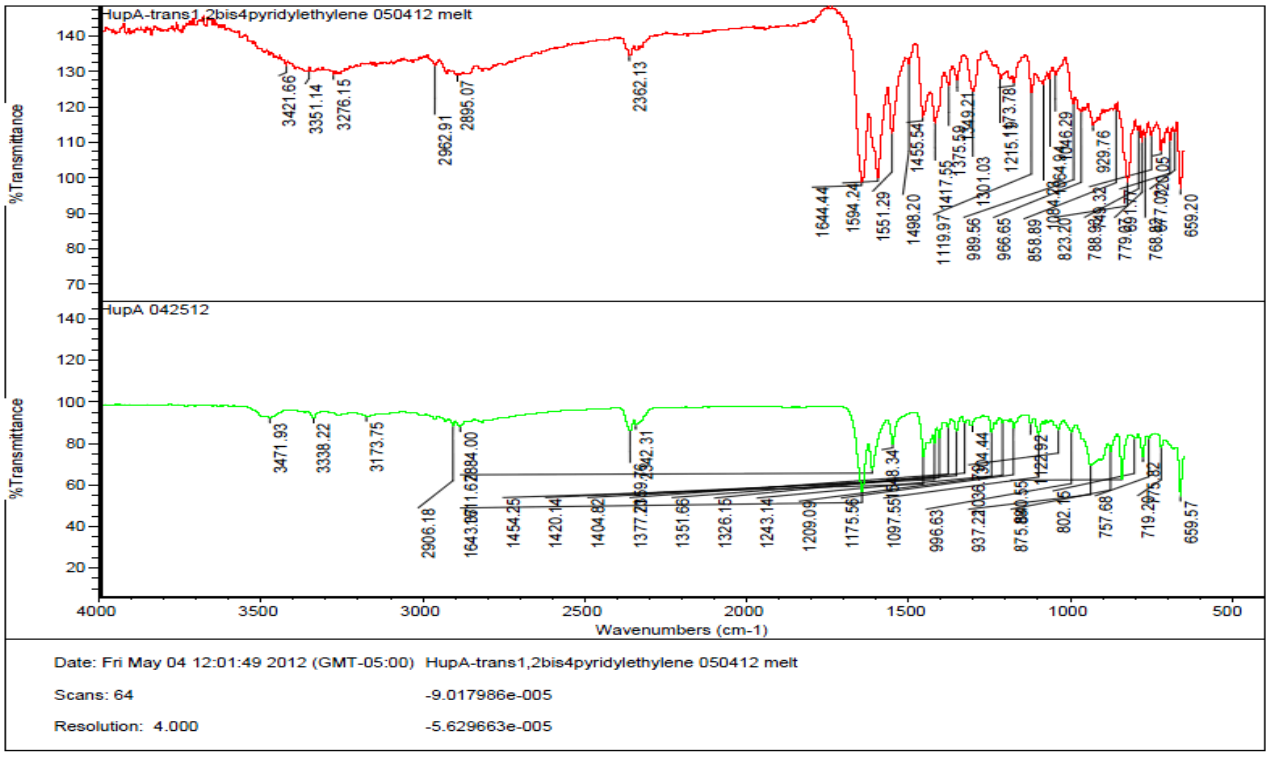
IR Spectrum 19: Huperzine A and 4,4dipyridyl Melt Sample



IR Spectrum 20: Huperzine A and 1,2bis4pyridylethane Melt Sample



IR Spectrum 21: Huperzine A and 4,4trimethylenedipyridine Melt Sample



IR Spectrum 22: Huperzine A and trans1,2bis4pyridylethylene Melt Sample

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3. Hualiang Jiang, X. L. (2003). *Progress in Clinical, Pharmacological, Chemical and Structural Biological Studies of Huperzine A: A Drug of Traditional Chinese Medicine Origin for the Treatment of Alzheimer's Disease.*

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6. Zaworotko, N. S. (May 2008). *The role of cocrystals in pharmaceutical science.*