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Automated Generation and Reactions of 3-Hydroxymethylindoles in Continuous-Flow Microreactors

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Dedicated to Professor R. N. Butler on the occasion of his retirement

Abstract: An automated sequential approach for the generation and reactions of 3-hydroxymethylindoles in continuous-flow microreactors is described. Consecutive halogen–magnesium exchanges of four 3-iodoindoles followed by addition to three aldehydes provided twelve 3-hydroxymethylindoles in a multi-microreactor setup. The synthetic flow strategy could be coupled with an in line continuous liquid–liquid extraction workup protocol for each reaction. Further elaboration of each of these indoles within the fluidic setup was achieved by acid-catalysed nucleophilic substitutions with allyltrimethylsilane and methanol used as nucleophiles. Overall, a set of four 3-iodoindoles was converted into thirty-six indole derivatives by a range of transformations including iodo–magnesium exchange/electrophile trapping and acid-catalysed nucleophilic substitution in a fully automated sequential fashion.

Keywords: automated synthesis · continuous flow · continuous liquid–liquid extraction · indoles · microreactors

Introduction

The tools of the trade for synthetic chemistry have significantly diversified from the era of round-bottomed flask and separating funnel. Nowadays a synthetic chemist can select from a wide range of reaction conditions and parameters accessible through the combination of batch/flow, sequential/parallel, homogenous/solid-supported and external/microwave heating. For example, among the major technology changes in the past decade, microwave irradiation is now a routinely used tool in synthetic laboratories.[1] However, the need for innovative approaches still encourages studies towards refined control and integrated systems for the synthesis–purification–analysis triad. Automated flow synthesis in microreactors has recently become more accessible and is now attracting great interest both from academia and industry.[2] In a microreactor, chemical reaction occurs in continuous flow in channels that are 50–500 μm in diameter, rather than in mixing vessels of conventional process technology. As a result of the channels size, heat transfer is highly efficient, which results in more precise temperature control.[3] Side reactions can be minimised and hazardous reactions can be handled more safely than with traditional batch procedures, as large quantities of reagents are not mixed. Short-lived reaction intermediates can be generated for new synthetically useful transformations or mechanism investigations.[4] Reactions carried out in flow rather than batch processes are readily optimised with low consumption of materials and give rise to a paradigm shift from current need to "scale up" a chemical reaction to a time "scale out" of a continuous flow synthesis for process development. This can be achieved without any further modifications of the reaction conditions being required, thus, offering scalable conditions by design and, therefore, providing a formidable bridge between fundamental research and the first stages of process development.[5] Several recent reports have combined flow reactions with heterogeneous supported catalysts utilising coated microchannels, packed-bed columns and monolithic reactors.[6] Our current goal is to develop automated, sequentially performed homogeneous reactions with in-line continuous liquid–liquid extraction of the products, thereby providing an operational link between the reaction and workup apparatus, conceptually comparable to physically linking the round-bottomed flask and separating funnel.

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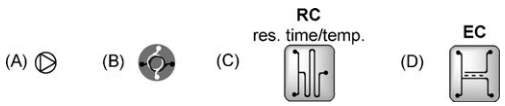
The importance of the indole scaffold in natural products and active pharmaceutical ingredients maintains a high level of research interest towards its synthesis and chemical modification—often with an emphasis on combinatorial strategies.[7] As part of an ongoing medicinal chemistry project for the biological evaluation of 3-substituted indole derivatives, we raised the challenging task of synthesising a collection of these compounds through a sequential approach by using an automated reagent store and a modular combination of micro-fluidic devices. Herein, we disclose our strategy to achieve the homogeneous and continuous multi-step generation of compounds that contain the 3-indolylmethyl motif by using automated micro-fluidic reactors and liquid–liquid extraction devices as depicted in Scheme 1.[8] It was envisaged that conversion of the starting 3-iodoindoles **1** to their corresponding Grignard compounds **2** and subsequent reaction of these 3-metallated indoles with aldehydes would provide the 3-hydroxymethylindoles **5**. The organometallic formation, electrophile reaction and aqueous product workup would be accessible in a three-step continuous-flow sequence. The versatility of these indoles **5** for further elaboration could be exploited by generating indoles **7** and **8** through acid-catalysed elimination–addition sequences via the intermediate electrophilic indolium cations **6**.

Results and Discussion

The microreactor system used for this study has four pumps that deliver flow rate ranges of 4 to 2500 μL min^{-1} (Scheme 2A). The flow streams are connected through poly(tetrafluoroethylene) (PTFE) tubing to: 1) an automated injection system with a liquid handler unit connected by a manifold to four individual automated injection loops with a pressurising pump to ensure no disruption of the system pressure during sample insertion (Scheme 2B), 2) a glass reactor chip (RC), with 0.2 mm inner diameter (ID), with a chip header that allows the connection of up to three inputs and one output tubings (Scheme 2C), 3) a continuous micro-fluidic liquid–liquid extraction chip (EC) module with a PTFE partitioning membrane[9] that is software-controlled to maintain

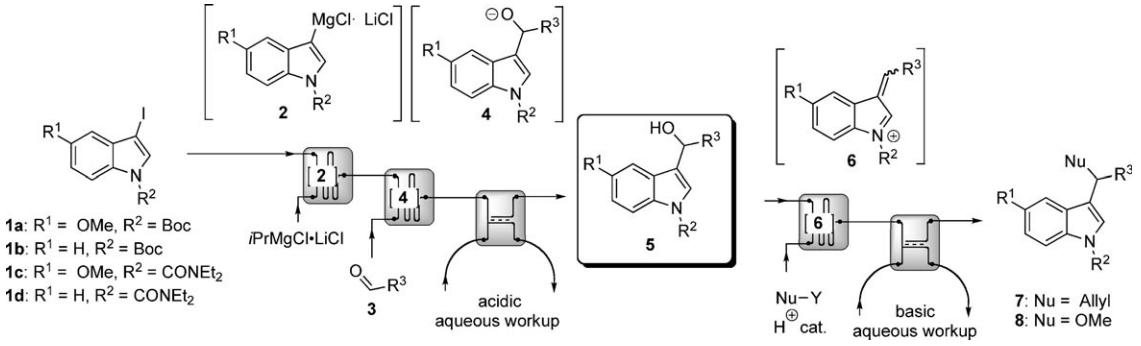


Scheme 2. Icons used for the description of the micro-fluidic experiments: A) pump, B) automated injection loops, C) reactor chip (RC) with residence time (res. time) and temperature and D) liquid–liquid extraction chip (EC).

the cross-membrane pressure (Scheme 2D). The RC temperature is controlled by a heating/cooling plate. The timings for the sequential injection of the reagents, extraction and collection of the products and all other reaction parameters were controlled by the system Reaction Manager v3.0 software[8] run from a dedicated computer. This software allows all reaction and workup parameters to be set prior to initiating a sequence of reactions.

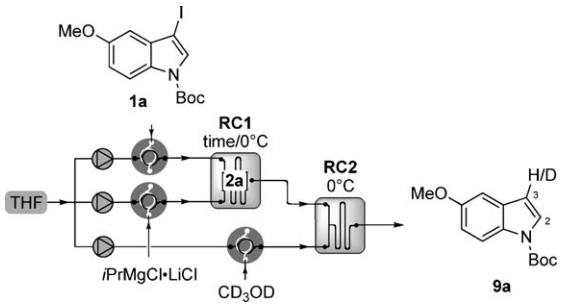
Our first objective was to define optimal metallation conditions for the starting 3-iodoindoles **1** within our continuous flow micro-fluidic setup. The utility of bromine–lithium exchange reactions in conjunction with microreactor technology was recently elegantly demonstrated.[10] However, reported examples of synthetic applications that use 3-lithiated indoles have shown that isomerisation to the thermodynamically favoured 2-metallated species readily occurs.[11] To avoid this potential complication, we chose to investigate magnesiated indole intermediates, which would offer higher thermal stability and could be generated by an iodine–magnesium exchange procedure from indoles **1a–d**. We envisaged that the utilisation of *i*PrMgCl·LiCl, developed by Knochel and co-workers,[12] would be a flow-compatible reagent for the generation of our indole Grignard reagents that could be subsequently converted in situ. Whereas the use of preformed Grignard reagents in flow reactions has been previously described, to the best of our knowledge, their generation by using *i*PrMgCl·LiCl and subsequent reaction has not been reported in the context of continuous microreactor technology.[13]

The iodine–magnesium exchange was investigated in our micro-fluidic setup by using three pumps combined with two reaction chips (Scheme 3).[14] The indole **1a** was chosen to



Scheme 1. Multi-step strategy for the continuous-flow synthesis of 3-hydroxymethylindoles **5** and their conversion to **7** and **8** by acid-catalysed nucleophilic substitution.

determine the reaction conditions and the chip residence time to achieve effective halogen–metal exchange. A solution of **1a** in THF was treated with *i*PrMgCl·LiCl at 0°C for a variable time in microreactor RC1.[15] The output flow was mixed with a solution of deuterated methanol in a second reactor RC2.



Scheme 3. Micro-fluidic setup for the investigation of halogen–magnesium exchange with 3-iodoindole **1a**.

Pleasingly, a satisfying conversion of 72% to deuterated [D]**9a** was obtained after 1 min residence time (Table 1, entry 1) and this could be improved to 85 and >95% by extending the time to 5 and 10 min, respectively (Table 1, entries 2 and 3). Prolonging the reaction time to 20 min gave an identical result as that found after a reaction time of 10 min, which shows good stability within the reaction timescale of the magnesiated indole **2a** at this temperature (Table 1, entry 4). In addition, no incorporation of deuterium at C-2 was observed, confirming that the migration process to the 2-metalated indole observed for halogen–lithium exchange was suppressed. A lowering of the stoichiometry of the reagent to 1.1 equiv resulted in a lowering of conversion (Table 1, entry 5). In all cases the deuterium incorporation into **9a** was greater than 95% as judged by ^{1}H NMR spectroscopy.

Table 1. Optimisation of the halogen–magnesium exchange conditions with 3-iodoindole **1a**.

