ChemCatChem

Research Article
doi.org/10.1002/cctc.202201289

Chemistry Europe
European Chemical Societies Publishing

www.chemcatchem.org

Special Collection

Development of an Automated Platform for C(sp^3)–C(sp^3) Bond Formation via XAT Chemistry

Brenda Pijper,*[a] Irini Abdiaj,[a] Daniele Leonori,[b] and Jesus Alcázar*[a]

Increasing Fsp^3 in drug molecules is of high importance in the pharmaceutical industry to escape the flatland. However, there is a lack of diverse methods to introduce C(sp^3) into a molecule in library synthesis. In this work, we report the combination of continuous flow chemistry with photochemistry to create an automated platform for library synthesis using halogen atom transfer (XAT) reaction to increase Fsp^3 in drug molecules. The chemistry has a broad scope of alkyl halides and electron deficient alkenes. We report a library synthesis of 84 compounds with a productivity of 1.5 reactions per hour, a scope of 51 isolated compounds and the reproducibility and scalability of the chemistry. Providing an efficient automated tool to synthesize drug-like molecules with increased Fsp^3 in drug discovery and development.

Introduction

One of the increasing challenges in the pharmaceutical industry is the delivery of bioactive molecules at an increased pace with the appropriate physicochemical properties.[1] A key feature to improve the rate of compound synthesis is utilizing high throughput library synthesis where a set of analogues can be made and screened in a single experiment accelerating the building of the structure-activity relationship (SAR) as well as the structure-properties relationship (SPR). These approaches have been dominated over the last decade by a set of transformations: reductive amination, sulfonamide formation, Suzuki coupling, amide formation and nucleophilic substitution.[2] This fact limits the capability of library synthesis to access novel chemical space. For instance, there is a strong need for methodologies to increase the fraction of C(sp^3) in drug-like compounds (Fsp^3). An increased Fsp^3 in drug-like molecules impacts molecule properties, such as solubility and crystallinity.[3]

Efforts in the automated synthetic platforms for library synthesis in drug discovery have proven to be impactful allowing for the exploration of broader chemical space. Not only limited to that, but it also allowed results to be generated in a more efficient and reproducible way.[4] Nowadays, library synthesis is progressing and incorporating robotic platforms with high-throughput experimentation (HTE) to develop synthetic methodologies and user-friendly automation platforms capable of broadening the accessible chemical space.[5] However, these methodologies are often limited to C(sp^2)–C(sp^2) and to some extent to C(sp^2)–C(sp^3). There is a clear need to expand the toolbox to robust methods introducing C(sp^3)–C(sp^3) bonds.[2c,e]

One approach that has allowed access to previously unattainable chemical space is photoredox catalysis. Due to the high energy transfer from the absorbance of light, it facilitates reaction pathways that are not accessible via conventional methods.[6] But reproducibility and scalability of photochemical reactions are limited by the light penetration as dictated by the Lambert-Beer law, which highlights the need for robust photochemistry tools for automated library synthesis able to precisely control reaction parameters, such as individual light intensity and temperature, to get reliable results.[7]

In this regard, a tool that allows this full control of reaction parameters as desired for photochemical reactions is flow chemistry. In flow chemistry the reaction mixtures circulate through small-diameter tubing, exponentially increasing the surface-to-volume ratio over batch reactors.[8] The increased surface-to-volume ratio is advantageous when running photochemical reactions as it can overcome the limitation of light penetration. This improved irradiation may affect reaction reproducibility as mixtures can be irradiated uniformly and may grant access to library synthesis if reactions are run sequentially in an automated manner.[9]

Recently published by our group is an end-to-end automated library synthesis using our previously described photo-Negishi cross-coupling protocol to increase the Fsp^3 in drug-like molecules.[10] However, this automated methodology is limited to C(sp^2)–C(sp^3). To increase the diversity and applicability of methods available for library synthesis in continuous flow photochemistry, we selected amino alkyl radicals as halogen atom transfer (XAT) agents to activate alkyl halides for adaption to flow chemistry.[11] This method uses an organic photocatalyst 4CzIPN that undergoes a single electron transfer (SET) with inexpensive trialkyl amines as a radical source that abstracts a

