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Button-Push On-Demand Synthesis for Rapid Optimization of Antiviral Peptidomimetics

Duanshuai Tian, Ting Wei Tan, Ronald Toh Kuan Hai, Gan Wang, Fadhil Peer Mohamed, Zhenyang Yu, Hwee Ting Ang, Weijun Xu, Qian Wen Tan, Pearly Shuyi Ng, Choon Heng Low, Boping Liu, Perlyn Quek Zekui, Joma Kanikadu Joy, Joseph Cherian, Frankie S Mak,* and Jie Wu*

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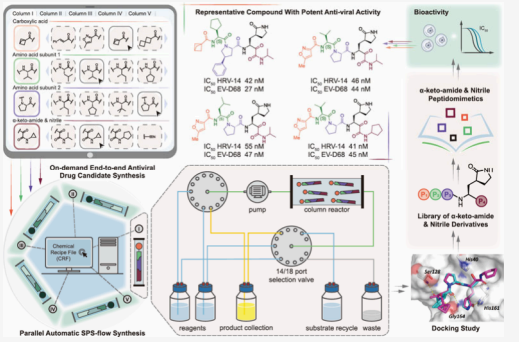
ABSTRACT: The optimization of hit compounds into drug candidates is a pivotal phase in drug discovery but often hampered by cumbersome manual synthesis of derivatives. While automated organic molecule synthesis has enhanced efficiency, safety, and cost-effectiveness, achieving fully automated multistep synthesis remains a formidable challenge due to issues such as solvent and reagent incompatibilities and the accumulation of side-products. We herein demonstrate an automated solid-phase flow platform for synthesizing α-keto-amides and nitrile peptidomimetics, guided by docking simulations, to identify potent broad-spectrum antiviral leads. A compact parallel synthesizer was built in-house, capable of producing 5 distinct molecules per cycle; 525 reactions could be finished within three months to generate 42 derivatives for a structure–activity relationship (SAR) investigation. Among these, ten derivatives exhibited promising target inhibitory activity (IC_{50} < 100 nM) including two with antiviral activity (EC_{50} < 250 nM). The platform, coupled with digital chemical recipe files, offers rapid access to a wide range of peptidomimetics, serving as a valuable reservoir for broad-spectrum antiviral candidates. This automated solid-phase flow synthesis approach expedites the generation of previously difficult complex molecular scaffolds. By integration of SPS-flow synthesis with medicinal chemistry campaign, >10-fold target inhibitory activity was achieved from a small set of derivatives, which indicates the potential to shift the paradigm of drug discovery.



INTRODUCTION

Since the initial outbreak of Severe Acute Respiratory Coronavirus (SARS-CoV-2) in early December 2019,[1] the world has witnessed over 690 million infections and nearly 7 million deaths.[2] This relentless pandemic has profoundly challenged healthcare systems and global economies, while significantly altering daily lives.[3,4] Meanwhile, infections caused by Enterovirus (EV) and Human Rhinovirus (HRV) have significantly impacted public health. Enteroviruses, a genus of positive-sense single-stranded RNA viruses, include polioviruses, coxsackieviruses, echoviruses, and newer enteroviruses such as EV-D68, which can cause illnesses ranging from mild respiratory infections to severe conditions such as aseptic meningitis, encephalitis, and acute flaccid paralysis. HRV, a member of the Picornaviridae family, is the most common viral infectious agent in humans and is the primary cause of the common cold. Insights gained from these infections are pivotal in reshaping the future of pharmaceutical development and public health strategy.[5] This situation underscores the critical need for a shift from conventional cumbersome and time-consuming drug discovery and development processes to more expeditious, streamlined approaches supported by innovative technologies.[6,7] Moreover, establishing a stockpile of broad-spectrum antiviral medications is crucial for quickly countering future viral outbreaks, enabling swift response and immediate availability of treatments.[8]

Promising compounds in the context of viral inhibition include peptidomimetics featuring α-keto-amide or nitrile groups as functional warheads.[9−12] These molecules are designed to mimic the natural substrates of viral proteases, which are crucial for viral replication. The α-keto-amides and nitrile warheads form reversible covalent bonds with viral proteases thereby disrupting viral replication leading to potent antiviral activity. Notable examples of α-keto-amide inhibitors include NS3 4A protease inhibitors such as boceprevir[13,14] and telaprevir,[15,16] both employed in the treatment of Hepatitis C Virus (HCV) infections. Another example is the class of chymotrypsin-related protease (3Cpro) or 3CLpro inhibitors, like GC375,[17] exhibiting activity against a range of viruses

