Towards a Pharmaceutical Cyber-Physical Systems Based Automated Drug Discovery Workcell

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Abstract: The global pharmaceutical industry, despite its growth, faces challenges in drug development, characterized by extensive timeframes and high costs. A significant bottleneck in this process is the labor-intensive and inefficient experimental synthesis in medicinal chemistry. The transition to automated methods offers a solution to these challenges, promising enhanced efficiency, scalability, and safety, while significantly reducing time and costs. This paper presents the development of an automated rotating bed reactor as part of an intelligent Cyber-Physical System-based automated drug discovery workcell. The automated rotating bed reactor is designed to be easily integrated as a component in the workcell, aiming to enable rapid adaptation to meet the specific needs of on-demand drug production. Experiments with the system shows that it has the potential to enhance the yield of the chemical reactions.

Keywords: automated drug discovery; cyber-physical system; pharmaceutical

1 Introduction

Global pharmaceutical markets have seen significant growth, propelled by factors such as the recent pandemic, a burgeoning global population, heightened healthcare requirements, and an aging demographic. Despite this, drug development remains an arduous and costly endeavor [1]. Taking upwards of a decade and billions in investment, the journey from concept to market-ready

medication is fraught with intricate phases, each presenting unique hurdles in terms of time and financial outlay [2]. A notable bottleneck is the protracted process of experimental synthesis in medicinal chemistry, which not only consumes time but also results in substantial waste from repeated reaction processes and purification steps. The evolution from hands-on chemical synthesis to a more automated approach is poised to revolutionize the field with heightened efficiency, scalability, and safety, while reducing time and costs, garnering attention from academic, industrial, and public sectors alike.

At the heart of drug development lies chemical synthesis, a process that has remained manually intensive, despite the rise of lab automation [3]. The exploration of synthetic routes is a daunting and often unpredictable endeavor. Current practices necessitate that chemists meticulously set up experimental synthesis platforms by hand, tailored to the specific chemical reactions being undertaken - a labour-intensive task that leads to inefficiencies within drug development. Nevertheless, robots and automation offer the potential for taking over rudimentary tasks such as handling and mixing, which not only alleviates the monotonous burden from chemists but also enables them to concentrate their expertise on more critical aspects of drug development [4].

Recent progress in pharmaceutical manufacturing have led to the development of an extremely flexible form of continuous manufacturing, specifically designed for on-demand production in small quantities [5, 6]. This approach is particularly beneficial for scenarios where setting up a full-scale production system could be prohibitively expensive and infeasible. For example, producing medications for patients with unique requirements or for drugs that have a limited shelf life. While functional prototypes for on-demand manufacturing have been created, their widespread adoption is still not a reality [7], even for drug discovery. One potential limitation would be that not all chemical reactions may be well-suited for continuous flow, due to the generation of solid by-products. This is particularly important in drug discovery, where the synthesis of new compounds often requires rapid iterative experimentation and refinement. An automated batch reactor fills this gap by offering versatility in handling diverse chemical reactions while providing an ideal environment for testing new reactions and processes on a smaller scale before scaling up. Additionally, batch reactors are generally easier to clean and reconfigure for different processes, making them more suitable for producing multiple products in facilities where production needs frequently change.

This paper introduces our work on the development of an intelligent CPS-based automated drug discovery workcell. As part of building up the capability of the workcell to handle a variance of reagents and reactants, we report our work on automating and integrating a special class of chemical reactor - the rotating bed reactor. This type of reactor uses centrifugal force to accelerate mass transfer and speed up reactions. These characteristics of the reactor has the potential to fit the needs of on-demand drug production.

This paper is structured as follows: In Section 2, a review of the current state of the art in Pharma 4.0 specific to drug discovery automation is presented. In Section 3, an intelligent CPS-Based framework for a drug discovery workcell is proposed. In Section 4, our work on an automated solid-liquid phase synthesis system as part of the proposed framework is described. In Section 5, our experimental results with the synthesis system are reported. Finally in Section 6, we present our conclusions.

