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Steric Modulation of Aromatic Compounds via Friedel–Craft Alkylation for Potential Reduction in Blood-Brain Barrier Permeability

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Abstract: Modulating blood–brain barrier (BBB) permeability is a crucial aspect of central nervous system (CNS) drug design. One strategy to decrease undesired BBB penetration involves the structural modification of drug molecules through the introduction of sterically bulky substituents. This study aimed to develop and evaluate a synthetic method for the selective introduction of tert-butyl groups onto an aromatic ring via Friedel-Craft alkylation, in order to investigate its potential to reduce BBB permeability. Acetanilide which synthesized from aniline was subjected to Friedel-Craft alkylation under mild conditions using tert-butyl chloride and aluminum chloride as reagents. Structural modification was confirmed via Fourier transform infrared spectrometer and nuclear magnetic resonance spectrometer. The tert-butyl group was successfully introduced, resulting in a substantial increase in molecular steric bulk. This approach may offer utility in the rational design of peripherally acting drugs by minimizing unintended CNS exposure.

Keywords: *Medicinal Chemistry, Freidel-Craft Alkylation, BBB Permeability.*

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I. INTRODUCTION

Due to the privatization of healthcare, the U.S. has a relatively expensive healthcare system, which increases the demand for over-the-counter drugs (OTC) over visiting a medical institution. Some of the most effective OTC medications for various types of colds and some other everyday health issues are DayQuil and NyQuil, which are pills consisting of pain relievers along with some other substances that help soothe symptoms. However, despite their high effectiveness, DayQuil and NyQuil are only available to legal adults.[1] This is a serious problem to international students in a boarding institution when they get sick, as schools are not usually equipped with those pain relievers. Both the age limit for buying DayQuil and NyQuil and the lack of those drugs in schools originate from the same issue: the easy organic synthesis of methamphetamine, a highly addictive stimulant and a recreational drug, from the already-existent substance in the pill, pseudoephedrine. The underlying reaction involves the reduction of the hydroxyl group (-OH) on the pseudoephedrine molecule to hydrogen, which involves a reducing agent.

One of the recent challenges of drug development is minimizing adverse side effects while preserving therapeutic efficacy. Over the past decade, medicinal chemistry has responded to this demand by implementing a suite of strategic design approaches. Structure modification such as stereochemistry optimization, biocompatible functional group addition have been common method to reduce off-target effect of drugs.[2,3] Prodrug strategy and on-demand drug delivery system establishment such as controlled release of drug molecule are also considered another drug development strategy. Not only experimental methods, but computational methods by artificial intelligence (AI)/machine learning (ML)-based prediction have been new approach for drug discovery.[4]

This research focuses on the prevention of the synthetic process of methamphetamine. Although it may be almost impossible to completely prevent the process, this research aims to make the product molecule larger by attaching a bulky substituent to the benzene ring of the molecule so that the resulting drug cannot act on the brain easily. However, it is illegal to use pseudoephedrine molecule for laboratory experiment because of the potential for methamphetamine

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synthesis.[5,6] Thus, aniline which has similar moiety with pseudoephedrine was used for the starting material and multi-step synthesis was performed. It is expected that this synthetic strategy may be used widely to prevent side effect of the drugs, especially blood brain barrier (BBB) penetration.

II. METHODS

➢ *Synthesis of Acetanilide*

Aniline was used as starting material of total synthesis procedure. First, 48 mL of distilled water and 16 mL of aniline was added into a 100 mL round flask with a magnetic stirrer and stirred thoroughly. While aniline solution stirring, 11.2 mL of acetic anhydride was added dropwise. When all of the acetic anhydride addition finished, mixture was stirred for an additional 15 minutes to allow crystals to grow. Grown crystals were filtrated and washed with 1 N hydrochloric acid followed by washing process with distilled water three times. The washed crystals were dissolved in two 500 mL beakers containing boiling water while remaining stirring. Solvent was minimized by gradually adding the crude solid until no additional solid dissolved in the boiling water for the first beaker, and by starting off with less water and gradually adding more boiling water under stirring in the second beaker. Both two beakers were cooled down to room temperature first, and then were placed in an ice bath and cooled down to 5°C, making the crude almost fully recrystallize. Finally obtained crystals were separated by vacuum filtration and vacuum drying. Synthesis result was confirmed by Fourier transform infrared spectrometer (FTIR) measurement and proton nuclear magnetic resonance spectrometer (NMR) measurement