[a] MSc. B. Pijper, Dr. I. Abdiaj, Dr. J. Alcázar
Discovery Chemistry
Janssen Pharmaceutical companies of J&J
Calle Jarama 75A, 45007 Toledo (Spain)
E-mail: bpijper2@its.jnj.com
jalcazar@its.jnj.com

[b] Prof. Dr. D. Leonori
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.202201289

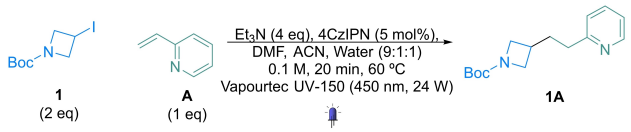
Special Collection *This publication is part of a Special Collection on "Catalysts in Industry". Please check the ChemCatChem homepage for more articles in the collection.*

halogen in the form of commercially available iodo alkanes (Supporting information, Figure S1).

Herein we report the adaptation of XAT chemistry in batch to automated library synthesis in continuous flow photochemistry to expand the library toolbox for the medicinal chemist to increase the Fsp^3 in drug discovery. Adaption from batch synthesis to flow is not straightforward. One key aspect is that everything is required to be in solution to avoid clogging the flow system and reactions need to be reoptimized to be adjusted to a flow format able to be used in library synthesis.[12] Screening the solubility of the different components allowed us to determine that DMF:ACN:H_2O (9:1:1) resulted in a homogeneous mixture suitable for running in a flow system and additionally showed the best conversion (Table 1 entry 1, 2, 3, Supporting information, Figure S2). After confirming the desired solvent mixture, we screened for optimal flow conditions by injecting the reaction mixture containing all components directly to the Vapourtec E-series equipped with a UV-150 photoreactor via a syringe pump. The outcoming solution was collected and analysed by LC/MS. We screened for temperature, and residence time, which were optimal at 20 minutes at 60 °C and 40 min 40 °C (Supporting information, Table S1). To increase the experimental throughput, we decided to run the reaction for 20 minutes at an elevated temperature. Photocatalysts were also assessed considering the new solvent system, however, the current catalyst was still the most suitable at 5 mol%. Base screening did confirm Et_3N as the best performing in the reaction (Supporting information Table S1). The main side product found in LC/MS analysis was the reaction of the radical intermediate formed after adding azetidine with the first molecule of 2-vinylpyridine to a second 2-vinylpyridine (Supporting information, Figure S3).[13]

This side-product indicated that the limiting step could be the second single electron transfer between the radical formed after the addition and the photocatalyst. To avoid forming this side product we opted to dilute the reaction from 0.1 M to 0.05 M, which resulted in a slightly improved conversion (Table 1, entry 6). However, the best results were obtained when the amount of **1** was reduced to 1 equivalent (Table 1, entry 9). Further optimization of equivalents of amine did not improve reaction outcomes. Control experiments without light, catalyst, base, or water showed no conversion to the desired product (Supporting information, Table S1).

Table 1. Optimization table.