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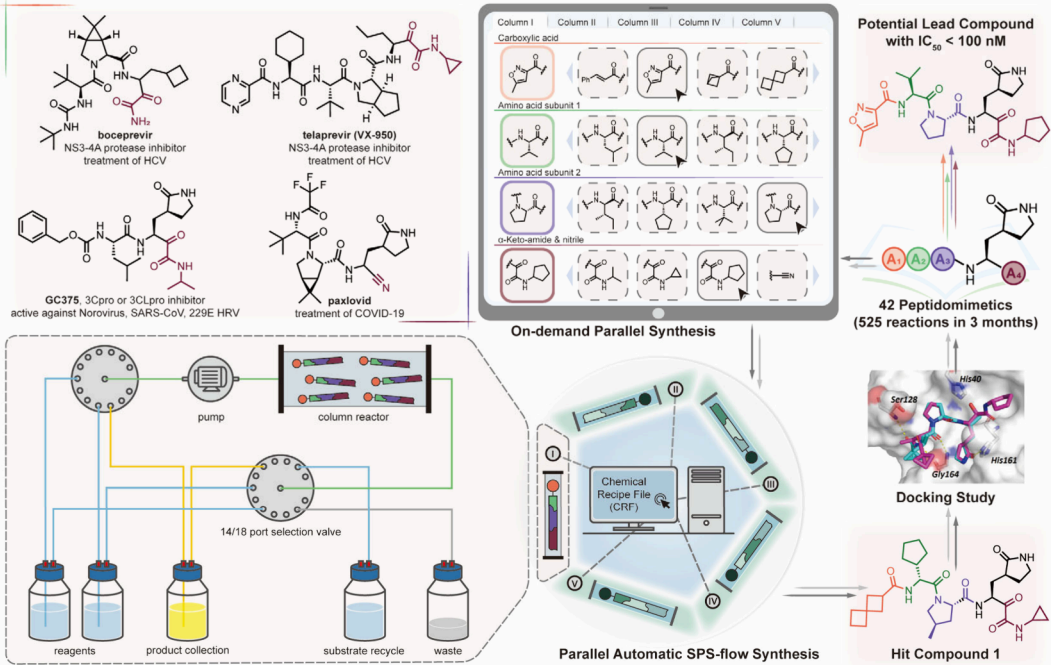

Figure 1. Development of a parallel automatic synthesis platform for the efficient synthesis of α-keto-amides and nitrile peptidomimetics with potent antiviral activity.

including norovirus, SARS-CoV, and Hand-Foot-and-Mouth Disease (HFMD) Virus. Nitrile-based peptidomimetics also exhibit broad-spectrum inhibition against 3CLpro from various coronavirus strains.[18] Of particular importance is paxlovid, a recently approved nitrile peptidomimetic, which has proven effective against SARS-CoV-2[19] (Figure 1).

While α-keto-amides and nitrile peptidomimetics hold significant potential as broad-spectrum antiviral agents, further investigations are needed to fully explore and optimize their therapeutic potential, considering the variability in the residues lining the binding pocket of the catalytic site of different viral proteases. Currently, the synthesis of these compounds predominantly relies on conventional batch solution-phase synthesis methods.[20] The inherent complexity of these compounds often leads to lengthy synthesis procedures with cumbersome postpurification campaign, largely limiting the synthetic efficiency and generating substantial waste. These challenges highlight the urgent need for innovative synthetic technologies that can enhance the efficiency and reduce waste generation. While transitioning from conventional batch solution-phase synthesis to automated pharmaceutical molecule assembly[21−26] is a promising solution, achieving fully automated multistep synthesis remains a formidable challenge. Issues such as incompatibility between different reaction steps, the accumulation of side-products, and the difficulties of implementing reliable automation systems capable of handling diverse reactions and reagents need to be overcome.

SPS-flow synthesis, a powerful amalgamation of solid-phase synthesis (SPS)—renowned for its widespread applications in the automated synthesis of peptides and oligonucleotides[27,28]—and flow reactor technology—increasingly recognized as an excellent tool for the automated synthesis of small molecule drugs[29]—presents a streamlined approach to automated multistep synthesis. The ease of purification between each step, facilitated by simple solvent washing in SPS, adeptly minimizes byproduct accumulation. This cohesive process not only enables efficient impurity removal but also effectively addresses challenges associated with compatibility between multiple reaction steps. On the other hand, due to the seamless integration with control systems, including pumps and valves, the flow system enhances the overall efficiency of SPS-flow synthesis, offering a convenient, efficient, and universally applicable methodology. This integration holds the promise of synergistically enhancing streamlined automation with broader reaction patterns and longer synthetic sequences. Compared with conventional SPS synthesis, SPS-flow synthesis offers several advantages. These include easy and precise process control, improved throughput, and enhanced consistency. Additionally, SPS-flow synthesis optimizes the mixing efficiency, leading to reduced reagent and solvent consumption. The Pentelute group has demonstrated the successful application of SPS-flow technology in the automated synthesis of peptides, proteins,[30] and oligonucleotide mimetics.[31] Recently, our group showcased the efficacy of this technology through a button-push, automated six-step synthesis of perxasertib and its derivatives.[32] The established Chemical Recipe File (CRF) can be seamlessly adapted for the on-demand automated synthesis of derivatives by strategically altering the starting building blocks at any step of the synthesis.

In contrast to traditional batch solution-phase synthesis, the SPS-flow platform demonstrates particular suitability for peptidomimetic synthesis, significantly reducing both time and manpower involvement by eliminating the need for laborious postpurification after each synthetic step. Moving forward, we anticipate that integration of SPS-flow technology with parallel synthesis and computer-aided drug design for the peptidomimetics synthesis holds the potential to significantly increase the chances of identifying effective drug candidates. This approach promises to expedite the hit optimization process, offering a time-efficient and resource-saving alternative to conventional resource-intensive combinatorial synthesis for chemical space exploration. The established digital CRF