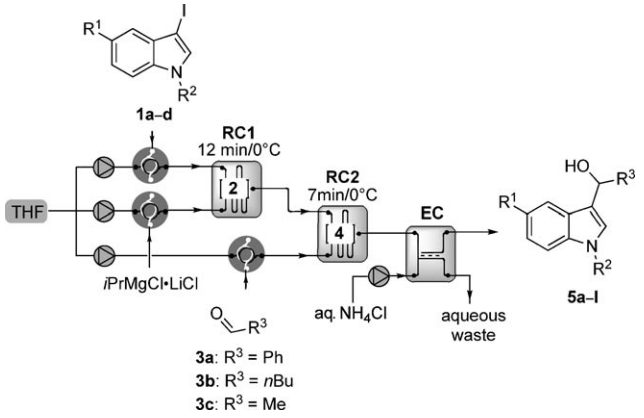
Entry	*i*PrMgCl·LiCl [equiv]	Time [min]	**1a**/[D]**9a**[a]
1	1.2	1	28:72
2	1.2	5	15:85
3	1.2	10	5:95
4	1.2	20	5:95
5	1.1	10	12:88

[a] As determined by integration of the H-2 peaks at $\delta = 7.69$ and 7.56 ppm, respectively, for compounds **1a** and **9a**. Deuterium incorporation was >95% as determined by integration of the H-3 NMR signal of **9a** at $\delta = 6.49$ ppm.

A similar optimisation by using benzaldehyde as the electrophile in reactions with magnesiated indole **2a** showed that effective electrophilic quench was achieved when 1.1 equiv of aldehyde was treated for 7 min.

The optimised magnesiation and subsequent aldehyde electrophilic quench were then applied to the automated sequential generation of library **5** (Table 2). The indoles **1a–d** were sequentially treated with a solution of *i*PrMgCl·LiCl in THF at 0°C for 12 min in microreactor RC1.[16] The output flow from RC1 was connected to an input port of RC2 to which a solution of aldehydes **3a–c** was also added with a residence time of 7 min at 0°C. The output flow of organic mixtures from RC2 continued directly into the continuous extraction module into which an aqueous solution of NH_4Cl was also introduced. The acidic wash and separation of aqueous and organic phases gave an organic and an aqueous output flow, whereas collection of the organic output was achieved by using an automated Gilson liquid handling system. This could be achieved by using the continuous flow EC module, in spite of the cross-solubility of THF and water. Once set up, the twelve sequential magnesiations, electrophile reactions and aqueous workups and product collections proceeded without intervention. All reaction combinations of four iodoindoles and three aldehydes were successfully achieved to give the products **5a–l** with isolated yields of 40 to 66%. The formation of indoles **9a–d** (ca. 5%) was observed in all cases but it could be easily removed by purification through short plugs of silica to afford the products with >95% purity.

Table 2. Micro-fluidic setup and results for the generation of 3-hydroxymethylindoles **5a–l**.

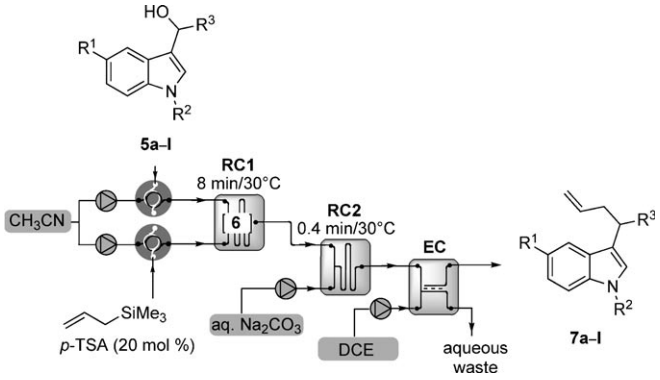


Product	R^1	R^2	R^3	Yield [%]
5a	MeO	CO_2tBu	Ph	48
5b	MeO	CO_2tBu	*n*Bu	52
5c	MeO	CO_2tBu	Me	59
5d	H	CO_2tBu	Ph	53
5e	H	CO_2tBu	*n*Bu	59
5f	H	CO_2tBu	Me	66
5g	MeO	$CONEt_2$	Ph	46
5h	MeO	$CONEt_2$	*n*Bu	59
5i	MeO	$CONEt_2$	Me	40
5j	H	$CONEt_2$	Ph	58
5k	H	$CONEt_2$	*n*Bu	50
5l	H	$CONEt_2$	Me	63

Next, we turned our attention to the further structural elaboration of **5a–l** by using modular micro-fluidic technolo-

gy. It was anticipated that diversification of the 3-indolylmethyl position could be achieved by extension of our previously reported acid-catalysed formation and in situ trapping of the indolium cations of type **6**.[17,18] Our first approach was to introduce an allyl substituent by using allyltrimethylsilane as the nucleophile and *p*-toluene sulfonic acid (*p*-TSA) as the catalyst (Table 3).

Table 3. Results for the generation of indoles **7a–l** by using two microreactors and a continuous extraction of the products.

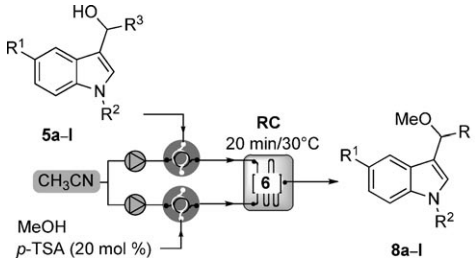


Product	R^1	R^2	R^3	Yield [%]
7a	MeO	CO_2tBu	Ph	50
7b	MeO	CO_2tBu	*n*Bu	45
7c	MeO	CO_2tBu	Me	43
7d	H	CO_2tBu	Ph	62
7e	H	CO_2tBu	*n*Bu	49
7f	H	CO_2tBu	Me	59
7g	MeO	$CONEt_2$	Ph	65
7h	MeO	$CONEt_2$	*n*Bu	46
7i	MeO	$CONEt_2$	Me	65
7j	H	$CONEt_2$	Ph	71
7k	H	$CONEt_2$	*n*Bu	54
7l	H	$CONEt_2$	Me	58

Optimisation of the nucleophilic displacement for substrate **5a** showed that complete allylation was achieved with a residence time (RC1) of 8 min when a solution of **5a** was treated in a microreactor with allyltrimethylsilane in the presence of 20 mol% of *p*-TSA in acetonitrile at 30°C (Table 3). To achieve an aqueous basic workup of product **7a**, the reaction output flow from RC1 was mixed with aqueous sodium carbonate solution in a second microreactor (RC2). The product was then continuously extracted with 1,2-dichloroethane (DCE) from the acetonitrile/water mixture by using the EC module. The allylated product **7a** was extracted (>98%) into in the organic output with complete separation of the acidic catalyst into the aqueous output. HPLC analysis of the aqueous output showed only the acidic catalyst together with traces of the starting hydroxyindole **5** (see the Supporting Information). With our reaction and extraction fluidic setup, the sequential continuous reaction of hydroxyindoles **5a–l** and product extractions were attempted (Table 3). After automated collection of the individual organic phases, the solutions in DCE were dried, evaporated and purified by silica gel chromatography to give compounds **7a–l**. In each case the desired product was isolated; this illustrates the generality of the automated fluidic setup to control an acid-catalysed dehydration, in situ allylation, aqueous basic workup, phase separation and product isolation for twelve sequential reactions.

As a further illustration of the reactivity of indoles **5a–l** in the context of micro-fluidic devices, we applied the *p*-TSA-catalysed nucleophilic displacement to the sequential generation of methoxy ether derivatives **8a–l** by using methanol as representative nucleophile (Table 4).

Table 4. Results for the generation of indoles **8a–l**.



Product	R^1	R^2	R^3	Yield [%]
8a	MeO	CO_2tBu	Ph	97
8b	MeO	CO_2tBu	*n*Bu	98
8c	MeO	CO_2tBu	Me	97
8d	H	CO_2tBu	Ph	97
8e	H	CO_2tBu	*n*Bu	90
8f	H	CO_2tBu	Me	92
8g	MeO	$CONEt_2$	Ph	94
8h	MeO	$CONEt_2$	*n*Bu	93
8i	MeO	$CONEt_2$	Me	96
8j	H	$CONEt_2$	Ph	90
8k	H	$CONEt_2$	*n*Bu	98
8l	H	$CONEt_2$	Me	97

In spite of the fact that ether-substituted indoles of this type are known to be relatively unstable and prone to re-elimination, this reaction was compatible with the micro-fluidic approach.[19] Solutions of indoles **5a–l** in acetonitrile were injected sequentially and treated for 20 min at 30°C with methanol in the presence of a catalytic amount of *p*-TSA. In this case removal of the acidic catalyst was readily achieved by using a post-chip Dowex resin extraction with compounds **8a–l** obtained in almost quantitative yields.

Conclusion

We have described an efficient automated access to 3-indolylmethyl derivatives by using homogenous continuous-flow microreactor technology. A primary set of four 3-iodoindoles was converted into thirty-six indole derivatives by a range of transformations, including iodo–magnesium exchange/electrophile trapping and acid-catalysed nucleophilic substitution in an automated sequential fashion. This investigation illustrates the broad future potential for multi-step, multi-chip reaction sequences in association with continu-

ous-flow extraction technology. Further applications of these micro-fluidic systems are ongoing and will be reported in due course.

Experimental Section

General methods: All commercially available reagents were used as supplied unless otherwise stated. Dry THF was obtained from a solvent purification system. The solution of *i*PrMgCl·LiCl (Acros, 1.10 M) was filtered through 0.2 μm pore size Acrodisc PTFE membrane and the concentration was determined by titration with menthol in THF by using 1,10-phenanthroline as indicator. Chromatography was performed on silica gel 60 PF_{254}. ^1H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz instrument. The microreactor used in this study was purchased from Syrris Ltd and was used without modification. The flow reactor consists of four Cavro-type syringe pumps with flow rates ranging from 4 to 2500 μL min^{-1}. Reagents were injected by using a Gilson injection robot connected to an automated injection module with four pressurised 1.0 mL PTFE sample loops. Glass chip reactors of 62.5, 250 or 1000 μL with inner diameters of 0.2 mm were used and the temperature was controlled by a cooling/heating plate with a working temperature of 0–150 °C. A flow liquid–liquid extraction module with a PTFE membrane was used and reaction mixtures were collected by using a modified Gilson FC204 collection robot fitted with a back-pressure regulator. Modules of the system were connected with 0.5 mm ID/1.6 OD PTFE tubing. The whole system was pressurised with dry nitrogen and computer controlled by using Reaction Manager v3.0.[8] Starting 3-iodoindoles **1a** and **1b** were synthesised by using established procedures.[20]

Procedure for investigation of the iodine–magnesium exchange: A representative procedure for entry 3, Table 1 is as follows: the solution of indole **1a** (0.50 M in THF, 394 μL, 65.0 μL min^{-1}) was treated with *i*PrMgCl·LiCl (1.10 M in THF, 212 μL, 35.0 μL min^{-1}) on microreactor RC1 (1000 μL, 10.0 min residence time) at 0 °C. A microreactor RC1 with an internal volume of 250 μL was used for experiments with shorter residence time (Table 1, entries 1 and 2) and flow rates were adjusted accordingly. The output flow was treated with a solution of deuterated methanol (3.0 M in THF, 394 μL, 65.0 μL min^{-1}) on microreactor RC2 (1000 μL, 6.0 min residence time) at 0 °C. The resulting solutions (1000 μL) were filtered through a plug of silica by using ether as eluent and dried over sodium sulfate. After filtration and evaporation of the solvent, samples were analysed by using ^1H NMR spectroscopy.