2 Current State of the Art in Automating Drug Discovery

2.1 Pharma 4.0

In recent times, 'Industry 4.0' has emerged as a term synonymous with the fourth industrial revolution, centered on advancing the intelligence of production systems. This revolution bridges the previous divide between information technology and operational technology, leveraging sophisticated tools such as the Internet of Things (IoT), Artificial Intelligence (AI), and cloud computing. As part of this evolution, the role of Cyber-Physical Systems (CPS) has become increasingly significant. CPS are complex networks of computational components closely intertwined with the physical environment [8]. These systems engage with their surroundings, concurrently offering and exploiting data services available through the Internet. A CPS integrates digital, analog, physical, and human components to execute its tasks [9]. They construct digital representations of physical processes using varied sensor networks, effectively virtualizing the physical world. These sensors are linked via networks to data processors, enabling enhanced decision making within the system. Presently, CPSs are applied in multiple sectors, ranging from manufacturing to plant management, promoting automation and augmenting process intelligence. The objective is to establish ‘Smart Factories’ where machines are able to communicate and cooperate with one another and are empowered to make autonomous decisions. This enables them to address emerging problems or challenges and adapt to changes, reducing the need for human interventions. Numerous companies are transitioning their manufacturing operations to such systems, enticed by the prospective gains in elevating productivity and adaptability, along with the opportunity for cost reduction.

Drawing inspiration from Industry 4.0, the pharmaceutical industry has been actively evolving towards greater intelligence and efficiency. This has led to the development of Pharma 4.0, a specialized adaptation for pharmaceutical manufacturing, offering enhanced flexibility, quality and safety, while reducing

costs [7, 10-12]. Pharma 4.0 focuses on integrating CPSs into pharmaceutical manufacturing, creating pharmaceutical CPSs (PCPSs). In such systems, interconnected embedded computers oversee and regulate the processes of drug discovery, development, and manufacturing, frequently utilizing feedback loops, where physical operations are informed and adjusted based on input from cloud-based computing units [13]. These PCPSs facilitate iterative simulation tests driven by data and knowledge for tasks such as design, control, or optimization within a virtual cyber environment. Moreover, as a crucial element in the upcoming landscape of pharmaceutical industrial systems, PCPSs offer significant promise in managing the intricacies and unpredictabilities in pharmaceutical quality control, consequently enhancing the efficiency of resource distribution [10]. It is clear that in the development of drug discovery platforms, incorporating and embracing aspects of Pharma 4.0 is essential. Such integration is necessary to ensure these platforms can seamlessly align with the broader pharmaceutical industry. This approach is vital for fostering progress and innovation within the sector.

2.2 Automatic Chemical Synthesis

There has been considerable advancement in the field of chemical process automation in recent times. Godfrey et al. developed a remotely operated laboratory, enabling chemists to direct the synthesis of chemicals from any global location, with the lab itself being primarily operated by robots [14]. This system incorporates comprehensive synthesis sequences, allowing the production of compounds in quantities ranging from 100 mg to 1 g. Although the synthesis process was not fully automated, was among the pioneering works that marked a substantial advancement towards automated drug discovery. Adamo et al. engineered a compact, adaptable system for the on-demand, continuous-flow manufacturing of pharmaceuticals, capable of producing diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam, and fluoxetine hydrochloride sufficient for hundreds to thousands of doses, in compliance with U.S. Pharmacopeia standards [5]. Lim et al. introduced a robotic arm-based automation system for conducting complex chemical reactions with minimal changes to the setups traditionally used by chemists [15]. Their system was versatile, excelled in precise liquid handling, mixing, and filtering, and was able to tailor production sequences by linking various tasks together. Liu et al. proposed a method that merges solid-phase synthesis with continuous-flow operations for the automated multistep synthesis of active pharmaceutical ingredients [16]. Their method provided a straightforward, compact, and flexible approach for the on-demand automated synthesis of drug molecules and their derivatives, potentially hastening lead optimization in drug discovery. Steiner et al. created an automated, lab-scale robotic system for organic synthesis, known as the Chemputer, which uses a chemical programming language to transform high-level synthetic protocols into

