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PROCESS INTENSIFICATION AND GREEN METRICS IN CONTINUOUS-FLOW SYNTHESES

PhD thesis

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List of Abbreviations

AE	atom economy
AI	artificial intelligence
API	active pharmaceutical ingredients
BAX	BCL2 associated x protein
BCL-2	B-cell lymphoma 2
CDK2	cyclin-dependent kinase 2
CF	continuous flow
CF-SPPS	continuous-flow solid-phase peptide synthesis
COX	cyclooxygenase
ΔHrxn	reaction enthalpy
ΔT	temperature difference
d	channel diameter; characteristic dimension
DABCO	1,4-diazabicyclo[2.2.2]octane
de	channel diameter
DIC	*N,N′*-diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DoE	design of experiments
E-factor	environmental factor
EPA	environmental protection agency
Fmoc	fluorenylmethyloxycarbonyl

FT-IR	Fourier transform infrared spectroscopy
GC	gas chromatography
GMP	good manufacturing practice
GSK	GlaxoSmithKline
GSK3β	glycogen synthase kinase 3 beta
h	heat transfer coefficient
HP	high performance
HPLC	high performance liquid chromatography
ICH	international council for harmonisation
ICP-MS	inductively coupled plasma mass spectrometry
IR	infrared spectroscopy
k	thermal conductivity
L	characteristic length; channel length
LCA	life cycle assessment
LCC	life cycle costing
LC-MS	liquid chromatography-mass spectrometry
LLM	large language models
5-LOX	5-lipoxygenase
μ	dynamic viscosity
MEF2D	myocyte enhancer factor 2D
ML	machine learning
MOF-808	metal-organic framework 808
MS	mass spectrometry

NMR	nuclear magnetic resonance
Nu	Nusselt number
OECD	organisation for economic co-operation and development
PAT	process analytical technology
PC	propylene carbonate
PDGFR	platelet-derived growth factor receptor
PEEK	polyetheretherketone
PI3-K	phosphoinositide 3-kinase
PMI	process mass intensity
Pr	Prandtl number
PTF	polytetrafluoroethylene
QbD	quality by design
QTPP	quality target product profile
ρ	fluid density
R&D	research and development
Ra-Ni	Raney nickel
Re	Reynolds number
RME	reaction mass efficiency
SPPS	solid-phase peptide synthesis
TEM	transmission electron microscopy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TOF	turnover frequency

TON	turnover number
UV	ultraviolet
v	velocity; average velocity
VEGFR	vascular endothelial growth factor receptor
VOC	volatile organic compounds
WHO	World Health Organization
XPS	x-ray photoelectron spectroscopy

1. Introduction

1.1 Short literary summary

The development of greener, safer, and more efficient synthetic technologies is a central priority in modern organic and pharmaceutical chemistry (1). As the demand for sustainable processes grows—driven by both environmental regulations and industrial needs—continuous-flow (CF) chemistry has emerged as a transformative tool (2, 3). Compared to traditional batch synthesis, flow chemistry offers numerous advantages, including enhanced heat and mass transfer, superior reaction control, shorter residence times, improved reproducibility, scalability, and a substantially reduced safety risk profile (4). These features make CF platforms particularly attractive for hazardous or highly exothermic transformations, as well as for the integration of process automation and online analytics (5-8).

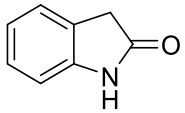

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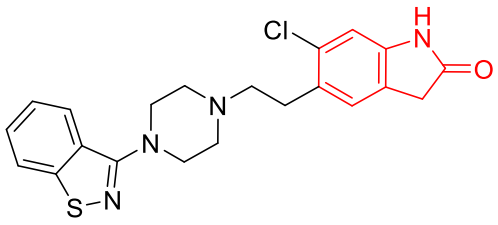
Figure 1.

Oxindole

Among heterocyclic scaffolds, oxindole (2-indolinone) represents a privileged core structure found in a wide array of natural products and active pharmaceutical ingredients (APIs), such as the anticancer agent sunitinib (**3**) and the antipsychotic ziprasidone(**2**) (9-12). The functionalization of the C-3 position of oxindole—particularly through alkylation—yields key building blocks for medicinal chemistry and drug design (13, 14). However, literature methods for regioselective 3-alkylation of oxindoles with alcohols typically require multistep procedures under extreme conditions (elevated temperature and pressure). These methods often use Raney nickel, a highly active but pyrophoric catalyst (15-17). These challenges limit the operational and environmental viability of the transformation, particularly on a larger scale (18).



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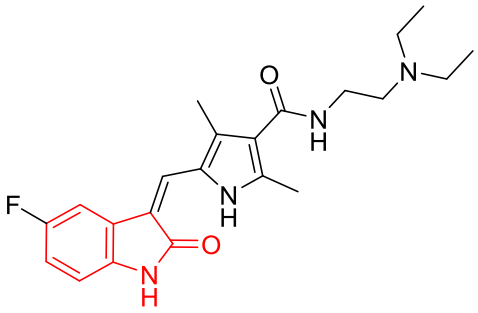

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Figure 2.

Sunitinib and ziprasidone

To address these limitations, the primary aim of this dissertation was the development of a time-, cost-, and atom-efficient CF protocol for the reductive 3-alkylation of oxindole with alcohols and aldehydes, utilizing Raney nickel under optimized and safe flow conditions (19-21). The developed process successfully replaces hazardous batch procedures and enables efficient catalyst handling, process intensification, and high-throughput production. Using this method thirteen structurally diverse 3-substituted oxindole derivatives were synthesized, including both simple alkyl and electronically rich aralkyl analogues. Notably, the CF setup allowed for long-term catalyst reuse; in a representative example, 20 g of 3-ethyl-oxindole was synthesized from oxindole and acetaldehyde in a single 16-hour run using only 800 mg of Raney nickel—demonstrating both sustainability and economic viability.

Beyond its direct application to oxindole chemistry, this work also explores the broader impact of CF methodologies in scalable synthesis, particularly in solid-phase peptide synthesis (SPPS) (22-24). The engineering principles and reactor design approaches optimized during this study—such as stable handling of slurries, control of heterogeneous catalysis, and minimization of pressure drops—are directly relevant to CF-SPPS, a field undergoing rapid evolution (25-27). Peptide synthesis remains a cornerstone of pharmaceutical R&D, but traditional batchwise SPPS is time-consuming and generates

substantial waste (28). Flow-based SPPS, in contrast, offers shorter cycle times, higher coupling efficiency, improved resin washing, and reduced solvent consumption (29). By transferring lessons learned from oxindole alkylation, including equipment configuration, back-pressure regulation, and inline monitoring, this dissertation contributes to the development of more robust, scalable peptide synthesis technologies.

1.2 Literature Survey on the Green Aspects of CF Technologies

CF technologies have emerged as a transformative approach in chemical synthesis, offering substantial environmental and operational benefits over traditional batch processes. This literature survey synthesizes key contributions from important studies, highlighting the green aspects of CF technologies, including their efficiency, safety, and sustainability in various chemical applications.

1.2.1 Introduction to CF Syntheses

The transition from batch processing to CF techniques represents a significant advancement in green chemistry, as emphasized by researchers and industry stakeholders alike (30-34). CF technologies are acclaimed for their capability to enhance operational efficiency while adhering to the principles of green chemistry, leading to reduced waste, energy consumption, and enhanced safety profiles during chemical synthesis (35-37).

1.2.2 Green Advantages of CF Technologies

1.2.2.1 Efficiency and Scalability

Several studies accentuate the operational advantages of CF systems, which include improved heat and mass transfer, leading to enhanced reaction rates and scalability (38-42). For instance, CF reactors facilitate precise control over reaction parameters, significantly increasing yield and consistency, as demonstrated in the hydrogenolysis studies conducted by Tu et al., where precise conditions were crucial for suppressing side reactions (30). The scalability of these technologies allows for rapid adaptation from lab to industrial applications, which is essential for pharmaceutical manufacturing (31, 43-55). Beyond pharmaceutical applications, CF chemistry has demonstrated exceptional versatility in materials science, enabling the ultrafast and cost-effective synthesis of advanced materials such as metal-organic frameworks like MOF-808, which represent another class of high-value compounds benefiting from flow chemistry's enhanced control and efficiency (56).

1.2.2.2 Reduction of Chemical Waste

The green credentials of CF chemistry are underscored by their capacity to minimize the generation of chemical waste (57-59). Studies indicate that flow processes can achieve higher conversions with lower quantities of starting materials (60, 61), thus decreasing by-products and the subsequent need for purification (62). An excellent example is the work of Li et al., which demonstrated how CF technology enabled the eco-friendly synthesis of 9-aryl-fluoren-9-ols with minimized wastage through optimized reaction pathways (60).

1.2.2.3 Safety and Handling of Hazardous Reactions

CF technologies enhance safety by decreasing the scale of hazardous reactions and allowing for the safe handling of toxic or unstable intermediates (30, 63, 64). The capability to maintain small reaction volumes reduces the potential hazards associated with large-scale batch reactions, offering a safer alternative, especially in the pharmaceutical industry where the handling of hazardous materials is critical (2, 36, 65). For instance, the safe generation of hydrazoic acid through CF reactors has been demonstrated, allowing for precise control of reaction parameters that would be unsafe in traditional batch settings (63). The advantages of flow chemistry compared to conventional batch methods are well established and extend seamlessly to flow photochemistry as well. A key reason for this is the exceptional precision with which reaction parameters—such as temperature, mixing, stoichiometry, and reaction time—can be regulated in flow systems. This heightened level of control enables more consistent and reproducible chemical transformations. In the context of flow photochemistry, these benefits are even more pronounced, allowing for greater optimization and fine-tuning than is possible with traditional batch photochemical setups (66-69).

1.2.2.4 Integration of Renewable Resources

Recent works have highlighted the integration of renewable sources in CF processes, further promoting sustainability in chemical manufacturing. Techniques such as microwave-assisted synthesis and biocatalysis in CF microreactors have shown promise for developing greener processes, as described in studies focusing on enzymatic transformations (70, 71). These advancements not only enhance efficiency but also align with sustainable practices by utilizing biodegradable catalysts and renewable feedstocks (72).

1.2.3 Limitations and Future Directions

Despite the ample advantages, CF technology faces challenges, including the need for specialized equipment and investment, which may limit its widespread adoption (31, 73-82). Among the most significant technical challenges is the effective handling of solids in CF processes, where issues such as clogging, fouling, and bridging can lead to complete system blockages and operational failures (83). Furthermore, life cycle assessments indicate that while CF methods reduce certain environmental impacts, a thorough evaluation is required to assess overall sustainability (73, 84). Future work should focus on integrating innovative materials and technologies that enhance the versatility and effectiveness of CF systems while addressing these challenges (85-90).

1.3 Synthesis of Oxindole Derivatives

The alkylation of oxindoles has become an area of significant interest in organic synthesis due to the relevance of oxindole derivatives in pharmaceuticals and biologically active compounds. This literature survey provides a comprehensive overview of the methodologies employed in the alkylation of oxindoles, underscoring the diversification of methods and new catalytic systems introduced in recent years.

1.3.1 The Significance of Oxindole Scaffold Molecules

Oxindole scaffold compounds represent a chemically and biologically significant family of molecules with diverse and versatile applications (16, 91). These heterocyclic compounds possess remarkable versatility in their therapeutic applications, with particularly extensive utilization in human medicine and the pharmaceutical industry, where they hold considerable importance (92, 93). The ability to synthesize pharmaceutical active compounds through structural modifications of the basic scaffold makes the study of oxindole-based compounds highly significant from a pharmaceutical science perspective (94).

Diverse Biological Applications and Pharmaceutical Presence

The biological utilization of oxindole derivatives is highly significant and multifaceted, with numerous representatives found among commercially available pharmaceutical compounds due to their varied biological activities. Beyond their pharmaceutical applications, oxindole derivatives are also discovered in natural alkaloids and serve as active ingredients in several plant protection products (95). Furthermore, these

compounds are found as intermediates in the synthesis of indole alkaloids, highlighting their fundamental role in natural product biosynthesis (96-98).

The broad spectrum of biological activities exhibited by oxindole derivatives includes antiviral, antifungal, antibacterial, antiproliferative, anticancer, anti-inflammatory, antihypertensive, and anticonvulsant properties. This diverse pharmacological profile has established oxindole as a privileged scaffold in medicinal chemistry, capable of providing high-affinity ligands for multiple receptor targets (99-101).

Greatest Significance in Human Medicine

However, oxindole compounds hold their greatest significance due to their role in human medicine. Oxindole scaffold compounds play a major role in drug research, with numerous oxindole-containing drug candidates currently in various stages of clinical trials (102, 103). The pharmaceutical industry has recognized the exceptional therapeutic potential of this scaffold, as evidenced by the extensive research and development activities focused on oxindole-based therapeutics.

Approved and Marketed Oxindole-Containing Pharmaceuticals

Several examples of approved and marketed active compounds from the oxindole-containing compound family demonstrate the clinical success of this scaffold:

Ziprasidone (**2**) is a second-generation atypical antipsychotic agent that represents a significant advancement in psychiatric medication. It functions as a dopamine and 5-HT2A receptor antagonist with a unique receptor binding profile, offering enhanced modulation of mood, notable negative symptom relief, and reduced motor dysfunction compared to other antipsychotics.

Ropinirole (**4**) acts as a dopamine agonist through D2/D3 receptor stimulation and is extensively used in the treatment of Parkinson's disease. It is also employed as an effective treatment for Restless Legs Syndrome. As a non-ergoline dopamine agonist with preferential affinity for D2-like receptors, ropinirole has demonstrated significant clinical efficacy in early Parkinson's disease patients.