3-Deuterio-5-methoxyindole-1-carboxylic acid *tert*-butyl ester ([D]9): ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.02$ (br d, $^3J_{7,6} = 9.0$ Hz, 1H; 7-H), 7.57 (s, 1H; 2-H), 7.03 (d, $^4J_{4,6} = 2.4$ Hz, 1H; 4-H), 6.93 (dd, $^3J_{6,7} = 9.0$, $^4J_{6,4} = 2.4$ Hz, 1H; 6-H), 3.85 (s, 3H; OCH_3), 1.67 ppm (s, 9H; $C(CH_3)_3$).

Procedure for the continuous-flow synthesis of compounds 5a–l: The solutions of indoles **1a–d** (0.55 M in THF, 776 μL, 52.0 μL min^{-1}), *i*PrMgCl·LiCl (1.10 M in THF, 470 μL, 31.5 μL min^{-1}) were injected on microreactor RC1 (1000 μL, 12 min residence time) at 0 °C by using an automated liquid handler. The output flow was treated with solutions of aldehyde **2** (0.5 M in THF, 932 μL, 62.5 μL min^{-1}) on microreactor RC2 (1000 μL, 7 min residence time) at 0 °C. The resulting flow was connected to the liquid–liquid extraction module and combined with an aqueous solution of NH_4Cl (50%, 300 μL min^{-1}). The back pressure was adjusted to 2.0 bar and the cross-membrane pressure set at 50 mbar. The minimum volume of solvent pumped through the system between injections was 450 μL. A total volume of 2200 μL was collected for each experiment. The solutions obtained were dried over sodium sulfate. Filtration and parallel evaporation of the solvent by using ActeVap Rack followed by purification on silica, with cyclohexane/diethyl ether as eluent (9:1 to 7:1 for **5a–f** or 9:1 to 1:1 for **5g–l**) gave analytically pure products (see Table 2).

3-(Hydroxyphenylmethyl)-5-methoxyindole-1-carboxylic acid *tert*-butyl ester (5a): The product (72 mg, 48%) was obtained as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.97$ (m, 1H; 7-H), 7.51–7.47 (m, 3H; 2-H, 2×H_{ortho}), 7.46–7.40 (m, 2H; 2×H_{meta}), 7.35–7.29 (m, 1H; H_{para}), 6.89–6.84 (m, 2H; 6-H, 4-H), 5.95 (br s, 1H; C*H*OH), 3.71 (s, 3H; OCH_3), 2.62 (br s, 1H; OH), 1.62 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 155.5$ (C), 149.6 (C), 142.3 (C), 129.4 (C), 128.4 (2×CH), 127.7 (CH), 126.8 (C), 126.6 (2×CH), 124.1 (CH), 123.4 (C), 115.8 (CH), 113.0 (CH), 102.8 (CH), 83.5 (C), 70.1 (CH), 55.5 (CH_3), 28.1 ppm (3×CH_3); IR (KBr disc): $\tilde{\nu} = 2984$, 1730, 1614, 1597, 1478, 1449 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{21}H_{23}NO_4$: 353.2; found: 336.1 $[M-OH]^+$; anal. calcd (%) for $C_{21}H_{23}NO_4$: C 71.37, H 6.56, N 3.96; found: C 71.53, H 6.76, N 3.82.

3-(1-Hydroxypentyl)-5-methoxyindole-1-carboxylic acid *tert*-butyl ester (5b): The product (74 mg, 52%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.10$–7.90 (m, 1H; 7-H), 7.49 (s, 1H; 2-H), 7.14 (d, $^4J_{4,6} = 2.3$ Hz, 1H; 4-H), 6.91 (dd, $^3J_{6,7} = 9.0$, $^4J_{6,4} = 2.3$ Hz, 1H; 6-H), 4.90 (m, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 1.98–1.88 (m, 2H; 2′-CH_2), 1.81 (br d, $^3J_{OH,1'} = 3.5$ Hz, 1H; 1′-OH), 1.66 (s, 9H; C-$(CH_3)_3$), 1.64–1.30 (m, 4H; 2×CH_2), 0.91 ppm (t, $^3J_{5',4'} = 6.6$ Hz, 3H; 5′-H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 155.6$ (C), 149.6 (C), 130.5 (C), 129.4 (C), 123.8 (C), 122.9 (CH), 116.0 (CH), 113.0 (CH), 102.6 (CH), 83.5 (C), 68.1 (CH), 55.7 (CH_3), 36.7 (CH_2), 28.1 (3×CH_3), 28.0 (CH_2), 22.5 (CH_2), 14.0 ppm (CH_3); IR (KBr disc): $\tilde{\nu} = 3054$, 2983, 2959, 2935, 1728, 1614, 1597, 1478, 1450 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{19}H_{27}NO_4$: 333.2; found: 356.4.5 $[M+Na]^+$, 316.4 $[M-OH]^+$; anal. calcd (%) for $C_{19}H_{27}NO_4$: C 68.44, H 8.16; N 4.20; found: C 68.58, H 8.23, N 4.02.

3-(1-Hydroxyethyl)-5-methoxyindole-1-carboxylic acid *tert*-butyl ester (5c): The product (73 mg, 59%) was obtained as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.10$–7.90 (m, 1H; 7-H), 7.50 (s, 1H; 2-H), 7.15 (d, $^4J_{4,6} = 2.4$ Hz, 1H; 4-H), 6.93 (dd, $^3J_{6,7} = 9.3$, $^4J_{6,4} = 2.4$ Hz, 1H; 6-H), 5.12 (m, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 1.84 (br s, 1H; OH), 1.65 (s, 9H; $C(CH_3)_3$), 1.64 ppm (d, $^3J_{2',1'} = 6.3$ Hz, 3H; 2′-H_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 155.7$ (C), 149.7 (C), 130.4 (C), 129.4 (C), 124.9 (C), 122.4 (CH), 116.0 (CH), 113.1 (CH), 102.6 (CH), 83.5 (C), 63.8 (CH), 55.7 (CH_3), 28.1 (3×CH_3), 23.2 ppm (CH_3); IR (KBr disc): $\tilde{\nu} = 3055$, 2982, 2933, 2836, 1728, 1614, 1597, 1478 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{16}H_{21}NO_4$: 291.1; found: *m/z* 314.4 $[M+Na]^+$, 274.4 $[M-OH]^+$; anal. calcd (%) for $C_{16}H_{21}NO_4$: C 65.96, H 7.27, N 4.81; found: C 65.77, H 7.40, N 4.54.

3-(Hydroxyphenylmethyl)indole-1-carboxylic acid *tert*-butyl ester (5d): The product (73 mg, 53%) was obtained as a colourless solid. M.p. 74–75 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.15$–8.05 (m, 1H; 7-H), 7.51–7.38 (m, 4H; 2-H, 2×H_{ortho}, 4-H), 7.36–7.30 (m, 2H; 2×H_{meta}), 7.30–7.22 (m, 2H; 5-H, 6-H), 7.15–7.13 (m, 1H; H_{para}), 6.07 (m, 1H; 1′-H), 2.24 (br s, 1H; OH), 1.65 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 149.9$ (C), 142.4 (C), 135.9 (C), 128.5 (C), 128.4 (2×CH), 127.9 (CH), 126.6 (2×CH), 124.5 (CH), 123.6 (C), 123.5 (CH), 122.6 (CH), 120.0 (CH), 115.3 (CH), 83.8 (C), 70.4 (CH), 28.1 ppm (3×CH_3); IR (KBr disc): $\tilde{\nu} = 1730$, 1452, 1373, 1254, 1158 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{20}H_{21}NO_3$: 323.1; found: 306 $[M-OH]^+$; anal. calcd (%) for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33; found: C 74.20, H 6.53, N 4.18.

3-(1-Hydroxypentyl)indole-1-carboxylic acid *tert*-butyl ester (5e): The product (75 mg, 59%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.13$ (br d, $^3J_{7,6} = 8.2$ Hz, 1H; 7-H), 7.67 (d, $^3J_{4,5} = 7.8$ Hz, 1H; 4-H), 7.53 (s, 1H; 2-H), 7.32 (m, 1H; 6-H), 7.23 (m, 1H; 5-H), 4.94 (m, 1H; 1′-H), 2.02–1.80 (m, 3H; 2′-H_2, OH), 1.67 (s, 9H; $C(CH_3)_3$), 1.50–1.25 (m, 4H; 3′-H_2, 4′-H_2), 0.91 ppm (m, 3H; 5′-H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 149.7$ (C), 135.8 (C), 128.6 (C), 124.4 (CH), 124.2 (C), 122.4 (CH), 122.3 (CH), 119.8 (CH), 115.3 (CH), 83.6 (C), 68.1 (CH), 36.9 (CH_2), 28.1 (3×CH_3), 28.0 (CH_2), 22.5 (CH_2), 14.0 ppm (CH_3); IR (KBr disc): $\tilde{\nu} = 3410$, 2957, 2932, 2861, 1734, 1453, 1371, 1255, 1159 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{18}H_{25}NO_3$: 303.2; found: 326.4 $[M+Na]^+$, 286 $[M-OH]^+$; anal. calcd (%) for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62; found: C 70.98, H 8.35, N 4.58.