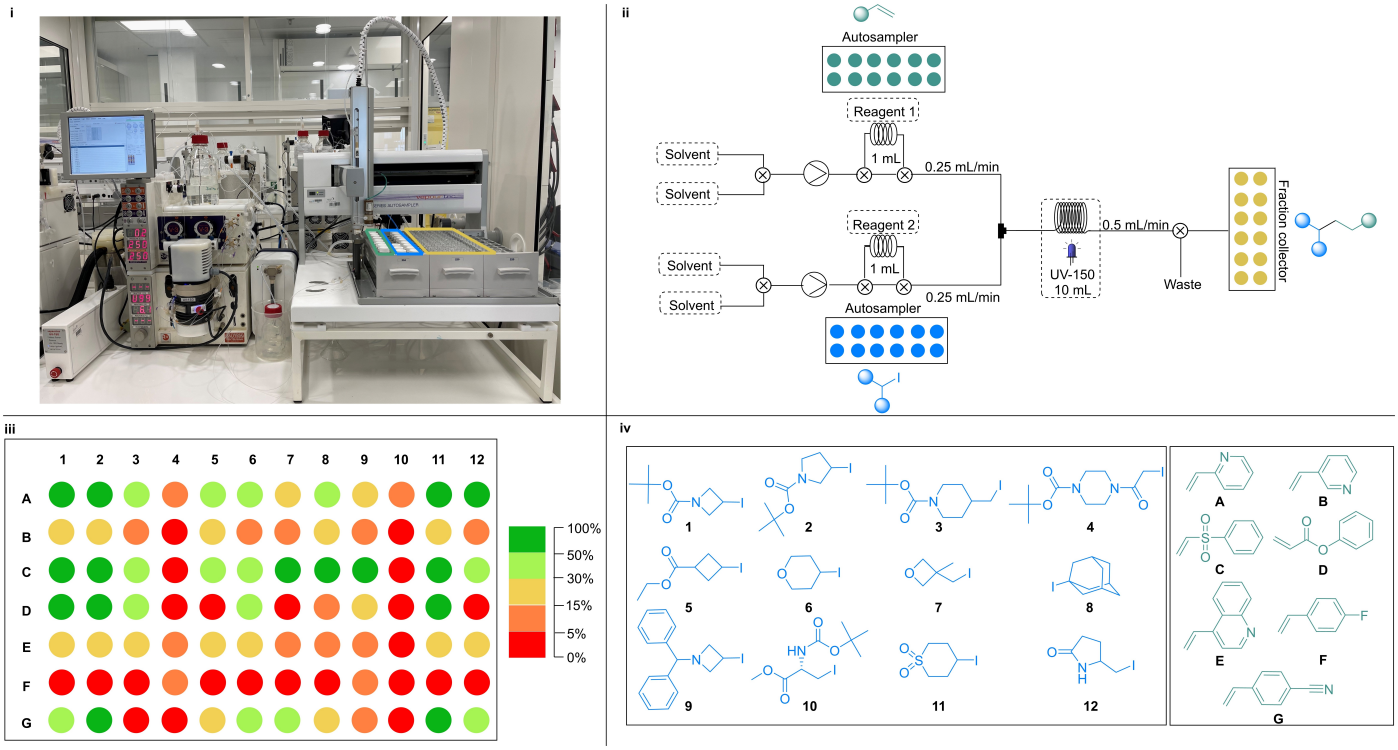
1 (2 eq) **A** (1 eq) **1A**

Entry	Variation	Conversion [%][a]
1	None	69
2	ACN:Water (10:1)	67
3	DMF:water (10:1)	68
4	2.5 mol% 4CzIPN	56
5	DIPEA	68
6	0.05 M	70
7	0.05 M, Et_3N:iodo (**1**) 3:1 (6 eq)	25
8	0.05 M, Et_3N: iodo (**1**) 1:1 (2 eq)	68
9	**0.05 M, 1:1 Iodo (1):Giese acceptor (A)**	**88**
10	0.05 M, 1:1.2 Iodo (1):Giese acceptor (**A**)	79

[a] LCMS conversion based on ratio between product/starting material/identified side-product.

After identifying the optimized conditions, we decided to explore the applicability of the reaction by developing a heatmap combining twelve alkyl iodides with seven vinyl derivatives. To allow all potential combinations to be run in a single experiment, reagents must be split into two lines. Placing the iodo-derivative in one solution and the other components in the other provided the best results (Supporting information, Table S2). For performing this heatmap, we used the automated Vapourtec instrument shown in Scheme 1i, where reagents were placed in the first rack (in blue), and reactions were collected in the other two racks (in yellow). The schematic set-up of the reaction is shown in Scheme 1ii. Twelve different iodo alkanes (blue) were selected based on their reactivity and substitution pattern (primary, secondary, and tertiary), and seven radical acceptors (turquoise) were selected on their electron-withdrawing nature (Scheme 1iv). Corresponding solutions were prepared and placed in the automated liquid handler. The software was programmed to do a matrix library combining all the alkyl iodides with all radical acceptors injected by the automated liquid handler. A total of 84 reactions were run over 56 hours, which equals 1.5 reaction output per hour. All the products were collected by the automated liquid handler and analysed by ^{1}H-NMR with an internal standard to measure conversion and create a representative heatmap (Scheme 1iii). NMR was used instead of LC/MS as UV absorption will depend on the final product structure. We decided that below 5% ^{1}H-NMR yield it would not be possible to isolate the product in high-throughput experimentation and thus results are presented in red. Above 5%–15% it is often still difficult but there is a possibility to get 1–5 mg for the biological tests in medicinal chemistry projects and thus we considered that as orange. The heatmap concludes that both **4** and **10** show little to no conversion with all vinyl analogues attempted (**A**–**G**). This could be explained by the lower nucleophilic character of their corresponding radicals to react with the electrophilic vinyl. Additionally, **F** showed that the electronegative character of fluorine is not enough to allow a radical addition step at the alkene. Moreover, the position of the nitrogen on the pyridine ring is important for the reaction. Alkene **A** provided higher yields than **B** because of the conjugation effect of the nitrogen towards the vinyl.