Sunitinib (**3**) and Nintedanib (**5**) represent targeted anticancer agents with multikinase inhibitory effects, specifically used for angiogenesis inhibition in cancer patient therapy.

Sunitinib is an oral oxindole multitargeted kinase inhibitor that inhibits specific receptor tyrosine kinases, including vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and stem cell factor receptor. Nintedanib, an oxindole derivative, functions as a triple kinase inhibitor with potent suppressing effects on VEGFR, PDGFR, and fibroblast growth factor receptors.

Tenidap (**6**) represents a historically significant example of oxindole-based anti-inflammatory therapy, belonging to the class of non-steroidal anti-inflammatory drugs. Although it is a compound that has not been approved but is registered in several countries, tenidap demonstrates the potential of oxindole derivatives in inflammatory conditions. It exerts its effect through non-selective cyclooxygenase (COX) enzyme inhibition, showing potent COX inhibition (104).

Figure 3.
Oxindole-Containing Pharmaceuticals

Contemporary Anticancer Research and Kinase Inhibition

Recent research has demonstrated the exceptional potential of oxindole derivatives as anticancer agents, particularly as kinase inhibitors targeting multiple pathways simultaneously. Novel oxindole-coumarin hybrids have shown broad spectrum of anticancer activity, with compounds displaying significant anticancer activity with mean growth inhibition concentrations in the micromolar range (105). These hybrid compounds revealed apoptosis-dependent mechanisms through the increase in the BAX/BCL-2 ratio and enhancement of expression levels of caspase-9 and tumor suppressor p53.

Oxindole-based inhibitors of cyclin-dependent kinase 2 have been extensively studied, with compounds showing potent inhibitory activity in the low nanomolar range (106). Members of this class of inhibitor cause cell cycle arrest and have shown potential utility in the prevention of chemotherapy-induced alopecia. Natural product-inspired spirooxindoles have emerged as dual anticancer agents, with compounds showing very good inhibition potency against both breast and colorectal cancer cell lines (107).

Anti-inflammatory and Analgesic Activities

Oxindole derivatives have demonstrated remarkable anti-inflammatory and analgesic activities through various mechanisms. A dual COX/5-LOX strategy has been adopted to develop new oxindole derivatives with superior anti-inflammatory activity, with some compounds showing up to 100% edema inhibition and writhing protection (108). Chiral oxindole-type analogues have been synthesized with potent anti-inflammatory and analgesic activities, with one compound showing remarkable in vivo anti-inflammatory activity approaching that of dexamethasone (109).

Spiro thiochromene-oxindoles have been developed as novel anti-inflammatory agents through sustainable synthesis methods. These compounds exhibited moderate to good efficacy in inhibiting heat-induced bovine serum albumin denaturation, with the most active compounds showing inhibition percentages of 90-95%. The mechanistic studies revealed binding affinities with cyclooxygenase-2 protein, demonstrating their potential as anti-inflammatory leads (105).

Natural Products and Biosynthetic Pathways

Oxindole alkaloids are widely distributed in nature, particularly in plants belonging to the Rubiaceae family, where species such as Uncaria serve as important sources of bioactive compounds. The biosynthesis of monoterpenoid oxindole alkaloids represents a unique oxidative process derived from monoterpenoid indole alkaloids, involving complex biosynthetic pathways that vary by species, organs, tissues, and growth stages (97). Recent advances in understanding these biosynthetic mechanisms have revealed the formation of spirooxindole scaffolds through specialized enzymatic processes (110).

Natural spirooxindole alkaloids have demonstrated significant biological activities, including apoptosis-inducing effects against acute lymphoblastic leukemia cells and

various cancer cell lines (111). These naturally occurring compounds serve as valuable lead structures for the development of synthetic derivatives with enhanced pharmacological properties.

Neuroprotective and Antioxidant Properties

Oxindole derivatives have shown remarkable neuroprotective activities through various mechanisms. Rhynchophylline, a tetracyclic oxindole alkaloid from Uncaria rhynchophylla, has been demonstrated to provide significant protection against neurotoxicity in cellular models associated with Parkinson's disease. The compound markedly enhanced the activity of transcription factor MEF2D and reversed inhibition caused by neurotoxic agents through PI3-K/Akt/GSK3β pathway activation (104).

Novel oxindole-curcumin hybrid compounds have been developed for antioxidative stress and neuroprotection. These compounds exhibited more potent neuroprotective activity than individual components and demonstrated less cytotoxicity. The compounds showed ferrous ion chelating activity and induced antioxidant response element transcriptional activity, contributing to their neuroprotective effects. The 5-fluoro-2-oxindole derivative has demonstrated antinociceptive, antioxidant, and anti-inflammatory effects during inflammatory pain conditions (112).

Antimicrobial and α-Glucosidase Inhibitory Activities

Virtual screening studies have identified novel oxindole derivatives as potential antimicrobial agents with significant binding affinity against targeted enzymes. Compounds showed superior binding affinity compared to standard antibiotics, with the best compounds demonstrating excellent stability through molecular dynamics simulation. These novel oxindole scaffolds could serve as promising leads for effective antibacterial drugs (91).

Oxindole derivatives have shown promising antidiabetic activity through α-glucosidase inhibition, representing an effective strategy for controlling post-prandial hyperglycemia in diabetic patients. Tetracyclic oxindole derivatives have been evaluated for α-glucosidase inhibitory activity, with the most potent compound exhibiting activity approximately 170 times greater than acarbose. The kinetic analysis revealed that active compounds inhibited α-glucosidase in an irreversible and mixed manner.

Green Chemistry and Sustainable Synthesis Approaches of Oxindoles

The development of efficient, economical synthetic methods for oxindole derivatives has become increasingly important, with recent advances in green chemistry leading to sustainable synthetic protocols. Microwave-assisted synthesis has emerged as an efficient method for obtaining novel oxindole derivatives, providing rapid heating and reaction rates while allowing reactions to proceed under environmentally friendly conditions (113). The microwave-assisted technique offers advantages including shorter reaction times, higher yields, and reduced environmental impact (114).

Microwave heated flow synthesis has been developed for spirooxindole derivatives, providing fast and convenient synthetic routes with residence times down to 168 seconds. The continuous microwave-flow routes provide smooth and scalable synthetic methodology towards various classes of bioactive compounds (115). These green protocols feature high yields, cost-efficiency, non-toxicity, atom economy (AE), and environmentally friendly synthesis conditions.

Oxindole derivatives represent a chemically and biologically significant family of compounds with diverse and versatile applications across multiple therapeutic areas(99). Their extensive utilization in human medicine and the pharmaceutical industry, combined with their presence in natural products and various biological activities, underscores their fundamental importance in chemical biology (16). The continued development of economical, efficient, and scalable synthetic methods for oxindole derivatives remains crucial for meeting the growing pharmaceutical demand and advancing therapeutic applications. The success of currently marketed oxindole-based drugs and the promising pipeline of compounds in clinical development strongly support the continued investment in oxindole research and development.

Building on the recognized pharmaceutical importance of oxindole derivatives and their established role in modern therapeutics, the development of sophisticated synthetic strategies has become essential to access these valuable scaffolds efficiently. Among the various synthetic approaches, alkylation reactions represent a particularly powerful tool for introducing structural diversity at key positions of the oxindole core. These transformations have been greatly enhanced by advances in transition metal catalysis, which provide improved selectivity, functional group tolerance, and synthetic efficiency

compared to traditional methods. The evolution of catalytic methodologies has not only expanded the scope of accessible oxindole derivatives but has also enabled the precise control of stereochemistry essential for biological activity, making these approaches indispensable in contemporary pharmaceutical synthesis (116).

One of the fundamental approaches to alkylation involves the use of transition metal catalysis. Trost and Zhang reported on Mo-catalyzed asymmetric allylic alkylation, demonstrating a method to construct quaternary stereocenters in 3-alkyloxindoles, which underscores the significance of such transformations in synthesizing biologically active molecules (117). This work complements findings by Dagar et al., who explored cerium-mediated decarboxylative alkylation, further expanding the catalytic methodology for producing oxindole derivatives (118). The utilization of transition metals enhances not only yield but also regio- and stereoselectivity, which is crucial when synthesizing complex molecules (119). Stereoselective synthesis methods have become particularly important in creating spirocyclic oxindole derivatives with precise control over their three-dimensional structure, which is crucial for their therapeutic applications (120).

Recent advances have also introduced novel catalytic systems that operate under milder conditions. For instance, Reddy et al. innovated a one-step C5-alkylation process using alcohols, which traditionally required a two-step acylation followed by reduction (121). This not only simplifies the synthetic route but also improves overall efficiency. Similarly, Chaudhari et al. presented a platinum-catalyzed method for C3 alkylation under additive-free conditions, showcasing the practicality of the reaction with various alcohols (122).

Moreover, the incorporation of photochemical methods has added a new dimension to oxindole alkylations. Shaw et al. described a photoinduced radical cascade for synthesizing CF3-containing oxindoles, illustrating how light can facilitate radical reactions for selective alkylation (123). This method signifies an innovative shift towards more sustainable practices in organic synthesis, moving away from harsher chemical environments.

The introduction of organocatalysts and alternative reaction conditions has also been a focus. Chen and He highlighted DABCO-catalyzed Michael/alkylation sequences, which provided rapid access to spirocyclopropyl oxindoles (124). Additionally, Chakraborty et

al. demonstrated methodologies optimizing alkylation strategies using secondary alcohols under cobalt catalysis, showing specific interest in developing greener synthetic pathways (125, 126).

Overall, the alkylation of oxindoles encompasses a range of strategies—transition metal catalysis, organocatalysis, and new methodologies that harness both photochemical and radical processes. This diversity allows for the fine-tuning of product formation, essential for developing new drugs and biologically relevant compounds. The continued innovation in this field promises to yield more selective, efficient, and sustainable synthetic techniques.

The evolution and optimization of solid-phase peptide synthesis (SPPS) for large-scale applications represent significant advancements in the field of peptide chemistry. This literature survey delves into the methodologies and innovations that have enabled the effective scaling-up of SPPS, highlighting key studies and findings that illustrate the progression in this area.

Historically, the development of SPPS was spurred by Bruce Merrifield's pioneering work in 1963, which introduced the concept of synthesizing peptides on a solid support (127). Since then, improvements have been made in various parameters to enhance the efficiency and output of SPPS. A notable approach has been the implementation of high shear mixing, as demonstrated by Alshanski et al., which significantly reduces the coupling times for peptide synthesis and minimizes side reactions, allowing for larger scales of peptide drugs to be manufactured efficiently (128). The ability to synthesize at multi-100-kg scales emphasizes the commercial viability of SPPS, contributing to the global sales of peptide therapeutics (128).

One of the challenges in scaling up SPPS is the need for effective solvation of peptide-resin complexes. Enhanced solvation techniques have been explored by Dang et al., who reported improved synthesis outcomes for elastin sequences through better solvation of peptides attached to resin (129). This enhances reaction kinetics, which is vital for larger-scale synthesis where diffusion limitations can hinder overall efficiency.

Temperature control also plays a critical role in the optimization of peptide coupling reactions. Schieck et al. noted that conducting coupling steps at elevated temperatures

(30–80 °C) yielded significant improvements for challenging peptide sequences, facilitating smoother reactions and higher yields (130). This technique holds promise for large-scale applications where reaction conditions can be adjusted to respond to the specific needs of difficult peptides.

Furthermore, the advent of microwave-assisted SPPS has been pivotal in improving reaction times and yields. Research conducted by Öhlander et al. highlighted that solvents like N-butylpyrrolidinone can match or surpass traditional solvents such as dimethylformamide (DMF) under microwave conditions, offering alternatives that may help mitigate environmental concerns associated with conventional SPPS (131). Moreover, the combination of ultrasonication with SPPS has been shown to further enhance synthesis efficiency, as discussed by Merlino et al., who reported a remarkable increase in the productivity of peptide synthesis using this approach (132).

Despite advancements, the need for accurate resin loading assessment remains crucial for maximizing yield and minimizing costs in SPPS. Torre et al. emphasized the importance of precise measurement techniques, such as online quantification via a refractometer, to improve the economic feasibility of large-scale syntheses (133). Overestimating resin loading leads to excess reagents, thus inflating costs without necessarily improving the quality of the product.

Recent trends also indicate a shift towards greener methods in solid-phase synthesis. Jadhav et al. explored the use of green binary solvent mixtures to replace traditional solvents like DMF, which can lead to significant reductions in side reactions commonly encountered in SPPS (134). This is part of a broader trend towards environmentally friendly practices in chemical synthesis, emphasizing the dual benefits of sustainability and efficiency for large-scale operations.

In conclusion, the scaling-up of SPPS involves a multifaceted approach that integrates novel synthesis methodologies, temperature management, solvation techniques, and greener practices. As demonstrated through various studies, these enhancements not only contribute to the yield and efficiency of peptide synthesis but also address economic and environmental concerns, positioning SPPS as a cornerstone in the production of peptide therapeutics.

1.4 Green Metrics in CF Chemistry

The quantitative assessment of environmental sustainability in chemical processes has become increasingly crucial for advancing green chemistry principles in both academic research and industrial applications. Green metrics provide standardized methodologies for evaluating the environmental impact of synthetic processes, enabling objective comparisons between different synthetic approaches and driving systematic improvements in process sustainability.

Process Mass Intensity and Environmental Factor

Process Mass Intensity (PMI) represents one of the most comprehensive metrics for evaluating overall process efficiency, calculated as the ratio of total mass input to product mass output. This metric encompasses all materials consumed during synthesis, including solvents, reagents, catalysts, and auxiliary materials. In continuous-flow systems, PMI values consistently demonstrate substantial improvements compared to batch processes, primarily due to enhanced reaction control, reduced solvent requirements, and the elimination of intermediate isolation steps.