3-(1-Hydroxyethyl)indole-1-carboxylic acid *tert*-butyl ester (5f): The product (73 mg, 66%) was obtained as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.13$ (br d, $^3J_{7,6} = 7.8$ Hz, 1H; 7-H), 7.67 (d, $^3J_{4,5} = 7.8$ Hz, 1H; 4-H), 7.52 (s, 1H; 2-H), 7.31 (m, 1H; 6-H), 7.23 (m, 1H; 5-H), 5.14 (dt, $^3J_{1',OH} = 6.8$, $^3J_{1',2'} = 6.3$ Hz, 1H; 1′-H), 1.99 (br s, 1H; OH), 1.66 (s, 9H; $C(CH_3)_3$), 1.63 ppm (d, $^3J_{2',1'} = 6.3$ Hz, 3H; 2′-H_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 149.7$ (C), 135.8 (C), 128.5 (C), 125.2 (C),

124.4 (CH), 122.5 (CH), 121.7 (CH), 119.7 (CH), 115.3 (CH), 83.6 (C), 63.8 (CH), 28.1 ($3\times CH_3$), 23.4 ppm (CH_3); IR (KBr disc): $\tilde{\nu}=3390$, 2977, 1723, 1372, 1256 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{15}H_{19}NO_3$: 261.1; found: 244.2 $[M-OH]^+$; anal. calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.64, H 7.22, N 5.13.

3-(Hydroxyphenylmethyl)-5-methoxyindole-1-carboxylic acid diethylamide (5g): The product (69 mg, 46%) was obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.51$ (d, $^3J_{7,6}=8.8$ Hz, 1H; 7-H), 7.46 (br d, $J=7.3$ Hz, 2H; $2\times H_{ortho}$), 7.37–7.31 (m, 2H; $2\times H_{meta}$), 7.31–7.26 (m, 1H; H_{para}), 6.97 (d, $^4J_{4,6}=2.4$ Hz, 1H; 4-H), 6.96 (s, 1H; 2-H), 6.88 (dd, $^3J_{6,7}=8.8$, $^4J_{6,4}=2.4$ Hz, 1H; 6-H), 6.01 (s, 1H; 1′-H), 3.75 (s, 3H; OCH_3), 3.39 (q, $J=7.4$ Hz, 4H; $2\times CH_2$), 2.66 (s, 1H; OH), 1.15 ppm (t, $J=7.4$ Hz, 6H; $2\times CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.1$ (C), 154.3 (C), 142.7 (C), 131.3 (C), 128.3 ($2\times$CH), 128.1 (C), 127.6 (CH), 126.5 ($2\times$CH), 124.6 (CH), 122.0 (C), 114.0 (CH), 113.1 (CH), 102.2 (CH), 70.0 (CH), 55.6 (CH_3), 42.3 ($2\times CH_2$), 13.2 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=3055$, 2980, 2939, 1673, 1477, 1450, 1424 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{21}H_{24}N_2O_3$: 352.1; found: 335.2 $[M-OH]^+$; anal. calcd (%) for $C_{21}H_{24}N_2O_3$: C 71.57, H 6.86, N 7.95; found: C 71.31, H, 6.90, N 7.81.

3-(1-Hydroxypentyl)-5-methoxyindole-1-carboxylic acid diethylamide (5h): The product (83 mg, 59%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.52$ (d, $^3J_{7,6}=8.8$ Hz, 1H; 7-H), 7.20 (s, 1H; 2-H), 7.16 (d, $^4J_{4,6}=2.4$ Hz, 1H; 4-H), 6.91 (dd, $^3J_{6,7}=8.8$, $^4J_{6,4}=2.4$ Hz, 1H; 6-H), 4.92 (m, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 3.46 (q, $J=7.4$ Hz, 4H; $2\times CH_2$), 1.94 (m, 2H; 2′-H_2), 1.87 (br s, 1H; OH), 1.53–1.30 (m, 4H; 3′-H_2, 4′-H_2), 1.23 (t, $J=7.4$ Hz, 6H; $2\times CH_3$), 0.91 ppm (t, $J=7.4$ Hz, 3H; 5′-H_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.1$ (C), 154.5 (C), 131.2 (C), 128.1 (C), 123.2 (CH), 122.3 (C), 114.0 (CH), 113.1 (CH), 102.2 (CH), 68.1 (CH), 55.8 (CH_3), 42.4 ($2\times CH_2$), 36.8 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 14.0 (CH_3), 13.4 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=$ 3055, 2984, 2960, 2937, 1675, 1477, 1450, 1423 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{19}H_{28}N_2O_3$: 332.2; found: 355.4 $[M+Na]^+$, 315.5 $[M-OH]^+$; HRMS: *m/z*: calcd for $C_{19}H_{28}N_2O_3Na$: 355.1998 $[M+Na]^+$, found: 355.2012,.

3-(1-Hydroxyethyl)-5-methoxyindole-1-carboxylic acid diethylamide (5i): The product (49 mg, 40%) was obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.51$ (d, $^3J_{7,6}=8.8$ Hz, 1H; 7-H), 7.20 (s, 1H; 2-H), 7.16 (d, $^4J_{4,6}=2.4$ Hz, 1H; 4-H), 6.91 (dd, $^3J_{6,7}=8.8$, $^4J_{6,4}=$ 2.4 Hz, 1H; 6-H), 5.14 (m, 1H; 1′-H), 3.85 (s, 3H; OCH_3), 3.46 (q, $J=$ 7.4 Hz, 4H; $2\times CH_2$), 2.00 (br s, 1H; OH), 1.64 (d, $J_{2',1'}=6.8$ Hz, 3H; 2′-H_3), 1.22 ppm (t, $J=7.4$ Hz, 6H; $2\times CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.1$ (C), 154.4 (C), 131.2 (C), 128.0 (C), 123.4 (C), 122.7 (CH), 114.0 (CH), 113.2 (CH), 102.1 (CH), 63.8 (CH), 55.8 (CH_3), 42.4 ($2\times CH_2$), 23.3 (CH_3), 13.4 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=3054$, 2977, 2937, 2835, 1668 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{16}H_{22}N_2O_3$: 290.2; found: 313.4 $[M+Na]^+$, 291.4 $[M+H]^+$, 273.4 $[M-OH]^+$; HRMS: *m/z*: calcd for : $C_{16}H_{22}N_2O_3Na$ $[M+Na]^+$: 313.1528; found: 313.1543.

3-(Hydroxyphenylmethyl)-indole-1-carboxylic acid diethylamide (5j): The product (80 mg, 58%) was obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.61$ (d, $^3J_{7,6}=8.3$ Hz, 1H; 7-H), 7.53 (d, $^3J_{4,5}=7.8$ Hz, 1H; 4-H), 7.48 (d, $J=7.4$ Hz, 2H; $2\times H_{ortho}$), 7.36 (t, $J=$ 7.4 Hz, 2H; $2\times H_{ortho}$), 7.32–7.22 (m, 2H; H_{para}, 6-H), 7.16–7.12 (m, 1H; 5-H), 7.06 (s, 1H; 2-H), 6.10 (d, $^3J_{1',OH}=4.2$ Hz, 1H; 1′-H), 3.43 (q, $J=$ 7.3 Hz, 4H; $2\times CH_2$), 2.29 (d, $^3J_{OH,1'}=4.2$ Hz, 1H; OH), 1.19 ppm (t, $J=$ 7.4 Hz, 6H; $2\times CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=142.7$ (C), 136.4 (C), 128.4 ($2\times$CH), 127.8 (CH), 127.3 (C), 126.6 ($2\times$CH), 124.1 (CH), 123.8 (CH), 122.2 (C), 121.6 (CH), 120.0 (CH), 113.2 (CH), 70.2 (CH), 42.4 ($2\times CH_2$), 13.3 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=3054$, 2978 2938, 2877, 1673, 1453, 1425 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{20}H_{22}N_2O_2$: 322.2; found: 345.4 $[M+Na]^+$, 323.4 $[M+H]^+$, 305.4 $[M-OH]^+$; HRMS: *m/z*: calcd for $C_{20}H_{22}N_2O_2Na$: 345.1579 $[M+Na]^+$; found: 345.1580; anal. calcd (%) for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found: C 74.19, H 7.05, N 8.78.

3-(1-Hydroxypentyl)indole-1-carboxylic acid diethylamide (5k): The product (64 mg, 50%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.71$ (d, $^3J_{7,6}=7.7$ Hz, 1H; 7-H), 7.61 (d, $^3J_{4,5}=7.7$ Hz, 1H; 4-H), 7.28 (t, $^3J_{5,6}=^3J_{5,4}=7.7$ Hz, 1H; 5-H), 7.23 (s, 1H; 2-H), 7.19 (t, $^3J_{6,5}=^3J_{6,7}=7.7$ Hz, 1H; 6-H), 4.97 (m, 1H; 1′-H), 3.47 (q, $J=7.3$ Hz, 4H; $2\times CH_2$), 1.95 (m, 2H; 2′-H_2), 1.86 (d, $J_{OH,1'}=3.4$ Hz, 1H; OH), 1.52–1.30 (m, 4H; 3′-H_2, 4′-H_2), 1.24 (t, $J=7.3$ Hz, 6H; $2\times CH_3$), 0.90 ppm (t, $^3J_{5',4'}=7.3$ Hz, 3H; 5′-H_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=154.3$ (C), 136.2 (C), 127.3 (C), 123.7 (CH), 122.7 (CH), 122.6 (C), 121.4 (CH), 119.9 (CH), 113.2 (CH), 68.2 (CH), 42.4 ($2\times CH_2$), 37.0 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 14.0 (CH_3), 13.4 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=3052$, 2959, 1657, 1418 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{18}H_{26}N_2O_2$: 302.2; found: 325.4 $[M+Na]^+$, 303.5 $[M+H]^+$, 285.5 $[M-OH]^+$; HRMS: *m/z*: calcd for $C_{18}H_{26}N_2O_2Na$: 325.1892 $[M+Na]^+$; found: 325.1908.