detailed instructions for a modular robotic platform [13]. Together with the Chempiler software that generates precise instructions for the hardware in the system, pharmaceutical compounds were produced with yields comparable to manual synthesis. Unfortunately, continuous-flow systems have some inherent limitations. First, all reagents have to be in liquid form to be passed through the system. Second, the type of reaction is limited, particularly those that results in solid precipitate, which have the potential to clog up the reactors, reducing and slowing the reaction and throughput.

A particular class of batch reactor that is of particular interest are the rotating bed reactors [17, 18], where these reactors can handle heterogeneous reactions, specifically solid-liquid reactions. These systems have the potential to make up for the limitations of continous-flow systems, but will require custom development to be integrated. We describe our efforts in automating one such system for integration into our workcell.

3 An Intelligent Pharmaceutical Cyber-Physical System-based Automated Drug Discovery Workcell

In view of the limitations mentioned in the previous section, we introduce our proposed framework for the automated drug discovery workcell.

3.1 Overview

A workcell is a configuration of resources dedicated to manufacturing a specific product or a group of related products [19]. In the context of a CPS workcell, the ability for self-configuration and self-organization among both cybernetic and physical resources is key, facilitating swift and frequent modifications for the generation of new products. This type of workcell is particularly advantageous in the Hit-to-Lead or lead optimization phase of drug discovery, where the rapid and efficient generation of potential chemical compounds for in-vitro testing is essential. An Intelligent CPS (iCPS) takes the concept of a CPS a step further by integrating an intelligence component. This addition plays a pivotal role in enabling high-level functions such as planning, decision making, and analytical processing within the CPS. It also opens possibilities for the transfer of intelligence across different CPSs, showcasing the system's adaptability and learning capabilities. A tool to develop multiple CPSs rapidly and in an interoperable manner is still needed. The components within these systems, similar to the intelligence component, need to be easily transferable. Figure 1 provides an overview of our proposed intelligent PCPS (iPCPS) framework.