➢ *Synthesis of 3-Tert-Butyl-Acetanilide*

3 g of synthesized acetanilide from previous procedure and 25 mL of anhydrous dichloromethane was added to a 100 mL flask with a stirrer and incubated at ice bath. 4.12 mL of tert-butyl chloride (t-BuCl) was added while stirring in an ice bath followed by dropwise addition of 2.96 g of anhydrous aluminum chloride ($AlCl_3$) while stirring in an ice bath. Stir the reaction mixture for 1 hour and slowly bring the temperature of the system back to room temperature and stir until thin layer chromatography (TLC) shows completion. When the reaction completed, pour the crude mixture over ice water and stir until the ice melts. After stirring, separate the organic layer using a separatory funnel and wash with saturated sodium bicarbonate solution, followed by another washing using brine. After washing, the organic layer is then dried over anhydrous Magnesium sulfate and then filtered using gravity. Synthesis result was confirmed by Fourier transform infrared spectrometer (FTIR) measurement and proton nuclear magnetic resonance spectrometer (NMR) measurement.

III. RESULTS

The results comprise the FTIR and proton NMR analyses at each stage of the synthesis scheme. A significant information to note is that the FTIR and proton NMR of acetanilide and t-butyl acetanilide were taken with a sample that consisted of the product dissolved in dichloromethane (DCM). This does not matter substantially for the FTIR spectroscopy since DCM was the common solvent for the FTIR spectroscopy, which means that the DCM traces will appear in every IR spectrum of all samples. Furthermore, the peaks due to DCM in the IR spectrum are also very predictable. Given the structure of the DCM molecule, DCM will result in a peak in the aliphatic C–H region (2850~3000 cm^{-1}), cause CH_2 bending (~1450 cm^{-1}), and show stretches in the C–Cl region (710~790 cm^{-1} and 1150~1260 cm^{-1}).

However, this does not stand for the proton NMR. The proton NMR used a distinct solvent, deuterated dimethyl sulfoxide (DMSO-D_6), and the sample of acetanilide and t-butyl acetanilide was the only sample that contained DCM as the solvent. Thus, it was required to take a proton NMR of pure DCM to refer to while analyzing the NMR spectrum for the t-butyl acetanilide sample. The proton NMR spectrum of pure anhydrous DCM used as the solvent for t-butyl acetanilide was shown as Figure 1.

For aniline, FTIR and proton NMR were both acquired. The FTIR sample used anhydrous DCM as the solvent, and the proton NMR sample used DMSO-D_6. The FTIR and proton NMR spectra were shown as Figure 2. This spectrum verifies the starting material, aniline, as it is consistent with the conventional spectrum of aniline. The IR spectrum shows the signs of a primary aromatic amine attached to a benzene ring. Peaks around 3460 and 3370 cm^{-1} show the symmetric and antisymmetric bands, which a typical primary amine shows. Furthermore, the weak bands from around 3000~3050 cm^{-1} show the aromatic C–H stretch. The absence of peaks in 2850~2950 cm^{-1} shows that there are no strong aliphatic C–H as expected for aniline. Strong peak around 1620 cm^{-1} shows the mix of NH_2 scissoring (δ NH_2) and aromatic C=C stretch contributions. The peaks along 1450~1500 cm^{-1} show the aromatic ring C–C stretches from the benzene ring of aniline. There are also moderate peaks from 1200-1300 cm^{-1}, which is due to the C–N stretching. Lastly, the out-of-plane C–H bends at ~750–700 cm^{-1} for the benzene ring is also visible. The starting substance is once more verified by proton NMR spectroscopy, and the results are labeled below with assigned peaks. The aromatic protons (5H total) are shown as the multiplets in the δ 6.5~7.3 ppm region, which shows a benzene ring structure. The NH_2 protons (2H total) are shown as a broad singlet along the δ 3.5~5 ppm region. The solvent residual peak for the residual DMSO-d_6 is at δ 2.50 ppm.

