PROCEEDINGS OF III. INTERNATIONAL AGRICULTURAL, BIOLOGICAL & LIFE SCIENCE CONFERENCE

AGBIOL 2021

SEPTEMBER 1-3, 2021

EDIRNE, TURKEY

PROCEEDINGS OF III. INTERNATIONAL AGRICULTURAL, BIOLOGICAL & LIFE SCIENCE CONFERENCE AGBIOL 2021

1 – 3 SEPTEMBER 2021,

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Organized by

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WELCOME NOTES

You are welcome to our III. AGBIOL Conference that is organized by Trakya University. The aim of our conference is to present scientific subjects of a broad interest to the scientific community, by providing an opportunity to present their work as oral or poster presentations that can be of great value for global science arena. Our goal was to bring three communities, namely science, research and private investment together in a friendly environment of Edirne, Turkey in order to share their interests and ideas and to benefit from the interaction with each other but we have to organize as online due to Covid_19 stiuation again. I hope next one we could host you in Edirne.

In September 2018, we organized the first AGBIOL Conference with more than 700 scientists and researchers from all over the world with over 800 scientific papers. Due to COVID-19 situation, II. AGBIOL 2020 has organized fully on-line event which was one of the biggest online conferences in recent years in the world with 499 papers and 1133 authors with 333 oral and 166 e-poster presentations from 55 countries. Therefore, this great interest gave ambition to organizers to make it a periodical event then we decided to organize 3rd one in this year.

The Organizing Committee of AGBIOL 2021 considers the health, safety, and security of its conference attendees and community as its top priority. Due to COVID-19 situation, which results in a very difficult travel restriction for most countries and the fact that there is no definite end in sight, with a careful consideration in all aspects**,** then AGBIOL 2021 has decided to move towards the organization of on-line again but with limited participation**.** There is a worldwide participation from 44 countries with 422 papers by contributing 1066 authors. Our AGBIOL 21 conference was organized with 288 oral, 134 e-poster presentations.

The participants with paid conference fee will be able to access all the virtual presentation talks in each session, as well as to visit the virtual poster hall via preliminary provided participant ID and codes. The selected ABSTRACTs will be published in the Conference ABSTRACT and Proceedings Book. Participants might send us their full papers, which based on their preferences will be published either in our Conference ABSTRACT and Proceedings Book or in selected International Indexed Scientific Journals.

Conference Topics:

Agriculture, Forestry, Life Sciences, Agricultural Engineering, Aquaculture and Biosystems, Animal Science, Biomedical science, Biochemistry and Molecular Biology, Biology, Bioengineering, Biomaterials, Biomechanics, Biophysics, Bioscience, Biotechnology, Botany, Chemistry, Chemical Engineering, Earth Sciences, Environmental Science, Food Science, Genetics and Human Genetics, Medical Science, Machinery, Pharmaceutical Sciences, Physics, Soil Science.

We would like to thank all of you for joining this conference and we would like to give also special thanks to our sponsors and collaborators for giving us a big support to organize this event.

Prof Dr Yalcin KAYA

Head of the Organizing Committee

METHODOLOGY FOR THE ALTERATION OF HAZARDOUS SOLVENTS IN DRUG SYNTHESIS

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ABSTRACT

Hazardous solvents have a high potential for causing acute health risks, including serious health problems such as cancer. They should be avoided or limited in pharmaceutical and chemical synthesis owing to the health hazards and safety issues. A method of amide coupling reaction was developed employing the recommended solvents to replace the hazardous solvents. The reactions were observed using the RP-HPLC method to detect reaction rate of aniline and benzoic acid to produce N-phenyl benzamide. 68.33%, 79.25% and 89.81% yields were synthesized using the solvents: acetone (Ace), dimethyl sulfoxide (DMSO), and ethanol (EtOH) respectively while 87.60% was produced by hazardous solvent: N, N-dimethyl formamide (DMF). Using this approach, adjusting the pH10 of the organic solvent increases reaction yield up to 34.67%, 4.65%, and 3.84% for Ace, DMSO, and EtOH, respectively. In drug synthesis, the proposed method can be applied in wide range to get the protection from the risks of hazardous solvents. The method can be anticipated in future to be an exciting basic method in synthetic chemistry.

Keywords: N-phenyl benzamide, Hazardous solvent, amide coupling reaction, Reaction yield, RP-HPLC method.

III. INTERNATIONAL AGRICULTURAL, BIOLOGICAL &
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Research Title

Methodology for the Alteration of Hazardous Solvents in Drug Synthesis

Presented by
Tariqul Islam

Tariqul Islam, Md. Zaidul Islam Sarker*, ABM Helal Uddin

الجامعة الإسلامية العالمية ماليزيا
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Garden of Knowledge and Virtue

Outlines

1. Background

2. Objective

3. Methodology

- ✓ Flowchart of methodology
- ✓ Solvent selection by Kamlet Taft (KT) parameters
- ✓ Synthesis procedure

4. Result and Discussion

- ✓ KT properties of pure solvents and solvent-pair mixtures
- ✓ Curve for KT properties
- ✓ Comparison of HPLC chromatograms between normal pH and pH adjusted synthesis
- ✓ Reaction conversion curve of pure solvents
- ✓ Yield curve of pure solvents
- ✓ Reaction conversion curve of solvent-pair mixtures
- ✓ Yield curve of solvent-pair mixtures

5. Conclusion

Background

1. Solvents are an unavoidable part of pharmaceutical and chemical synthesis
2. 80-90% solvents of the non-aqueous volume is used in the synthesis of APIs in routine GSK development processes
3. 83% of the 680000 amidation reactions performed by DMF, DCM
4. Majority of crucial solvents have a high potential for causing acute health risks, including safety and environmental hazards and also makes the problem in pharmaceutical preparation