The Environmental Factor (E-factor), defined as the mass ratio of waste to desired product, serves as a complementary metric that specifically quantifies waste generation efficiency. Continuous-flow processes typically achieve E-factors below 20 for pharmaceutical intermediates, compared to batch processes that often exceed 100, representing a transformative improvement in waste minimization.

Atom Economy and Reaction Mass Efficiency

AE provides a theoretical framework for evaluating the efficiency of chemical transformations by calculating the percentage of reactant atoms incorporated into the desired product. While AE represents an intrinsic property of the chemical transformation itself, continuous-flow systems enable closer approach to theoretical AE through enhanced reaction control and reduced byproduct formation.

Reaction Mass Efficiency (RME) integrates multiple factors including yield, stoichiometry, and molecular weight considerations, providing a holistic assessment of synthetic efficiency. Flow chemistry enables improved RME through precise

stoichiometric control, enhanced mixing, and the ability to operate under optimized conditions that maximize selectivity.

Solvent and Energy Efficiency Metrics

Solvent efficiency metrics gain particular significance in continuous-flow processes where dramatic reductions in solvent consumption are achievable through process intensification. The implementation of green solvents, such as propylene carbonate in peptide synthesis, demonstrates how flow chemistry can simultaneously improve environmental performance while maintaining synthetic efficiency.

Energy efficiency considerations in flow systems encompass both the direct energy requirements for heating and mixing, as well as the indirect energy benefits achieved through process intensification and reduced downstream processing requirements. The miniaturization inherent in flow systems often results in lower absolute energy consumption while providing superior reaction control.

1.5 Green Metrics in SPPS

Solid-phase peptide synthesis presents unique challenges for environmental sustainability assessment due to the iterative nature of the process, high solvent consumption, and the requirement for excess reagents to drive coupling reactions to completion. Traditional SPPS protocols typically achieve PMI values exceeding 10,000, making peptide synthesis one of the most resource-intensive areas of pharmaceutical chemistry.

Challenges in Traditional SPPS Green Metrics

The environmental impact of classical SPPS stems from multiple contributing factors that compound throughout the synthesis cycle. Each coupling and deprotection step requires substantial solvent volumes for resin swelling, washing, and product isolation. The typical requirement for 3-5 equivalents of amino acid reagents to achieve quantitative coupling further contributes to poor AE, while the use of hazardous solvents such as DMF poses additional environmental and safety concerns.

The iterative nature of SPPS means that environmental inefficiencies are multiplicative rather than additive, with each additional amino acid residue proportionally increasing the overall environmental impact. This scaling relationship makes the development of

green SPPS methodologies particularly crucial for longer peptide sequences and large-scale production applications.

Environmental Advantages of Continuous-Flow SPPS

The implementation of continuous-flow technology in SPPS achieves dramatic improvements across multiple green metrics through process intensification and enhanced reaction control. PMI values for CF-SPPS typically range from 400-700, representing a 15-25 fold reduction compared to classical batch methods. This improvement stems from reduced solvent consumption (measured in milliliters rather than liters), decreased reagent requirements (1.5 equivalents versus 3-5 equivalents), and elimination of intermediate isolation steps.

The temporal efficiency of CF-SPPS contributes significantly to overall environmental performance, with synthesis times reduced from days to hours compared to classical methods. This acceleration results from enhanced mass transfer in flow systems, optimized residence times, and the ability to conduct reactions at elevated temperatures and pressures that would be impractical in batch systems.

Green Solvent Implementation in CF-SPPS

The replacement of traditional hazardous solvents with environmentally benign alternatives represents a critical advancement in SPPS sustainability. Propylene carbonate emerges as an ideal green solvent for CF-SPPS applications, offering low toxicity, high boiling point, and favorable solvation properties for peptide synthesis. The synthesis of propylene carbonate through CO_2 utilization reactions provides additional environmental benefits by converting greenhouse gases into useful chemical feedstocks.

The implementation of green solvents in CF-SPPS demonstrates the synergistic relationship between flow technology and green chemistry principles. The enhanced mass transfer and mixing achieved in flow systems compensate for any potential reduction in reaction efficiency associated with green solvent use, enabling the achievement of both environmental and performance objectives simultaneously.

Scalability and Industrial Implementation

The scalability of green CF-SPPS methodologies presents significant opportunities for industrial peptide production, where environmental performance directly impacts economic viability. The linear scaling of PMI values with production volume, combined with the ability to implement numbering-up strategies for capacity expansion, provides a clear pathway for sustainable peptide manufacturing at commercial scales.

The integration of green metrics assessment into CF-SPPS development enables data-driven optimization of both environmental and economic performance. Real-time monitoring of resource consumption and waste generation facilitates continuous improvement of process sustainability while maintaining the high yields and purity requirements essential for pharmaceutical applications.

These green metrics improvements in CF-SPPS represent a paradigmatic shift toward sustainable peptide synthesis, demonstrating how advanced process technologies can simultaneously address environmental concerns and manufacturing efficiency requirements. The quantitative framework provided by green metrics enables systematic optimization and provides benchmarks for future technological developments in sustainable pharmaceutical synthesis.

2. Objectives

The overarching objective of this dissertation is to advance sustainable continuous-flow methodologies for the synthesis of pharmaceutically relevant compounds, with primary emphasis on oxindole derivatives and secondary focus on peptide synthesis, both addressing critical environmental and operational challenges through comprehensive green chemistry implementation. A fundamental component of this research involves the rigorous application of green metrics—including PMI, E-factor, and AE—to quantitatively assess and validate the sustainability improvements achieved through flow chemistry approaches. This research is fundamentally motivated by the urgent need for environmentally responsible synthetic processes that align with the twelve principles of green chemistry while maintaining pharmaceutical-grade efficiency and scalability.

2.1 Green Chemistry Integration through CF Oxindole Synthesis

The central goal is to demonstrate how CF chemistry serves as an enabling technology for achieving fundamental green chemistry objectives through the development of sustainable methodologies for oxindole derivative synthesis. Oxindole compounds represent a critically important pharmaceutical scaffold found in several marketed drugs including sunitinib, ziprasidone, and nintedanib, making their sustainable synthesis of considerable industrial relevance. Traditional batchwise oxindole alkylation requires extreme reaction conditions (150-220°C, >40 bar) that pose significant safety risks, scalability challenges, and environmental concerns. The methodology aims to implement innovative CF process intensification strategies using packed-bed reactor configurations with pyrophoric Raney nickel catalyst, enabling safe handling of dangerous materials while maximizing catalytic efficiency through enhanced mass transfer and optimal residence time distribution.

The research targets exceptional environmental performance through quantitative green metrics validation, with PMI values dramatically reduced compared to conventional batch methodologies. The borrowing hydrogen mechanism exemplifies elegant AE by eliminating external hydrogen requirements while maintaining high conversion efficiency, directly addressing multiple green chemistry principles including waste prevention, AE enhancement, safer synthetic methods, and energy efficiency through miniaturization. Extended continuous operation processing over 20 grams of starting

material using minimal catalyst loading (800 mg) will establish benchmarks for industrial scalability while demonstrating turnover numbers (TON) of 29 and turnover frequencies (TOF) of 1.45 h^{-1}, representing remarkable catalyst productivity for an inexpensive heterogeneous system.

2.2 Green Solvent Implementation in CF Peptide Synthesis

A complementary objective focuses on advancing green chemistry principles through the implementation of propylene carbonate (PC) as an eco-friendly solvent replacement for DMF in CF solid-phase peptide synthesis (CF-SPPS). PC represents an ideal green solvent choice according to the GSK solvent selection guide, being synthesized through CO_2 utilization reactions that mitigate greenhouse gas emissions while providing low toxicity and minimal volatile organic compound emissions. The methodology targets dramatic improvements in environmental efficiency, with PMI values ranging between 434-693 for CF-SPPS compared to classical SPPS values exceeding 10,000, representing fundamental improvements that approach the efficiency levels observed in small-molecule drug synthesis.

The research will validate solvent consumption reductions of approximately two orders of magnitude compared to traditional methodologies, with gram-scale peptide synthesis requiring minimal solvent quantities measured in milliliters rather than liters. The integration demonstrates how flow chemistry maximizes efficiency through telescoping capabilities while minimizing waste generation, with enhanced reaction control enabling quantitative conversions using only 1.5 equivalents of amino acids compared to traditional excess requirements. This approach directly addresses green chemistry principles of safer solvents and auxiliaries, energy efficiency through reduced synthesis times, and waste prevention through enhanced AE and process intensification.

Anticipated Outcomes and Broader Impact

By integrating these research objectives, the dissertation aims to provide comprehensive demonstration of how CF methodologies can revolutionize pharmaceutical synthesis while advancing sustainable chemical manufacturing principles. The anticipated outcomes include methodological innovations establishing new standards for environmentally efficient synthesis, detailed green metric analyses providing concrete benchmarks for future development, and scalability validation demonstrating industrial

viability through economic assessment and environmental impact quantification. The research will establish CF chemistry as a paradigmatic example of green chemistry implementation, providing foundations for widespread adoption of sustainable synthetic technologies in pharmaceutical and fine chemical industries while contributing to the broader transition toward environmentally responsible chemical manufacturing practices.

3. Methods

Packed-Bed Reactor Configuration for Oxindole Reductive Alkylation

For the execution of oxindole reductive alkylation reactions, a CF packed-bed reactor system was employed. These systems consist of packed columns or cartridges - which can be made from glass, polymer, or stainless steel - with lockable end closures containing filter plates and/or frits. In packed beds, typically the entire column or channel is filled with solid material, thereby limiting particle movement. The bed can be randomly filled with small particles that can serve as catalysts or modify flow patterns, or it can contain other specific packing materials embedded between filter units through which the reaction mixture passes.

Direct Alkylation of Oxindoles: Challenges and the Raney Nickel Solution

Despite numerous methods for direct alkylation of deprotonated oxindole, controlling regiochemistry remains difficult, often yielding mixtures of N-, C-, di-, or trialkylated products. In 1958, Wenkert and co-workers introduced a landmark approach using Raney nickel and alcohols under prolonged reflux ("borrowing hydrogen" mechanism), which selectively delivers 3-alkyloxindoles and laid the groundwork for modern catalyst design(135).

Raney nickel—a porous nickel–aluminium alloy produced by NaOH activation—combines high surface area (50–150 m^2/g) and abundant active sites to perform three roles in a single pot:

- Dehydrogenation of the alcohol to its carbonyl derivative, storing hydrogen on the catalyst surface.
- Base-catalyzed aldol condensation between the in situ carbonyl and the oxindole's C-3 methylene, yielding a 3-alkylideneoxindole.
- Hydrogenation of that intermediate to the 3-alkyloxindole product(136).

This method's extraordinary regioselectivity arises from generating and consuming the alkyl donor in situ, avoiding over-alkylation. Moreover, using simple alcohols broadens accessible substituents without handling toxic alkyl halides.

However, early protocols required days of reflux, large catalyst loadings (10 equivalent), and gave variable yields, limiting scalability. Subsequent improvements employed high-pressure autoclaves (150–220 °C, 1–5 h), reducing reaction times, catalyst amounts, and boosting yields—demonstrating the method's industrial promise(137).

Further mechanistic insights came from diol alkylations: ethylene glycol or 1,4-butanediol undergo oxidation on Raney nickel, and the generated hydrogen suffices to complete reduction in open vessels, revealing the catalyst's inherent hydrogen-storage capability(138).

Today, "borrowing hydrogen" catalysis has evolved with iron and supported noble metals, while flow reactors offer improved heat and mass transfer. Nonetheless, the Raney nickel paradigm—combining dehydrogenation, condensation, and hydrogenation in one vessel—remains a cornerstone of 3-alkyloxindole synthesis.

The particle size of the packing material is crucial, as larger particles have relatively small surface-to-volume ratios. Since the reaction occurs at the surface, this can impair the efficiency of the synthesis. However, excessive reduction of particle size is also not recommended, as this can create significant resistance in the column, making the system unusable, potentially causing pump shutdown due to overpressure, or even rupturing PEEK tubing that carries solvents.

The CF reductive alkylation of oxindole derivatives was performed using a packed-bed reactor system optimized for high-temperature (150–300°C) and high-pressure (40–160 bar) conditions. The core component consisted of a stainless-steel HPLC column (4.6 mm inner diameter × 250 mm length) packed with 800 mg of Raney nickel (Ra-Ni) catalyst (Sigma-Aldrich, 50% Ni/Al basis). The reactor column was integrated into a temperature-controlled GC oven (JASCO) for precise thermal regulation, while a semi-preparative HPLC pump (JASCO PU-2080) delivered reagents at flow rates of 0.1–1.0 mL/min. A back-pressure regulator (ThalesNano, 0–300 bar) maintained system pressure, ensuring pressurized liquid-phase conditions throughout the reaction zone.

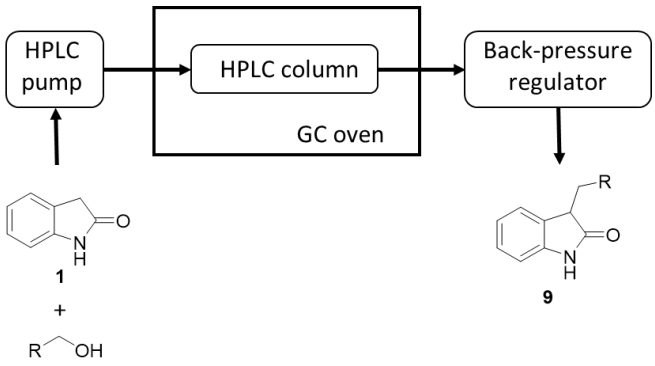


Figure 4.
Schematic illustration of the packed-bed CF reactor system

The column used was a 4.6 mm inner diameter and 250 mm length HPLC column, which was packed with 800 mg of Ra-Ni catalyst (product number: 72240; purum, 50% aluminium-based, 50% nickel-based) purchased from Sigma-Aldrich. The reactor system was designed to safely handle the pyrophoric nature of Raney nickel while maximizing catalytic efficiency through enhanced mass transfer and optimal residence time distribution.