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For acetanilide, FTIR and proton NMR were both taken. The FTIR sample used anhydrous DCM as the solvent, and the proton NMR sample used DMSO-D_6 solvent on a sample that contained acetanilide dissolved in DCM. The FTIR and proton NMR spectra were shown as Figure 3. This spectrum is consistent with what would be expected from an acetanilide sample, as the secondary amine N–H sample is visible as a broad band around 3300 cm^{-1}. The C=O stretch at the acetyl group is shown as a strong band near 1650–1690 cm^{-1}, and the N–H bend and the C–N stretch are shown around 1550 cm^{-1}. The aromatic features still show: The C–H stretches near 3050 cm^{-1}, the ring skeletal vibrations 1500~1600 cm^{-1}, and the out-of-plane C–H bends at ~750–700 cm^{-1} are all visible. The C–N stretch due to the amine group is at 1250~1300 cm^{-1}. It is also noticeable that the primary amine doublets at 3370~3460 cm^{-1}, which were present in aniline, are now gone. The middle product is once more verified by proton NMR spectroscopy, and the results are labeled below with assigned peaks. The amine proton at δ 9 ppm is visible. The aromatic protons of monosubstituted benzene are shown as clusters around δ 7.0~7.6 ppm, and the methyl protons at the acetyl group are shown as a singlet at δ ~2.0 ppm. The residual DMSO-d_6 peak and the DCM peaks also exists

The FTIR and proton NMR spectra of the final product were shown as Figure 4. This spectrum is consistent with what would be expected from meta-substituted tert-butyl acetanilide, or 3-tert-butyl-acetanilide. The amine functional group and acetyl is visible by the single band N–H stretch at 3300 cm^{-1} and the amide stretch at 1550 cm^{-1}. The acetyl group is evident due to the C=O peaks found in 1650–1680 cm^{-1}, while all signs of the aromatic ring: C–H stretches near 3050 cm^{-1}, the ring skeletal vibrations 1500~1600 cm^{-1}, and the out-of-plane C–H bends at ~750–700 cm^{-1} are still remaining. The tert-butyl group was newly added and is shown in the IR spectrum. The aliphatic C–H stretches at 2850–2960 cm^{-1} and the intense C–H bending of tert-butyl group near 1360–1380 cm^{-1} suggest the existence of a substituted t-butyl group. This spectrum is indeed consistent with the expected product. The tert-butyl protons are available as the singlets (9H total) around δ 1.25~1.35 ppm, and the acetamide protons are available as a singlet in δ 2.00~2.15 ppm. The meta-disubstituted benzene ring pattern shows around δ 7.0~7.6 ppm, and the amine NH protons are shown in δ 9~10 ppm. The solvent peaks still exist.

IV. DISCUSSION

This study successfully implemented Friedel–Craft alkylation to introduce a sterically demanding tert-butyl substituent onto an aromatic ring under mild conditions. This synthetic strategy allowed for efficient installation of a bulky moiety, enabling exploration of its structural consequences. Although direct experimental evidence is not available for tert-butyl-substituted moiety, several lines of indirect but compelling rationale support its potential to attenuate passive diffusion across the BBB. First, Faramarzi et al. developed two robust quantitative structure-activity relationship (QSAR) models based on *in vivo* rodent data for over 900 compounds, achieving high predictive accuracy for BBB permeability outcomes. These models underscore the predictive power of molecular descriptors related to structure—indicating that certain physicochemical properties are key determinants for BBB transport.[7] Moreover, Zhang et al. employed support vector machine (SVM) and k-nearest neighbor (k-NN) approaches using a diverse set of descriptors, including lipophilicity, polar surface area, and steric factors. Notably, their findings highlight that steric descriptors contribute significantly to BBB permeability predictions, reinforcing the concept that increased steric bulk may impede barrier crossing.[8] In addition, Janicka et al. reviewed key determinants of BBB penetration—identifying hydrogen bonding capacity, lipophilicity, and molecular size as critical factors. While lipophilicity generally enhances permeability, increased molecular size can counteract this effect, particularly impacting passive diffusion pathways.[9]

It is important to note that our study did not involve genuine drug molecules but rather model compounds bearing similar moieties. Consequently, while the synthetic methodology is validated, the direct relevance to drug efficacy or pharmacodynamics remains unclear. To translate these findings into therapeutic contexts, further *in vitro* or *in vivo* BBB permeability assays are necessary. Nevertheless, Friedel-Craft alkylation enabling the introduction of bulky substituents onto aromatic ring serve as a generalizable tool for modulating BBB permeability in drug design. Specifically, applying this strategy to central nervous system (CNS)-inactive drugs could help reduce unintended CNS exposure while retaining peripheral efficacy, thereby contributing to improved safety profiles in clinical candidates.