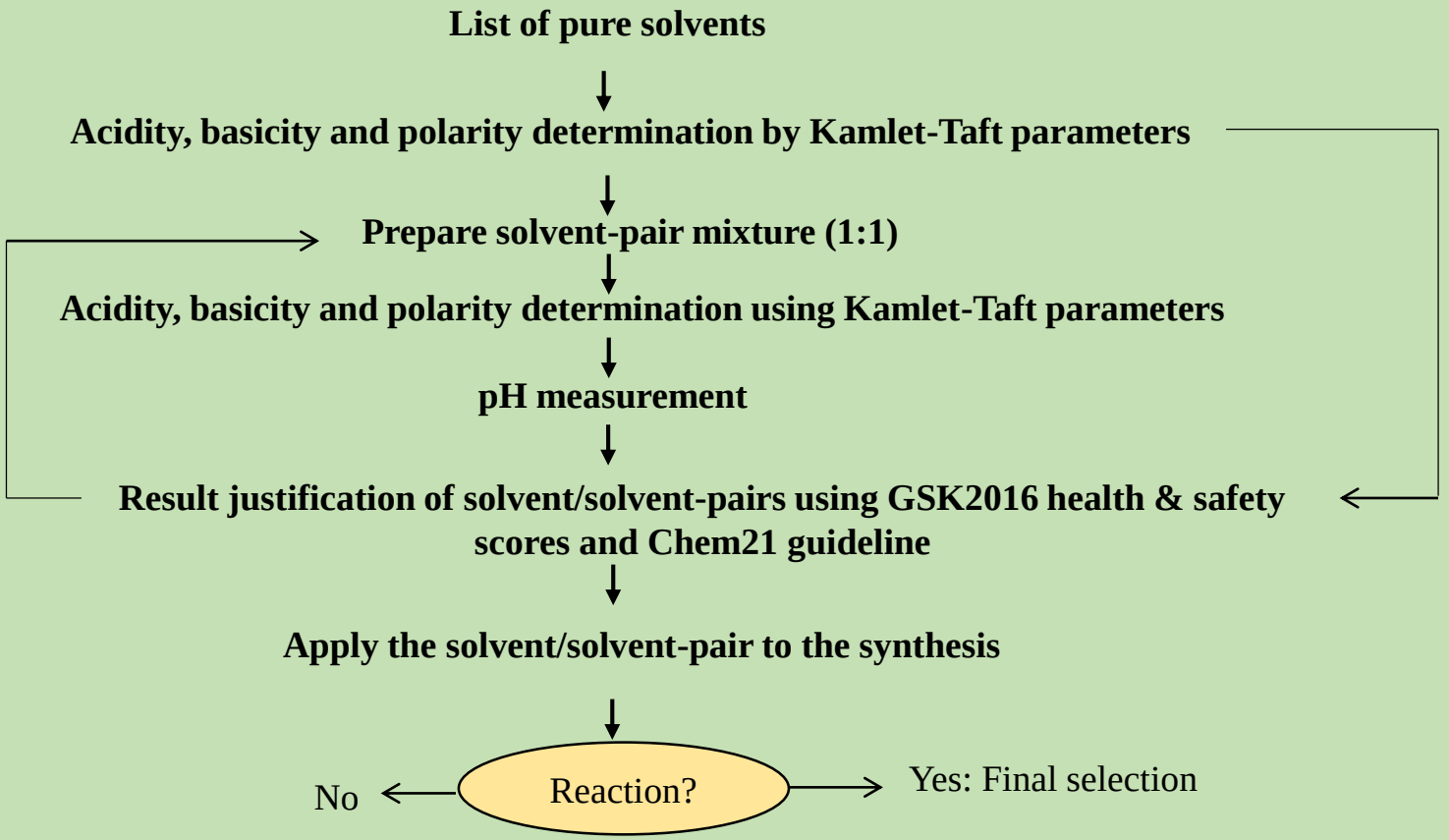
Solvent	**Concern (comment)**			
Most used solvents	**Pfizer**	**GSK**	**Sanofi**	**ICH**
DMF	Undesirable	Major issues	Substitution requested	To be limited
DMAC	Undesirable	Major issues	Substitution requested	To be limited
NMP	Undesirable	Major issues	Substitution requested	To be limited
DCM	Undesirable	Major issues	Substitution advisable	To be limited
Chloroform	Undesirable	Major issues	No comment	To be limited
Dioxane	Undesirable	Major issues	Substitution requested	To be limited
Pyridine	Undesirable	No comment	Substitution advisable	To be limited
IPE	Undesirable	Major issues	Substitution advisable	Unknown