Temperature and Pressure Control Systems

CF synthesis was performed under high temperature and high-pressure conditions according to flow chemistry protocols. The high pressure enabled reactions to be carried out at temperatures nearly four times the normal atmospheric boiling point of the solvent used, tetrahydrofuran, which has a boiling point of 64°C at standard atmospheric pressure. The reactor constructed and used by the research group consisted of a GC oven capable of providing high temperatures, containing an HPLC column filled with Raney nickel catalyst where the heterogeneous catalytic reaction took place.

The system also included an external pressure control unit and an HPLC pump that maintained CF and was capable of controlling and modifying the solvent flow rate. Solvents and reagents were introduced into and removed from the reaction chamber using PEEK tubing and high-temperature resistant stainless-steel tubing. The CF reactor system was located in a fume hood, further enhancing the safety of the reactions.

Reagent Preparation and Optimization Procedures

Reagents and the solvent necessary for their dissolution were measured together in a graduated cylinder, with ultrasonic sonication assisting their dissolution. After complete dissolution of the sample, it was introduced to the pump via a suction tube attached to PEEK tubing, which could then transport it to the temperature-controlled oven. The reagent then passed through the HPLC column located in the oven. At a flow rate of 0.5 mL/min, it remained in the Raney nickel-filled column for 5 minutes and 30 seconds, during which time the substitution of the hydrogen molecule at the 3-position of oxindole with an alkyl group occurred.

The reagents used included 97% purity oxindole (Sigma-Aldrich), as well as aldehydes and solvents for the reactions, which were also obtained from Sigma-Aldrich. Comprehensive optimization studies revealed optimal reaction conditions of 220°C, 120 bar pressure, and 0.5 mL/min flow rate, corresponding to a residence time of 2.7 minutes. Temperature optimization demonstrated a maximum conversion plateau at 220°C followed by significant degradation at 300°C due to thermal decomposition and 7-methylation side reactions.

Process Parameter Optimization and Control

The optimization process carefully considered thermal expansion effects in residence time calculations, ensuring accurate process control parameters throughout the investigation. Flow rate optimization revealed critical relationships between mixing efficiency and residence time, with the optimal 0.5 mL/min flow rate providing maximum conversion of 97% for the model ethylation reaction. Pressure dependence studies showed optimal performance at 120 bar, with productivity reaching 1.2 g/h in optimized conditions.

After passing through the external pressure control unit located at the end of the reaction path, which exerts a pressure-increasing effect on the reaction chamber through changing the tension of a PTFE membrane. Subsequently, a sample collection vessel was placed at the end of the continuous reactor to collect the product arriving drop by drop. The system allowed precise control over temperature, pressure, and flow, which was critical to

maximize conversion and regioselectivity while minimizing side reactions such as 7-methylation.

Catalyst Performance and Mechanistic Studies

The catalyst demonstrated remarkable stability, maintaining activity for up to 19 hours of continuous operation, enabling the transformation of over 20 grams of oxindole with minimal catalyst loading of approximately 800 mg. The TON of 29 and TOF of 1.45 h^{-1} indicate remarkable catalyst efficiency, particularly significant given the use of an inexpensive, widely available heterogeneous catalyst.

Mechanistic studies using deuterium labelling confirmed that water, introduced with the aqueous Ra-Ni catalyst and generated during condensation steps, served as the hydrogen source for the reduction of the C=C bond. X-ray photoelectron spectroscopy (XPS) analysis revealed important catalyst deactivation mechanisms, with complete disappearance of metallic aluminium content and dramatic reduction in surface Ni-Al ratio from 0.9:1 to 0.05:1. The investigation confirmed progressive catalyst degradation through aluminium oxidation and nickel leaching, providing essential understanding for rational catalyst improvement approaches.

Substrate Scope and Product Isolation

Post-reaction, products were isolated by solvent evaporation followed by flash chromatography using a CombiFlash NextGen 300+ System with a 12 g HP Silica RediSep® Gold column using a hexane-ethyl acetate solvent system. The process achieved high isolated yields (up to 96%) across a variety of oxindole derivatives, including 3-alkyl and 3-aralkyl substituted compounds.

For large-scale CF reactions, oxindole (1) was dissolved either in the corresponding alcohol (serving simultaneously as both solvent and alkylating agent) or in THF, to which both the corresponding alcohol and the corresponding aldehyde (2.0 equivalents) were added as reactants. The solution was homogenized by sonication for 5 minutes, then pumped through the CF reactor under the established conditions. Conversion was tested by NMR investigations every 30 minutes, and when conversion dropped, the reaction was stopped.

The substrate scope investigation demonstrated broad applicability across diverse alcohol and aldehyde partners, with isolated yields ranging from 40% to 96% depending on substrate structure and reaction conditions. Alcohol-based alkylations showed decreasing efficiency with increasing chain length: 95% for methanol, 96% for ethanol, 77% for propanol, and 46% for butanol, reflecting increasing steric hindrance and potential for competing side reactions.

CF Solid-Phase Peptide Synthesis Integration

A complementary CF solid-phase peptide synthesis (CF-SPPS) methodology was employed using propylene carbonate (PC) as an eco-friendly solvent. The reactor setup consisted of a semi-preparative stainless-steel HPLC column packed with TentaGel® R RAM resin, an HPLC pump providing pulse-free and precise flow control, an autosampler for reproducible reagent delivery, a column thermostat to maintain elevated reaction temperatures, and a back-pressure regulator to ensure stable system pressure.

Propylene carbonate was selected as the solvent due to its favourable environmental profile, including low toxicity, high boiling point, and sustainable synthesis from CO_2, aligning with green chemistry principles. The synthesis parameters were extensively optimized using model peptides to achieve high coupling efficiency and crude purity. Optimal conditions included a reaction temperature of 70°C, a backpressure of 60 bar, a flow rate of 0.3 $mL \cdot min^{-1}$, and a residence time of approximately 5 minutes per coupling or deprotection step.

Environmental Factor and Atom Economy Improvements

E-factor improvements demonstrated substantial waste reduction across our CF processes. The E-factor, calculated as the ratio of waste mass to product mass, offers a direct measure of environmental efficiency. In our CF reductive alkylation of oxindole, elimination of intermediate isolations and precise in situ reagent generation reduced solvent and reagent waste, achieving E-factors in the range of 2–20 for pharmaceutical intermediates, compared to typical batch values of 36–2245. These reductions stem from minimized solvent usage, elimination of work-up steps, and enhanced reaction selectivity inherent to CF platforms.

AE calculations revealed further efficiency gains through CF implementation. AE is defined as the percentage of reactant atoms incorporated into the final product, calculated by dividing the molecular weight of the desired product by the sum of molecular weights of all reactants. CF enabled operation under optimized stoichiometry and improved reaction control, reducing by-product formation and allowing AE values to approach theoretical maxima more closely than in batch syntheses. By combining high AE with reduced E-factors, our CF methodology establishes a robust framework for sustainable and scalable pharmaceutical manufacturing.

Safety Protocols and Environmental Considerations

The CF approach afforded exceptional PMI values as low as 1.36, reflecting the efficient use of reagents and solvent recycling (95% ethanol recovery). The closed system design minimized safety risks associated with handling pyrophoric Raney nickel and high-pressure, high-temperature conditions. The methodologies developed integrate the principles of green chemistry with advanced flow technology to deliver efficient, scalable, and safer synthetic routes for both peptides and oxindole derivatives. The precise control over reaction parameters, enhanced heat and mass transfer, and minimized waste generation underscore the advantages of CF synthesis as a transformative platform in modern chemical manufacturing (139).

4. Results

4.1 Process Intensification in CF Systems

CF chemistry demonstrated remarkable improvements in fundamental transport phenomena through miniaturization effects that transform reaction dynamics. The geometric advantages of microreactors created unprecedented opportunities for process intensification, where surface area scales as length squared while volume scales as length cubed, yielding surface-to-volume ratios proportional to 1/d where d represents the characteristic dimension. Microreactors achieved surface-to-volume ratios of 8,000-15,000 m^{-1} compared to approximately 60 m^{-1} for conventional batch reactors, facilitating rapid heat transfer with coefficients approaching 2,200 $W/(m^2 \cdot K)$ versus approximately 100 $W/(m^2 \cdot K)$ in batch systems.

The enhanced heat transfer capabilities enabled precise temperature control even during highly exothermic reactions, with complete mixing achieved in microseconds compared to seconds or minutes required in batch systems. Mass transfer enhancement results showed dramatic improvements in microreactors due to shortened diffusion distances typically ranging from 10-500 μm, with diffusion times scaling proportionally to the square of the diffusion path length.

4.2 Oxindole Reductive Alkylation Results

Process Development and Optimization Outcomes

Comprehensive optimization studies for oxindole reductive alkylation revealed optimal reaction conditions of 220°C, 120 bar pressure, and 0.5 mL/min flow rate, corresponding to a residence time of 2.7 minutes. Temperature optimization demonstrated a maximum conversion plateau at 220°C followed by significant degradation at 300°C due to thermal decomposition and 7-methylation side reactions. The optimization process carefully considered thermal expansion effects in residence time calculations, ensuring accurate process control parameters throughout the investigation.

Catalyst Performance and Sustainability Metrics

Exceptional catalyst productivity was demonstrated with 800 mg of Raney nickel enabling the processing of approximately 20-23 g of oxindole during continuous operation periods of 16-19 hours. The turnover number (TON) of 29 and turnover

frequency (TOF) of 1.45 h^{-1} indicated remarkable catalyst efficiency, particularly significant given the use of an inexpensive, widely available heterogeneous catalyst. Extended operation validation showed that continuous processing could be maintained for up to 19 hours without significant conversion loss, with 22.8 g of oxindole transformed to the corresponding 3-ethyl derivative using only approximately 800 mg of Raney nickel.

Substrate Scope and Synthetic Applications

Substrate scope investigation demonstrated broad applicability across diverse alcohol and aldehyde partners, with isolated yields ranging from 40% to 96% depending on substrate structure and reaction conditions. Alcohol-based alkylations showed decreasing efficiency with increasing chain length: 95% for methanol, 96% for ethanol, 77% for propanol, and 46% for butanol, reflecting increasing steric hindrance and potential for competing side reactions. Aldehyde-based alkylations demonstrated more consistent

performance across the substrate range, with aliphatic aldehydes generally providing good to excellent yields.

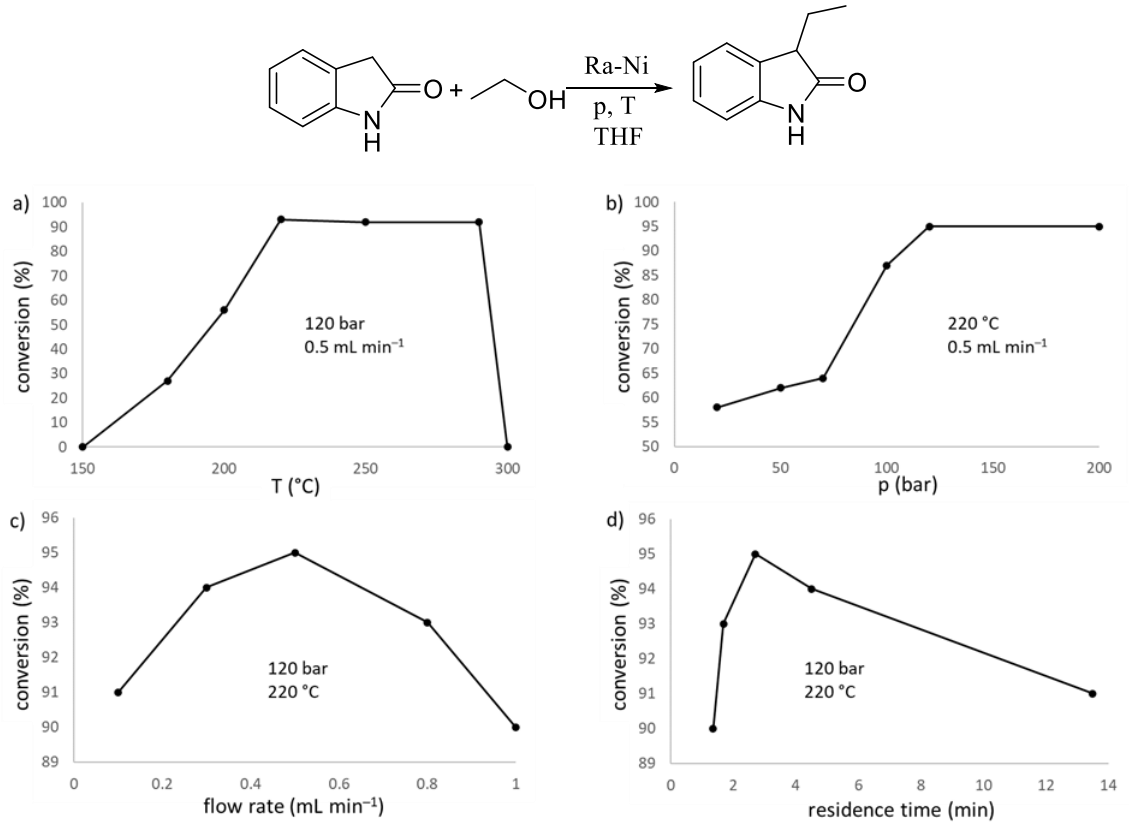


Figure 5.
The effect of temperature (a), pressure (b), flow rate (c) and residence time (d) on the reaction conversion

Process Efficiency and Throughput

The continuous flow methodology significantly enhanced space-time yield compared to conventional batch processing, particularly relevant for pharmaceutical manufacturing where reactor volume efficiency is critical. The 82% isolated yield achieved for 22.6 g of 3-ethyloxindole during 19 hours of continuous operation demonstrates both process efficiency and scalability potential for this transformation.