From results obtained in the heatmap we observed a discrepancy between LC/MS conversion used in Table 1 and NMR yield in Scheme 1. To clarify this difference, we wanted to determine if this could be due to lack of robustness of flow systems. For this purpose, we designed a set of experiments using the automated device with sample splitting to obtain compounds **28** and **29** and measure the conversion by ^{1}H-NMR using internal standard. Two different lamps (24 W and 60 W) were used to determine if low quantum yield of the reaction can influence final conversion at 0.2 mmol scale (Figure 1, blue bars).[11] We also wanted to compare these results with the



Scheme 1. i. Picture of the R2–R4 automated Vapourtec system with a liquid handler. ii. Schematic overview of the R2–R4 automated Vapourtec system with the iodo alkanes in blue and Michael Acceptors in turquoise, a UV-150 photoreaction with a 10 mL coil and the fraction collector in yellow. iii. Heatmap created with 12 iodo alkyl on row 1–12 and Michael acceptors on row A–G. iv. Corresponding structures of the heatmap.

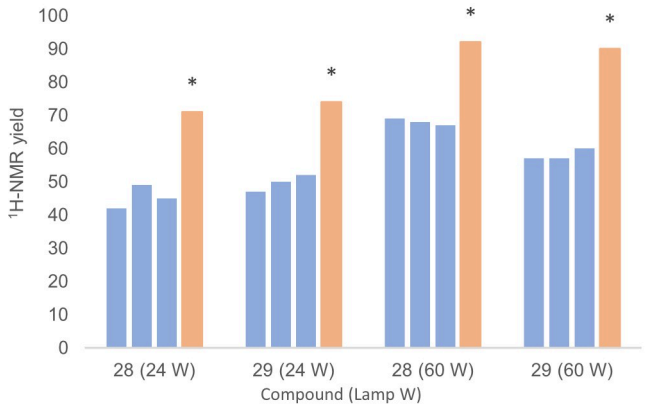
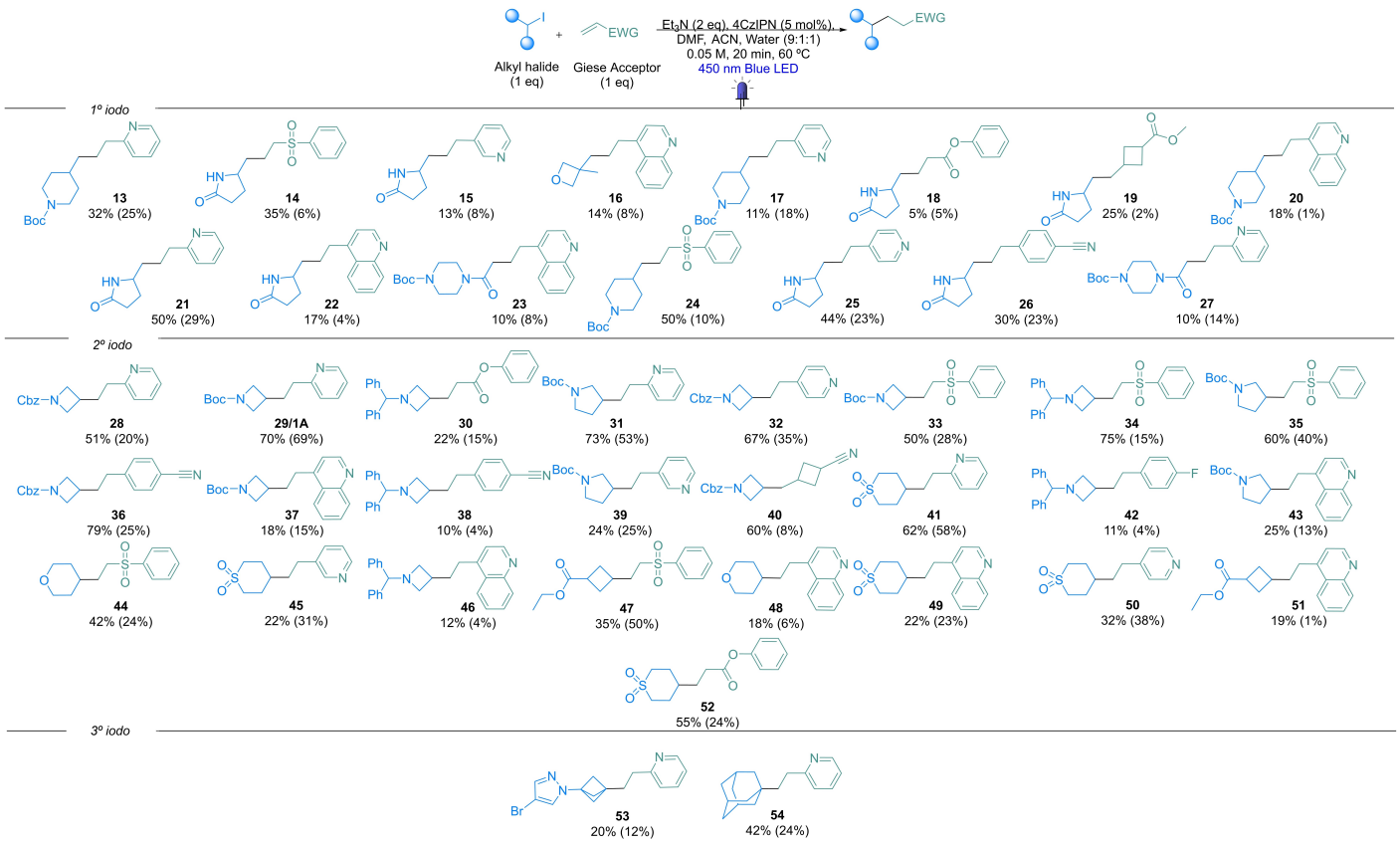