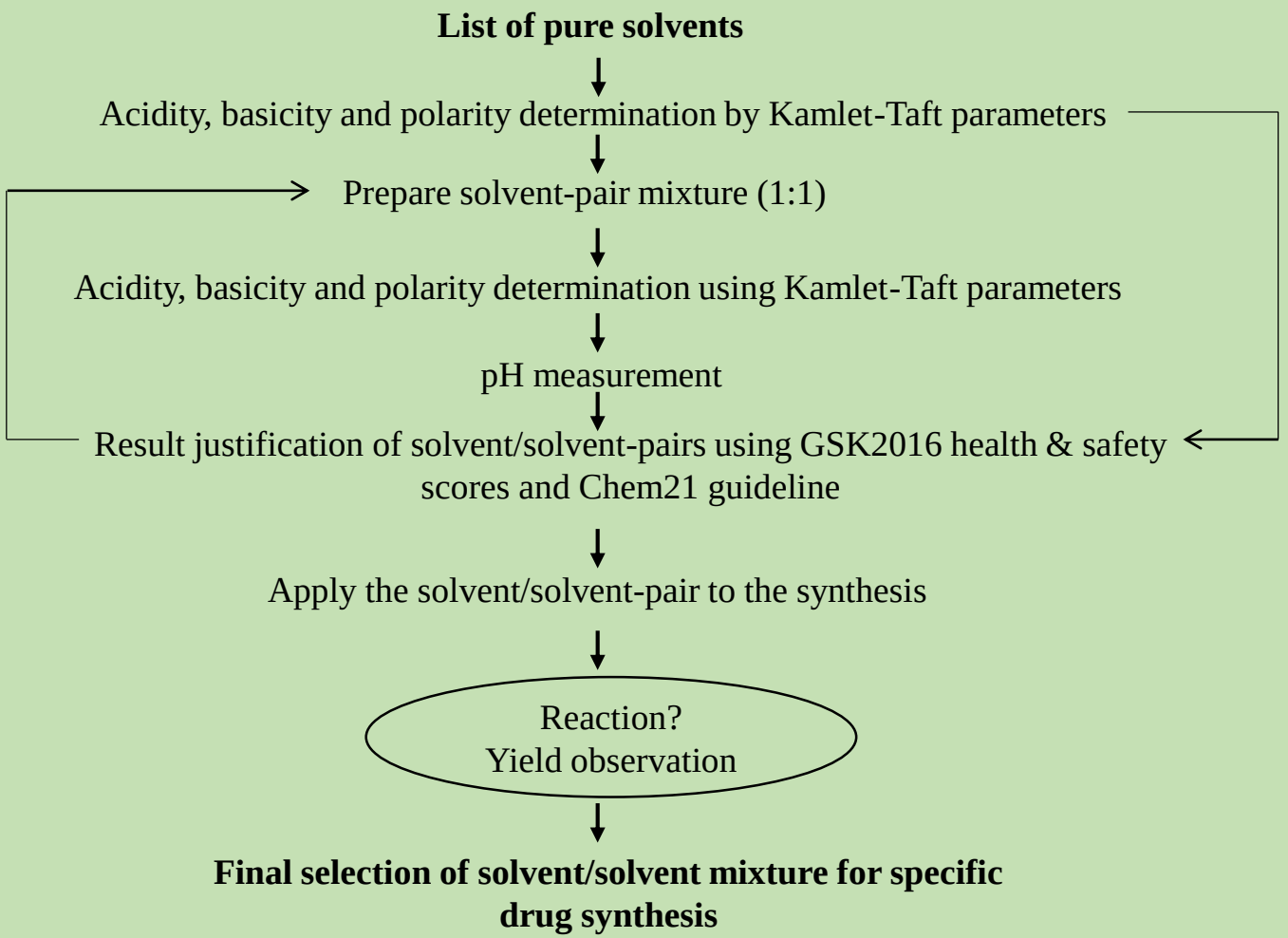
Objectives

- ✓ Our target to replace the dipolar aprotic solvents containing hydrogen bond acceptor solvent (HBA)
- ✓ Since present HBA solvents (e.g. NMP, DMF) are used for processing API have both severe health and safety issues, we propose to study one or more common amide coupling reactions with solvent-pair mixtures and pure solvent to understand the comparison of solvent replacement according to reaction kinetics.
- ✓ Application of pure solvent and solvent-pair mixture in N-phenylbenzamide synthesis

Methodology

Flowchart




List of pure solvents
Acidity, basicity and polarity determination by Kamlet-Taft parameters
Prepare solvent-pair mixture (1:1)
Acidity, basicity and polarity determination using Kamlet-Taft parameters
pH measurement
Result justification of solvent/solvent-pairs using GSK2016 health & safety scores and Chem21 guideline
Apply the solvent/solvent-pair to the synthesis
Reaction?
Yield observation
Final selection of solvent/solvent mixture for specific drug synthesis

Methodology

Kamlet-Taft (KT) solvatochromic parameters (For 10 pure solvents and 16 solvent-pairs)

1. Double beam UV-VIS spectrophotometer with 0.2 nm resolution was applied to determine the absorbance of the solvent with indicator at temperature of 25 ± 0.1 °C.
2. The concentration was for indicator 1: N,N-dimethyl-4-nitroaniline (0.03 mM to 0.05 mM), indicator 2: 4-nitroaniline (0.03 mM to 0.05 mM), and indicator 3: 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio) phenolate (0.1mM) in the solvent or solvent mixture.

- Indicator 1: Polarity (π) = $(28.10 - V_{max1}) / 3.52$ (eq. 1)
- Indicator 2: Basicity (β) = $(0.984V_{max1} + 3.49 - V_{max2}) / 2.759$ (eq. 2)
- Indicator 3: Acidity (α) = $(1.318V_{max1} - 47.7 + V_{max3}) / 5.47$ (eq. 3)

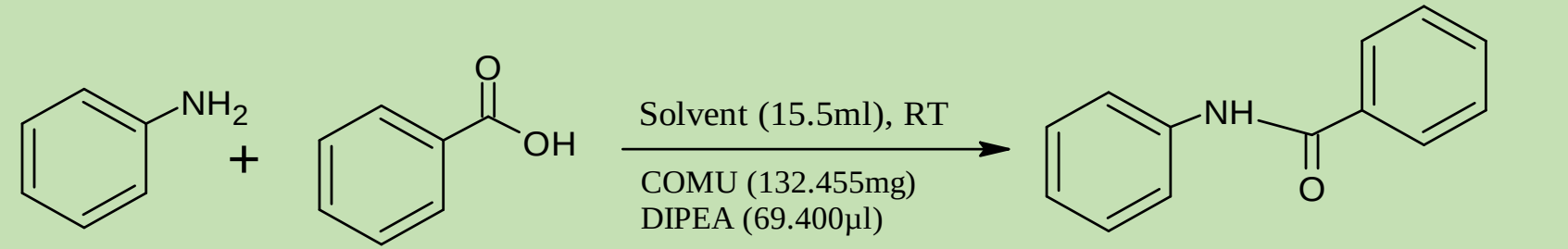
The wavenumber (Vmax) from wavelength (nm) is converted into KiloKaiser unit (1KK = 1000 cm^{-1} = $10000/\lambda_{max}$ (nm) require to calculate the π^*, β, α.