Scale-up Validation and Industrial Applicability

The demonstration of sustained catalytic activity over extended periods represents a critical validation of the methodology's practical utility. The 16–19-hour continuous operation periods without significant conversion loss indicate exceptional process robustness, essential for potential industrial implementation. The consistent conversion

maintenance during these extended runs demonstrates the stability of both the catalyst system and the overall process parameters.

Catalyst Performance and Deactivation

XPS analysis of fresh and used catalysts revealed that loss of metallic aluminum and a sharp decrease in the surface Ni-Al ratio (from 0.9:1 to 0.05:1) reflect catalyst degradation via aluminum oxidation and nickel leaching. These findings clarify key deactivation pathways and provide a basis for targeted catalyst improvement and process optimization.

The mechanistic study of the borrowing hydrogen pathway, including isotopic labeling and catalyst analysis, enables reliable prediction of substrate compatibility and helps optimize reaction conditions. This foundational understanding supports the efficient and sustainable expansion of substrate scope in future developments.

Process Mass Intensity Achievements in CF Oxindole Alkylation

Across the aldehyde series, PMI values clearly demonstrate the substantial material-efficiency benefit of the continuous-flow protocol, with distinct structure–efficiency relationships evident throughout the substrate scope.

The PMI values span a remarkably narrow range of 33.70–59.27, with all thirteen substrates delivering exceptional performance compared to conventional batch processes (typically PMI ≥100). The most efficient substrates—phenylacetaldehyde (33.70), citronellal (34.80), and benzaldehyde (36.89)—achieve outstanding material economy, while even the highest PMI value (formaldehyde, 59.27) represents at least 2-fold superior efficiency compared to typical batch benchmarks.

Aromatic aldehydes demonstrate consistently excellent performance across diverse electronic environments. Unsubstituted benzaldehyde (36.89) and both trifluoromethyl-substituted derivatives (36.55–37.57) achieve nearly identical PMI values, indicating that electron-withdrawing substituents do not compromise material efficiency. The hydroxyl-substituted 4-hydroxybenzaldehyde (38.22) performs equally well, while p-anisaldehyde

(43.67), despite requiring elevated stoichiometry (1:4 ratio) due to its electron-rich nature, still maintains favorable material economy.

Aliphatic aldehydes show more pronounced structure–efficiency correlations. Longer-chain substrates like valeraldehyde (39.47) excel through high conversion rates and minimal side reactions, while branched derivatives such as isobutyraldehyde (48.85) and butyraldehyde (47.70) maintain good performance despite increased steric demands. Short-chain volatile aldehydes—formaldehyde (59.27), acetaldehyde (51.93), and propionaldehyde (51.95)—exhibit the highest PMI values in the series, likely reflecting volatility-related losses or competing side reactions, yet still dramatically outperform conventional synthetic approaches.

Overall Assessment

Remarkably, ten of thirteen substrates (77%) achieve PMI values below 50, while all entries remain well below conventional batch thresholds. This comprehensive superiority underscores both the broad applicability of the continuous-flow approach across structurally diverse aldehydes and its transformative impact on sustainable synthesis, where even the most challenging substrates deliver substantial improvements in material efficiency.

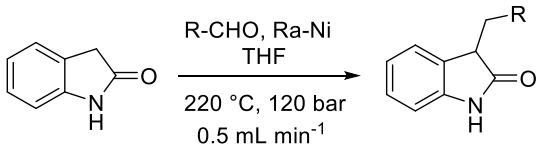


Figure 6.
Reaction with aldehydes

Table 1.

Conversions, Yields and PMIs of CF Reductive Alkylations of Oxindole with Aldehydes Resulting in 3-Alkyloxindoles

reagent (R-CHO)	oxindole: reagent ratio	conversion; yield	PMI
Formaldehyde	1:2	87%; 45%	59,27
Acetaldehyde	1:2	91%; 83%	51,93
Propionaldehyde	1:2	84%; 71%	51,95
Butyraldehyde	1:2	85%; 80%	47,70
Valeraldehyde	1:2	96%; 89%	39,47
Isobutyraldehyde	1:2	83%; 77%	48,85
Benzaldehyde	1:2	94%; 86%	36,89
4-Hydroxybenzaldehyde	1:2	85%; 81%	38,22
p-Anisaldehyde	1:4	73%; 42%	43,67
Phenylacetaldehyde	1:2	97%; 90%	33,70
Citronellal	1:2	83%; 78%	34,80
3-(Trifluoromethyl)benzaldehyde	1:2	74%; 68%	36,55
4-(Trifluoromethyl)benzaldehyde	1:2	72%; 67%	37,57

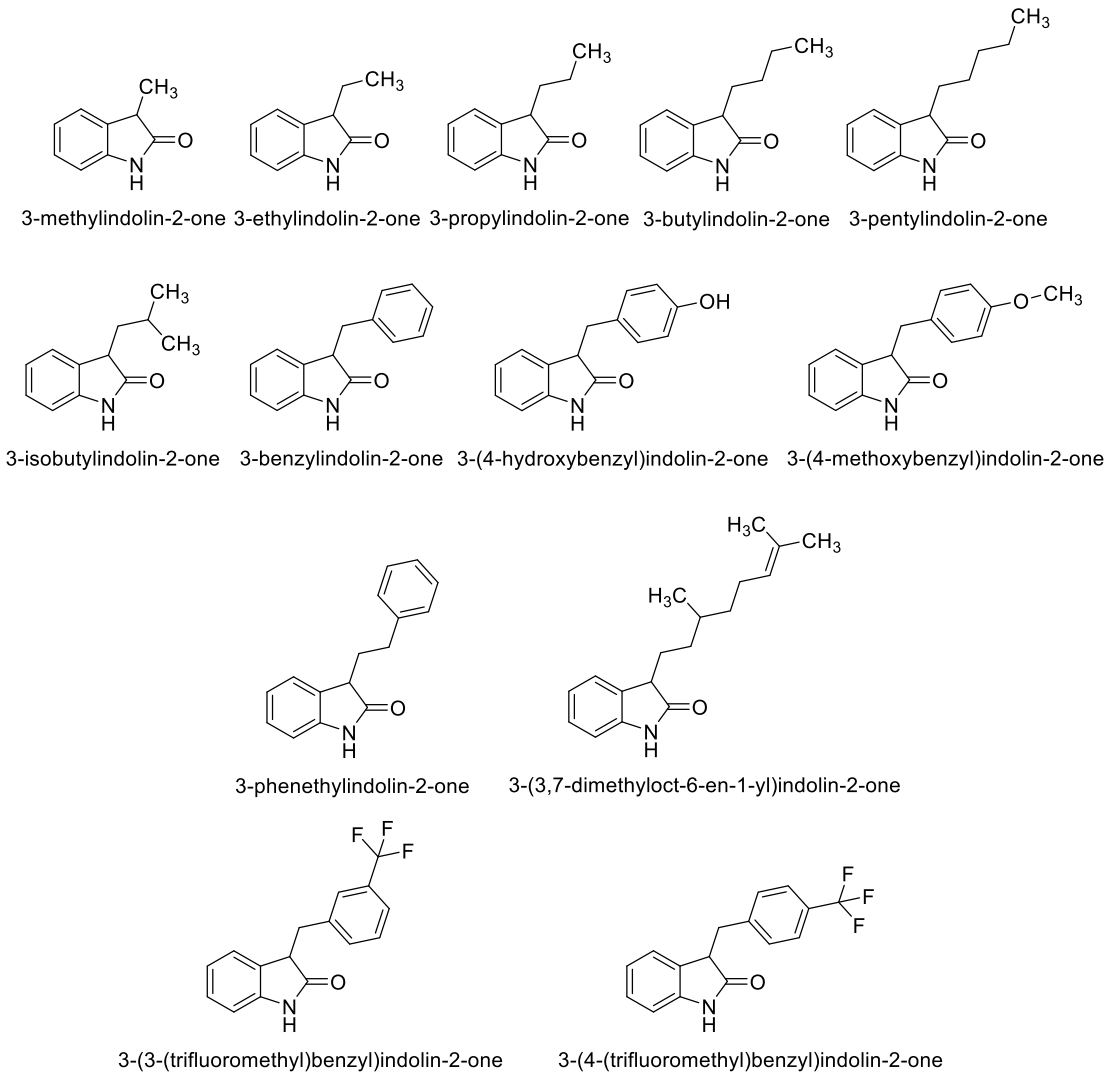


Figure 7.
3-alkyloxindoles

The synthetic versatility of the developed continuous-flow methodology was demonstrated through the successful preparation of thirteen structurally diverse 3-alkyloxindole derivatives using aldehyde substrates. All thirteen compounds were synthesized using the optimized reaction conditions (220°C, 120 bar, 0.5 mL/min flow rate) in the packed-bed reactor system, showcasing the broad applicability and robustness of the borrowing hydrogen approach.

The complete series of thirteen oxindole derivatives encompasses both aliphatic and aromatic substituents, demonstrating the method's tolerance for diverse electronic and steric environments. Each derivative was successfully synthesized with isolated yields

ranging from 42% to 90%, confirming the general applicability of the continuous-flow protocol across structurally varied aldehyde partners.

4.3 Scale-Up and Green Metrics of CF-SPPS

Scale-up validation demonstrated exceptional scalability from 0.07 mmol laboratory scale to 1.5 mmol production scale, maintaining consistent high purity and yield while preserving green chemistry advantages. Production at gram scale (>4 g of peptide isolated in less than 6 hours) maintained minimal solvent usage measured in milliliters rather than liters, confirming industrial viability of the approach. The established optimal conditions utilized 70°C temperature, 60 bar pressure, 5 min residence time with only 1.5 equivalents of amino acids using OxymaPure®/DIC as coupling agents in PC at 100 mM concentration.

Time and Efficiency Comparisons

Synthesis time comparisons demonstrated remarkable efficiency improvements, with peptide chain construction times of 5-8 hours compared to 35-140 hours in traditional methods. For α-peptides, the CF-SPPS methodology achieved impressive results: compound 1 with >98% raw purity and 96% yield, compound 2 with >96% raw purity and 94% yield, compound 3 with >97% raw purity and 93% yield, and compound 4 with >95% raw purity and 91% yield. The consistent PMI values ranging between 434-693 regardless of peptide complexity or production volume validated the fundamental sustainability advantages of the CF approach.

Process Mass Intensity Achievements in CF-SPPS

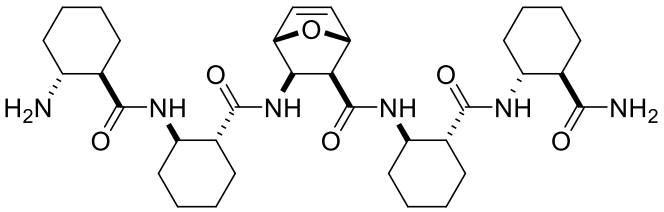
The integration of propylene carbonate (PC) as an eco-friendly solvent in CF solid-phase peptide synthesis (CF-SPPS) achieved dramatic improvements in environmental efficiency. PMI values under classical SPPS conditions exceeded 10,000 for all investigated compounds, while optimized CF-SPPS conditions achieved PMI values ranging between 434 and 693. This approximately 20-fold reduction in PMI represents a paradigm shift in peptide synthesis sustainability, approaching efficiency levels observed in small-molecule pharmaceutical synthesis.

The PMI improvements stemmed from multiple synergistic factors: reduced solvent consumption (approximately two orders of magnitude lower than classical methods),

minimal reagent usage (1.5 equivalents versus traditional 3-5 equivalents), and elimination of intermediate purification steps. Direct comparison of solvent requirements showed complete peptide chain assembly required approximately 18-75 mL in CF-SPPS versus 1,680-6,960 mL in traditional approaches.