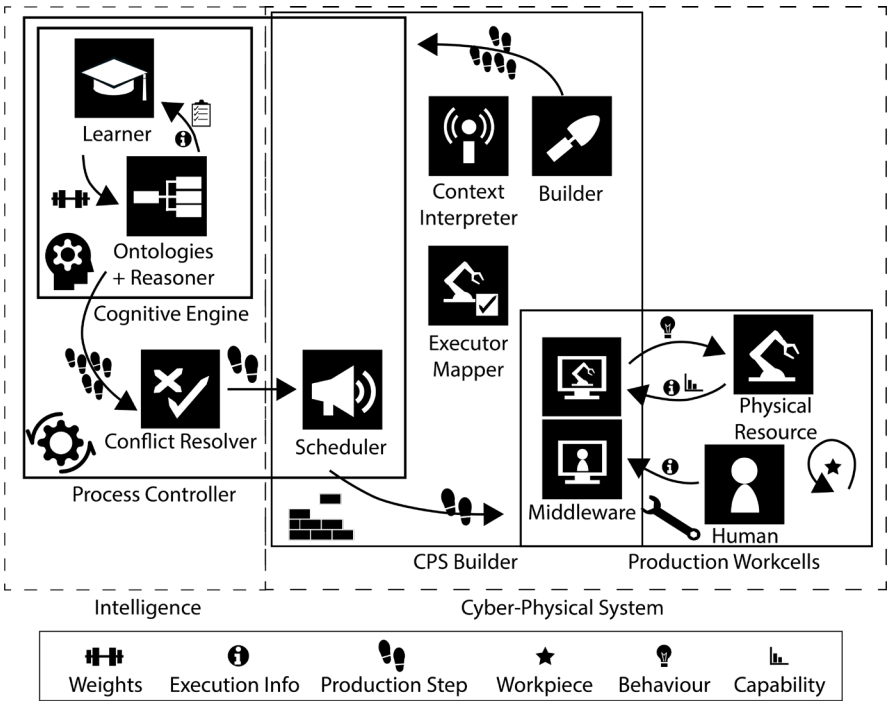

Figure 1
iCPS Framework for a Drug Discovery Workcell

A process controller is composed of a Cognitive Engine (CE) and a conflict resolver. Within the CE, ontologies serve as the memory component. Specifically, the CEPC incorporates two types of ontologies: the process control ontology (PCO) and the process monitor ontology (PMO). The process classes of a manufacturing task are Step, Objective Layer, and Task. The base units of the CPS are the production workcells, which execute production steps to generate the chemicals. These workcells transmit execution data to the process controller's cognitive engine. This data encompasses the status of resources, materials, and chemicals. The learning component of the CE uses this information to refine the weights used in predicting the most effective subsequent steps. Concurrently, the ontological components update the status of the State classes with this data. Following this, the PMO deduces the status of the process classes, determining whether a process class is complete, incomplete, or needs disposal due to failure. In parallel, the PCO suggests a range of potential next steps. The conflict resolver's role is to ensure that the next production step assigned to the production workcells is free from conflicts with other ongoing processes. The production workcells then execute the given production step and relay the results back to the cognitive engine. This cycle of process control is repeated continuously until the

production task is completed. An example of a component can be used in this framework is described in the next section.

The development of an automated batch reactor is an essential step in the development of a drug discovery workcell. This reactor is designed to automate the multi-step process where a solid agent successively reacts with different liquid chemicals, without the need for changing the solid agent between steps.

In rotating bed reactors (RBRs), granular solid reactant is placed in fine-meshed steel containers (rotating beds). These rotating beds are then submerged and rotated sequentially in different reagents, with agitation over extended periods. This method ensures the precise location of the solid reactant throughout the entire process. The RBR is specifically designed to maintain constant exposure of the solid reactant to a steady flow of reaction fluid, thanks to its rotation, thus creating optimal reaction conditions. When the rotation speed is high enough, centrifugal forces expel the fluid from the reactor chambers, while the solid agent is retained by the fine-meshed stainless-steel net, allowing continuous fluid intake through the reactor's bottom opening.

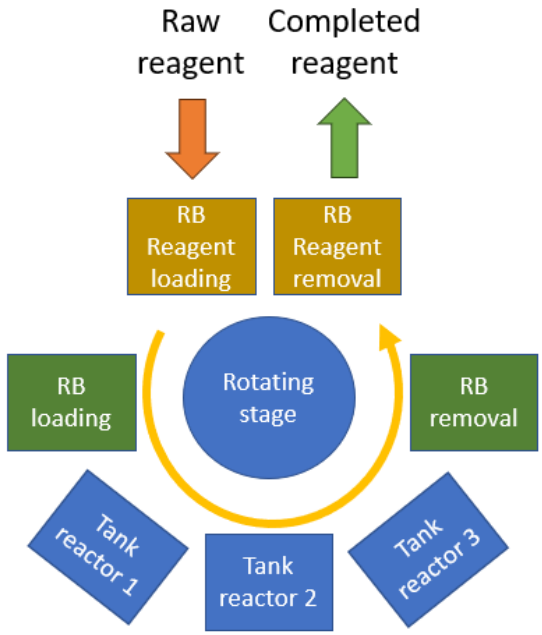

Figure 2
Schematic Diagram of the Multi-Stage Automated RBR

To automate this synthesis process, the steps can be executed either sequentially in different reaction vessels or consecutively in the same vessel, with emptying and refilling for each new chemical. The solid agent, held within the rotating beds, facilitates this process even when the reactor containing the solid agent remains

inside the vessel. For enhanced flexibility, the system developed is designed to use multiple reaction vessels, with the option to flush and reuse them. Additional modules for the loading and unloading of the rotating bed to the rotating stage, loading and unloading the reagent is proposed to further modularize the system. Figure 2 depicts the overview of such a system with multiple reaction vessels.