Methodology

Synthesis procedure of N-phenylbenzamide (N-PBA)

At room temperature, benzoic acid (24.448 mg), a amide coupling reagent (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU, 132.455 mg)) and then a base N,N-Diisopropylethylamine (DIPEA, 69.400 µL) were added in the solvent mixture (1:1, 15.5 mL) respectively. Then, aniline (10.637 µL) was added in the mixture after 15 min proper stirring. Reactions were observed using the HPLC at 0 hour (approx. 1 min.), 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h.

The procedure was applied to the synthesis of N-PBA with **8 solvent-pair mixtures** and **4 pure solvents** in triplicate



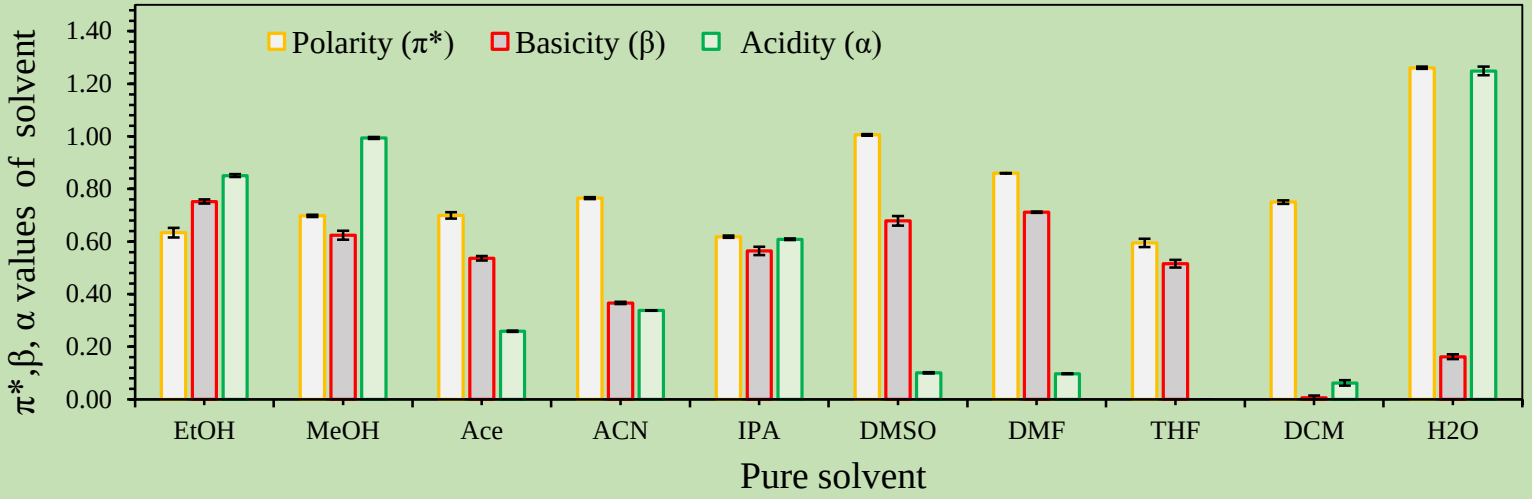
Aniline (10.637µl)

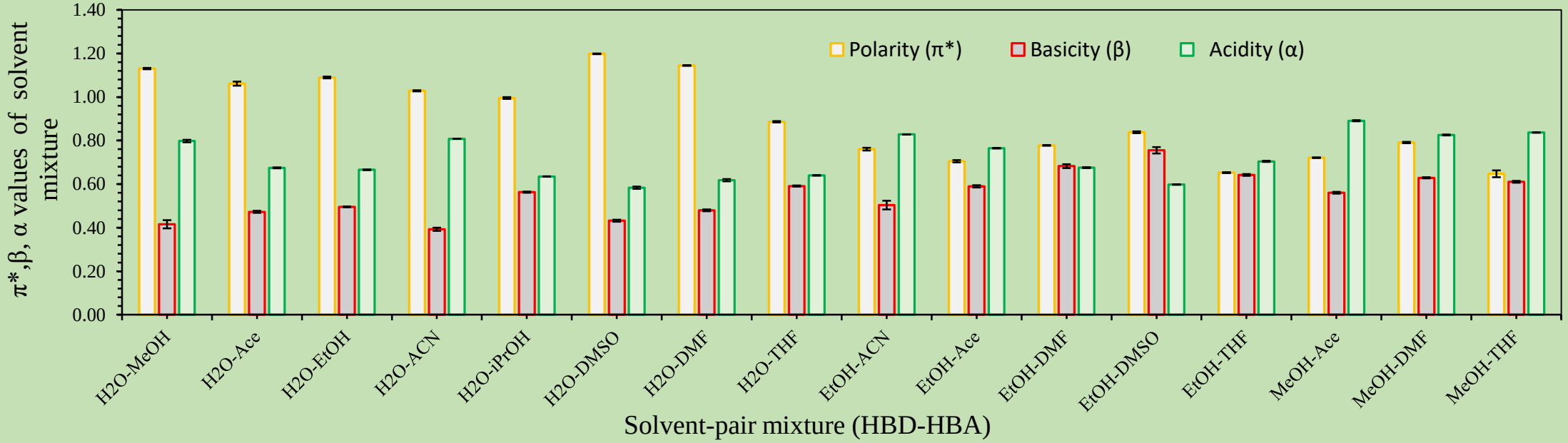
Benzoic acid (24.448mg)