3-(1-Hydroxyethyl)indole-1-carboxylic acid diethylamide (5l): The product (70 mg, 63%) was obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta=7.72$ (d, $^3J_{7,6}=7.8$ Hz, 1H; 7-H), 7.60 (d, $^3J_{4,5}=8.3$ Hz, 1H; 4-H), 7.32–7.27 (m, 1H; 5-H), 7.25 (br s, 1H; 2-H), 7.22–7.18 (m, 1H; 6-H), 5.20 (m, 1H; 1′-H), 3.48 (q, $J=7.3$ Hz, 4H; $2\times CH_2$), 1.85 (d, $J_{OH,1'}=4.4$ Hz, 1H; OH), 1.66 (d, $^3J_{2',1'}=6.3$ Hz, 3H; 2′-H_3), 1.24 ppm (t, $J=7.3$ Hz, 6H; $2\times CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=154.3$ (C), 136.2 (C), 127.3 (C), 123.7 (CH), 123.6 (C), 122.2 (CH), 121.5 (CH), 119.9 (CH), 113.1 (CH), 63.9 (CH), 42.4 ($2\times CH_2$), 23.5 (CH_3), 13.4 ppm ($2\times CH_3$); IR (KBr disc): $\tilde{\nu}=3053$, 2975, 2877, 1672, 1475, 1453 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{15}H_{20}N_2O_2$: 260.4; found: 283.4 $[M+Na]^+$, 261.4 $[M+H]^+$, 243.4 $[M-OH]^+$; HRMS: *m/z*: calcd for $C_{15}H_{21}N_2O_2$: 261.1603 $[M+H]^+$; found: 261.1597.

Procedure for the continuous-flow synthesis of compounds 7a–l: The solutions of indoles **5a–l** (0.25 M in CH_3CN, 800 μL, 80 μL min^{-1}) were sequentially injected by using the automated liquid handler and treated with a solution that contains allyltrimethylsilane (0.1 M in CH_3CN, 400 μL, 40 μL min^{-1}) and *p*-TSA (1.0 M in CH_3CN, 400 μL, 40 μL min^{-1}) on microreactor RC1 (1000 μL, 8.3 min residence time) at 30°C. The output flow was mixed with an aqueous solution of Na_2CO_3 (2%, 240 μL min^{-1}) on microreactor RC2 (1000 μL, 2.8 min residence time). Products were extracted with a flow of 1,2-dichloroethane (360 μL min^{-1}) by using the liquid–liquid extraction module with 2.0 bar back-pressure and 150 mbar cross-membrane pressure. A total volume of 3600 μL was collected for each experiment. The minimum slug spacing was 450 μL. The solutions obtained were dried over sodium sulfate. After filtration and parallel evaporation of the solvent by using an ActeVap rack, products were obtained as described in Table 3. Samples of product **7a–c** and **7g–i** were purified on silica gel with cyclohexane/diethyl ether as eluent (9:1 for **7a,b** and 1:1 for **7g–i**) prior to NMR spectroscopy analysis. Products **7d–f** and **7j–l** were analysed without purification.

5-Methoxy-3-(1-phenylbut-3-enyl)-indole-1-carboxylic acid *tert*-butyl ester (7a): The product (38 mg, 50%) was obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.94$ (br s, 1H; 7-H), 7.49 (br s, 1H; 2-H), 7.30–7.23 (m, 4H; ArH), 7.21–7.13 (m, 1H; ArH), 6.85 (dd, $^3J_{6,7}=8.9$, $^4J_{6,4}=2.7$ Hz, , 1H; 6-H), 6.72 (d, $^4J_{4,6}=2.3$ Hz, , 1H; 4-H), 5.79 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.10–5.03 (m, 1H; 4′-H), 5.00–4.94 (m, 1H; 4′-H_{trans}), 4.11 (t, $^3J_{1',2'}=7.0$ Hz, 1H; 1′-H), 3.74 (s, 3H; OCH_3), 2.91 (m, 1H; 2′-H_A), 2.75 (m, 1H; 2′-H_B), 1.69 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.5$ (C), 149.8 (C), 143.3 (C), 136.6 (CH), 131.0 (C), 128.4 ($2\times$CH), 127.9 ($2\times$CH), 126.4 (CH), 123.5 (C), 123.2 (C), 116.4 (CH_2), 115.8 (CH), 112.5 (CH), 102.9 (CH), 83.4 (C), 55.6 (CH_3), 42.8 (CH_2), 40.0 (CH), 28.2 ppm ($3\times$ CH_3); IR (KBr disc): $\tilde{\nu}=2978$, 1725, 1476, 1448, 1381, 1281 cm^{-1}; HRMS: *m/z*: calcd for $C_{24}H_{28}NO_3$: 378.2069 $[M+H]^+$; found: 378.2060.

3-(1-Allylpentyl)-5-methoxy-indole-1-carboxylic acid *tert*-butyl ester (7b): The product (32 mg, 45%) was obtained as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.98$ (br s, 1H; 7-H), 7.30 (br s, 1H; 2-H), 7.00 (d, $^4J_{4,6}=2.3$ Hz, 1H; 4-H), 6.90 (dd, $^3J_{6,7}=8.9$, $^4J_{6,4}=$ 2.7 Hz, 1H; 6-H), 5.75 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3'',2''}=7.0$ Hz, 1H; 3′-H), 5.01–4.95 (m, 1H; 4′-H_{cis}), 4.95–4.90 (m, 1H; 4′-H_{trans}), 3.86 (s, 3H; OCH_3), 2.82–2.87 (m, 1H; 1′-H), 2.52–2.38 (m, 2H; CH_2), 1.75–1.62 (m, 2H; CH_2), 1.66 (s, 9H; $C(CH_3)_3$), 1.34–1.20 (m, 4H; $2\times CH_2$), 0.85 ppm (t, $J=7.0$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.4$ (C), 137.0 (CH), 124.2 (C), 122.8 (C), 115.9 (CH_2), 112.1 (CH), 102.8 (CH), 83.2 (C), 55.7 (CH_3), 39.5 (CH), 36.3 (CH_2), 34.1 (CH_2), 29.5 (CH_2), 28.2 ($3\times CH_3$), 22.7 (CH_2), 14.0 ppm (CH_3); IR (KBr disc): $\tilde{\nu}=$

2930, 1724, 1474, 1450, 1386 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{22}H_{31}NO_3$: 357.2; found: 370.5 $[M+Na]^+$; HRMS: *m/z*: calcd for $C_{22}H_{32}NO_3$ 358.2382 $[M+H]^+$; found: 358.2394.

5-Methoxy-3-(1-methylbut-3-enyl)-indole-1-carboxylic acid tert-butyl ester (7c): The product (27 mg, 43%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.98$ (brs, 1H; 7-H), 7.31 (brs, 1H; 2-H), 7.00 (d, $^4J_{4,6}=2.5$ Hz, 1H; 4-H), 6.90 (dd, $^3J_{6,7}=8.9$, $^4J_{6,4}=2.5$ Hz, 1H; 6-H), 5.81 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.07–5.01 (m, 1H; 4′-H_{cis}), 5.01–4.97 (m, 1H; 4′-H_{trans}), 3.86 (s, 3H; OCH_3), 2.97–3.03 (m, 1H; 1′-H), 2.54 (m, 1H; 2′-H_A), 2.33 (m, 1H; 2′-H_B), 1.66 (s, 9H; $C(CH_3)_3$), 1.32 ppm (t, $J=7.0$ Hz, 3H; 1′-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta=155.5$ (C), 136.9 (CH), 132.0 (C), 125.9 (C), 122.0 (C), 116.1 (CH_2), 115.9 (CH), 115.8 (C), 112.3 (CH), 102.5 (CH), 83.1 (C), 55.7 (CH_3), 40.9 (CH), 30.3 (CH_2), 28.2 (3×CH_3), 19.9 ppm (CH_3); IR (KBr disc): $\tilde{\nu}=2971$, 1724, 1474, 1384 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{19}H_{25}NO_3$: 315.2; found: 316.2 $[M+H]^+$; HRMS: *m/z*: calcd for $C_{19}H_{26}NO_3$: 316.1913 $[M+H]^+$; found: 316.1993.

3-(1-Phenylbut-3-enyl)-indole-1-carboxylic acid *tert*-butyl ester (7d):[17] The product (43 mg, 62%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=8.15$–7.90 (m, 1H; 7-H), 7.51 (m, 1H; 2-H), 7.35–7.00 (m, 8H; 2×H_{ortho}, 2×H_{meta}, H_{para}, 4-H, 5-H, 6-H), 5.79 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.1$, $^3J_{3',2'}=6.6$ Hz, 1H; 3′-H), 5.07 (dd, $^3J_{trans}=17.2$, $^4J_{cis,2'}=1.5$ Hz, 1H; 4′-H_{cis}), 4.98 (brd, $^3J_{cis}=10.1$ Hz, 1H; 4′-H_{trans}), 4.17 (t, $^3J_{1',2'}=7.4$ Hz, 1H; 1′-H), 2.97–2.85 (m, 1H; 2′-H_A), 2.82–2.70 (m, 1H; 2′-H_A), 1.68 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=$ 149.9, 143.4, 136.7, 130.2, 128.4, 128.0, 126.4, 124.2, 123.8, 122.5, 122.3, 119.7, 116.4, 115.2, 83.5, 43.4, 42.8, 40.1, 28.2 ppm; LRMS (ES): *m/z*: calcd for $C_{23}H_{25}NO_2$: 347.1; found: 370.5 $[M+Na]^+$.

3-(1-Allylpentyl)-indole-1-carboxylic acid *tert*-butyl ester (7e): The product (32 mg, 49%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=8.20$–7.90 (m, 1H; 7-H), 7.56 (d, $J=7.8$ Hz, 1H; ArH), 7.35–7.15 (m, 3H; ArH), 5.74 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.1$, $^3J_{3',2'}=6.8$ Hz, 1H; 3′-H), 5.04–4.97 (m, 1H; 4′-H_{cis}), 4.96–4.91 (m, 1H; 4′-H_{trans}), 2.87–2.91 (m, 1H; 1′-H), 2.46 (m, 2H; CH_2), 1.77–1.65 (m, 2H; CH_2), 1.67 (s, 9H; $C(CH_3)_3$), 1.35–1.20 (m, 4H; 2×CH_2), 0.84 ppm (t, $J=7.0$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=149.9$ (C), 137.0 (CH), 135.6 (C), 130.4(C), 124.4 (C), 124.0 (CH), 122.1 (CH), 119.4 (CH), 115.8 (CH_2), 115.2 (CH), 83.4 (CH), 39.5 (C), 36.3 (CH_2), 34.2 (CH_2), 29.6 (CH_2), 28.2 (3×CH_3), 22.7 (CH_2), 14.0 ppm (CH_3); IR (KBr disc): $\tilde{\nu}=$ 2959, 2929, 2865, 1728, 1453, 1375, 1254, 1160 cm^{-1}; LRMS (EI): *m/z*: calcd for $C_{21}H_{29}NO_2$: 327.2; found: 230.5 $[M-t\text{Bu}-(\text{allyl})]$, 186.5 $[M-CO_2t\text{Bu}-(CH_2CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{18}H_{24}NO_2$: 286.1807 $[M-(CH_2CHCH_2)]^+$; found: 286.1860.

