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Synthesis of substituted indoles using continuous flow micro reactors

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ABSTRACT

Continuous flow micro fluidic devices for organic synthesis ('*micro reactors*') are becoming established in a number of facets of modern applied chemistry. As part of a concurrent research project with a pharmaceutical company for generation of materials of pharmaceutical interest within continuous flow environments, we present here, for the first time a series of indoles that have been produced within micro reactor systems. We have developed three different approaches to the synthesis, which are compared with traditional batch synthesis as well as each other in terms of ease of optimization, chemical suitability and versatility, and implications as to throughput. Typical throughputs of approach 1 (simulated classical synthesis) were in the region of 2 mgh^{-1} of indoles such as tetrahydrocarbazole and cyclopentaindole. The second approach (based on Elk's modification of Fischer indole synthesis) gave throughputs of 5.7–8.9 mgh^{-1} and the final approach (using heterocatalytic flow reactors) gave the highest throughputs of 12.7–20.1 mgh^{-1}. All throughputs are per single channel reactor system (i.e., one single reactor set up), and the latter two approaches produce viable output quantities for the syntheses of radiolabelled materials (where typically minute amounts of high purity materials are required from a rapid and safe production environment).

1. Introduction

Micro reactors are comprised of a series of channels etched into a solid substrate through which fluids are manipulated so as to create a continuous flow reaction environment. In recent years there has been much development in technologies used within micro reactor groups, from the construction materials, to novel pumping systems and elaborate micro- and nano-architecture. In the work outlined in this paper, glass micro reactors are used due to their chemical inertness and robust physical strength. These reactors are typically etched using HF to give channels of the dimensions in the range of 50–200 μm wide by 50–75 μm deep and are prepared as per the method outlined by McCreedy.[1] Typical channel shape and dimensions are shown in Figure 1.

Using micro reactors for synthesis offers a number of advantages over conventional batch procedures, such as lower reagent consumption (and thus lower waste generation), faster mixing times due to minute diffusion distances, better thermal control brought about by very large surface area to volume ratios of the reactor, and the fact that the reactor array is a sealed system where there is no risk of losses to the environment, and minimal human exposure to hazardous reagents (being that the micro reactor itself acts as a primary engineering control).[2,3] For these reasons pharmaceutical companies are looking towards micro reactors as a possible platform on which to perform radiolabelled synthesis, where typically small amounts of high purity materials are required rapidly with low human exposure.

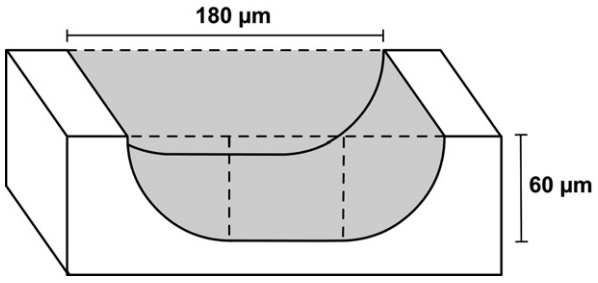

Figure 1. Micro reactor cross section demonstrating shape and typical dimensions.

In-line with a parallel investigation on the above topic of radio synthesis, we have developed three methods for the synthesis of the indole core. The indole unit is a well established pharmacophore due to the fact that many biological species include the indole nucleus, including serotonin ('5-HT', a neurotransmitter **1**) and melatonin (a master regulatory hormone **2**) and as such the indole unit is realised in many classes of pharmaceuticals from beta blockers (e.g., Pindolol **3**), *anti*-inflammatory drugs (e.g., Indomethacin **4**) and migraine management (e.g., Zolmitriptan and Almotriptan) as well

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as their use in *anti*-depressives and treatments for schizophrenia and other psychological conditions.[4–8]