Benzanilide or. N-phenylbenzamide

Result and Discussion

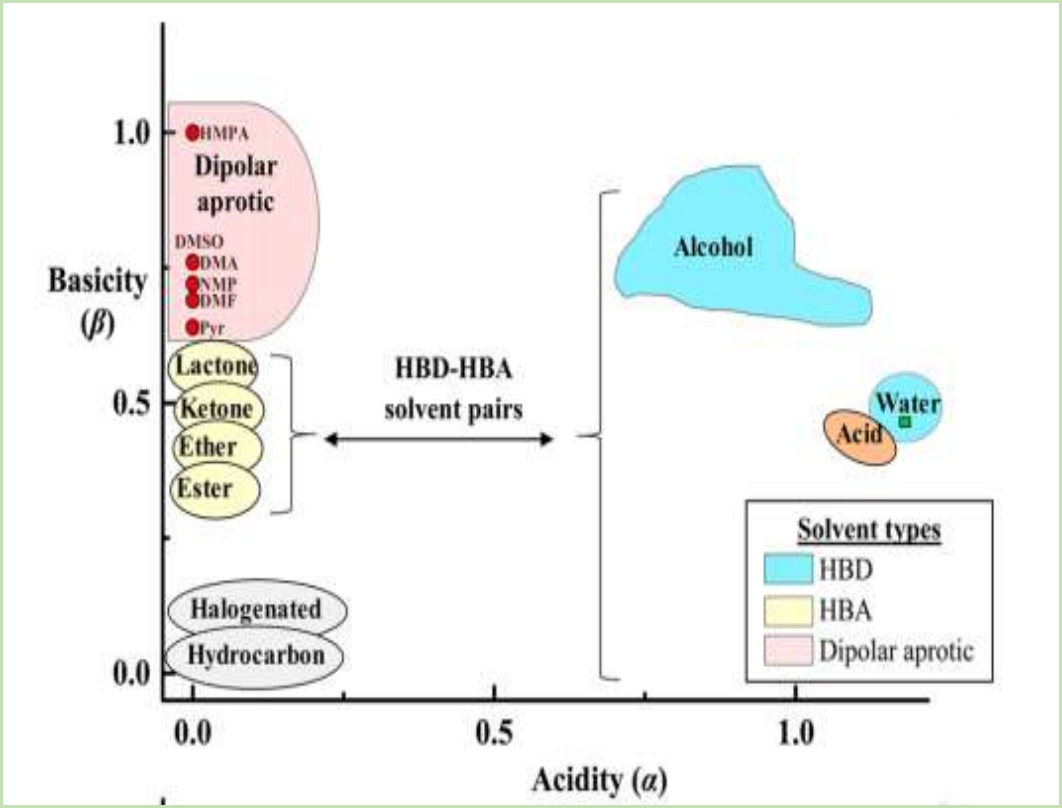
KT solvatochromic properties (π^*, β, α) of the pure solvent (10) and solvent-pairs (16)