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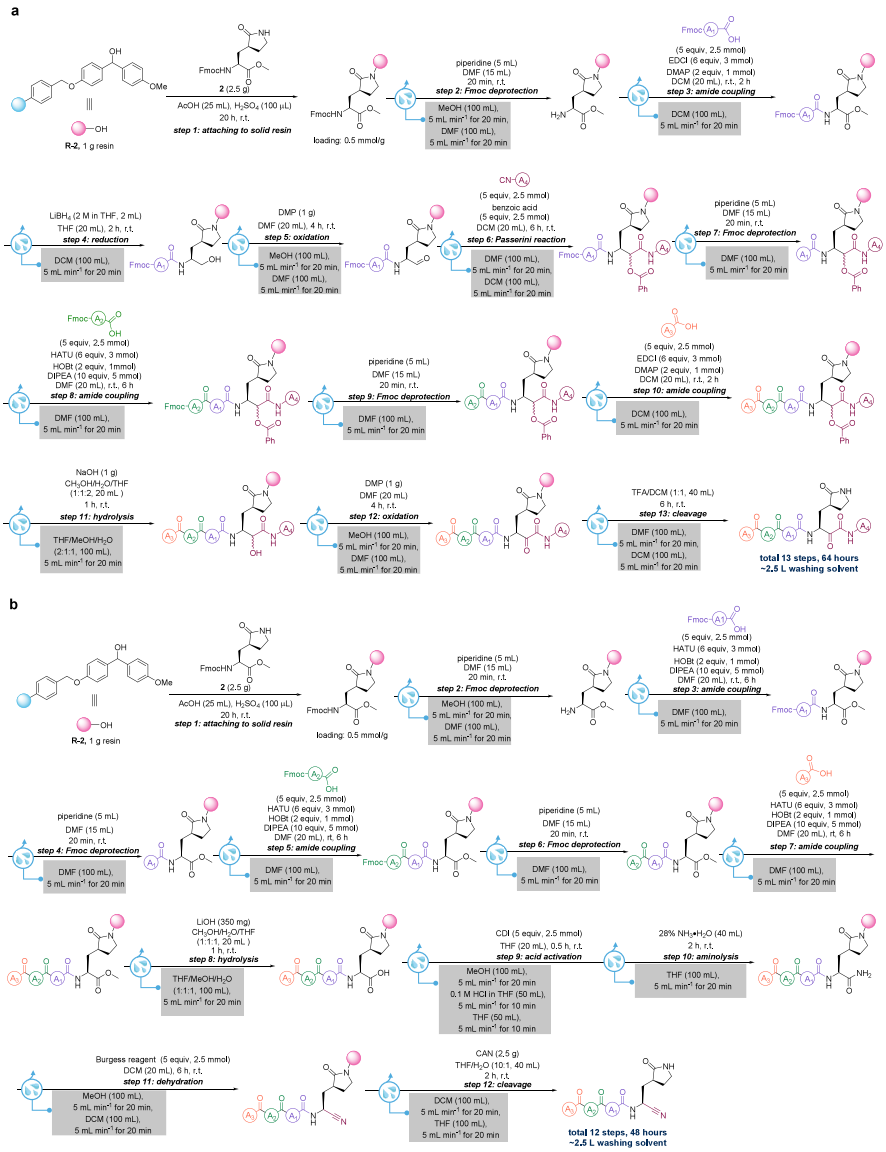

Figure 2. Schematic scheme of the established CRFs for the synthesis of α-keto-amide and nitrile compounds. (a) CRF for the synthesis of *a*-keto-amides. (b) CRF for the synthesis of nitrile compounds. Loading of the first step was confirmed by analysis of the ^{1}H NMR spectrum of the cleaved compound with 1,3,5-trimethoxybenzene as an internal standard. DMF, dimethylformamide; THF, tetrahydrofuran; DCM, dichloromethane; TFA, trifluoroacetic acid; EDCI, 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide; HATU, hexafluorophosphate azabenzotriazole tetramethyl uronium; DMAP, 4-dimethylaminopyridine; DMP, Dess−Martin periodinane; HOBt, 1-hydroxybenzotriazole; r.t., room temperature; DIPEA, *N*,*N*-diisopropylethylamine; CDI, 1,1′-carbonyldiimidazole; CAN, ceric ammonium nitrate.

provides the capability to directly generate any desired peptidomimetic compounds within the defined scaffold scope in a button-push fashion. These capabilities position this integrated platform as a valuable reservoir of candidate compounds for broad-spectrum antiviral agents, strategically prepared to address future pandemic challenges.

We herein report the successful implementation of SPS-flow technology for automated parallel on-demand synthesis of α-keto-amide and nitrile peptidomimetics guided by computational docking simulations, accelerating the hit-to-lead campaign for broad spectrum antiviral therapies (Figure 1). Our in-house-built compact synthesis platform, featuring five parallel column reactors, facilitated the simultaneous production of five distinct target compounds in a single run, allowing us to access a library of related structures within 3 months and thus perform a detailed SAR investigation. Out of 42 synthesized derivatives on this automated platform, ten compounds exhibited notable inhibitory activity (IC_{50} values below 100 nM) against 3Cpro in both Enteroviruses (EV) and Human Rhinovirus (HRV) (Figure S18), including two with antiviral activity (EC_{50} < 250 nM, Figure 4d). Additionally, the same platform, along with the established CRF, is readily applicable for scaling up the synthesis of potential lead compounds to several hundred milligrams for *in vivo* pharmacokinetics and pharmacology studies.