Figure 1. Reproducibility experiments measured in the automated Vapourtec of **28** and **29** and a comparison of 24 W and 60 W LED light. ^{1}H-NMR yield is measured with 1,3,5-trimethoxybenzene as internal standard. * Direct injection to the Vapourtec E-series equipped with the UV-150 photoreactor.

direct injection into the Vapourtec E-series equipped with a UV-150 photoreactor (Figure 1, orange bars). Results showed that reactions were reproducible depending on light intensity, improved with the 60 W light source. The difference in NMR yield observed between direct injection and automated mode can be explained by the combination of two factors: reactions were not run under steady state conditions and the larger dispersion in the automated system, as more tubbing was required due to splitting of reagents. Even though the reaction were not run under ideal conditions, the automated system proved to be robust.[14]

With all this information in hand, the focus was shifted towards the scope of the reaction. As the 60 W lamp performed slightly better than 24 W, scope exploration was executed in the automated instrument with the higher power lamp at 0.2 mmol scale, suitable for library synthesis. A wide variety of functionalized alkyl iodides can be introduced by this procedure, such as protected amine, heterocycles, cyclic sulfone, cyclic amide, cyclobutyl ester, oxetane and tetrahydrofuran (Scheme 2). Primary, secondary, and tertiary alkyl iodides of high interest in medicinal chemistry can be obtained with moderate to good yields. Not only selected examples of the heatmap are described, but also additional examples to expand the diversity such as the bicyclopentane (BCP) iodide provided the corresponding product **53**. BCP motif have been identified as bio isosteres of the phenyl ring, and methods to derivatize this structure are highly valued in drug discovery.[15]

In the case of the radical acceptors, we introduced various heterocycles, conjugated sulfones, and ring systems with conjugated electron withdrawal groups.[11] As shown in Scheme 2, styrenes were also found as suitable acceptors as long as they contain an electron-withdrawing group at the aromatic *para* position (CN: **26**, **36**, and **38**) or aliphatic cyclobutyl with an electron-withdrawing group *para* (ester: **19**, CN: **40**). Additionally, it is interesting to note the importance of