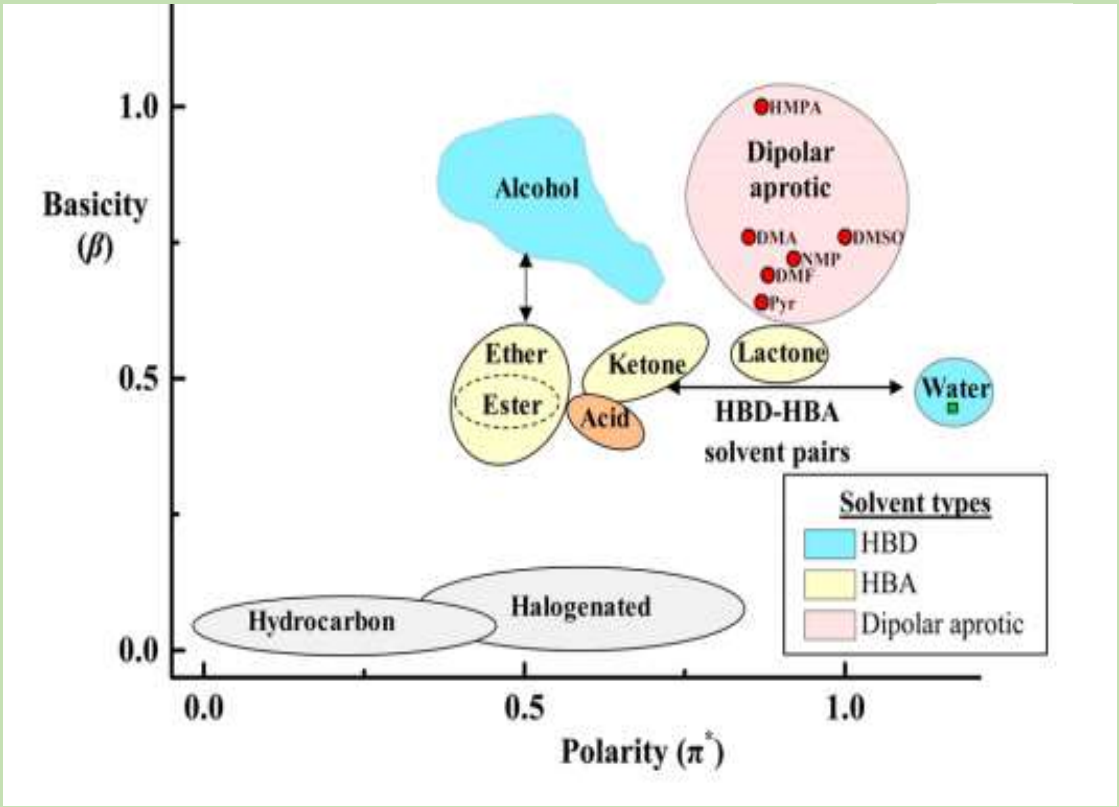




Results and Discussion

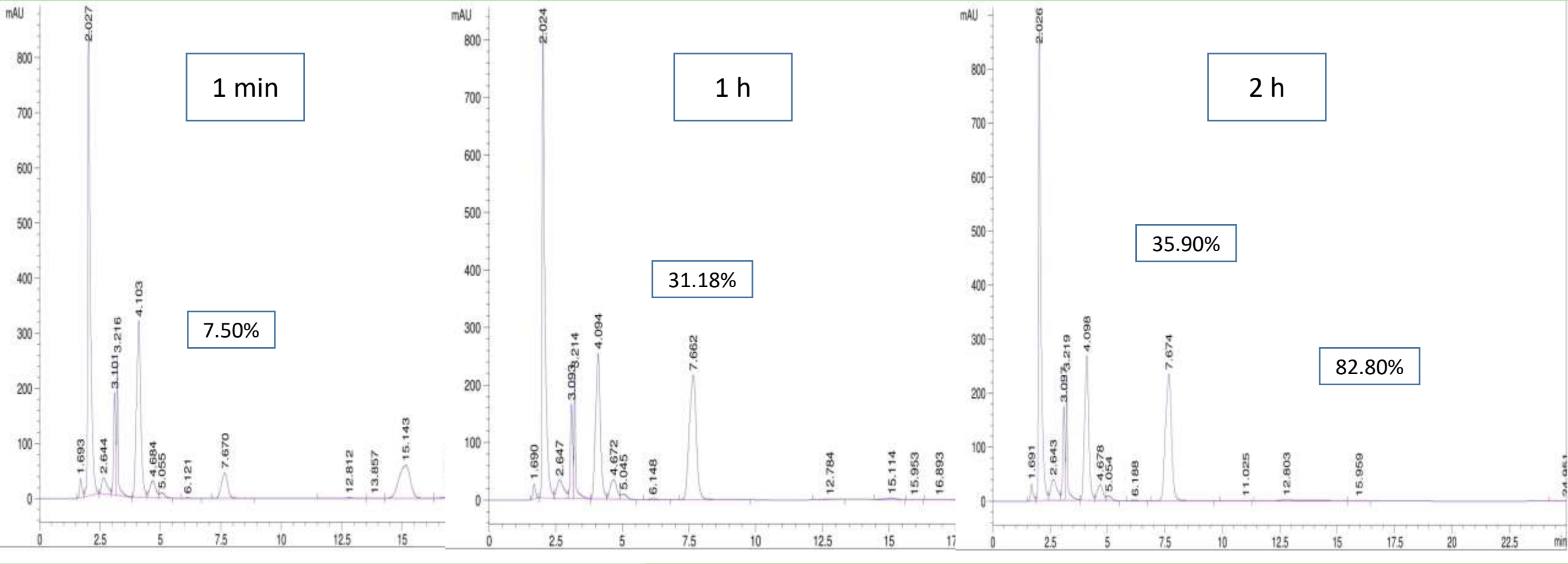
KT properties (π*, β, α) of the organic solvents