3-(1-Methylbut-3-enyl)-indole-1-carboxylic acid *tert*-butyl ester (7f): The product (34 mg, 59%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=8.25$–8.00 (m, 1H; 7-H), 7.56 (d, $^3J_{4,5}=$ 7.4 Hz, 1H; 4-H), 7.34 (brs, 1H; 2-H), 7.30 (dt, $J=7.0$, 1.2 Hz, 1H; ArH), 7.22 (dt, $J=7.0$, 1.0 Hz, 1H; ArH), 5.82 (ddt, $^3J_{trans}=17.0$, $^3J_{cis}=$ 10.0, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.09–5.02 (m, 1H; 4′-H_{cis}), 5.02–4.98 (m, 1H; 4′-H_{trans}), 3.02–3.07 (m, 1H; 1′-H), 2.56 (m, 1H; 2′-H_A), 2.34 (m, 1H; 2′-H_B), 1.67 (s, 9H; $C(CH_3)_3$), 1.33 ppm (d, $J=7.0$ Hz, 3H; 1′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=149.9$ (C), 136.9 (CH), 130.0 (C), 126.1 (C), 124.1 (CH), 122.1 (CH), 121.3 (C), 119.3 (CH), 116.1 (CH_2), 115.3 (CH), 83.3 (C), 41.0 (CH), 30.4 (CH_2), 28.2 (3×CH_3), 20.0 ppm (CH_3); IR (KBr disc): $\tilde{\nu}=2977$, 1726, 1456, 1375, 1255, 1158 cm^{-1}; LRMS (EI): *m/z*: calcd for $C_{18}H_{23}NO_2$: 285.4; found: 188.4 $[M-t\text{Bu}-(CH_2-CHCH_2)]^+$, 144.4 $[M-CO_2t\text{Bu}-(CH_2CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{18}H_{24}NO_2$: 286.1807 $[M+H]^+$; found: 286.1796.

5-Methoxy-3-(1-phenylbut-3-enyl)-indole-1-carboxylic acid diethylamide (7g): The product (49 mg, 65%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.53$ (d, $^3J_{7,6}=8.9$ Hz, 1H; 7-H), 7.27 (m, 4H; ArH), 7.18 (m, 1H; ArH), 7.12 (brs, 1H; ArH), 6.85 (dd, $^3J_{6,7}=8.9$, $^4J_{6,4}=2.7$ Hz, 1H; 6-H), 6.75 (d, $^4J_{4,6}=2.7$ Hz, 1H; 4-H), 5.80 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.07–5.01 (m, 1H; 4′-H_{cis}), 4.99–4.95 (m, 1H; 4′-H_{trans}), 4.17 (t, $^3J_{1',2'}=7.4$ Hz, 1H; 1′-H), 3.72 (s, 3H; OCH_3), 3.45 (q, $J=7.0$ Hz, 4H; 2×CH_2), 2.91 (m, 1H; 2′-H_A), 2.76 (m, 1H; 2′-H_B), 1.22 ppm (t, $J=7.0$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=154.9$ (C), 154.7 (C), 143.5 (C), 136.7 (CH), 131.1 (C), 129.5 (C), 128.3 (2×CH), 127.9 (2×CH), 126.3 (CH), 123.6 (CH), 121.8 (C), 116.2 (CH_2), 113.9 (CH), 112.5 (CH), 102.3 (CH), 55.6 (CH_3), 42.7 (CH), 42.4 (2×CH_2), 40.0 (CH_2), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}=2976$, 1673, 1474, 1422 cm^{-1}; HRMS: *m/z*: calcd for $C_{24}H_{29}N_2O_2$: 377.2229 $[M+H]^+$; found: 377.2233.

3-(1-Allylpentyl)-5-methoxyindole-1-carboxylic acid diethylamide (7h): The product (33 mg, 46%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.58$ (d, $^3J_{7,6}=8.9$ Hz, 1H; 7-H), 7.01 (d, $^4J_{4,6}=2.7$ Hz, 1H; 4-H), 6.99 (brs, 1H; 2-H), 6.91 (dd, $^3J_{6,7}=8.9$, $^4J_{6,4}=$ 2.7 Hz, 1H; 6-H), 5.75 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.01–4.97 (m, 1H; 4′-H_{cis}), 4.96–4.92 (m, 1H; 4′-H_{trans}), 3.86 (s, 3H; OCH_3), 3.45 (q, $J=7.0$ Hz, 4H; 2×CH_2), 2.89 (p, $J=6.8$ Hz, 1H; 1′-H), 2.52–2.40 (m, 2H; CH_2), 1.77–1.65 (m, 2H; CH_2), 1.32–1.20 (m, 4H; 2×CH_2), 1.23 (t, $J=7.0$ Hz, 6H; 2×CH_3), 0.84 ppm (t, $J=7.0$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=154.8$ (C), 137.1 (C), 131.1 (CH), 129.7 (C), 123.0 (CH), 122.2 (C), 115.8 (CH_2), 114.0 (C), 112.2 (CH), 102.2 (CH), 92.2 (CH), 55.8 (CH_3), 42.4 (2×CH_2), 39.6 (CH), 36.1 (CH_2), 34.2 (CH_2), 29.5 (CH_2), 22.7 (CH_2), 14.0 (CH_3), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}=2931$, 1672, 1472, 1422, 1270 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{22}H_{32}N_2O_2$: 356.2; found: 357.5 $[M+H]^+$, 315.5 $[M-(CH_2CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{22}H_{33}N_2O_2$: 357.2542 $[M+H]^+$; found: 357.2533.

5-Methoxy-3-(1-methylbut-3-enyl)-indole-1-carboxylic acid diethylamide (7i): The product (41 mg, 65%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.56$ (d, $^3J_{7,6}=9.0$ Hz, 1H; 7-H), 7.02 (d, $^4J_{4,6}=2.3$ Hz, 1H; 4-H), 7.01 (brs, 1H; 2-H), 6.91 (dd, $^3J_{6,7}=9.0$, $^4J_{6,4}=2.3$ Hz, 1H; 6-H), 5.81 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.07–5.03 (m, 1H; 4′-H_{cis}), 5.02–4.98 (m, 1H; 4′-H_{trans}), 3.86 (s, 3H; OCH_3), 3.46 (q, $J=7.2$ Hz, 4H; 2×CH_2), 3.04–3.08 (m, 1H; 1′-H), 2.55 (m, 1H; 2′-H_A), 2.34 (m, 1H; 2′-H_B), 1.33 (d, $J=7.0$ Hz, 3H; 1′-CH_3), 1.23 ppm (t, $J=7.2$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=154.9$ (C), 136.9 (CH), 131.0 (C), 129.4 (C), 124.2 (C), 122.3 (CH), 116.0 (CH), 114.1 (CH), 112.4 (CH), 102.0 (CH), 92.1 (CH), 55.8 (CH_3), 42.4 (2×CH_2), 41.1 (CH), 30.3 (CH_2), 20.1 (CH_3), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}=2973$, 1672, 1473, 1422 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{19}H_{26}N_2O_2$: 314.2; found: 315.5 $[M+H]^+$, 273.4 $[M-(CH_2-CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{19}H_{27}N_2O_2$: 315.2073 $[M+H]^+$; found: 315.2067.

3-(1-Phenylbut-3-enyl)-indole-1-carboxylic acid diethylamide (7j): The product (49 mg, 71%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.62$ (d, $^3J_{7,6}=8.2$ Hz, 1H; 7-H), 7.34 (d, $^3J_{4,5}=7.8$ Hz, 1H; 4-H), 7.30–7.15 (m, 6H; ArH), 7.14 (brs, 1H; ArH), 7.06 (m, 1H; ArH), 5.80 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=6.8$ Hz, 1H; 3′-H), 5.08–5.04 (m, 1H; 4′-H_{cis}), 4.99–4.95 (m, 1H; 4′-H_{trans}), 4.23 (t, 1H; $J=7.4$ Hz, 1′-H), 3.46 (q, $J=7.0$ Hz, 4H; 2×CH_2), 2.93 (m, 1H; 2′-H_A), 2.77 (m, 1H; 2′-H_B), 1.22 ppm (t, $J=7.0$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=154.6$ (C), 143.6 (C), 136.8 (CH), 136.1 (C), 128.7 (C), 128.3 (2×CH), 127.9 (2×CH), 126.3 (CH), 123.5 (CH), 123.0 (CH), 122.1 (C), 121.2 (CH), 119.7 (CH), 116.2 (CH_2), 113.1 (CH), 42.6 (CH), 42.4 (2×CH_2), 40.1 (CH_2), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}=$ 2977, 1676, 1450, 1422, 1343 cm^{-1}; LRMS (GCMS): *m/z*: calcd for $C_{23}H_{26}N_2O$: 346.2; found: 305.5 $[M-(CH_2CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{23}H_{27}N_2O$: 347.2123; found: 347.2109 $[M+H]^+$.

3-(1-Allylpentyl)-indole-1-carboxylic acid diethylamide (7k): The product (35 mg, 54%) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.66$ (d, $^3J_{7,6}=8.2$ Hz, 1H; 7-H), 7.59 (d, $^3J_{4,5}=7.8$ Hz, 1H; 4-H), 7.26 (m, 1H; ArH), 7.17 (m, 1H; ArH), 7.00 (s, 1H; 2-H), 5.74 (ddt, $^3J_{trans}=17.2$, $^3J_{cis}=10.2$, $^3J_{3',2'}=7.0$ Hz, 1H; 3′-H), 5.00–4.96 (m, 1H; 4′-H_{cis}), 4.94–4.90 (m, 1H; 4′-H_{trans}), 3.45 (q, $J=7.0$ Hz, 4H; 2×CH_2), 2.94 (p, $J=6.8$ Hz, 1H; 1′-H), 2.55–2.40 (m, 2H; CH_2), 1.85–1.60 (m, 2H; CH_2), 1.35–1.15 (m, 4H; 2×CH_2), 1.23 (t, $J=7.0$ Hz, 6H; 2×CH_3), 0.83 ppm (t, $J=7.0$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=154.7$ (C), 137.1 (CH), 136.1 (C), 128.9 (C), 123.3 (CH), 122.5 (C), 122.4 (CH), 121.0 (CH), 119.4 (CH), 115.8 (CH_2), 113.2 (CH), 42.4 (2×CH_2), 39.7 (CH), 36.2 (CH_2), 34.3 (CH_2), 29.6 (CH_2), 22.7 (CH_2), 14.0 (CH_3), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}=2963$, 2930, 2870, 1676, 1450, 1423 cm^{-1}; LRMS (ES): *m/z*: calcd for $C_{21}H_{30}N_2O$: 326.2; found: 327.5 $[M+H]^+$, 285.5 $[M-(CH_2CHCH_2)]^+$; HRMS: *m/z*: calcd for $C_{21}H_{31}N_2O$: 327.2436; found: 327.2422 $[M+H]^+$.