V. CONCLUSION

In this study, we successfully applied Friedel–Crafts alkylation to introduce a tert-butyl substituent onto an aromatic scaffold, with the aim of modulating blood–brain barrier (BBB) permeability. The tert-butyl group, characterized by its pronounced steric bulk, was selected based on its known ability to increase molecular size and induce conformational constraints, both of which are physicochemical properties frequently associated with reduced BBB penetration.

This synthetic strategy offers a generalizable and accessible methodology for modifying drug-like molecules with the intent of limiting central nervous system (CNS) exposure, particularly valuable in the development of peripheral-acting agents. Future work should focus on *in vitro* and *in vivo* validation of BBB transport properties to further substantiate the utility of this approach in medicinal chemistry.

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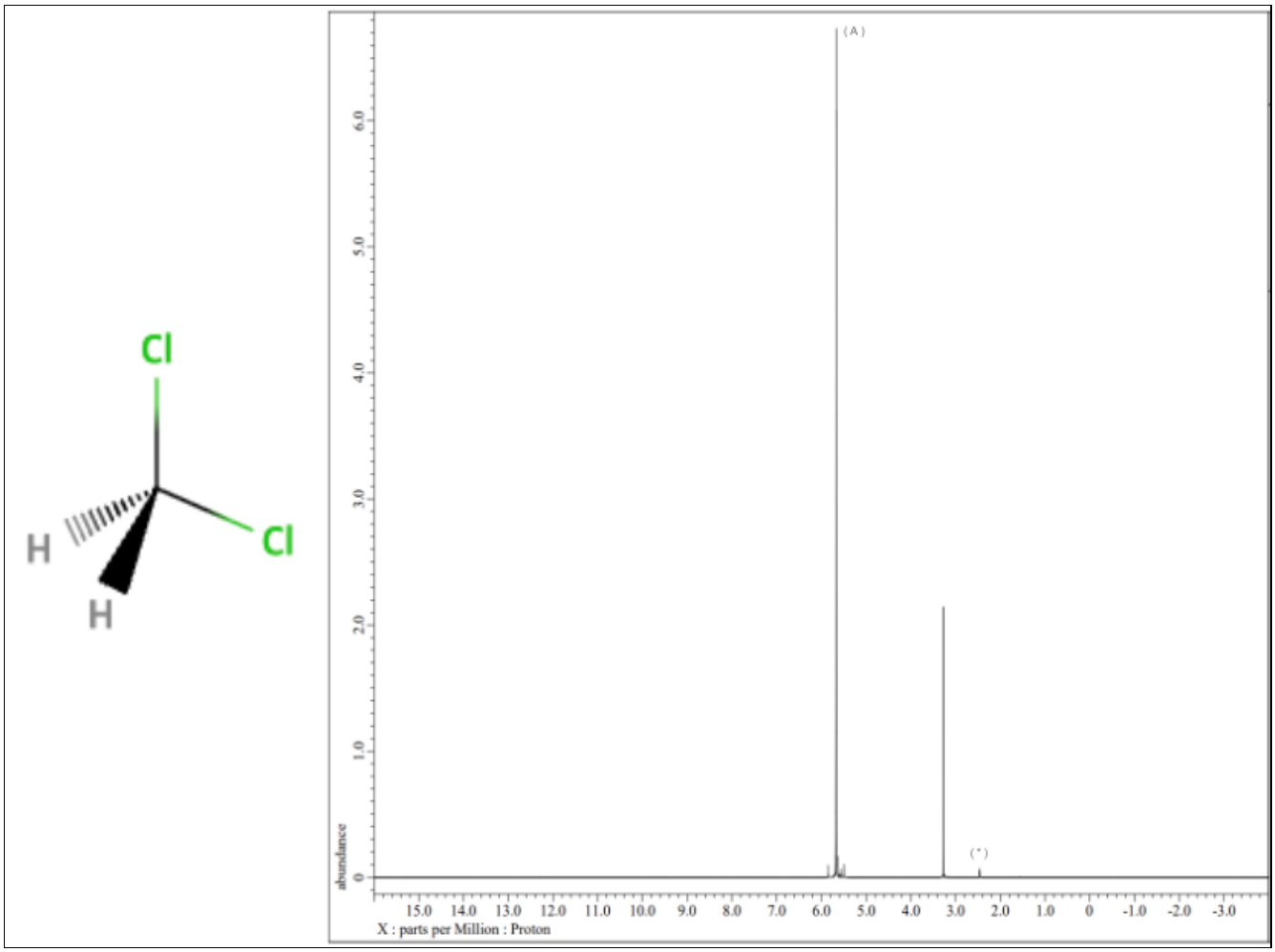