Substituted indoles (such as those shown in Fig. 2) have been a topic of interest for over a century since Fischer's first report some 120 years ago.[9] Today, there are a number of routes to the indole unit but the most commercially used is still the Fischer method Fig. 3 as its versatility, availability of the starting reagents and the range of suitable catalysts and solvents make it viable on an industrial scale. The development of continuous flow systems for the synthesis of indoles has been briefly touched upon in the innovative works of Bagley et al. who developed a novel microwave-irradiated continuous flow system for the synthesis of 1,2,3,4-tetrahydro-1*H*-carbazole **5**,[10] and also the works of Kappe et al., who utilised high temperature and high pressure to produce **5** using custom pressurised continuous flow reactors to allow solvent temperatures to exceed their normal boiling points.[11]

We have focused our efforts on the development of the Fischer indole synthesis for continuous flow micro reactor environments using conventional heating and simpler, more available devices and we now present our results.

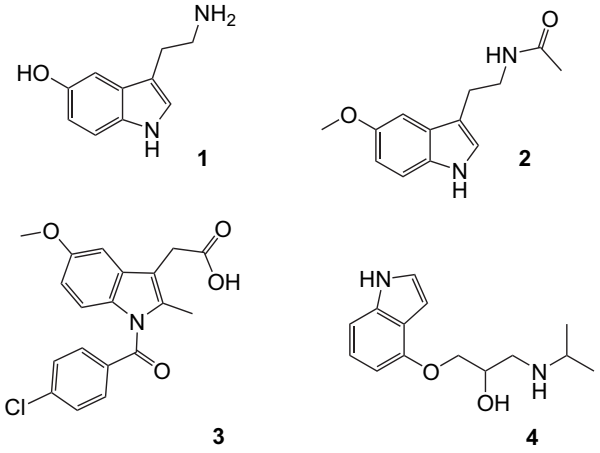


Figure 2. Selected pharmaceutically important indoles.

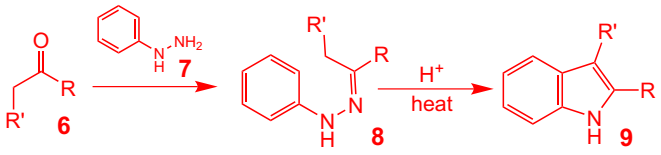


Figure 3. Fischer indole synthesis where the ketone (**6**), is reacted with phenylhydrazine (**7**) to form the phenylhydrazone (**8**), which is cyclised via a [3,3]-sigmatropic rearrangement to form the substituted indole (**9**).

2. Results and discussion

In the course of our investigation into the adaptation of Fischer indole synthesis for micro reactor environments we undertook three separate approaches.

For this piece of work, a reasonably simple reaction system was set up using a syringe pump (so as to drive the system hydrodynamically, as at the low pH involved in the use of strong acids, electro kinetic methods such as electro osmotic flow become ineffective). A schematic of the set up is shown in Figure 4.

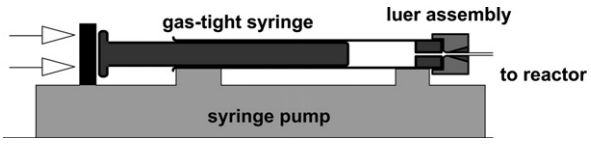


Figure 4. Schematic of syringe pump.

Gas tight syringes are loaded with the reagents, which are pumped using a syringe pump (a simple motorized worm drive, which provides a continuous, relatively pulse free driving force). The syringes are linked to microbore tubing via low dead-volume luer assemblies, which provide the step down in diameter from the syringe luer to the tubing diameter. The tubing then led directly into the micro reactors via the ports drilled in the top plate of the reactor. The tubing is supported in place using an epoxy based adhesive.

The first and simplest of the three approaches discussed in this report is the direct conversion of the commonly used classical batch methodology to a homogenous continuous flow system. Figure 5 demonstrates the micro reactor set up used to indolise the ketone series **10**–**13** (Table 1).