Table 2.
Comparison of PMI values for classic SPPS and under the CF-SPPS conditions carried out in PC as solvent

Compound	PMI value for classic SPPS	PMI value for classic SPPS per AA residue	PMI value for CF-SPPS	PMI value for CF-SPPS per AA residue
ALFEK-NH_2	58027	11605	658	132
KRLFKKLLFSLRKY-NH_2	39370	2812	434	31
RQIKIWFQNRRMKWKK-NH_2	51062	3191	564	35
GMASKAGAIAGKIAKVALKAL-NH_2	63326	3016	693	33
7	57895	11579	659	132
8 and 9	66279	11046	757	126
10	56768	9461	658	110
11	60302	10050	681	113



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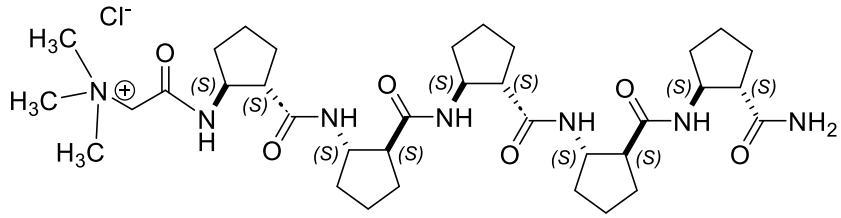

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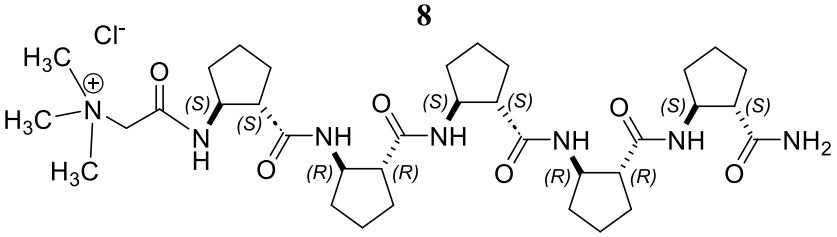

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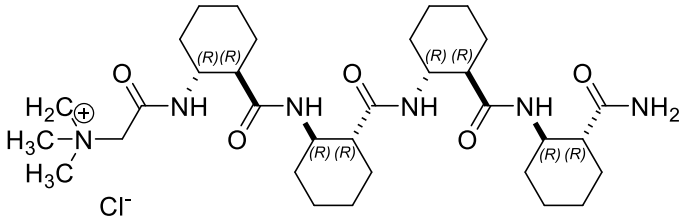

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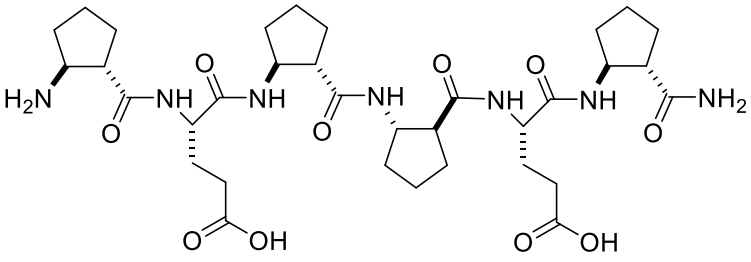

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Figure 8.
Structures of the synthesised β-peptide foldamers using PC as solvent

5. Discussion

5.1 Green Chemistry Principles and Flow Systems Integration

CF chemistry represents a paradigm shift that fundamentally aligns with the twelve principles of green chemistry, offering inherent advantages that extend far beyond conventional batch processing capabilities. The integration of flow systems with green chemistry principles creates synergistic effects that manifest in multiple dimensions of process optimization, waste reduction, and energy efficiency enhancement.

The precision control achievable in CF systems enables remarkable waste reduction through highly controlled stoichiometry and reaction conditions. This precision emerges from the laminar flow regimes typically encountered in microreactors, characterized by Reynolds numbers (Re) ranging from 100 to 1000, where

$$\mathrm{Re} = \frac{\rho v L}{\mu}$$

(ρ = fluid density, v = velocity, L = characteristic length, μ = dynamic viscosity). The predominant laminar flow conditions facilitate predictable mixing patterns and eliminate the chaotic mixing variability inherent in batch systems, resulting in more consistent product formation and reduced byproduct generation.

Energy efficiency in flow systems stems from the fundamental advantage of miniaturization, where the surface-to-volume ratio increases dramatically as reactor dimensions decrease. For a reactor with characteristic dimension d, the surface area scales as d^2, while volume scales as d^3, yielding a surface-to-volume ratio proportional to 1/d . This relationship enables microreactors to achieve surface-to-volume ratios of 8,000-15,000 m^{-1}, compared to 60 m^{-1} for conventional batch reactors, facilitating rapid heat transfer with coefficients approaching 2,200 $W/(m^2 \cdot K)$ versus approximately 100 $W/(m^2 \cdot K)$ in batch systems.

The safety enhancements achievable through flow chemistry extend beyond simple containment advantages to encompass fundamental changes in reaction dynamics and hazard mitigation. The small hold-up volumes typical of microreactors (often <1 mL) dramatically reduce the consequences of potential reaction runaway scenarios, while the continuous nature of the process enables real-time monitoring and immediate response to

process deviations. Furthermore, the excellent heat transfer characteristics of microreactors allow for precise temperature control even during highly exothermic reactions, with the dimensionless parameter

$$\beta = \frac{-\Delta Hrxn \times de}{4\Delta T \times k}$$

(where ΔHrxn is reaction enthalpy, de is channel diameter, ΔT is temperature difference, and k is thermal conductivity) serving as a criterion for thermal runaway prevention.

Solvent reduction and replacement strategies in flow chemistry benefit from the enhanced mass transfer characteristics inherent to miniaturized systems. The reduced diffusion distances in microchannels, typically on the order of 10-500 μm, enable complete mixing in microseconds compared to seconds or minutes required in batch systems. This enhanced mixing efficiency permits the use of less aggressive solvents or solvent-free conditions, while the telescoping capabilities of flow systems eliminate intermediate isolation steps that would otherwise require additional solvents for workup and purification.

5.2 Green Metrics Analysis and Quantitative Assessment

The quantitative assessment of environmental impact through green metrics provides essential tools for evaluating and optimizing the sustainability of chemical processes, with particular relevance to CF synthesis methodologies. The most fundamental and widely applied metrics include the E-factor, PMI, AE, and RME, each offering unique perspectives on process greenness and efficiency.

The E-factor, defined as E = (Total waste mass)/(Product mass), serves as the primary metric for waste quantification, providing a direct measure of process efficiency from an environmental perspective. In CF systems, E-factors consistently demonstrate dramatic improvements compared to batch processes, primarily due to reduced solvent usage, elimination of intermediate isolation steps, and enhanced reaction selectivity. The relationship between E-factor and other metrics becomes apparent through the equation PMI ≈ E + 1 (when all in-process water is counted as waste, otherwise minor deviations occur), highlighting the interconnected nature of these assessment tools.

PMI represents a comprehensive measure that accounts for all materials input into a process, calculated as PMI = (Total input mass)/(Product mass). The pharmaceutical industry has adopted PMI as a standard benchmarking tool, with typical values ranging from 25-200 for complex active pharmaceutical ingredients. CF processes consistently achieve lower PMI values through several mechanisms: reduced solvent requirements due to enhanced mass transfer, elimination of chromatographic purification steps, and the ability to telescope multiple synthetic steps without intermediate isolation.

AE provides a theoretical upper limit for process efficiency, calculated as AE = (Molecular weight of desired product)/(Molecular weight of all reactants) × 100%. While AE represents an intrinsic property of the chemical transformation, flow chemistry can approach theoretical AE more closely than batch processes through improved reaction control and reduced side product formation. The enhanced selectivity achievable in flow systems stems from precise temperature control, optimized residence time distribution, and the ability to rapidly quench reactions at optimal conversion levels.

RME integrates multiple factors including yield, AE, and stoichiometric efficiency, providing a holistic assessment of process performance. The calculation of RME involves complex considerations of catalyst recovery, solvent recycling, and auxiliary material usage, making it particularly valuable for evaluating the overall sustainability impact of process modifications. Flow chemistry enables improved RME through enhanced catalyst utilization (particularly in packed-bed configurations), solvent recycling capabilities, and reduced auxiliary material requirements.

The dramatic improvements achievable through flow chemistry become evident when comparing quantitative metrics across different synthetic methodologies, as demonstrated in comprehensive case studies of complex organic transformations.

5.3 Reactor Design and Process Intensification Fundamentals

The fundamental principles governing reactor design in CF systems encompass complex interactions between fluid dynamics, heat and mass transfer, and chemical kinetics, requiring sophisticated understanding of transport phenomena at the microscale. The design optimization process must consider multiple competing factors including pressure drop, residence time distribution, mixing efficiency, and heat transfer performance.

Microreactor design begins with the fundamental relationship governing pressure drop in microchannels, described by the Hagen-Poiseuille equation for laminar flow:

$$\Delta P = \frac{32\mu L v}{d^2}$$

where μ is dynamic viscosity, L is channel length, v is average velocity, and d is channel diameter. This relationship demonstrates that pressure drop scales inversely with the fourth power of channel diameter, creating significant design constraints for very small channels while highlighting the importance of optimizing channel geometry for specific applications.

Heat transfer in microreactors follows the relationship

$$Nu = \frac{hd}{k}$$

where Nu is the Nusselt number, h is the heat transfer coefficient, d is the characteristic dimension, and k is thermal conductivity. For developing laminar flow in microchannels, correlations such as

$$Nu = 1.86\left(\frac{Re \times Pr \times d}{L}\right)^{\frac{1}{3}}$$

apply, where Pr is the Prandtl number. The enhanced heat transfer achievable in microreactors enables the use of reaction conditions that would be impractical in batch systems, including superheated solvents, cryogenic conditions, and rapid thermal cycling.

Mass transfer enhancement in microreactors results from the combination of short diffusion distances and optimized flow patterns. The mass transfer coefficient km scales approximately as $km \propto D/\delta$, where D is the molecular diffusivity and δ is the characteristic diffusion distance. In microchannels with dimensions of 100-500 μm, diffusion times scale as $\tau \propto \delta^2/D$, yielding mixing times on the order of milliseconds compared to seconds or minutes in batch systems.

Packed-bed microreactors represent a specialized category that combines the advantages of heterogeneous catalysis with the benefits of CF processing. The design of packed-bed systems requires careful consideration of the relationship between particle size, channel

diameter, and void fraction to optimize both catalytic performance and transport properties. The catalyst effectiveness factor η = (observed reaction rate)/(reaction rate without mass transfer limitations) provides a key design parameter, with values approaching unity indicating optimal design.

The selection of reactor materials becomes critical in microreactor design due to the high surface-to-volume ratios and potential for enhanced corrosion or fouling. Common materials include stainless steel, Hastelloy, and various ceramic compositions, each offering specific advantages for particular applications. The surface properties of reactor materials can significantly influence both heat transfer performance and catalyst stability in packed-bed configurations.

5.4 Advanced Flow Reactor Configurations and Applications

The evolution of flow reactor technology has led to increasingly sophisticated designs that address specific challenges in process chemistry while maintaining the fundamental advantages of continuous processing. These advanced configurations include multi-stage reactor systems, integrated separation units, and hybrid reactor designs that combine multiple unit operations within a single continuous process.

Multi-stage reactor systems enable the implementation of complex synthetic sequences through telescoping strategies that eliminate intermediate isolation and purification steps. The design of such systems requires careful consideration of residence time requirements for each reaction stage, compatibility of reaction conditions, and the potential for intermediate degradation or side reactions. Successful implementation of multi-stage systems can result in dramatic improvements in overall process efficiency, with space-time yields often exceeding those of corresponding batch processes by factors of 10-100.

Integrated separation and purification within flow systems represents a significant advancement in process intensification, enabling real-time product isolation and solvent recovery. Techniques such as continuous extraction, membrane separation, and crystallization can be integrated directly into the flow stream, eliminating the need for separate unit operations. The implementation of integrated separations requires careful design to maintain steady-state operation while achieving acceptable separation efficiency.

Temperature and pressure management in advanced flow systems enables access to novel process windows that are impractical or impossible in batch systems. Superheated processing, where solvents are maintained above their normal boiling points through pressurization, enables accelerated reaction kinetics while maintaining solution-phase conditions. The precise pressure control achievable in flow systems, typically using back-pressure regulators, enables operation at pressures ranging from vacuum to hundreds of bar with excellent stability.

Real-time monitoring and control systems represent essential components of advanced flow reactor implementations, enabling autonomous operation and real-time optimization. Analytical techniques including online HPLC, IR spectroscopy, and NMR can be integrated directly into flow streams to provide continuous feedback on reaction progress and product quality. This real-time information enables implementation of closed-loop control systems that can automatically adjust reaction conditions to maintain optimal performance.

5.5 Oxindole Derivatives via CF Reductive Alkylation

The CF reductive alkylation of oxindole represents a paradigmatic example for how advanced flow chemistry can transform traditionally challenging synthetic transformations into highly efficient, environmentally sustainable processes. This methodology demonstrates the comprehensive integration of green chemistry principles, advanced reactor design, and quantitative sustainability assessment in a single, coherent synthetic approach that addresses critical pharmaceutical intermediates.

5.5.1 Process Development and Reactor Engineering Fundamentals

The development of the CF oxindole alkylation methodology focused on the implementation of a packed-bed reactor system utilizing Raney nickel catalyst, enabling safe handling of this pyrophoric material while maximizing catalytic efficiency. The reactor configuration employed an HPLC column (4.6 mm inner diameter, 250 mm length) packed with approximately 800 mg of Raney nickel, integrated with a GC oven for temperature control and a back-pressure regulator for pressure management.

The comprehensive optimization study revealed optimal reaction conditions of 220°C, 120 bar pressure, and 0.5 mL/min flow rate, corresponding to a residence time of 2.7 minutes. These conditions represent a carefully balanced compromise between reaction

efficiency and catalyst stability, with temperature optimization showing a maximum conversion plateau at 220°C followed by significant degradation at 300°C due to thermal decomposition and 7-methylation side reactions. The pressure dependence study demonstrated optimal performance at 120 bar, with further pressure increases providing no additional benefit.

The flow rate optimization revealed a critical relationship between mixing efficiency and residence time, with the optimal 0.5 mL/min flow rate providing maximum conversion of 97% for the model ethylation reaction. This optimization considered thermal expansion effects in residence time calculations, ensuring accurate process control parameters. The productivity achieved under these conditions reached 1.2 g/h, representing a significant improvement over traditional batch processing methods.

Building upon these carefully optimized reaction conditions, the environmental and economic advantages of the CF methodology become clearly evident through comprehensive sustainability analysis. The integration of green chemistry principles with advanced process control enables quantitative assessment of environmental benefits that extend far beyond simple yield optimization, demonstrating how process intensification translates directly into measurable sustainability improvements.