RESULTS AND DISCUSSION

Targeted Peptidomimetics Identification. EV and HRV infections are increasingly associated with severe outcomes, including neurological complications and fatalities, capturing the attention of the public and medical researchers.[33] However, there remains a lack of approved antiviral therapies

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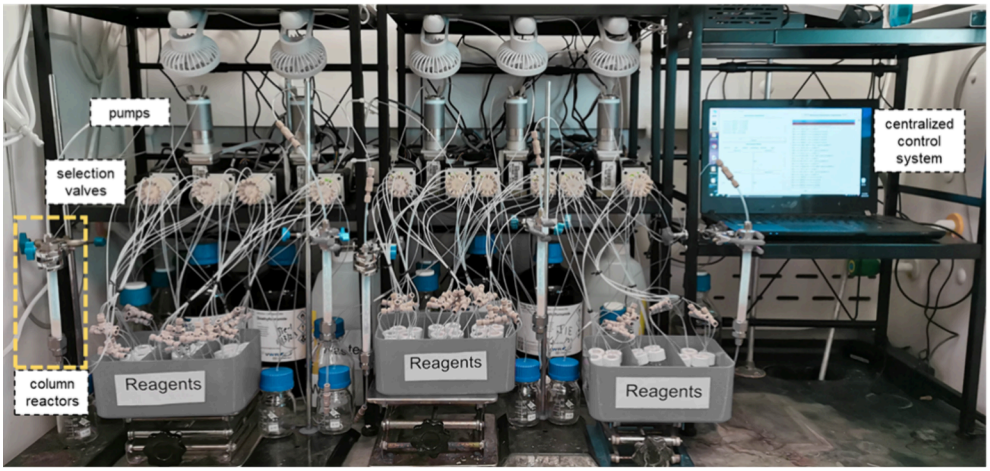

- ✓ Enabling automation with long synthetic steps: 13 steps for α-ketoamides; 12 steps for nitriles
- ✓ Enhanced productivity: 5 distinct target products within 2-4 days
- ✓ Minimized labour requirement: only 1 offline purification needed for each target derivative
- ✓ Reduced solvent usage: only ~2.5 liters of solvents needed for each target
- ✓ Compact footprint: within a single fume hood size

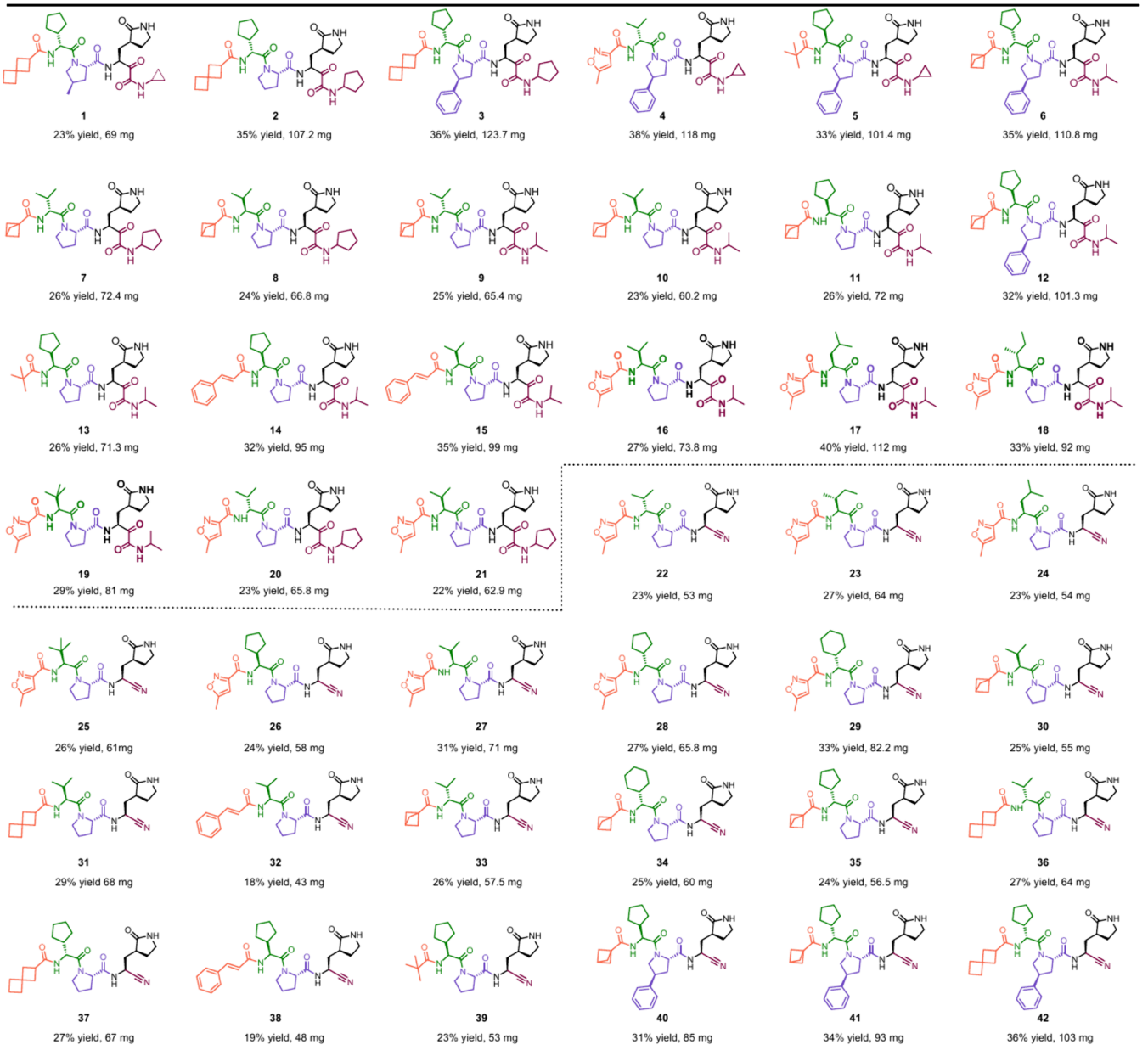

Figure 3. Setup of the SPS-flow synthesizer and automated synthesis of targeted 42 derivatives. For reagent/solvent-port connections, see Figure S11. The products were obtained from 1 g of the resin. The yields were based on loading of the starting materials (0.5 mmol/g).