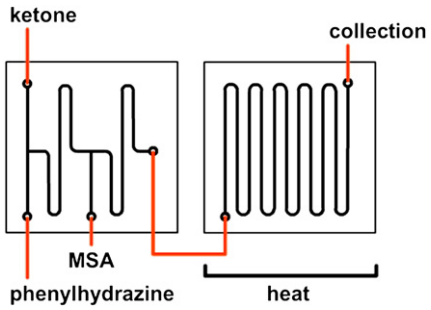
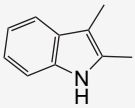
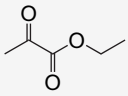
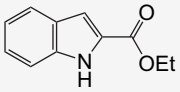
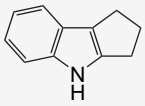
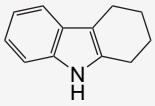


Figure 5. Schematic of micro reactor set up for homogeneous indolisation (approach 1).

The reactor allowed for a mixing period in which the ketone and phenylhydrazine could react in order to form the phenylhydrazone in situ, and then mixed methanesulfonic acid (MSA) as a catalyst, which on heating rendered the indole at the channel output. This system gave reasonable first results (e.g., 98% conversion from cyclohexanone to 1,2,3,4-tetrahydro-1*H*-carbazole at 160 °C, 2.3 mgh^{-1}) but there were problems associated with high backpressures and insolubility at high concentrations, which led to channel blocking and seal breaches at the luer and syringe plunger. Protic solvents such as alcohols make good reaction solvents for indolisation; however the low boiling points of short chain alcohols (C≤4) limited the temperature of the system. Larger alcohols have issues solubilising the intermediates. High boiling solvents tend to have higher viscosities (e.g., DMSO vs ethanol, ν_{20}=2.14 and 1.20 mPa, respectively), which did not alleviate the pressure problems. A compromise of DMSO doped with 10% EtOH allowed for solubility and the required protic nature of the solvent to be fulfilled. Reagent concentration was limited to 0.1 M as solubility of the phenylhydrazone species was restrictive. In the case of cyclohexanone and cyclopentanone (ketones **11** and **12**, respectively) temperatures were capped at 175 °C, and discolouration of the solution stream was seen. Throughputs were limited by the back-pressures generated within the system, but high conversions of the simpler ketones such as butan-2-one **10** were as high as 98%, offering throughputs of 2.0 mgh^{-1}). Both the cyclic ketones cyclised efficiently (cyclopentanone gave 86% conversion to the cyclopentaindole **15**, and cyclohexanone gave 98% conversion to the tetrahydrocarbazole **5** (giving throughputs of 2.3 and 1.9 mgh^{-1}, respectively). However ethyl pyruvate would not cyclise. In the application for which these reactors were developed, the throughputs produced by this method were considered non-viable.

With the problems associated with the first method, a second approach was devised, using harsher chemical conditions so that milder environmental conditions could be employed – allowing the reduction of the backpressures, which would increase system throughput by allowing faster flow rates. This approach, adapted from Elk et al.,[12] used neat glacial acetic acid as a highly protic solvent, and 10% (v/v) sulfuric acid as the catalyst. This strategy is not

Table 1
Comparison of micro fluidic indolisation versus classical synthesis

Ketone		Indole		Batch (%)[a]	Homogeneous approach (1) (%)[b]	Elks' approach (2) (%)[b]	Heterogeneous approach (3) (%)[b]
	**10**		**14**	88	98	96	98
	**11**		**5**	68	98	88	98
	**12**		**15**	69	86	68	74
	**13**		**16**	76	0	52	56

[a] Isolated yield.
[b] Conversion (chromatographic yield).

commonly used industrially due to the hazardous nature of the strong acids, however within sealed glass micro reactors, the risks of exposure to such solvents was minimal, and no damage to the reaction vessels are observed. The micro reactor set up can be seen in Figure 6.

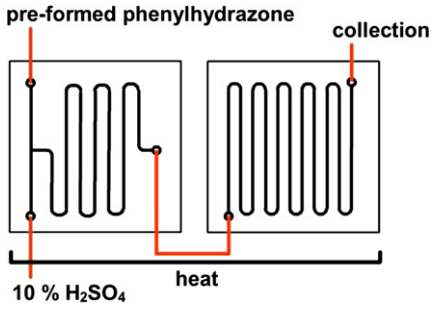


Figure 6. Schematic of set up for approach 2.