Sustainability Metrics and Environmental Impact Assessment

The environmental benefits of the CF methodology become evident through comprehensive green metrics analysis, demonstrating substantial improvements across multiple sustainability indicators. The catalyst utilization efficiency represents a particularly impressive achievement, with 800 mg of Raney nickel enabling the processing of approximately 20-23 g of oxindole during continuous operation periods of 16-19 hours.

The turnover number (TON) of 29 and turnover frequency (TOF) of 1.45 h^{-1} indicate exceptional catalyst productivity, particularly significant given the use of an inexpensive, widely available heterogeneous catalyst. These metrics demonstrate the fundamental advantage of CF processing in maximizing catalyst utilization while minimizing waste generation.

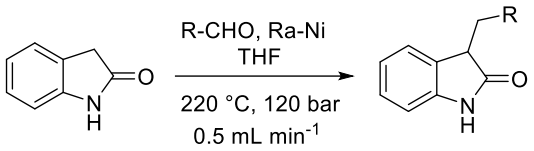

Figure 9.
Alkylation of oxindoles

Table 3.
Yields of CF alkylations of oxindole with alcohols

R	yield of isolated product (%)
H	95
Me	96
Et	77
Pr	46

PMI calculations reveal dramatic improvements compared to traditional batch methodologies, with the CF approach achieving PMI values of 50-65 for alcohol-based alkylation reactions, representing a 150-200 fold reduction compared to conventional oxindole alkylation procedures which typically exceed PMI values of 10,000. These values are consistent with the aldehyde series PMI range (33.70-59.27), demonstrating the method's uniform efficiency across different substrate classes.

The alcohol-based reactions demonstrated remarkably consistent environmental profiles with PMI values (50-65) that closely parallel the aldehyde series (33.70-59.27), confirming the uniform efficiency of the borrowing hydrogen mechanism across different substrate classes. The slight increase in PMI for longer alcohols reflects the higher stoichiometric excess required (1:5 ratio) compared to aldehydes (1:2 ratio), while still maintaining exceptional sustainability compared to batch processes. These PMI calculations account for all input materials including catalyst, solvents, and reagents, providing a comprehensive assessment of the environmental impact per unit of product generated.

For aldehyde-based alkylations, PMI values ranged from 33.70–59.27 depending on substrate complexity and required purification procedures. The higher PMI values for

certain aldehyde reactions reflect the need for additional equivalents and more extensive purification protocols yet still maintain substantial advantages over conventional synthetic approaches. Notably, the borrowing hydrogen mechanism in aldehyde reactions relies on water decomposition for hydrogen generation, contributing to overall process sustainability while maintaining excellent AE through the elimination of external hydrogen sources.

Systematic analysis of substrate performance reveals important structure-activity relationships that guide both substrate selection and reaction optimization strategies. Aliphatic aldehydes consistently demonstrate superior performance compared to aromatic counterparts, with yields of 71-89% reflecting the electronic neutrality that facilitates both condensation kinetics and subsequent reduction efficiency.

The dramatic yield difference between benzaldehyde (86%) and 4-methoxybenzaldehyde (42%) highlights the profound sensitivity of the Knoevenagel condensation step to electronic effects. The electron-donating methoxy group reduces the electrophilicity of the carbonyl center, thereby lowering the efficiency of condensation and diminishing the overall reaction performance. Conversely, electron-withdrawing trifluoromethyl-substituted benzaldehydes promote the condensation by increasing carbonyl activation, as evidenced by the favorable yields (67–68%). In addition to these electronic factors, superior yields with benzaldehyde may also result from enhanced surface interaction with the catalyst: benzaldehyde's nearly planar structure allows effective adsorption onto the Ra–Ni surface, whereas the three-dimensional shape of trifluoromethyl-substituted derivatives impedes efficient alignment and interaction. Furthermore, the yield of reactions involving fluorinated substrates can be influenced by the presence and reactivity of aluminum species within the catalyst, potentially affecting outcomes with fluorine-containing reagents.

Chain length effects in aliphatic aldehydes show minimal impact on reaction efficiency, with C2-C5 substrates maintaining consistently high yields (71-89%). This performance consistency validates the mechanistic robustness and suggests broad applicability across pharmaceutical intermediate structures. The slight decrease observed with longer chains likely reflects increased steric hindrance during the condensation step rather than fundamental mechanistic limitations.

Notably, the formation of dimethylated byproducts with formaldehyde represents a unique challenge attributed to competing 7-methylation reactions, as previously observed in batch studies. This selectivity issue necessitates careful optimization for methylation reactions or consideration of alternative synthetic approaches for this specific transformation.

The space-time yield improvements become particularly evident in the context of pharmaceutical manufacturing, where the CF methodology enables processing rates that would require significantly larger reactor volumes in batch mode. The 82% isolated yield achieved for 22.6 g of 3-ethyloxindole during the 19-hour continuous run demonstrates both process efficiency and scalability potential.

5.5.2 Mechanistic Elucidation and Reaction Pathway Analysis

The mechanistic investigation of the CF reductive alkylation reveals a sophisticated multi-step process involving sequential oxidation, condensation, and reduction transformations. For alcohol-based alkylations, the Raney nickel catalyst functions simultaneously as an oxidizing agent (converting alcohols to aldehydes), a basic catalyst (promoting Knoevenagel condensation), and a reducing agent (hydrogenating the resulting alkene intermediate).

The "borrowing hydrogen" mechanism represents a particularly elegant aspect of this transformation, where hydrogen generated during alcohol oxidation is subsequently consumed in the reduction step, eliminating the need for external hydrogen sources. This integrated approach significantly reduces both the environmental footprint and operational complexity of the process.

For aldehyde-based alkylations, the mechanism involves direct Knoevenagel condensation followed by catalytic reduction, with deuterium labelling experiments confirming water as the hydrogen source. The deuteration studies using D_2O-washed Raney nickel demonstrated extensive deuterium incorporation, yielding products with Gaussian-like mass distributions centred around M = 229, indicating the presence of mono- to nonadeuterated molecules.

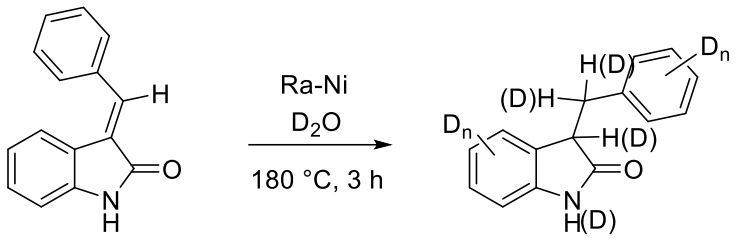

Figure 10.
The reduction of benzylidene derivative (isolated as a single isomer) was executed in an autoclave with aqueous Ra-Ni catalyst rinsed several times with D2O prior to the reaction.

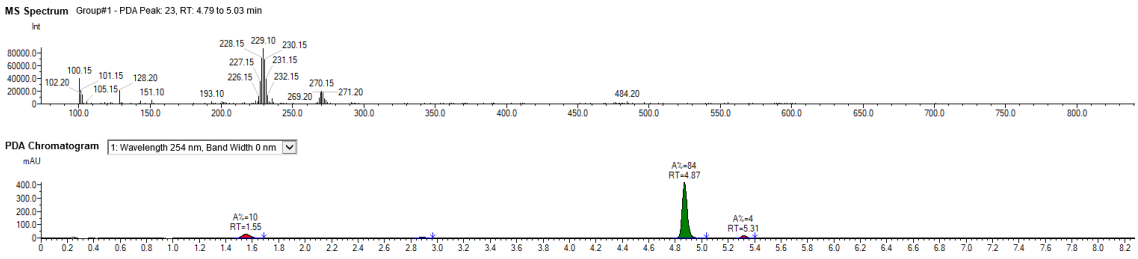

Figure 11.
LC-MS data of deuterated 3-benzyloxindole

The deuterium incorporation pattern observed in LC-MS analysis provides definitive evidence for the proposed borrowing hydrogen mechanism, with the Gaussian-like mass distribution (centred around M = 229) indicating statistical hydrogen/deuterium exchange during the reduction step. This exchange pattern confirms that multiple hydrogen atoms from the catalyst-bound water source participate in the reduction process, supporting the hypothesis that water decomposition generates the reducing equivalents necessary for efficient C=C bond saturation.

The complete absence of monodeuterated products when using D_2O-washed catalyst demonstrates the exclusive reliance on catalyst-bound water for hydrogen generation, effectively eliminating alternative hydrogen sources such as solvent decomposition or preexisting catalyst surface hydrides. This mechanistic clarity enables rational optimization strategies for different substrate classes and provides confidence in process scalability and reproducibility.

Furthermore, the statistical nature of deuterium incorporation suggests rapid equilibration between hydrogen sources, indicating that the reduction step proceeds through multiple hydrogen transfer events rather than a single concerted process. This insight has important

implications for understanding catalyst requirements and optimizing reaction conditions for maximum efficiency.

5.5.3 Catalyst Performance and Deactivation Mechanisms

XPS analysis of fresh and used catalyst samples provided crucial insights into catalyst deactivation mechanisms. The complete disappearance of metallic aluminium content and dramatic reduction in the surface Ni-Al ratio from 0.9:1 to 0.05:1 indicated progressive catalyst degradation through aluminium oxidation and nickel leaching.

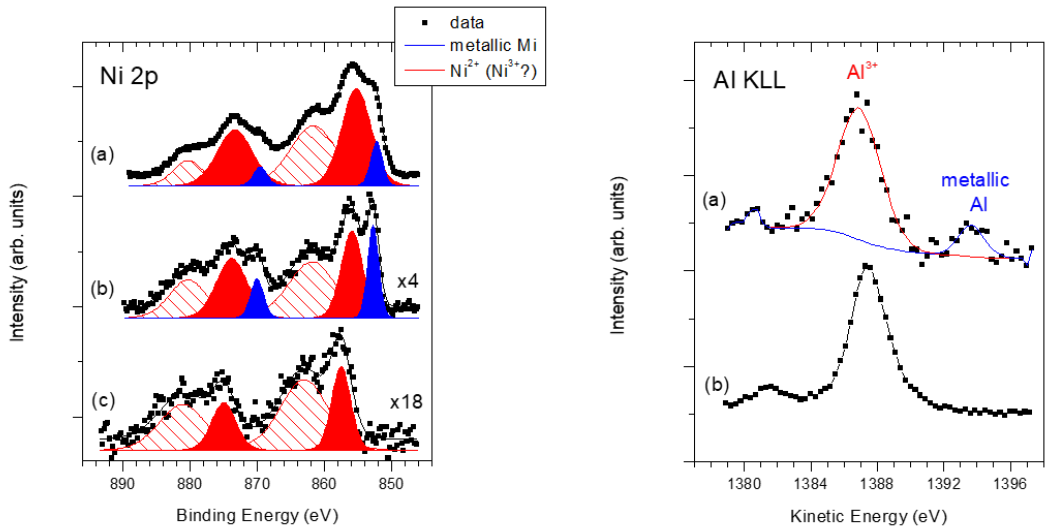

Figure 12.
Ni 2p and Al KLL spectra of the samples are compared

The left panels display Ni 2p XPS spectra of (a) the initial Ra-Ni catalyst; (b) the used catalyst recovered after the reaction and (c) the crude reaction product. The spectra were normalized to the same intensity for comparability by using the factors indicated on the right. Red features are assigned to ionic Ni (predominantly to Ni^{2+} although a mixture of Ni^{2+} and Ni^{3+} states cannot be ruled out); shaded bands are satellites accompanying the main peaks.

The right panels present Al KLL Auger electron spectra of (a) the initial Ra-Ni catalyst; (b) the used catalyst recovered after the reaction.

This mechanistic understanding enables rational approaches to catalyst improvement and process optimization.

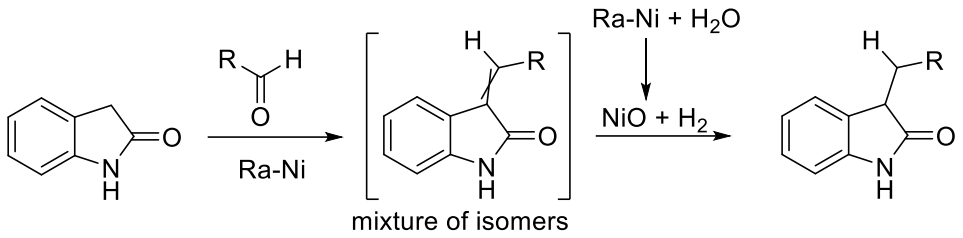

Figure 13.
Exploration of the hydrogen source of the C=C reduction step

The comprehensive mechanistic understanding of the borrowing hydrogen pathway, supported by deuterium labelled studies and catalyst characterization, provides essential insights for predicting substrate compatibility and optimizing reaction conditions across diverse molecular architectures. This fundamental knowledge enables systematic exploration of substrate scope while maintaining the environmental and efficiency advantages established through rigorous process optimization.

5.5.4 Substrate Scope and Synthetic Applications

The substrate scope investigation demonstrates broad applicability across diverse alcohol and aldehyde partners, with isolated yields ranging from 40% to 96% depending on substrate structure and reaction conditions. Alcohol-based alkylations showed decreasing efficiency with increasing chain length, yielding 95% for methanol, 96% for ethanol, 77% for propanol, and 46% for butanol. This trend reflects the increasing steric hindrance and potential for competing side reactions with longer-chain alcohols.

Aldehyde-based alkylations demonstrated more consistent performance across the substrate range, with aliphatic aldehydes generally providing good to excellent yields. Aromatic aldehydes showed variable performance, with benzaldehyde achieving 84% yield while 4-methoxybenzaldehyde yielded only 42% due to electronic effects influencing the condensation step. The successful alkylation with 4-trifluoromethyl and 3-trifluoromethyl benzaldehydes (67% and 69% yields respectively) demonstrates tolerance for electron-withdrawing substituents.