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targeting these viruses, highlighting an urgent need for broad-spectrum antiviral compounds that target conserved elements that are essential for viral replication. In this case, our study started with identifying inhibitors of 3Cpro in EV and HRV. The 3Cpro enzyme is critical for proteolytic cleavage, transforming large proteins into functional proteins and enzymes essential for viral replication.[34] In our preliminary investigations of novel inhibitors of the SARS-CoV-2 3CLpro, we discovered that compound **1** effectively inhibited HRV 3Cpro, albeit with limited inhibitory activity against the SARS-CoV-2 3Clpro (IC_{50} > 100 μm). To explore the potential of compound **1** for broad-spectrum antiviral agents targeting 3Cpro, we performed a structural alignment and comparison based on a 3D superimposition of the active sites of 3C proteases across HRV-16, Coxsackie (COX)-B3, EV-D68, and EV-71. Using the rupintrivir-bound EV-D68 cocrystal structure as a reference (pdb: 7L8H), we observed a high degree of similarity in the amino acids surrounding the ligand (Figure S17). Armed with these insights, we embarked on a hit-to-lead campaign for compound **1**. The targeted compound structures include one carboxylic acid, two amino acids, and one α-keto-amide subunit, providing four variables for generating various derivatives in the hit-to-lead campaign. Additionally, although compound **1** is a α-keto-amide peptidomimetic, we leveraged the capabilities of the SPS-flow platform to explore compounds containing alternate warheads, such as a nitrile group, as a subseries.

Generation of Digital Chemical Recipe Files (CRFs) for the SPS-Flow Synthesis of α-Keto-Amide and Nitrile Peptidomimetics. The key to the success of automated SPS-flow synthesis lies in the rapid generation of robust and general CRFs. Despite the seemingly straightforward assembly of the scaffolds in compound **1**, we faced multiple challenges in establishing the CRFs. The first obstacle arises from the low reactivity of the amide functional groups in the targeted scaffolds, complicating the attachment of starting materials to solid resin. Additionally, the presence of several chiral centers in the scaffolds requires cautious synthetic conditions to prevent racemization.

Our study began with the development of an effective protocol for attaching the starting material to a solid resin and the subsequent convenient cleavage of the final product from the resin matrix (Figure S1). Notably, lactam **S-2** underwent an S_N1 reaction with diaryl alcohol in acetic acid to form compound **S-3** while preserving the chiral stereocenters. In the cleavage step, the C−N bond could be efficiently cleaved in TFA/DCM (1:1) without affecting the labile keto-amide functional group. These results suggested that using this approach to bind the initial lactam to a solid resin containing a diaryl alcohol linker and cleave the final product from the resin is feasible. Thereafter, to achieve the optimal reaction conditions for SPS, we established a 13-step synthetic protocol for batch solution-phase synthesis of the model α-keto-amide compound **2**, achieving an overall yield of 18.0% (Figure S4). However, the postreaction treatment is cumbersome, requiring a total of 10 rounds of column chromatography for purification. Noteworthily, all synthetic procedures were conducted under ambient conditions, which helps to suppress the epimerization of chiral centers and simplifies the subsequent setup of the SPS-flow system.

To transform the batch solution-phase synthesis into the SPS-flow synthesis, we modified Wang resin by introducing a diaryl alcohol linker, which was used as the solid matrix for the subsequent study (Figure S3). Gratifyingly, the pre-established conditions in batch solution-phase synthesis could be directly adapted to SPS-flow synthesis by incorporating simple solvent washing steps in between each step. It is worth noting that the remarkable solvent cleaning efficiency enables strategic use of excess reagents to ensure high yields (Figure S7 and Table S1). Significantly, the SPS-flow synthesis, comprising 13 steps, required only a single postpurification step following the final cleavage, where the crude reaction mixture was purified with preparative thin-layer chromatography (prep-TLC) to afford the pure target product **2** (107 mg from 1 g of resin) with an improved overall yield of 35%. Moreover, the entire process required only 2.5 L of solvent, marking a substantial reduction compared to that used in the batch solution-phase synthesis protocol. With the SPS-flow protocol established for compound **2**, a CRF was easily established for synthesizing α-keto-amide peptidomimetic derivatives (Figure 2a). Additionally, we successfully developed a CRF for the nitrile compounds without resorting to batch solution-phase synthesis by modifying the SPS-flow synthesis protocol of keto-amide **2**. Although the cleavage of nitrile peptidomimetics from the solid presented a unique challenge due to the instability of the nitrile group under acidic conditions, it was successfully addressed by employing oxidative cleavage ceric ammonium nitrate (CAN) as the oxidant (Figure 2b, Figure S9 and Table S2).