Fig 1. Proton NMR Spectrum of DCM. Asterisk Indicates Solvent Peak (DMSO-D_6)

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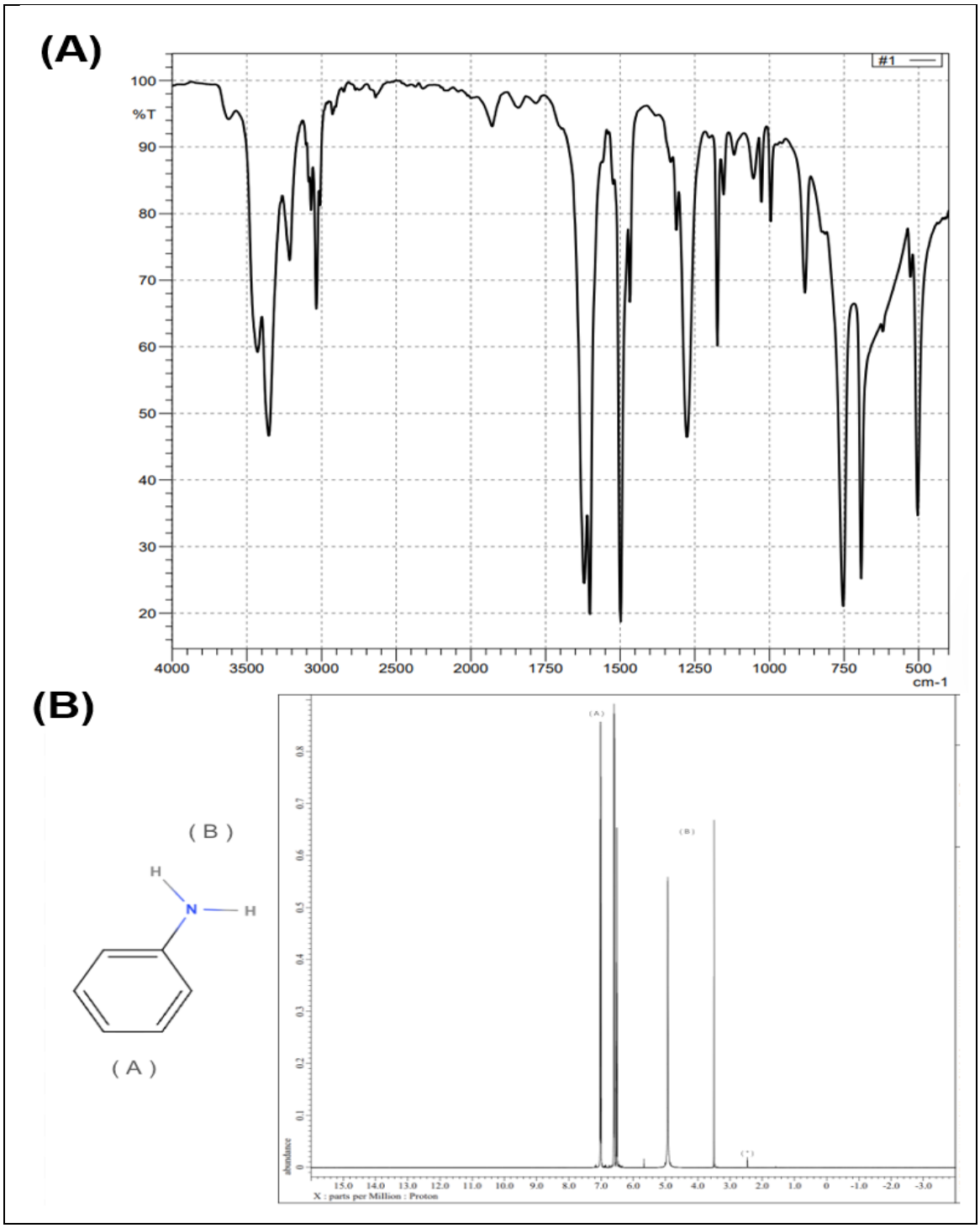