3-(1-Methylbut-3-enyl)-indole-1-carboxylic acid diethylamide (7l): The product (33 mg, 58%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.64 (d, $^3J_{7,6}$ = 8.6 Hz, 1H; 7-H), 7.59 (d, $^3J_{4,5}$ = 7.8 Hz, 1H; 4-H), 7.26 (m, 1H; ArH), 7.18 (m, 1H; ArH), 7.03 (s, 1H; 2-H), 5.81 (ddt, $^3J_{trans}$ = 17.2, $^3J_{cis}$ = 10.2, $^3J_{3',2'}$ = 7.0 Hz, 1H; 3′-H), 5.06–5.02 (m, 1H; 4′-H_{cis}), 5.01–4.97 (m, 1H; 4′-H_{trans}), 3.46 (q, J = 7.4 Hz, 4H; 2×CH_2), 3.08–3.12 (m, 1H; 1′-H), 2.56 (m, 1H; 2′-H_A), 2.35 (m, 1H; 2′-H_B), 1.34 (d, $^3J_{1',2'}$ = 6.8 Hz, 3H; 1′-CH_3), 1.23 ppm (t, J = 7.4 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 154.7 (C), 137.0 (CH), 136.1 (C), 128.7 (C), 124.4 (C), 123.3 (CH), 121.7 (CH), 121.0 (CH), 119.3 (CH), 116.0 (CH_2), 113.2 (CH), 42.4 (2×CH_2), 41.2 (CH), 30.4 (CH_2), 20.2 (CH_3), 13.4 ppm (2×CH_3); IR (KBr disc): $\tilde{\nu}$ = 2974, 2933, 1675, 1451, 1422 cm^{-1}; LRMS (ES): m/z: calcd for $C_{18}H_{24}N_2O$: 284.2; found: 307.4 $[M+Na]^+$, 285.5 $[M+H]^+$, 243.4 $[M-(CH_2CHCH_2)]^+$; HRMS: m/z: calcd for $C_{18}H_{25}N_2O$: 285.1967; found: 285.1980 $[M+H]^+$.

Procedure for the continuous flow synthesis of compounds 8a–l: The solutions of indoles **5a–l** (0.25 M in CH_3CN, 800 μL, 30 μL min^{-1}) were sequentially injected by using the automated liquid handler and treated with a solution of *p*-TSA (0.05 M in MeOH, 800 μL, 30 μL min^{-1}) on microreactor RC1 (1000 μL, 16.6 min residence time) at 30°C. The output flows (1600 μL) were collected, on Dowex 1X8.100 (200 mg) and agitated for 10 min. Filtration and parallel evaporation of the solvent by using ActeVap Rack gave the products as described in Table 4.

5-Methoxy-3-(methoxyphenylmethyl)indole-1-carboxylic acid *tert*-butyl ester (8a): The product (72 mg, 97%) was obtained as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.07–7.90 (m, 1H; 7-H), 7.50–7.42 (m, 3H; 2-H, 2×H_{ortho}), 7.36 (m, 2H; 2×H_{meta}), 7.32–7.27 (m, 1H; H_{para}), 6.96 (d, $^4J_{4,6}$ = 2.3 Hz, 1H; 4-H), 6.91 (dd, $^3J_{6,7}$ = 8.9, $^4J_{6,4}$ = 2.3 Hz, 1H; 6-H), 5.46 (s, 1H; 2-H), 3.78 (s, 3H; OCH_3), 3.44 (s, 3H; OCH_3), 1.66 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.6, 149.6, 140.5, 130.6, 129.6, 128.3, 127.7, 127.1, 124.6, 121.4, 115.8, 112.9, 103.1, 83.5, 79.3, 56.8, 55.6, 28.1 ppm; IR (KBr disc): $\tilde{\nu}$ = 2981.1, 2936.0, 2828.1, 1727.1, 1599.8 cm^{-1}; LRMS (ES): m/z: calcd for $C_{22}H_{25}NO_4$: 367.2; found: 390.42 $[M+Na]^+$, 336.5 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{21}H_{22}NO_3$: 336.1600; found: 336.1602 $[M-OMe]^+$.

5-Methoxy-3-(1-methoxypentyl)indole-1-carboxylic acid *tert*-butyl ester (8b): The product (70 mg, 98%) was obtained as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.10–7.90 (m, 1H; 7-H), 7.46 (s, 1H; 2-H), 7.17 (d, $^3J_{4,6}$ = 2.7 Hz, 1H; 4-H), 6.93 (dd, $^3J_{6,7}$ = 8.9, $^3J_{6,4}$ = 2.7 Hz, 1H; 6-H), 4.34 (t, $^3J_{1',2'}$ = 6.6 Hz, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 3.26 (s, 3H; OCH_3), 2.05–1.92 (m, 1H; 2′-H_A), 1.89–1.72 (m, 1H; 2′-H_A), 1.67 (s, 9H; $C(CH_3)_3$), 1.45–1.20 (m, 4H; 2×CH_2), 0.88 ppm (t, J = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.6, 149.6, 130.6, 129.6, 124.2, 121.0, 115.9, 113.0, 103.0, 92.1, 83.4, 77.6, 56.2, 55.7, 35.5, 28.2, 22.5, 14.0 ppm; IR (KBr disc): $\tilde{\nu}$ = 2935.3, 2866.8, 1727.3, 1473.8, 1450.7, 1387.5, 1328.8, 1255.5 cm^{-1}; LRMS (ES): m/z: calcd for $C_{20}H_{29}NO_4$: ;347.2 found: 316.5 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{19}H_{26}NO_3$: 316.1913; found: 316.1911 $[M-OMe]^+$.

5-Methoxy-3-(1-methoxyethyl)-indole-1-carboxylic acid *tert*-butyl ester (8c): The product (59 mg, 97%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.10–7.90 (m, 1H; 7-H), 7.48 (s, 1H; 2-H), 7.17 (d, $^3J_{4,6}$ = 2.3 Hz, 1H; 4-H), 6.93 (dd, $^3J_{6,7}$ = 8.9, $^3J_{6,4}$ = 2.7 Hz, 1H; 6-H), 4.59 (q, $^3J_{1',2'}$ = 6.2 Hz, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 3.30 (s, 3H; OCH_3), 1.66 (s, 9H; $C(CH_3)_3$), 1.59 ppm (d, J = 6.2 Hz, 3H; 1′-H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.6, 149.6, 130.6, 129.5, 123.6, 122.2, 115.9, 113.0, 102.9, 83.4, 72.8, 56.0, 55.7, 28.1, 21.6 ppm; IR (KBr disc): $\tilde{\nu}$ = 2979.7, 2934.2, 1727.7, 1609.5, 1473.7 cm^{-1}; LRMS (ES): m/z: calcd for $C_{17}H_{23}NO_4$: 305.4; found: 274.0 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{16}H_{20}NO_3$: 274.1443; found: 274.1451 $[M-OMe]^+$.

3-Methoxyphenylmethylindole-1-carboxylic acid *tert*-butyl ester (8d): The product (66 mg, 97%) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.13 (m, 1H; ArH), 7.52 (d, J = 7.8 Hz, 1H; ArH), 7.50–7.46 (m, 3H; ArH), 7.36 (m, 2H; ArH), 7.30 (m, 2H; ArH), 7.18 (m, 1H; ArH), 5.50 (s, 1H; 1′-H), 3.44 (s, 3H; OCH_3), 1.67 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 149.7, 140.5, 135.8, 128.8, 128.3, 127.7, 127.1, 124.4, 123.9, 122.5, 121.8, 120.2, 115.2, 83.7, 79.3, 56.8, 28.1 ppm; IR (KBr disc): $\tilde{\nu}$ = 2981.2, 2934.4, 1731.5, 1451.9, 1373.9, 1256.4, 1158.0 cm^{-1}; LRMS (ES): m/z: calcd for $C_{21}H_{23}NO_3$: 337.2; found: 306.5 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{20}H_{20}NO$: 306.1494; found: 306.1492 $[M-OMe]^+$.

3-(1-Methoxypentyl)indole-1-carboxylic acid *tert*-butyl ester (8e): The product (57 mg, 90%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.14 (br d, J = 7.8 Hz, 1H; ArH), 7.70 (d, J = 7.8 Hz, 1H; ArH), 7.49 (s, 1H; 2-H), 7.31 (m, 1H; ArH), 7.22 (m, 1H; ArH), 4.38 (t, J = 6.6 Hz, 1H; 1′-H), 3.31 (s, 3H; OCH_3), 2.05–1.92 (m, 1H; 2′-H_A), 1.90–1.78 (m, 1H; 2′-H_B), 1.47–1.20 (m, 4H; 2×CH_2), 1.68 (s, 9H; $C(CH_3)_3$), 0.88 ppm (t, J = 7.4 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 149.7, 135.8, 128.9, 124.3, 123.5, 122.4, 121.4, 120.3, 115.2, 83.6, 77.6, 56.3, 35.7, 28.2, 28.1 22.5, 14.0 ppm; IR (KBr disc): $\tilde{\nu}$ = 2934.5, 2866.4, 1729.2, 1452.7, 1369.5, 1259.3 cm^{-1}; LRMS (ES): m/z: calcd for $C_{19}H_{27}NO_3$: 317.2; found: 286.2 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{18}H_{24}NO_2$: 286.1807; found: 286.1873 $[M-OMe]^+$.