Establishment of the Parallel Automated Synthesizer and Automated Synthesis of Targeted 42 Derivatives. To further enhance the efficiency of the synthesis process and enable on demand button-push synthesis, an automated SPS-flow synthesizer featuring five parallel column reactors was established (Figure 3). The system is composed of five milligat pumps, ten multiway selection valves, five perfluoroalkoxy (PFA) column reactors (each equipped with frits featuring 200 mesh pores; Figure S6), and a Python-interfaced computer system (Figure S11). The synthetic protocol was digitally encoded using Python programming, outlining the process modules, fluid paths, stock solution and solvent locations, and flow rates. Based on the codes, the computer system manages the seamless coordination of all units, ensuring efficient transfer of reagents and solvents from designated stock locations to the column reactors. This process therefore enables the digital storage of the CRF, allowing for easy retrieval and implementation in the synthesis of peptidomimetic molecules, with the flexibility to modify any fragment on demand.

This custom-built platform is remarkably compact and can be fitted within a standard fume hood (70 cm width × 150 cm length × 90 cm height). The working process of this platform was showcased in the Supplementary Video. With this system, five distinct target compounds could be prepared within 4 days, each requiring only a single final purification, underscoring a significant improvement in efficiency and a substantial reduction in labor and resource expenditure compared to traditional batch solution-phase synthesis methods. In total, 525 reactions were thus operated within 3 months to afford 21 α-keto-amide and 21 nitrile peptidomimetics in moderate to good yields (Figure 3). Unlike current high-throughput systems limited to one- or two-step reactions, our platform handles multistep syntheses—13 steps for α-ketoamides and 12 steps for nitriles—which can modify different parts of the scaffold and not just a single point, surpassing existing capabilities and establishing it as a powerful tool for lead derivatization.

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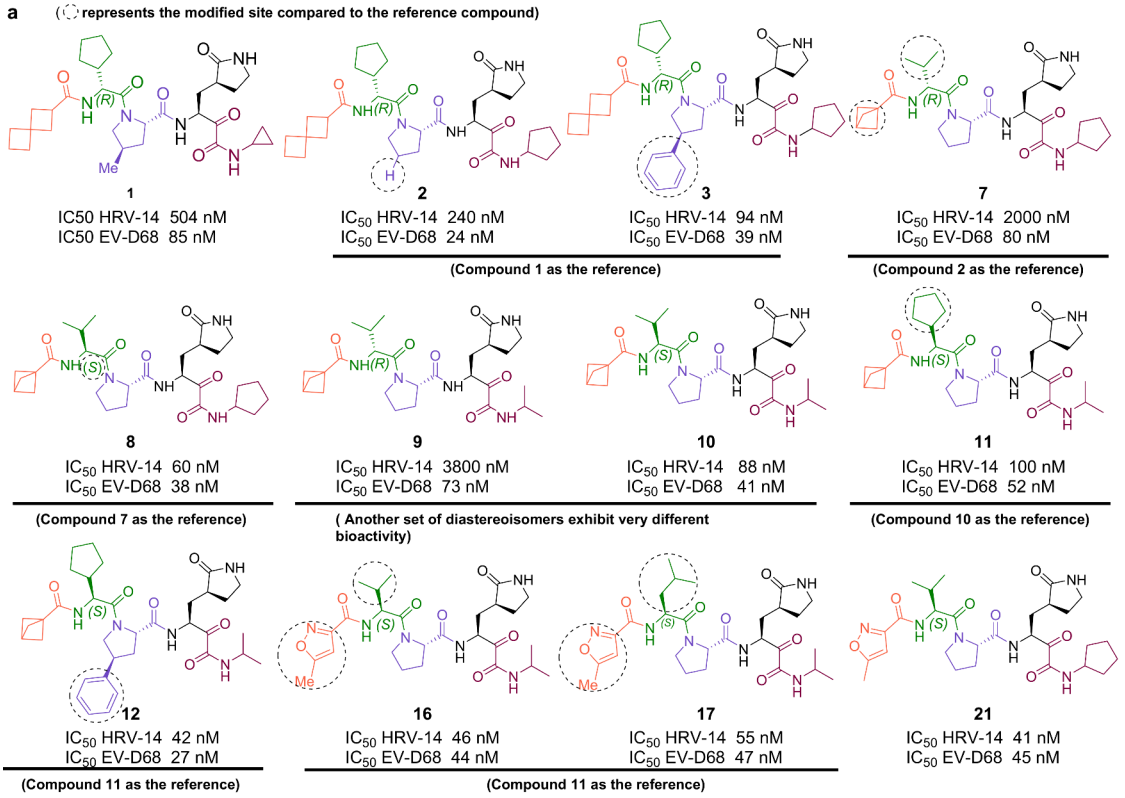

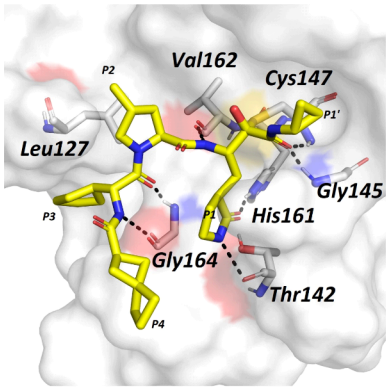

c

	Compound **3**	Compound **21**
Measured LogD pH 7.4	4.7	1.0
Thermodynamic solubility pH 7.4 (μg/mL)	110.3	979.4
PAMPA Pe 10-6 (cm/sec)	38.08	0.18
Cl_{int} HLM, RLM (μL/min/mg)	142, 62	0, 1
Plasma Stability H, R ($T_{1/2}$ - min)	>240	>240
PPB H, R (% unbound)	1.76, 0.64	50.7, 45.4

d

Compounds	EV virus assay EC_{50} (nM)	HRV virus assay EC_{50} (nM)	50% cytotoxicity concentrations CC_{50} (μM)
3	< 50	< 50	25
8	< 50	1400	> 50
11	< 50	1600	> 50
12	< 50	1400	> 50
21	< 50	220	> 50