Formaldehyde presented unique challenges due to the formation of dimethylated byproducts, likely involving 7-methylation reactions as observed in previous batch studies. The formation of 3,7-dimethyloxindole as a significant byproduct necessitates careful optimization for methylation reactions or alternative synthetic approaches.

The broad substrate applicability demonstrated across structurally diverse alcohol and aldehyde partners validates the fundamental robustness of the CF methodology and the versatility of the borrowing hydrogen mechanism. However, long-term operational stability represents a critical parameter for industrial implementation, requiring systematic evaluation of catalyst performance and process durability under extended reaction conditions to establish clear benchmarks for manufacturing viability.

5.5.5 Process Scale-up and Industrial Implementation

Catalyst deactivation studies reveal gradual performance degradation after approximately 16-19 hours, attributed to aluminium oxidation and framework disruption rather than simple poisoning effects. This mechanistic understanding suggests potential improvement strategies through catalyst reformulation or regeneration procedures. The ability to process 20-23 g of starting material with a single catalyst charge represents remarkable efficiency for a heterogeneous catalytic system.

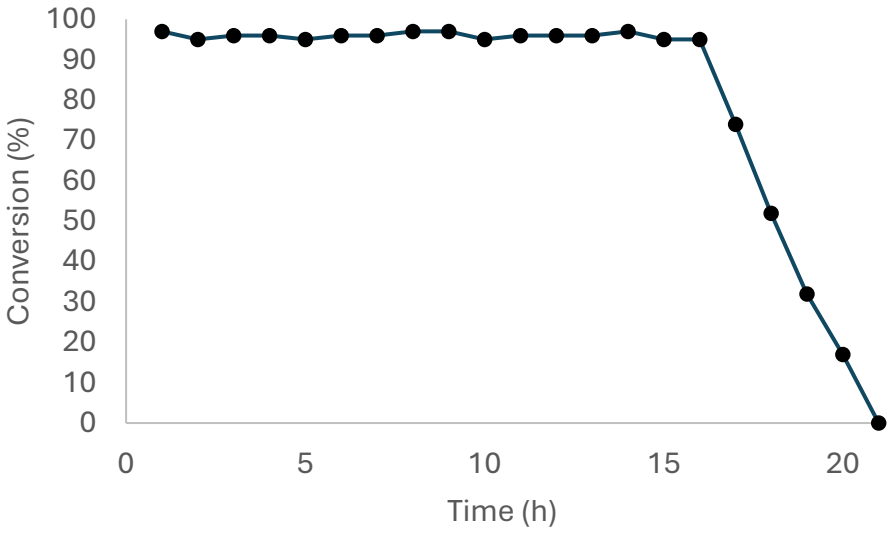

Figure 14.
The conversion values found in continuous running of the reaction of oxindole and acetaldehyde under the optimized conditions

The sustained conversion maintenance over 16-19 hour operational periods represents exceptional performance for a heterogeneous catalytic system operating under demanding reaction conditions. The demonstrated ability to process 22.8 g of starting material with a single 800 mg catalyst charge establishes clear benchmarks for industrial viability, with catalyst productivity metrics (TON = 29, TOF = 1.45 h^{-1}) comparing favourably with

precious metal catalysts while maintaining the significant economic advantages of readily available Raney nickel.

The gradual decline in activity after extended operation, from 95% to approximately 75% conversion over the final operational hours, correlates directly with XPS-observed changes in catalyst composition. This performance profile suggests primarily reversible catalyst deactivation rather than catastrophic poisoning, indicating significant potential for catalyst regeneration strategies that could further extend operational lifetime and improve overall process economics.

The linear nature of the activity decline supports the aluminium oxidation mechanism proposed based on surface analysis, where progressive loss of metallic aluminium reduces the catalyst's basic character necessary for efficient Knoevenagel condensation promotion. Understanding this deactivation pathway enables rational approaches to catalyst improvement through aluminium stabilization or alternative support materials.

Scale-up validation through numbering-up approaches demonstrates clear pathways for larger-scale implementation while maintaining the fundamental advantages of microreactor operation. The modular reactor design enables flexible capacity adjustment based on production requirements, providing a practical bridge between laboratory development and industrial manufacturing.

The scalability demonstration through numbering-up approaches indicates potential for larger-scale implementation through parallel reactor operation. This strategy maintains the advantages of microreactor operation while achieving production rates suitable for pilot-scale or manufacturing applications. The modular nature of the system enables flexible capacity adjustment based on production requirements.

6 Conclusions

6.1 Conclusions from Green Chemical CF Synthesis

Process Intensification Through Miniaturization

CF chemistry achieves dramatic improvements in heat and mass transfer through miniaturization, with microreactors providing surface-to-volume ratios of 8,000-15,000 m^{-1} compared to 60 m^{-1} for batch reactors. The geometric advantage where surface area scales as length squared while volume scales as length cubed enables rapid temperature control and enhanced safety. This miniaturization allows access to novel process windows including superheated conditions and flash chemistry applications. The precise control over residence time and reaction parameters leads to increased selectivity and reduced waste generation.

Telescoping and AE Enhancement

Multi-step synthesis telescoping in flow eliminates intermediate isolation steps, dramatically reducing solvent consumption and improving overall process efficiency. The integration of solid-supported reagents, catalysts, and scavengers within flow systems enables quantitative conversions while minimizing catalyst waste. Real-time in-line analytics provide continuous feedback enabling immediate optimization and reduced byproduct formation. This approach achieves significant improvements in E-factors with some applications showing 80-90% waste reduction compared to batch methods.

Catalysis Integration and Safety Enhancement

Packed-bed microreactors enable safe handling of pyrophoric catalysts while maximizing interfacial area and improving catalyst lifetime through reduced environmental exposure. The continuous removal of products minimizes catalyst poisoning and side reactions while enabling high reagent excess to drive reactions to completion. The closed-system operation with minimal headspace eliminates safety risks associated with dangerous intermediates. Heterogeneous catalysis in flow systems demonstrates superior performance with enhanced mass transfer and simplified product isolation.

Future Directions and Standardization Needs

The integration of artificial intelligence with flow chemistry enables autonomous optimization and real-time process control, dramatically reducing experimental requirements for optimization. Standardization of green metrics and assessment methodologies remains crucial for enabling meaningful cross-platform comparisons. The development of renewable energy integration and circular economy principles represents the next frontier for sustainable flow chemistry. The combination of these advances positions flow chemistry as a transformative technology for sustainable chemical manufacturing.

6.2 Conclusions from the CF Reductive Alkylation of Oxindole

Process Robustness and Catalyst Efficiency

The CF methodology demonstrates exceptional robustness with sustained operation for 16-19 hours processing over 20 g of starting material using only 800 mg of Raney nickel catalyst. The TON of 29 and TOF of 1.45 h^{-1} represent remarkable catalyst productivity for an inexpensive heterogeneous system. The packed-bed reactor configuration enables safe handling of pyrophoric catalysts while optimizing mass transfer and residence time distribution. The productivity of 1.2 g/h establishes clear benchmarks for economic viability and industrial scalability.

Mechanistic Understanding and Hydrogen Economy

The borrowing hydrogen mechanism elegantly eliminates external hydrogen requirements through integrated oxidation-reduction cycles utilizing water as the hydrogen source. Deuterium labelling experiments confirm the reaction pathway and demonstrate extensive deuterium incorporation from D_2O-washed catalyst. X-ray photoelectron spectroscopy reveals catalyst deactivation mechanisms through aluminium oxidation and nickel framework disruption. This mechanistic understanding provides rational approaches for catalyst improvement and process optimization while enabling prediction of catalyst lifetime.

Substrate Scope and Reaction Limitations

The methodology demonstrates broad applicability across diverse alcohol and aldehyde substrates with isolated yields ranging from 40-96% depending on substrate structure. Alcohol-based alkylations show decreasing efficiency with increasing chain length while

aromatic aldehydes exhibit variable performance based on electronic effects. The formation of dimethylated byproducts with formaldehyde reveals reaction limitations requiring optimization. The consistent regioselectivity at the C(3) position across all substrates confirms the method's predictable nature for synthetic planning.

Scalability and Industrial Potential

The successful scale-up demonstration through extended continuous operation addresses critical industrial adoption concerns while maintaining conversion efficiency. The numbering-up approach enables proportional scaling without compromising microreactor advantages, providing a pathway to larger production scales. The straightforward reactor design using commercially available components reduces implementation barriers. The combination of high productivity, catalyst efficiency, and operational robustness demonstrates clear industrial viability for pharmaceutical and fine chemical applications.

6.3 Conclusions from Peptide Synthesis Using Propylene Carbonate Research

Green Solvent Implementation and PMI

The successful replacement of DMF with propylene carbonate (PC) achieves dramatic reductions in PMI from over 10,000 for classical SPPS to 434-693 for CF methodology. PC selection based on GSK solvent guidelines demonstrates compatibility with automated peptide synthesis while maintaining high yields and purity. The two-order-of-magnitude reduction in solvent consumption compared to classical methods represents a paradigmatic shift toward sustainable peptide manufacturing. These PMI values approach those of small molecule synthesis, positioning peptides as viable pharmaceutical candidates.

Synthesis Time and Efficiency Optimization

CF peptide synthesis achieves 5-8 fold reductions in synthesis time compared to classical batch methods through optimized residence times and automated operation. The optimized conditions of 70°C, 60 bar pressure, and 5-minute residence time enable quantitative coupling with minimal amino acid equivalents (1.5 equivalent). The elimination of manual intervention and continuous processing significantly reduces overall synthesis time while maintaining product quality. This efficiency gain enables rapid peptide library synthesis and accelerated drug discovery timelines.

Scale-up Validation and Column Geometry Optimization

Successful scale-up from 0.07 mmol to 1.5 mmol scale demonstrates linear scalability while maintaining consistent PMI values and product quality. Column geometry calculations enable precise control over resin loading and flow rates to maintain optimal residence times across different scales. The production of >4 g peptide quantities in less than 6 hours synthesis time validates industrial applicability. The consistent performance across multiple scales confirms the robustness of the methodology for pharmaceutical manufacturing applications.

Environmental Impact and Sustainability Metrics

The quantitative environmental assessment demonstrates that CF methodology using PC achieves sustainability metrics comparable to small molecule synthesis. Solvent consumption measured in milliliters rather than liters represents a fundamental improvement in environmental footprint. The combination of reduced synthesis time, minimal solvent use, and high efficiency aligns with green chemistry principles while maintaining pharmaceutical-grade quality. These improvements position the methodology as a sustainable alternative for large-scale peptide production in pharmaceutical applications.

7 Summary

This dissertation demonstrates how continuous-flow (CF) technology transforms oxindole 3-alkylation and solid-phase peptide synthesis into environmentally superior processes through quantitative green chemistry metrics.

The oxindole program employed a packed-bed CF reactor successfully synthesizing ten 3-alkyloxindoles in 67-96% isolated yields from alcohols/aldehydes without external H_2. For alcohol substrates, direct use as both solvent and alkyl source achieved PMI values of 50-65 with productivity reaching 1.2 g/h, while aldehyde reactions in THF with 2 equiv. substrate delivered 67-91% yields using water from Ra-Ni as the H_2 source via borrowing hydrogen mechanism confirmed through D_2O labeling studies. The catalyst demonstrated remarkable efficiency (TON 29, TOF 1.45 h^{-1}) during 16-19 h continuous operations processing >20 g substrate with minimal deactivation tracked by XPS analysis revealing Ni-Al surface ratio decline from 0.9:1 to 0.05:1.

The SPPS program utilized propylene carbonate as green solvent in a CF achieving synthesis of four α-peptides (91-96% yields, ≥95% crude purity) and five challenging β-/α-β-peptides (86-93% yields, ≥96% purity) using only 1.5 equiv. amino acids. This methodology delivered PMI values of 434-693, representing 20-fold reduction vs. batch SPPS (PMI >10,000), while gram-scale syntheses maintained linear PMI retention, validating industrial scalability. Solvent consumption dropped by two orders of magnitude with synthesis times reduced to 5-8 h compared to 35-140 h in batch processing.

Both programs exemplify CF's environmental superiority through quantitative assessment: E-factors dropped below 20 (vs. 10-110 batch) and PMI values fell to pharmaceutical-relevant ranges through telescoped sequences, inline purification, and elimination of intermediate isolations. Process intensification enabled space-time yields of 1.2 $g \cdot h^{-1}$ for oxindole and 0.7 $mmol \cdot h^{-1}$ for peptides, validating industrial scalability through numbering-up strategies. This work establishes CF processing as a mature platform for sustainable pharmaceutical synthesis, jointly satisfying nine of the twelve principles of green chemistry while providing quantitative benchmarks for industrial adoption and positioning CF chemistry as the foundation for next-generation pharmaceutical manufacturing.

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9. Bibliography of the candidate's publications

9.1 Full papers related to the thesis

I. **András Mándoki**, György Orsy, Zoltán Pászti, Márta Porcs-Makkay, Dóra Bogdán, Gyula Simig, István Mándity, Balázs Volk
Continuous-Flow Regioselective Reductive Alkylation of Oxindole with Alcohols and Aldehydes in a Fast and Economical Manner
Synthesis, **2023**, 55.23: 4025-4033. IF.:2,2
DOI: doi.org/10.1055/a-2122-4080

II. Nikolett Varró, Beáta Mándityné Huszka, Eszter Erdei, **András Mándoki**, István M. Mándity
Upscaled Synthesis of α- and β-Peptides in a Continuous-Flow Reactor Using Propylene Carbonate as an Eco-Friendly Solvent
Chemistry-Methods, **2025**, 2500010. IF.:3,6*
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