3-(1-Methoxyethyl)indole-1-carboxylic acid *tert*-butyl ester (8f): The product (50 mg, 92%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br d, J = 7.8 Hz, 1H; ArH), 7.71 (d, J = 7.8 Hz, 1H; ArH), 7.51 (s, 1H; 2-H), 7.32 (m, 1H; ArH), 7.24 (m, 1H; ArH), 4.63 (q, J = 6.2 Hz, 1H; 1′-H), 3.26 (s, 3H; OCH_3), 1.68 (s, 9H; $C(CH_3)_3$), 1.60 ppm (d, J = 6.2 Hz, 3H; 1′-H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 149.7, 135.9, 128.7, 124.4, 122.9, 122.6, 122.5, 120.1, 115.2, 83.6, 72.8, 56.1, 28.2, 21.7 ppm; IR (KBr disc): $\tilde{\nu}$ = 2980.4, 2932.5, 1730.5, 1452.5, 1371.2 cm^{-1}; LRMS (ES): m/z: calcd for $C_{16}H_{21}NO_3$: 275.1; found: 244.1 $[M-OMe]^+$, 188.0 $[M-OMe-tBu]^+$, 144.1 $[M-OMe-CO_2tBu]^+$; HRMS: m/z: calcd for $C_{15}H_{18}NO_2$: 244.1338; found: 244.1420 $[M-OMe]^+$.

5-Methoxy-3-methoxyphenylmethylindole-1-carboxylic acid diethylamide (8g): The product (69 mg, 94%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.53 (d, $^3J_{7,6}$ = 9.0 Hz, 1H; 7-H), 7.47–7.43 (m, 2H; ArH), 7.36 (m, 2H; ArH), 7.29 (m, 1H; ArH), 7.00 (br d, $^4J_{4,6}$ = 2.3 Hz, 1H; 4-H), 6.95 (br s, 1H; 2-H), 6.89 (dd, $^3J_{6,7}$ = 9.0, $^4J_{6,4}$ = 2.3 Hz, 1H;6-H), 5.49 (s, 1H; 1′-H), 3.79 (s, 3H; OCH_3), 3.46–3.33 (m, 4H; 2×CH_2) overlapped with 3.43 (s, 3H; OCH_3), 1.17 ppm (t, J = 7.0 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.1, 154.3, 140.6, 131.3, 128.4, 128.3, 127.7, 127.2, 125.0, 120.1, 114.0, 112.9, 102.5, 79.3, 56.8, 55.7, 42.4, 13.3 ppmm; IR (KBr disc): $\tilde{\nu}$ = 2974.4, 2938.2, 1673.3, 1474.0, 1450.2 cm^{-1}; LRMS (ES): m/z: calcd for $C_{22}H_{26}N_2O_3$: 366.2; found: 389.4 $[M+Na]^+$, 367.4 $[M+H]^+$; HRMS: m/z: calcd for $C_{22}H_{26}N_2O_3Na$: 389.1841; found: 389.1855 $[M+Na]^+$.

5-Methoxy-3-(1-methoxypentyl)indole-1-carboxylic acid diethylamide (8h): The product (65 mg, 93%) was obtained as a light colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.56 (d, $^3J_{7,6}$ = 9.0 Hz, 1H; 7-H), 7.18–7.15 (m, 2H; ArH), 6.92 (dd, $^3J_{6,7}$ = 9.0, $^4J_{6,4}$ = 2.3 Hz, 1H; 6-H), 4.38 (t, J = 6.6 Hz, 1H; 1′-H), 3.85 (s, 3H; OCH_3), 3.52–3.41 (m, 4H; 2×CH_2), 3.27 (s, 3H; OCH_3), 2.03–1.92 (m, 1H; 2′-H_A), 1.91–1.80 (m, 1H; 2′-H_B), 1.45–1.20 (m, 4H; 2×CH_2) overlapped with 1.23 (t, J = 7.0 Hz, 6H; 2×CH_3), 0.87 ppm (t, J = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.0, 154.5, 131.2, 128.2, 124.3, 119.2, 114.0, 113.0, 102.4, 77.6, 56.1, 55.8, 42.4, 35.6, 28.2, 22.5, 14.0, 13.4 ppm; IR (KBr disc): $\tilde{\nu}$ = 2935.6, 1675.3, 1615.4, 1470.0, 1423.4, 1273.9 cm^{-1}; LRMS (ES): m/z: calcd for $C_{20}H_{30}N_2O_3$: 346.2; found: 369.5 $[M+Na]^+$, 315.5 $[M-MeO]^+$; HRMS: m/z: calcd for $C_{20}H_{30}N_2O_3Na$: 369.2154; found: 369.2162 $[M+Na]^+$.

5-Methoxy-3-(1-methoxyethyl)indole-1-carboxylic acid diethylamide (8i): The product (58 mg, 96%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.53 (d, $^3J_{7,6}$ = 9.0 Hz, 1H; 7-H), 7.19 (s, 1H; 2-H), 7.17 (d, J = 2.3 Hz, 1H; 4-H), 6.92 (dd, $^3J_{6,7}$ = 9.0, $^4J_{6,4}$ = 2.3 Hz, 1H; 6-H), 4.62 (q, J = 6.6 Hz, 1H; 1′-H), 3.86 (s, 3H; OCH_3), 3.52–3.41 (m, 4H; 2×CH_2), 3.31 (s, 3H; OCH_3), 1.60 (d, J = 6.6 Hz, 3H; CH_3), 1.23 ppm (t, J = 7.0 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.1, 154.5, 131.2, 128.2, 123.8, 120.6, 114.0, 113.0, 102.3, 72.8, 55.9, 55.8, 42.4, 21.6, 13.4 ppm; IR (KBr disc): $\tilde{\nu}$ = 2977.5, 2936.4, 1674.5, 1472.2, 1422.4 cm^{-1}; LRMS (ES): m/z: calcd for $C_{17}H_{24}N_2O_3$: 304.2; found: 327.4 $[M+Na]^+$, 273.4 $[M-MeO]^+$; HRMS: m/z: calcd for $C_{17}H_{24}N_2O_3Na$: 327.1685; found: 327.1669 $[M+Na]^+$.

3-Methoxyphenylmethylindole-1-carboxylic acid diethylamide (8j): The product (60 mg, 90%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.61 (d, $^3J_{7,6}$ = 8.6 Hz, 1H; 7-H), 7.57 (d, $^3J_{4,5}$ = 7.4 Hz, 1H; 4-H), 7.46 (m, 2H; ArH), 7.38–7.32 (m, 2H; ArH),

7.32–7.22 (m, 2H; ArH), 7.14 (m, 1H; ArH), 6.98 (brs, 1H; ArH), 5.52 (brs, 1H; 1′-H), 3.47–3.35 (m, 4H; 2×CH_2) overlapped with 3.43 (s, 3H; OCH_3), 1.18 ppm (t, J=7.0 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 1 C missing δ=154.3, 140.7, 136.3, 128.3, 127.8, 127.7, 127.2, 124.4, 123.7, 121.6, 120.4, 120.1, 113.1, 79.3, 56.8, 42.4, 13.3 ppm; IR (KBr disc): $\tilde{\nu}$=2979.0, 1678.7, 1449.8, 1422.9, 1273.5 cm^{-1}; LRMS (ES): m/z: calcd for $C_{21}H_{24}N_2O_2$: 336.2; found: 359.5 $[M+Na]^+$, 337.5 $[M+H]^+$, 305.5 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{20}H_{21}N_2O_2$: 305.1654; found: 305.1666 $[M-OMe]^+$.

3-(1-Methoxypentyl)indole-1-carboxylic acid diethylamide (8k): The product (62 mg, 98%) was obtained as a light colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.72 (d, $^3J_{7,6}$=7.8 Hz, 1H; 7-H), 7.64 (d, $^3J_{4,5}$=8.2 Hz, 1H; 4-H), 7.28 (m, 1H; ArH), 7.21–7.15 (m, 2H; ArH), 4.42 (t, $^3J_{1',2'}$=6.6 Hz, 1H; 1′-H), 3.52–3.42 (m, 4H; 2×CH_2), 3.27 (s, 3H; OCH_3), 2.05–1.94 (m, 1H; 2′-H_A), 1.93–1.82 (m, 1H; 2′-H_B), 1.45–1.22 (m, 4H; 2×CH_2), 1.24 (t, J=7.0 Hz, 6H; 2×CH_3), 0.87 ppm (t, J=6.6 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=154.4, 136.3, 127.6, 123.7, 123.6, 121.4, 120.2, 119.6, 113.1, 77.6, 56.3, 42.4, 35.8, 28.2, 22.5, 14.0, 13.4 ppm; IR (KBr disc): $\tilde{\nu}$=2935.0, 1677.2, 1450.8, 1425.2 cm^{-1}; LRMS (ES): m/z: calcd for $C_{19}H_{28}N_2O_2$: 316.2; found: 339.5 $[M+Na]^+$, 285.5 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{19}H_{28}N_2O_2Na$: 339.2048; found: 339.2055 $[M+Na]^+$.

3-(1-Methoxyethyl)indole-1-carboxylic acid diethylamide (8l): The product (54 mg, 97%) was obtained as a light colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.72 (d, $^3J_{7,6}$=7.8 Hz, 1H; 7-H), 7.62 (d, $^3J_{4,5}$=8.2 Hz, 1H; 4-H), 7.28 (m, 1H; ArH), 7.23–7.15 (m, 2H; ArH), 4.42 (q, J=6.6 Hz, 1H; 1′-H), 3.55–3.40 (m, 4H; 2×CH_2), 3.31 (s, 3H; OCH_3), 1.61 (d, J=6.6 Hz, 3H; CH_3), 1.24 ppm (t, J=7.0 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=154.4, 136.2, 127.5, 123.6, 123.2, 121.4, 120.9, 120.1, 113.1, 72.8, 56.1, 42.4, 21.8, 13.4 ppm; IR (KBr disc): $\tilde{\nu}$=2979.0, 2934.2, 1676.8, 1449.9, 1422.3 cm^{-1}; LRMS (ES): m/z: calcd for $C_{16}H_{22}N_2O_2$: 274.2; found: 297.4 $[M+Na]^+$, 243.4 $[M-OMe]^+$; HRMS: m/z: calcd for $C_{16}H_{22}N_2O_2Na$: 297.1579; found: 297.1581 $[M+Na]^+$.

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[16] The microreactors were washed with 1000 μL of solvent prior to the automated injection of another set of reagents (see the Supporting Information for details of parameters used). The minimum volume of solvent being pumped through the system between two experiments equalled the time between two injections × the lowest flow rate used in the system.

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