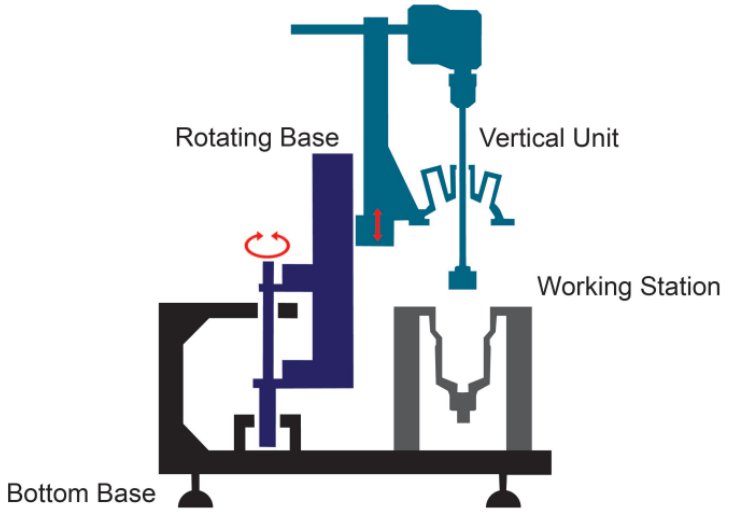

Figure 3
Components of the Automated RBR

The automated system is designed around the components of the SpinChem RBR S2 reactor. The cross-section of the automated system is depicted in Figure 3. The rotating base is mounted on a central shaft that is installed on a base frame. The lid of the reaction vessel is mounted to the slide of a linear actuator (EZSM4E020MK, Orientalmotor), together with the rotating bed reactor and the stirrer motor. This allows opening the lid and moving the rotating bed reactor into a different reaction vessel. The shaft's rotation is driven by a brushless DC motor (BLM230-GFV2, Orientalmotor), using a timing belt for power transmission from the motor to the shaft. The reaction vessel is designed for up to 0.5 bar internal pressure. This force must be sufficiently resisted during the reaction process. Therefore, two toggle clamps are installed, which press down on the lid in addition to the vertical slide during the reaction process. A Raspberry Pi is used as an edge computing device, controlling the actuators of the system and retrieving sensor data from the reactor. The detailed 3D drawing of the system is depicted in Figure 4.

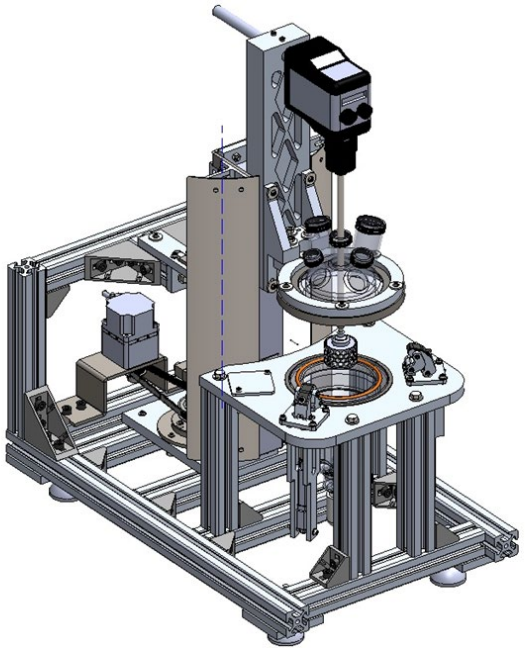

Figure 4
Detailed design of the Automated RBR

4 Experiments and Results

Two chemical reactions, the SN2 and SN1 reactions, were conducted using the automated system (Figure 5). The SN2 reaction was carried out first. This reaction, also known as the bimolecular nucleophilic substitution reaction, is a fundamental chemical reaction in organic chemistry. It is common in the synthesis of various organic compounds, such as alcohols, ethers, and amines, and it is also a step in the synthesis of the enzalutamide, also known as the drug Xtandi used in cancer treatment. The process used in this reaction is detailed as follows:

1) Preparation of Starting Materials: Carboxylate anion was first deprotonated by treating 4-amino-2-fluorobenzoate and 4-amino-2-fluorobenzoic acid with Triethylamine. Concurrently, the alkyl halide was prepared by brominating wang resin.