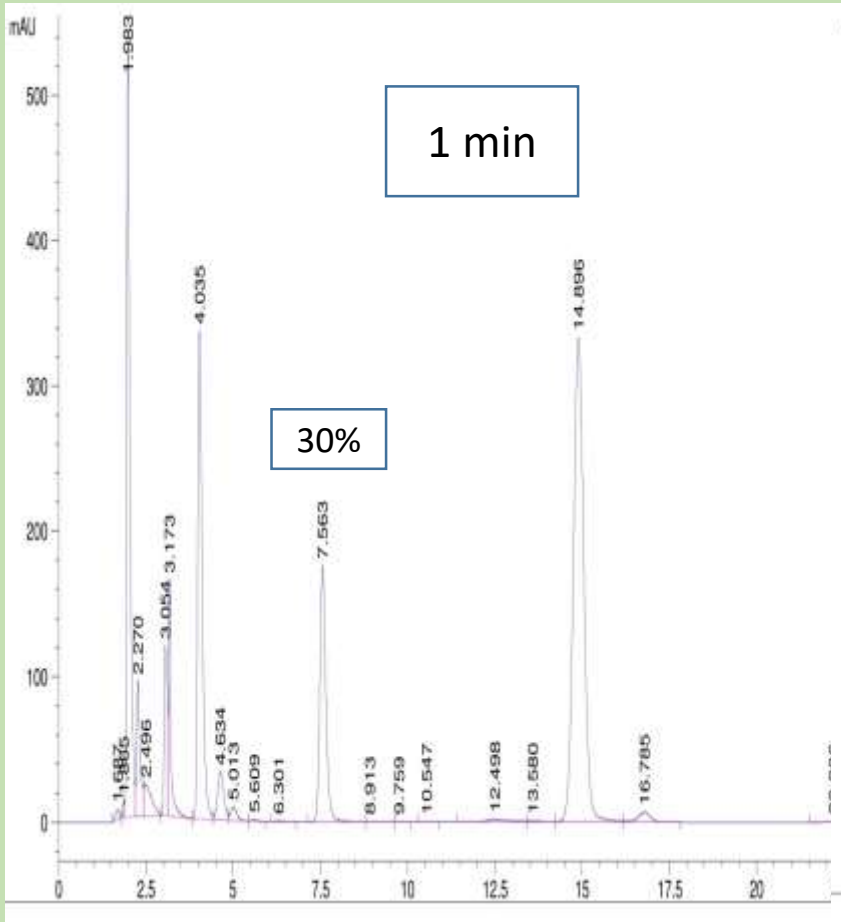
Result and Discussion

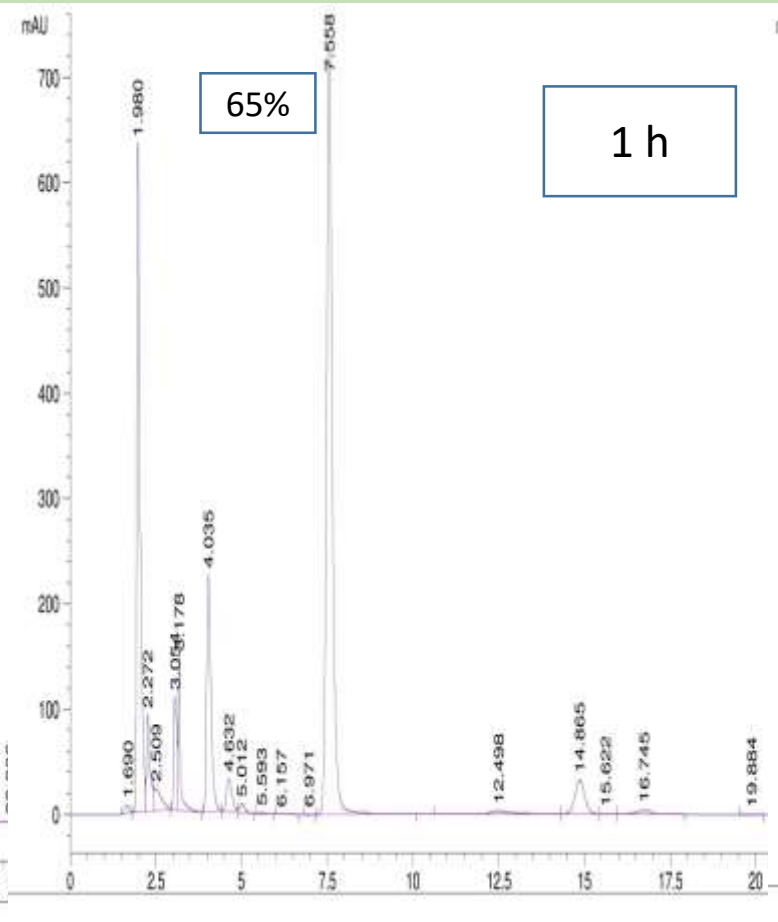
HPLC chromatograms of N-PBA synthesis using the H_2O-THF mixture (Normal pH 7.10)

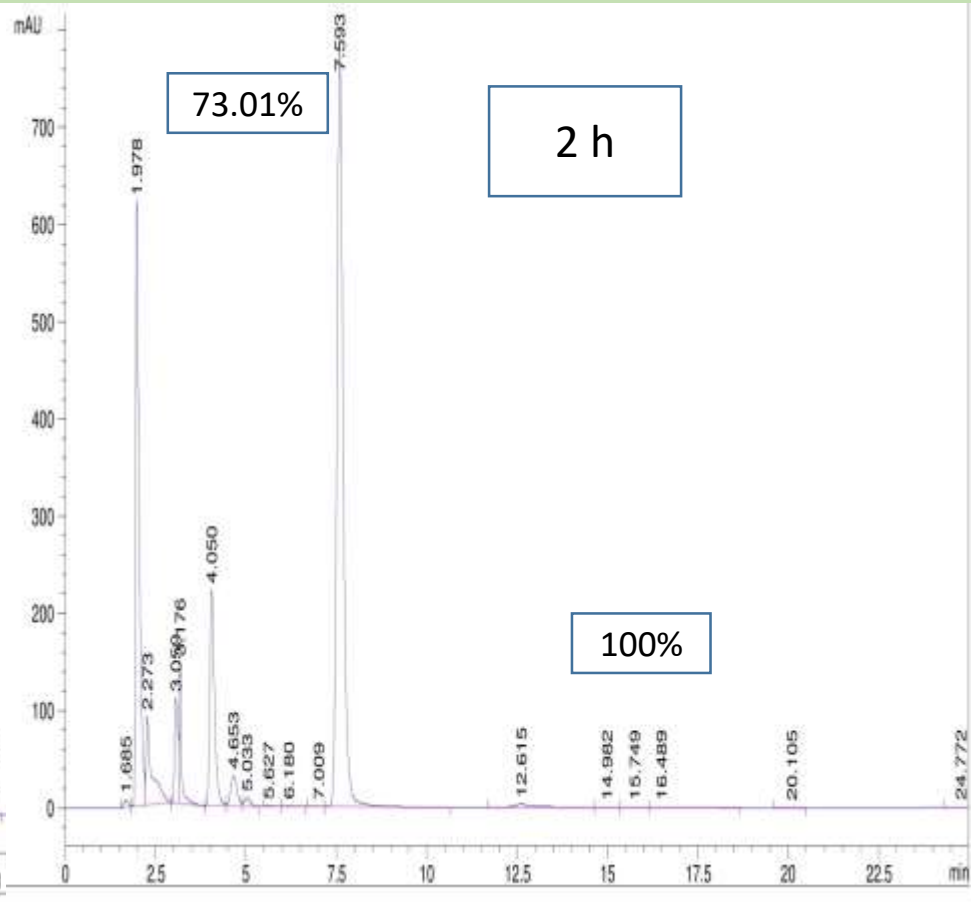


Result and Discussion

HPLC chromatograms of N-PBA synthesis using the H_2O-THF solvent (pH 10.80 adjust)