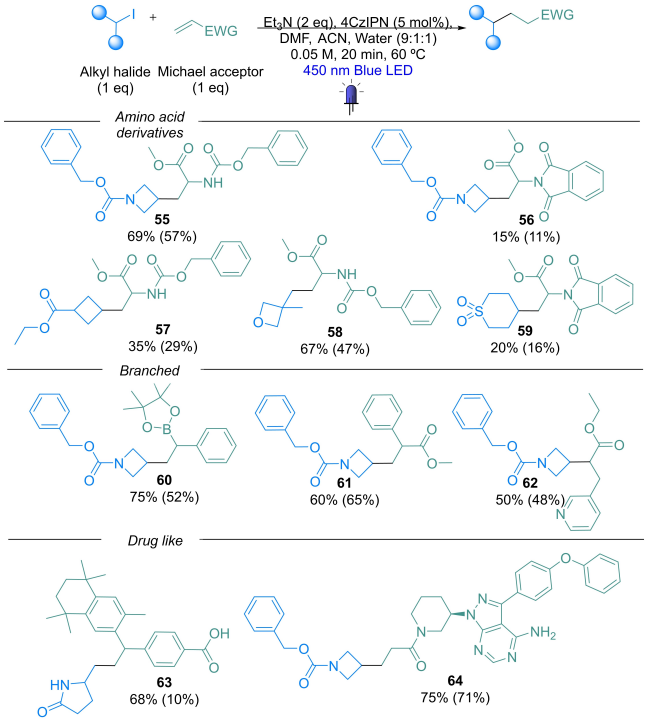


Scheme 2. Scope of 1° 2° and 3° iodo alkanes with various heterocycles, conjugated sulfones, and cyclobutenes. ^{1}H NMR yield (Isolated yield after reversed phase preparative LC/MS purification).[10a]

the nitrogen atom in pyridine derivatives. 2-vinylpyridine (**41**) provided higher yields than 3- (**45**) or 4-vinylpyridines (**50**). However, all the isomers provided the desired compounds.

We evaluated amino acid derivatives in this methodology, branched examples, and drug-like molecules to further expand the scope (Scheme 3). Unnatural amino acids are becoming important tools for modern drug discovery research as part of peptide chemistry or potential drugs on their own.[16] In previous work, Leonori and co-workers demonstrated the use of Boc-protected dehydroanaline as Giese acceptors.[11] We show that various amino-protecting groups are accepted in the system, such as Cbz (**55**, **57**, **58**) or phthalimide (**56**, **59**). Branched acceptors were also evaluated to expand the scope beyond terminal ones. Desired compounds were obtained in good yields (**60**–**62**). Finally, drug-like compounds, bexarotene, (**63**), a free acid used against cutaneous T cell Lymphoma (CTCL),[17] and kinase inhibitor Ibrutinib[18] (**64**) were selected to validate late-stage functionalization.

Finally, a scale-up experiment was performed to validate the relationship between ^{1}H-NMR yield and isolated yield (supporting information Figure S5). Compound **36** was selected as a suitable example to be scaled up due to the high NMR yield at 0.2 mmol scale in the scope. The experiment was performed in a Vapourtec E-series at a 7.7 mmol scale, an increase of 38 times in scale. The isolated yield of the reaction



Scheme 3. Scope of relevant amino acid derivatives, branched compounds, and drug like molecules purified by flash column chromatography. H NMR yield (isolated yield).

was 75% in accordance with the NMR yield measured at 0.2 mmol scale, 79%. 1.85 g of compound **36** was isolated, corresponding to 0.38 g/h or 1.5 mmol/h productivity. This successful scale-up highlights the scalability of the chemistry and the capability to move the chemistry among different machines.

Conclusion

In summary, we have demonstrated a robust and easy-to-implement approach for library synthesis to increase the Fsp^3 in drug discovery projects. The possibility of performing 84 reactions over 56 hours equals 1.5 products per hour productivity. The total isolated products in this study were 51, with a high diversity of functional group tolerance and a wide variety of primary, secondary, and tertiary alkyl iodides. Additionally, we have demonstrated that the chemistry is reproducible, transferable from one instrument to another, and easily scalable with a productivity of 1.5 mmol/h. We believe this approach will be of high value to increase Fsp^3 in library format for drug-like compounds to gain rapid access to novel structures.