Using an acid as the solvent meant that the cyclisation from the phenylhydrazone to the indole was faster than the first method, allowing the shortening of the reactor length. This therefore reduced the back pressure of the system and allowed slightly improved flow rates (and hence throughputs) of the system. Lower temperatures were required (experiments were conducted at 105 °C, just under the boiling point of acetic acid). It must be noted that the phenylhydrazone had to be pre-synthesised and purified to use as the starting material; it was no longer a '1-pot' synthesis. Phenylhydrazones are often unstable in air and autooxidise (even more so if they are impure), which made this approach less than satisfactory.[13] In the case of ethyl pyruvate **13**, a number of side products were produced, which thus reduced the maximum yield. Typical throughputs were much improved over the first method (for example 2,3-dimethylindole **14** was synthesised at 8.3 mgh^{-1}, and ethyl pyruvate **13**, which failed to cyclise to ethyl indole-2-carboxylate **16** in the previous method converted at 5.7 mgh^{-1}). The strongly acidic solvent stream had an extensive work-up. This method was not suitable for sequential ('*in-line*') reactions as glacial acetic acid is not a suitable solvent for many other reactions. Attempts to clean the solvent stream using a specialised in-line phase separation system (whereby the product is flowed into laminar flowing streams of dichloromethane and water, so as to perform an organic extraction) were unsuccessful as glacial acetic acid will persist in the organic layer for several washes.

The third and final approach investigated the use of heterogeneous catalysis. Although Fischer indole synthesis employs the use of an acid 'catalyst' it has been a point of debate that the acid is in fact not regenerated as a true catalyst would.[14] Traditionally the indolisation would be performed in excesses of acids, even with heterogeneous acids, a large excess is usually used. In a study to assess acid suitability, the nature of this untrue catalysis was conducted with the use of Amberlyst A-15, whereby the acid efficacy reduced rapidly over time in the generation of indole **16** (Fig. 7).

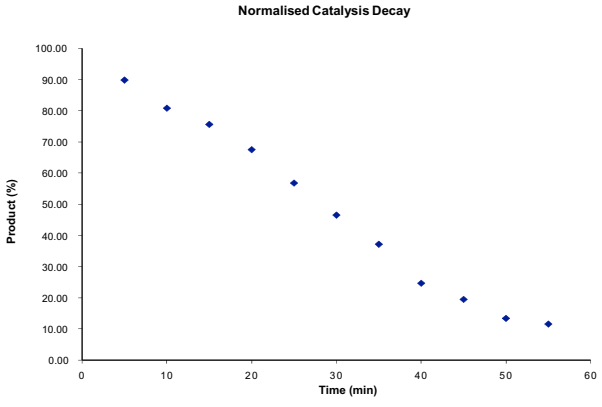


Figure 7. Catalytic decay of Amberlyst A-15 during indolisation in ethanol.

It is documented that Amberlite IR-120 is replenishable in situ as is routinely performed in the purification of water on an industrial scale. This inexpensive and easy to handle solid supported acid catalyst did not exhibit the same loss of activity in ethanol and as such was packed into a flow reactor and used as in the set up shown in Figure 8.

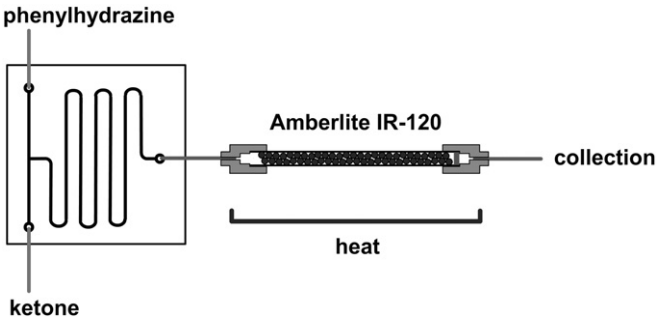


Figure 8. Schematic of micro reactor set up for heterogeneous indolisation (approach 3).