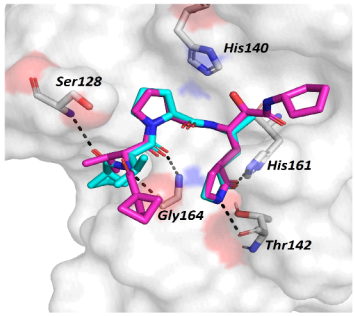

Figure 4. Structure−activity relationship (SAR) exploration. (a) IC_{50} values of selected compounds against HRV-14 and EV-D68 3C protease. (b) The docked pose of compound **1** with the crystal structure of HRV-16 3C protease (PDB code: 5FX6). The 5-membered lactam formed H-bond interactions with Thr142 and His161; amide oxygen of the ketoamide warhead interacted with the backbone NH group of both Gly145 and Cys147; NH of the amide bond between P2 proline and P1 glutamine made a H-bond contact with the backbone carbonyl oxygen of Val162, while the NH of the P3 amino acid residue formed a H-bond interaction with the backbone carbonyl oxygen from Gly164. The cyclopropyl moiety of the ketoamide warhead was surrounded by hydrophobic residues and likely formed beneficial van der Waal interactions. (c) *In vitro* ADME profile of compounds **3** and **21**. PAMPA: Parallel Artificial Membrane Permeability Assay; Cl_{int} HLM, RLM: intrinsic clearance Human Liver Microsomes, Rat Liver Microsomes; PPB H, R: Plasma Protein Binding Human and Rat. (d) EC_{50} values of selected compounds against HRV-14 and EV-D68 virus; 50% cytotoxicity concentrations (CC_{50}) of selected compounds. (e) Docked pose of **7** (purple) and **8** (cyan) with **8** showing additional interaction with Ser128.

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SAR Exploration. Developing structure−activity relationships (SARs) is paramount in the initial phases of drug discovery. By systematically altering the chemical structures of molecules and observing the resulting changes in their activity, researchers can identify key functional groups or structural motifs crucial for the desired biological effect. This process guides hit exploration and facilitates the identification and refinement of promising lead compounds with the potential to become viable drug candidates. Given the promising inhibitory activity of compound **1** against the EV-D68 3Cpro (IC_{50} 85 nM), our medicinal chemistry efforts pivoted toward identifying a lead compound with improved inhibitory activity against the HRV-14 3Cpro (Figure 4a).

Comparative bioactivity assessments revealed that α-keto-amide peptidomimetics outperformed nitrile peptidomimetics in target inhibitory activity (Figure S18). Out of the 21 synthesized α-keto-amide peptidomimetics, 12 representative compounds were shown to illustrate key SARs established from two rounds of optimization guided by computational modeling. Initial docking studies suggested that compound **1** formed a network of H-bond interactions with the HRV-16 3C protease (Figure 4b). While replacing the methyl group in compound **1** with a hydrogen and phenyl substituent showed only marginal improvements in IC_{50} values (**2** and **3**), compound **3** demonstrated potent antiviral activity against the HRV-14 virus with an EC_{50} value below 50 nM and low cytotoxicity, evidenced by a CC_{50} value of 25 μM (Figure 4d). Subsequent *in vitro* ADME (Absorption, Distribution, Metabolism and Excretion) profiling of **3** revealed its undesirable profile for *in vivo* studies, likely due to its high lipophilicity (Figure 4c). Reducing the size of cyclopentyl and spiro [3.3] heptyl in compound **2** to modulate lipophilicity resulted in significantly reduced potency (**7** - IC_{50} 2000 nM). Interestingly, the *S*-diastereomer of compound **7** was more potent (**8** - IC_{50} 60 nM), but it showed only modest activity against HRV-14 virus (EC_{50} 1400 nM, Figure 4d). This observation was further supported by testing another diastereomeric pair, where the *S*-diastereomer (**10** - IC_{50} = 88 nM) was again significantly more potent than its *R*-diastereomer (**9** - IC_{50} = 3800 nM). The observed increase in potency could be attributed to the specific interactions between Ser128 and Gly164 residues and the terminal peptide associated with the *S*-configuration. These interactions likely stabilize the binding conformation, enhancing the affinity of the compound for the active site. This was demonstrated by comparing the docking results of compounds **7** and **8** (Figure 4e). Compound **8**, featuring the *S*-configuration, exhibited a deeply embedded bicyclo-butyl group in the enzyme's S4 subpocket, along with the formation of an additional hydrogen bond with the backbone NH of Ser128. In contrast, compound **7**, possessing the *R*-configuration, showed a reorientation of its P3 amide bond and bicyclo-butyl group toward the solvent, likely diminishing favorable enthalpic interactions with the binding site residues. These results underscore the critical influence of terminal peptide stereochemistry on binding affinity and overall potency, emphasizing the need for precise stereochemical control in the design of potent peptidomimetic inhibitors. Based on these findings, a second round of optimization focused on derivatives that all possess the *S*-configuration. Notably, a close analogue to compound **10** with a cyclopentyl of *S*-configuration resulted in no potency and antiviral activity improvement (**11** - IC_{50} 100 nM; EC_{50} 1600 nM) and exploration of the P2 pocket in **12** with a phenyl substituent also showed a similar profile (IC_{50} 42 nM; EC_{50} 1400 nM). Subsequent efforts to replace the bicyclo[1.1.1]-pentyl group in compound **11** with a methyl isoxazole group and substituting the cyclopentyl group with an isopropyl or isobutyl group to increase conformational flexibility (**16** and **17**) did not lead to significant potency improvement. However, a closely related analogue **21** demonstrated good target potency, antiviral activity, and low cytotoxicity (IC_{50} 41 nM, EC_{50} 220 nM, CC_{50} > 50 μM, Figure 4d) with an improved *in vitro* ADME profile compared to compound **3** (Figure 4c). Based on the hit compound **1**, it is encouraging to identify a compound **21** with good antiviral activity and a decent *in vitro* ADME profile from a small set of analogues, which will guide the next phase of optimization leveraging our parallel automatic SPS-flow synthesis platform in a resource- and time-efficient manner.