Experimental Section

General procedure

Two solutions, vinyl (1 eq), Et_3N (2 eq), 4CzIPN (5 mol%) in a mixture of DMF, water, and ACN (0.1 M, 9:1:1) and Iodo alkyl (1 eq, 0.1 mmol) in DMF, water and ACN (0.1 M, 9:1:1). Both solutions were placed in the Autosampler of the Automatic R2–R4 Vapourtec reactor. Solution A was loaded to loop A and pumped at the flow rate of 0.250 ml/min. Solution B was loaded in loop B and pumped at the flow rate of 0.250 ml/min. Solution A and B were mixed in a T-mixer at a combined flowrate of 0.500 ml/min and was irradiated with blue LEDs 450 nm with 24 or 60 W, through a UV-150 Photoreactor with a coil of 10 ml (20 min of residence time) at 60 °C. The outcoming solution was collected into a fraction collector using the Autosampler. Then the solvent was evaporated in the GENEVAC. The solid was dissolved in $CDCl_3$ and 25% was taken for NMR yield, 75% was purified by preparative HPLC reversed phase separation.

Acknowledgements

We would like to thank Alberto Fontana, Marta Serrano Torne, Raquel Rodriguez Rodriguez, and Sergio Fernández Trujillo for providing support with the analysis and purification of the compounds, and Jose Manuel Alonso for the NMR support. Thanks to the European Union for the funding under the PhotoReAct Project, H2020 Marie Sklodowska-Curie grant agreement No 956324 (MSCA ITN: PhotoReAct).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Flow chemistry · Photochemistry · Library synthesis · Automation · Fraction sp^3

[1] a) J. P. Hughens, S. Rees, S. B. Kalindjian, K. L. Philpott, *Br. J. Pharmacol.* **2011**, *162*, 1239–1249; b) J. Lyu, S. Wang, T. E. Balius, I. Singh, A. Levit, Y. S. Moroz, M. J. O'Meara, T. Che, E. Algaa, K. Tolmachova, A. A. Tolmachev, B. K. Shoichet, B. L. Roth, J. J. Irwin, *Nature* **2019**, *566*, 224–229.

[2] a) A. W. Dombrowski, A. L. Aguirre, A. Shrestha, K. A. Sarris, Y. Wang, *J. Org. Chem.* **2022**, *87*, 1880–1897; b) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479; c) Y. Wang, I. Haight, R. Gupta, A. Vasudevan, *J. Med. Chem.* **2021**, *64*, 17115–17122; d) G. D. Brown, J. J. Boström, *Med. Chem.* **2016**, *59*, 4443–4458; e) A. W. Dombrowski, A. L. Aguirre, A. Shrestha, K. A. Sarris, Y. Wang, *ACS Med. Chem. Lett.* **2020**, *11*, 597–604.

[3] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756; b) W. Wei, S. Cherukupalli, L. Jing, X. Liu, P. Zhan, *Drug Discovery Today* **2020**, *25*, 1839–1845; c) T. Tsukamoto, *ACS Med. Chem. Lett.* **2013**, *4*, 369; d) W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.* **2011**, *54*, 6405; e) J. Meyers, M. Carte, N. Y. Mok, N. Brown, *Future Med. Chem.* **2016**, *8*, 1753; f) F. Lovering, *MedChemComm* **2013**, *4*, 515–519.

[4] a) G. Schneider, *Nat. Rev. Drug Discovery* **2018**, *17*, 97–113; b) L. van Hijfte, G. Marciniak, N. Froloff, *J. Chromatogr. B* **1999**, *725*, 3–15.

[5] a) C. N. Prieto Kullmer, J. A. Kautzky, S. W. Krska, T. Nowak, S. D. Dreher, D. W. C. MacMillan, *Science* **2022**, *376*, 532–539; b) N. Carson, *Chem. Eur. J.* **2020**, *26*, 3194–3196; c) A. Buitrago Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L. C. Campeau, J. Schneeweis, S. Berritt, Z. C. Shi, P. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher, *Science* **2015**, *347*, 49–53.

[6] a) T. Noël, E. Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468–476; b) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926; c) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103; d) T. Bach, J. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045; *Angew. Chem.* **2011**, *123*, 1032–1077; e) B. König, *J. Org. Chem.* **2017**, *2017*, 1979–1981; f) R. Cannalire, S. Pelliccia, L. Sancineto, E. Novellino, G. C. Tron, M. Giustiniano, *Chem. Soc. Rev.* **2021**, *50*, 766–897; g) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Chem. Rev.* **2017**, *1*, 0052.