Fig 2. (A) FTIR and (B) Proton NMR Spectrum of Aniline. Asterisk Indicates Solvent Peak (DMSO-D_6)

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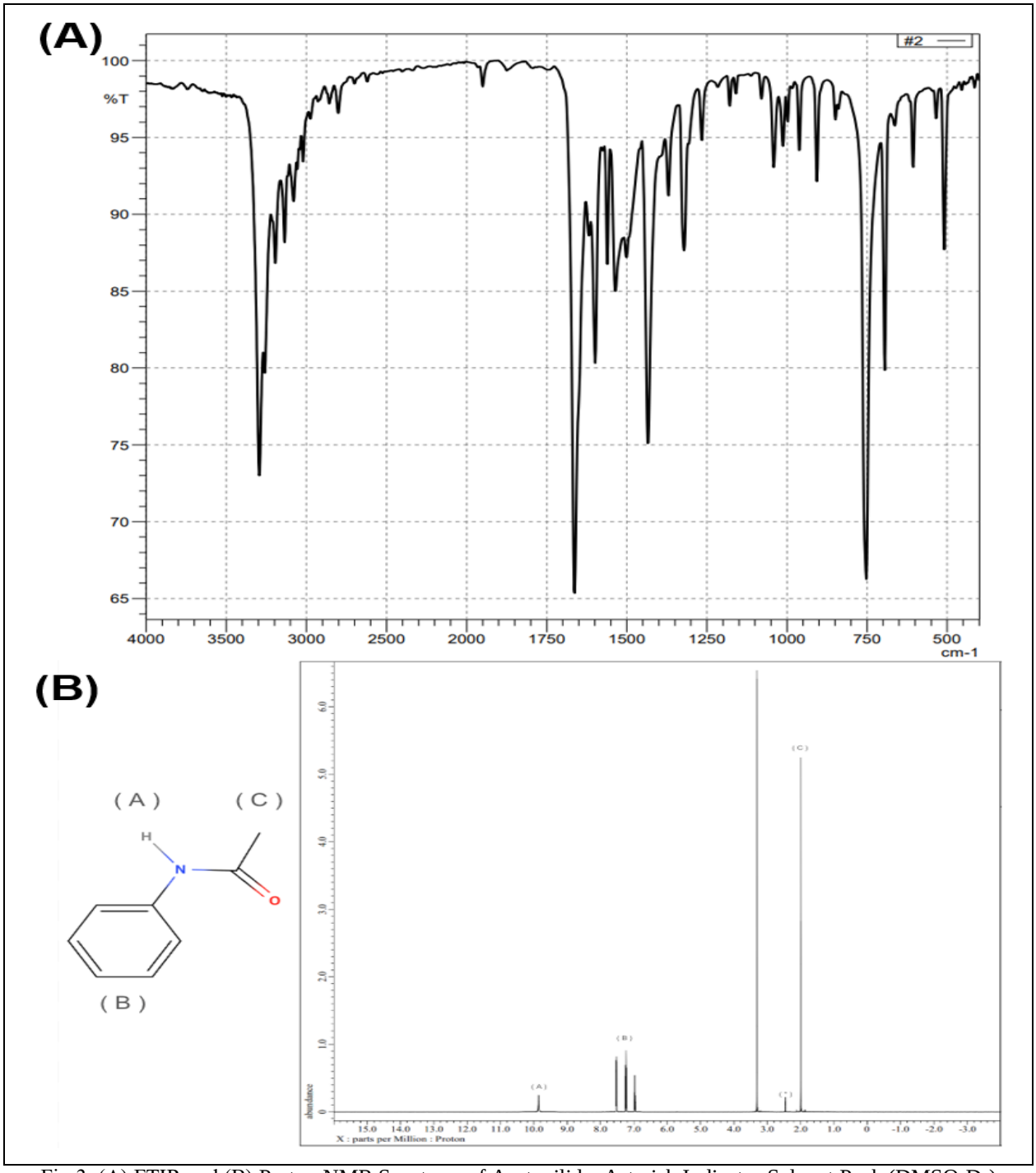