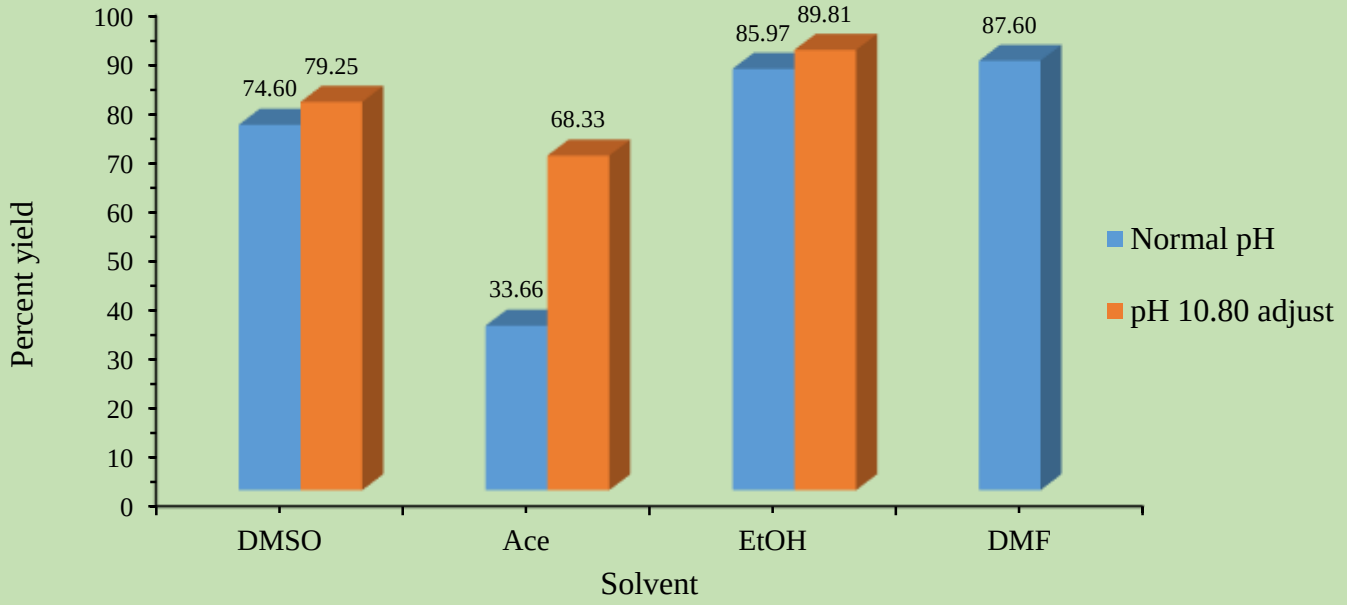






Results and Discussion

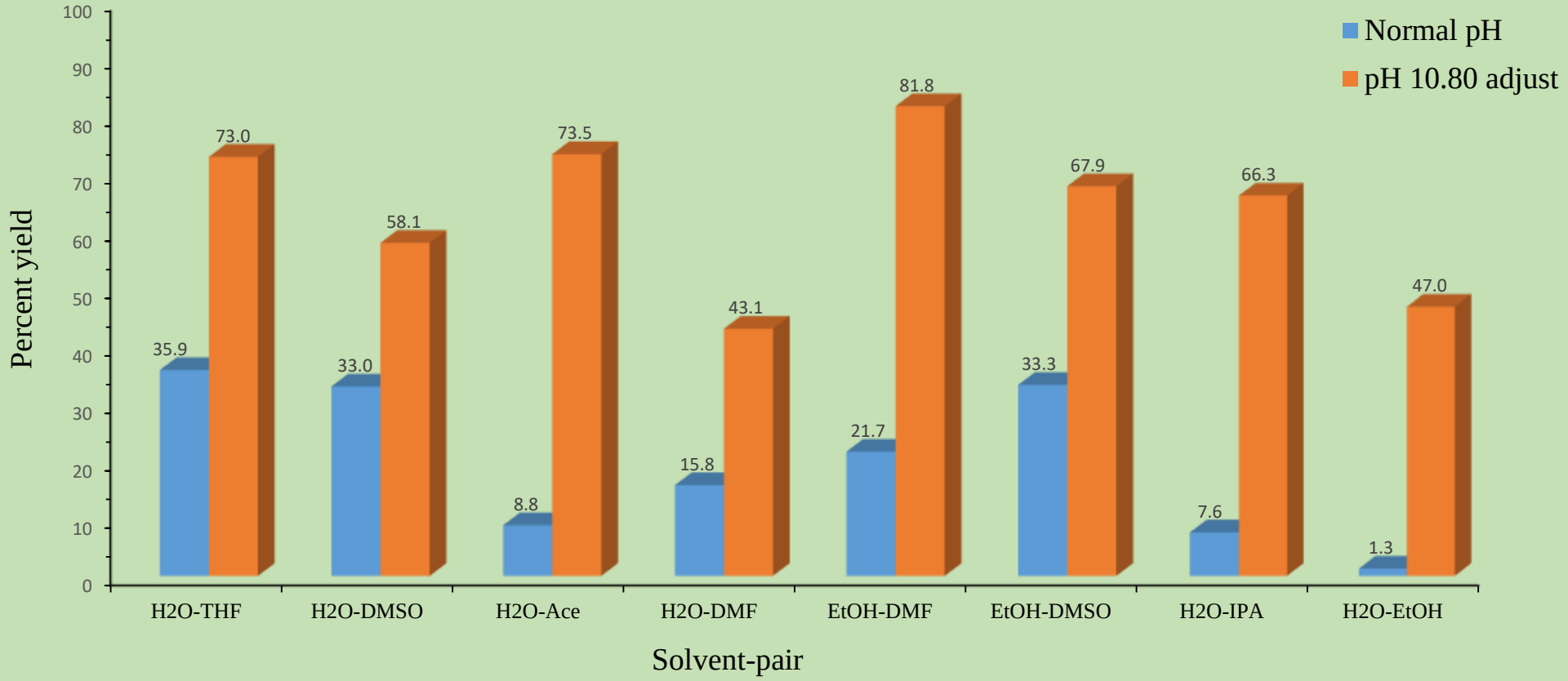
Yield comparison between the two types of synthesis (Normal pH and pH 10.80 adjusted solvent)



Mean (n=3), *P values of 0.05 or less were regarded as significant.

Results and Discussion

Yield comparison between the two types of synthesis (Normal pH and pH 10.80 adjusted solvent media)



Mean (n=3), *P values of 0.05 or less were regarded as significant.

Conclusion

It can be concluded that……..

1. Solvent-pair mixture/ HBD solvent able to replace the hazardous solvents
2. pH adjustment also increase the yield of reaction