[7] a) A. Yavorskyy, O. Shvydkiv, N. Hoffmann, K. Nolan, M. Oelgemöller, *Org. Lett.* **2012**, *14*, 4342–4345; b) K. Donnelly, M. Baumann, *J. Flow Chem.* **2021**, *11*, 223–241; c) K. C. Harper, E. G. Moschetta, S. V. Bordawekar, S. J. Wittenberger, *ACS Cent. Sci.* **2019**, *5*, 109–115; d) T. Noël, *J. Flow Chem.* **2017**, *7*, 87–93.

[8] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893; b) M. Guidi, P. H. Seeberger, K. Gilmore, *Chem. Soc. Rev.* **2020**, *49*, 8910–8932; c) M. Baumann, I. R. Baxendale, C. Kuratli, S. V. Ley, R. E. Martin, J. Schneider, *ACS Comb. Sci.* **2011**, *13*, 405–413; d) T. Fukuyama, T. Rahman, M. Sato, I. Ryu, *Synlett.* **2008**, *2*, 151–163; e) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318.

[9] a) E. López, M. L. Linares, J. Alcázar, *Future Med. Chem.* **2020**, *12*, 1–16; b) N. J. W. Straathof, T. Noël, in *Visible light Photocatalysis in Organic chemistry*, (Eds: C. Stephenson, T. Yoon, D. W. C. MacMillan), Wiley-VHC, Weinheim, Germany, **2018**, Chapter 13; c) K. Gilmore, P. H. Seeberger, *Chem. Rec.* **2014**, *14*, 410–418; d) C. Sambiagio, T. Noël, *Trends Chem.* **2020**, *2*, 92–106; e) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noël, *Chem. Rev.* **2022**, *122*, 2752–2906; f) A. Gioiello, A. Piccino, A. M. Lozza, B. Cerra, *J. Med. Chem.* **2020**, *63*, 6624–6647; g) A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* **2019**, *62*, 6422–6468; h) D. L. Hughes, *Org. Process Res. Dev.* **2018**, *22*, 13–20.

[10] a) I. Abdiaj, S. Cañellas, A. Diéguez-Vázquez, M. L. Linares, B. Pijper, A. Fontana, R. Rodriguez, A. Trabanco, E. Palao, J. Alcázar, *J. Med. Chem.* **2023**, *66*, 716–732; b) A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *20*, 7429; c) M. Tissot, N. Body, S. Petiti, J. Claessens, C. Genicot, P. Pasau, *Org. Lett.* **2018**, *20*, 8022.

[11] T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021–1026.
[12] M. González-Esguevillas, D. F. Fernández, J. A. Rincón, M. Barberis, O. de Frutos, C. Mateos, S. Garciá-Cerrada, J. Agejas, D. W. C. MacMillan, *ACS Cent. Sci.* **2021**, *7*, 1126–1134.
[13] a) S. Xia, B. Yang, G. Li, X. Zhu, A. Wang, J. Zhu *Polym. Chem.* **2011**, *2*, 2356–2359; b) J. G. Kennemur, *Macromolecules* **2019**, *52*, 1354–1370; c) G. T. Lewis, v. Nguyen, Y. Cohen, *J. Polym. Sci.* **2007**, *45*, 5748–5758.
[14] a) J. Alcazar, G. Diels, B. Schoentjes, *QSAR Comb. Sci.* **2004**, *23*, 906–910; b) J. Alcazar, *J. Comb. Chem.* **2005**, *7*, 353–355.
[15] M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046–14128.
[16] a) M. A. T. Blaskovich, *J. Med. Chem.* **2016**, *59*, 10807–10836; b) K. N. Amarasinghe, L. De Maria, C. Tyrchan, L. A. Eriksson, J. Sadowski, D. Petrovic, *J. Chem. Inf. Model.* **2022**, *62*, 2999–3007.
[17] L. T. Farol, K. B. Hymes, *Expert Rev. Anticancer Ther.* **2004**, *4*, 180–188.
[18] E. D. Deeks, *Drugs* **2017**, *77*, 225–236.

Manuscript received: October 25, 2022
Revised manuscript received: December 13, 2022
Accepted manuscript online: December 21, 2022
Version of record online: January 23, 2023