2) The Reaction Step: The prepared alkyl halide was then introduced into the rotating bed reactor. Following this, the solvent and additional reagents were added to the reaction vessel. In the vessel, the carboxylate anion derivative was generated to undergo the SN2 reaction. The stirring

speed of the reaction was maintained at 200 rpm, and the reaction was allowed to proceed for 12 hours at room temperature.

3) Reaction Workup: Upon completion of the reaction, the reaction mixture was quenched with methanol to halt the reaction process.

4) Purification: The final product, enzalutamide, was isolated and purified using preparative High-Performance Liquid Chromatography (Prep-HPLC).

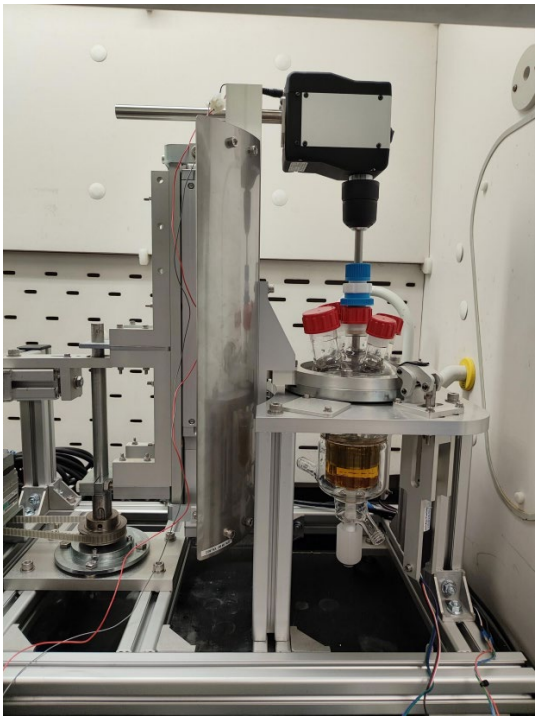

Figure 5
Experimental Testing of the Automated RBR

Subsequently, using the resin from the SN2 reaction as a substrate, the SN1 reaction was carried out next. The SN2 reaction is a concerted nucleophilic substitution process, characterized by one-step atom exchange and stereochemistry inversion. This bimolecular reaction is essential to organic synthesis, pharmaceuticals, and environmental degradation. The process used in this reaction is detailed as follows:

1) Nucleophile, and Solvent: The nucleophile, 2-methylpropan-2-yliumoate, was synthesized through the reaction of 2-bromo-2-methylpropanoic acid with triethylamine, serving as the base. Dichloromethane (DCM) was selected as the solvent for its efficacy in this context.

2) Reaction Setup: The enzalutamide resin was carefully placed within the rotating bed reactor. Subsequently, the prepared nucleophile and other necessary reagents were methodically introduced into the reaction vessel, ensuring proper mixing and reaction conditions.

3) Execution of the Reaction: The reaction was conducted at ambient room temperature. The rotating bed was set to stir the mixture at a consistent speed of 200 rpm, and this stirring was maintained for a duration of 4 hours to ensure adequate reaction time and mixing.

4) Quenching the Reaction: Upon completion of the reaction, the mixture was quenched with a combination of dichloromethane (DCM) and methanol. This step was crucial to halt the reaction process effectively. Following the quenching, the resultant solution was carefully extracted from the bottom of the vessel for further analysis and processing.