By utilising a flow reactor packed with a solid supported acid, it was possible to greatly reduce backpressures, and thus increase the flow rate by 10-fold. The output solution stream was acid free and required little or no work-up. In practice the product was collected into ice water, in which the product precipitated. Temperatures afforded by heating ethanol were suitable for indolisation (which in the first approach, were not enough) due to the greatly increased physical exposure to the acid—experiments in all cases were conducted at 70 °C.

Of the three approaches considered, it is clear that the use of the heterogeneous acid system was the most beneficial in synthetic terms. As the system output is free of acid and is low boiling (ethanol, bp 78 °C) compared with glacial acetic acid (bp 118 °C) and DMSO (bp 189 °C), using a heterogeneous catalyst rendered the system more amenable for sequential reactions such as further functionalisation of the indole structure. The reduced backpressures of the capillary based heterogeneous catalysis allowed greater flow rates to be applied and thus the throughput was significantly increased over the other methods. Typical throughputs of this method were nearly an order of magnitude greater than the first method, due to increased flow rates (e.g., 2,3-dimethylindole **14** was produced at a rate of 17.1 mgh^{-1} compared with just 2.0 mgh^{-1} in the first method, tetrahydrocarbazole **5** was produced at 20.1 mgh^{-1}, compared with 2.3 mgh^{-1}, and ethyl pyruvate **13**, which would not cyclise in the first method, converted to ethyl indole-2-carboxylate **16** at 12.7 mgh^{-1}). The comparison of throughputs is shown in Table 2.

Table 2
Throughputs comparison of micro reactor approaches

Indole	Throughput (mgh^{-1})		
	Homogenous approach (1)	Elks' approach (2)	Heterogeneous approach (3)
13	2.0	8.3	17.1
14	2.3	8.9	20.1
15	1.9	6.3	14.0
16	—	5.7	12.7

3. Conclusions

Micro reactors can be used for the cyclisation of ketones to indoles via Fischer indole synthesis. The different approaches employed demonstrate the versatility of the micro reactor platform for synthesis. The problems of back pressure associated with high throughput synthesis have been considered as well as the adaptability for further sequential reactions.

To this end, the heterogeneous approach using Amberlite IR-120 was deemed the most useful of the three methods as minimal work-up of the product and higher throughputs were possible. Synthesis of various indoles with throughputs of up to 20.1 mgh^{-1} per single channel reactor array (running from a single pump) was possible. This is a viable level of production for the application for which these systems were developed (rapid and safe synthesis of radiolabelled materials).

4. Experimental procedures

4.1. General experimental procedures

All materials were obtained from commercial sources and used without further purification. Column chromatography was performed using Kieselgel 60 (Fluka) and the components were eluted from ethyl acetate/hexane mixtures. Thin layer chromatography was conducted using Kieselgel 60, HF_{254} aluminium backed TLC plates (Merck) and ethyl acetate/hexane mixtures as mobile phase. Separation was visualised by irradiating with 254 nm ultra violet light.

Nuclear magnetic resonance (NMR) spectra were recorded at room temperature in deuterated DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. All spectra were recorded on a Jeol GX400 spectrometer (with the chemical shifts given in parts per million (ppm) and coupling constants in Hertz (Hz)), ^{1}H spectra were taken at 400 MHz, and ^{13}C taken at 100 MHz. Melting points were determined using a Stuart SMP10 melting point apparatus and were uncorrected. Mass spectrometry was performed using a Varian 2100 T GC–MS. High performance liquid chromatography (HPLC) was performed with a Shimadzu LC-6A single solvent pump and an Applied Biosystems 759A UV detector on a Phenomenex Luna column (5 μm, 100 Å, 4.60×250 mm C_{18}), and integrated with Datalys Azur 4.0.2.0 software.

4.2. General micro reactor procedures

Technical data for the micro reactor arrays are presented in the Electronic Supplementary data.