Scaling up Synthesis. With compound **21** identified as the potential lead from this set of analogues, a larger amount of compound **21** is needed for upcoming *in vivo* pharmacokinetic and pharmacology studies. Through the established system with the CRF, we could directly synthesize over 350 mg of compound **21** by running the parallel reactors in one cycle by using the automated synthesizer.

CONCLUSION AND OUTLOOK

We have successfully established a SPS-flow parallel automatic synthesis platform that conveniently fits within a 1.5 m long fume hood. This platform encompasses five column reactors, enabling the simultaneous production of five distinct target products in a single operational cycle. This technological advancement significantly accelerates the lead optimization process by facilitating direct access to specifically designed derivatives for SAR studies within a short time frame. Two general CRFs were generated, leading to the synthesis of 21 α-keto-amides and 21 nitrile peptidomimetics within three months in a streamlined, button-push, on-demand fashion. The digitalized CRFs enable the rapid generation of targeted peptidomimetics by modifying any specific amino acid fragments, thereby positioning these CRFs as a valuable reservoir of broad-spectrum antiviral agents. Notably, ten out of the 42 synthesized compounds exhibited good bioactivity, exhibiting IC_{50} values of HRV-14 protease below 100 nM, including two with antiviral activity (EC_{50} < 250 nM). Additionally, the platform was directly applied to produce over 350 mg of compound **21** for future *in vivo* pharmacokinetics and pharmacology studies.

In conclusion, our platform has demonstrated its potential in establishing an extensive reservoir of peptidomimetics, thereby positioning itself as a pivotal tool for drug discovery scientists to facilitate the comprehensive investigation of the potential applications of these compounds in the antiviral field. This study also underscores the profound impact of integrating SPS-flow synthesis technology with medicinal chemistry-guided optimization; a >10-fold target inhibitory activity was achieved from a small set of derivatives, illustrating the potential to revolutionize drug discovery processes in pharmaceutical endeavors. Hence, our methodology represents a significant step forward in refining strategies to enhance human preparedness and response to future viral disease outbreaks.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c12834.

Full experimental procedures (PDF)

A video of the SPS-flow automated synthesis (MP4)

Accession Codes

The Python code for operating the SPS-flow automated synthesis in this study is available at https://github.com/tian-auto/automatic-SPS-Flow-synthesis-of--keto-amide-and-nitrile-peptidomimetics-.

■ AUTHOR INFORMATION

Corresponding Authors

Jie Wu − *Department of Chemistry, National University of Singapore, Singapore 117543; National University of Singapore (Chongqing) Research Institute, Chongqing 401120, China;* orcid.org/0000-0002-9865-180X; Email: chmjie@nus.edu.sg

Frankie S Mak − *Experimental Drug Development Centre, Singapore 138670*; Email: frankie_mak@eddc.sg

Authors

Duanshuai Tian − *Department of Chemistry, National University of Singapore, Singapore 117543*

Ting Wei Tan − *Department of Chemistry, National University of Singapore, Singapore 117543*

Ronald Toh Kuan Hai − *Experimental Drug Development Centre, Singapore 138670*

Gan Wang − *Department of Chemistry, National University of Singapore, Singapore 117543*

Fadhil Peer Mohamed − *Department of Chemistry, National University of Singapore, Singapore 117543*

Zhenyang Yu − *Department of Chemistry, National University of Singapore, Singapore 117543; National University of Singapore (Chongqing) Research Institute, Chongqing 401120, China*

Hwee Ting Ang − *Department of Chemistry, National University of Singapore, Singapore 117543*

Weijun Xu − *Experimental Drug Development Centre, Singapore 138670;* orcid.org/0000-0002-3566-1082

Qian Wen Tan − *Experimental Drug Development Centre, Singapore 138670*

Pearly Shuyi Ng − *Experimental Drug Development Centre, Singapore 138670;* orcid.org/0000-0002-2276-7953

Choon Heng Low − *Experimental Drug Development Centre, Singapore 138670*

Boping Liu − *Experimental Drug Development Centre, Singapore 138670*

Perlyn Quek Zekui − *Experimental Drug Development Centre, Singapore 138670*

Joma Kanikadu Joy − *Experimental Drug Development Centre, Singapore 138670*

Joseph Cherian − *Experimental Drug Development Centre, Singapore 138670*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c12834

Notes

The authors declare no competing financial interest.

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