By employing 1H NMR spectroscopy technique, the result of the SN2 reaction was confirmed. This measurement is also referred to as loading, which indicates the number of acid compounds linked to the resin. The obtained data in the Top graph of Figure 6 shows a loading of 0.90 mmol per gram. This yield compared with other reactors show that the automated system has the potential to increase the yield of this step in the reaction. This can be attributed to the effective mixing conditions provided by the rotating bed reactor. The automated system has demonstrated the capability to effectively replicate the SN2 reaction carried out in conventional reactors.

Similarly, from the bottom graph of Figure 6, two peaks can be seen. The left peak corresponds to the product of the SN1 reaction, while the right peak represents both the product of SN2 reaction. Using 19F NMR spectroscopy technique, the results of the SN1 reaction can be confirmed, showing that the system can enhance the yield of this step reaction. This again can be attributed to the effective mixing conditions provided by the rotating bed reactor.

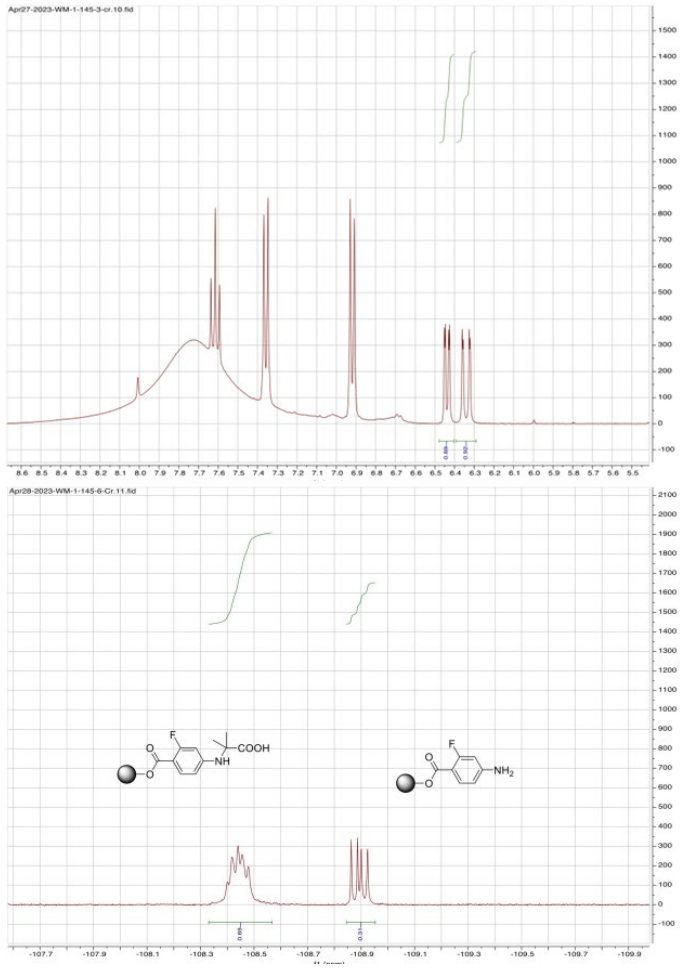

Figure 6
Experimental Results of the Automated RBR. (Top) SN2 Reaction, (Bottom) SN1 Reaction

Conclusion and Future Work

An iPCPS-based framework for automated drug discovery has been proposed. As part of this workcell, we have successfully automated a solid-liquid phase synthesis reactor, which is intended to be seamlessly integrated into the workcell structure. We have conducted experiments on this reactor, demonstrating its promising capabilities for automation. In the future, we plan to expand the workcell by incorporating various physical resources, including automated continuous-flow reactors. These additions will be complemented by robotic arms to enable exchange between systems, all under the coordinated management of the

iPCPS. This expansion is aimed at enhancing the workcell's versatility and efficiency in the automated drug discovery process.

Acknowledgement

This research is supported by the Singapore National Research Foundation (NRF) under its Competitive Research Programme (CRP) Grants (NRF-CRP29-2022-0004, NUS WBS: A-8001763-04-00) and (NRF-CRP25-2020RS-0002, NUS WBS: A-0008485-05-00)

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