Fig 3. (A) FTIR and (B) Proton NMR Spectrum of Acetanilide. Asterisk Indicates Solvent Peak (DMSO-D_6)

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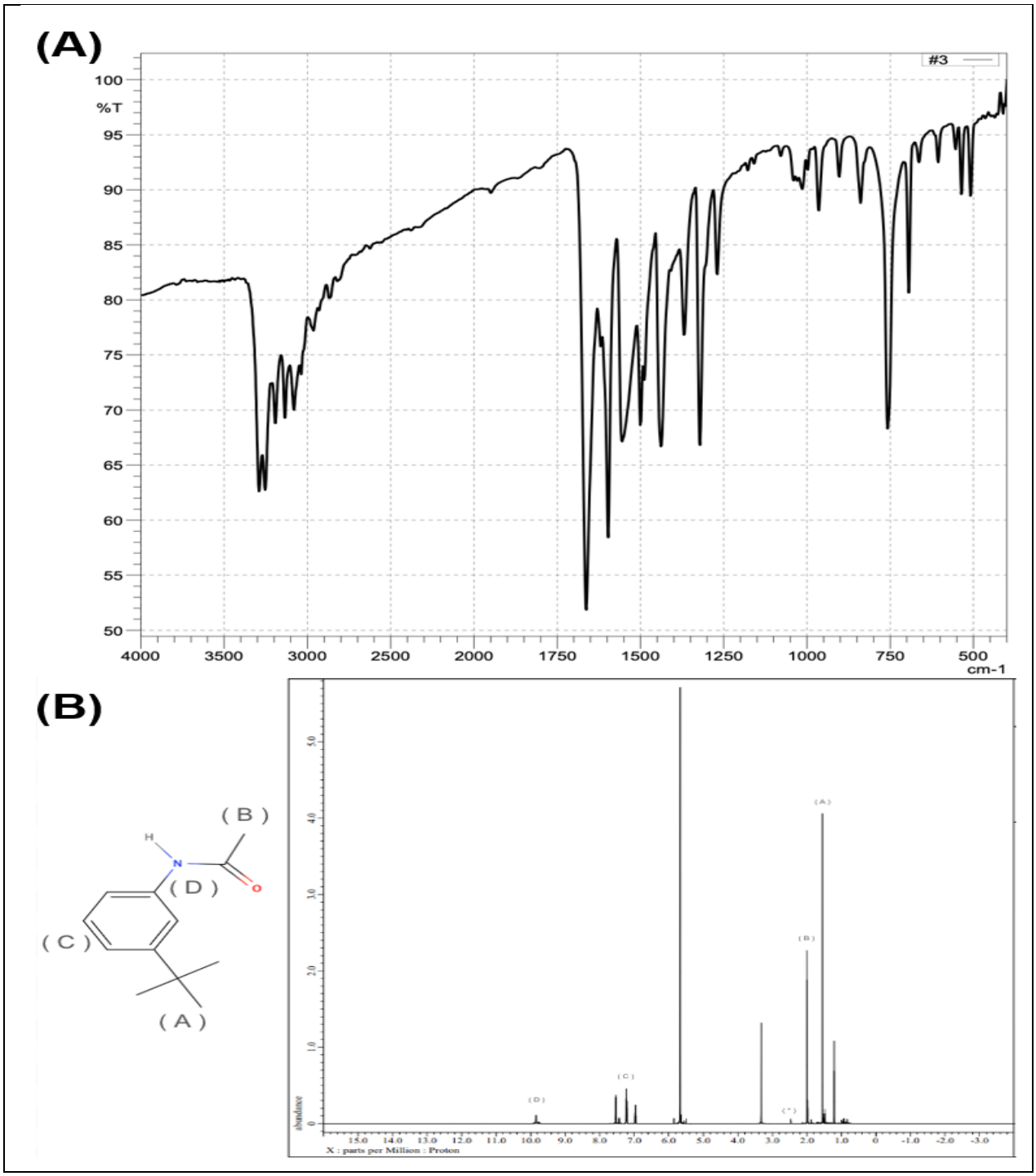

Fig 4. (A) FTIR and (B) Proton NMR Spectrum of Crude (3-Tert-Butyl-Acetanilide). Asterisk Indicates Solvent Peak (DMSO-D_6)