4.2.1. Approach 1: homogenous catalysis. Separate solutions of the ketones and phenylhydrazine were made to 0.1 M, and the MSA solution was made to 0.05 M in the solvent mixture of DMSO/ethanol (9:1) and sonicated for 10 min to remove gases then taken up into luer-lock syringes (Hamilton). The micro reactor array used was a mixing 'double T' chip, and a long wide-bore serpentine, joined by suitable PEEK™ (DuPont) microbore tubing. The total length of the channel array was 1.06 m, with a volume of 19.60 μL giving a residence time in the system of 19.60 min at the bulk operational flow rate of 1 $\mu L\,min^{-1}$. The reactors were primed by pumping the solvent mixture through for 20 min, to ensure all channel surfaces were wetted. The reagents were then connected to the reactors via low dead-volume luers and flow was provided by a syringe drive (BASi Bee, MD1001, controlled with the BASi Bee Hive, MD1020). The flow was set to 1 $\mu L\,min^{-1}$ and the output stream was collected for a set period. The solution collected was then diluted with ethanol for quantitative HPLC analysis (products and intermediates calibrated versus starting materials, mobile phase 65% acetonitrile in water).

4.2.2. Approach 2: neat acid catalysis. The relevant phenylhydrazone was solubilised in glacial acetic acid to 0.1 M, sonicated for 10 min to remove gases, and then taken up in a luer-lock syringe. The sulfuric acid was made up to 10% (v/v) in glacial acetic acid, sonicated and taken up into a separate syringe. The reactor array used for this approach was a mixing T-chip and a wide-bore serpentine with a total reaction length of 0.74 m, and a volume of 12.47 μL giving a residence time of 6.24 min at the bulk operational flow rate of 2 $\mu L\,min^{-1}$. The micro reactors were joined with acid impervious fused silica. The array was held in a custom built aluminium cradle to prevent

the reactors moving and stressing the relatively inflexible fused silica, and thus reduce risk of mechanical damage to the tubing. The reactors were primed with glacial acetic acid for 10 min and the reagents were introduced to the array using low dead-volume luers. The flow was set to 2 μL min^{-1} and the output stream was collected for a set period. The produced solution was then diluted with ethanol for quantitative HPLC analysis.

4.2.3. Approach 3: heterogeneous catalysis. Separate solutions of the ketones and phenylhydrazine were made to 0.1 M in ethanol and sonicated for 10 min to remove gases then taken up into luer-lock syringes. The micro reactor array comprised of a T-chip and a capillary, which was packed with Amberlite IR 120H (60 mg, 265 μmol), joined with suitable PEEK™ microbore tubing and connected by low dead-volume luers and unions. The total reaction length was 0.38 m, with a volume of 69.43 μL giving a residence time of 3.47 min at the bulk operational flow rate of 20 μL min^{-1}. The system was primed with ethanol for 5 min and then connected to the reagents via luers. The reagents were pumped through the system at up to 20 μL min^{-1} (bulk), and the output stream was collected for a set period. The solution collected was then diluted with ethanol for quantitative HPLC analysis.

4.3. Batch reactions

*4.3.1. General procedure for batch synthesis of indoles **8**, **9** and **10**.* Ketone (2.5 mmol) was added to a solution of phenylhydrazine (1 equiv) in ethanol, and stirred for 10 min at room temperature. *p*-TSA (1 equiv) was added and the solution was heated to reflux for 4 h. The solution was then allowed to cool, and concentrated in vacuo to remove the solvent, before diluting in water (50 mL) and extracting into dichloromethane (50 mL). The organic layer was washed with water (50 mL), ammonium chloride solution (0.1 M, 50 mL) and then sodium hydrogen carbonate solution (saturated, 50 mL). The organic layer was then dried over magnesium sulfate and concentrated in vacuo to render the crude indole product. The indole was purified by either recrystallisation (ethanol/water) or by flash chromatography on silica gel.

*4.3.2. 2,3-Dimethyl-1H-indole (**14**)*[15]. The reaction was carried out in accordance with general procedure for batch synthesis (4.3) using butan-2-one **10** and phenylhydrazine **7** to give the title compound **14** as a white solid, mp 105–106 °C (lit.,[16] 106 °C); δ_H 2.13 (3H, s, CH_3), 2.29 (3H, s, CH_3), 6.90 (1H, t, *J*=7.04 Hz, ArH), 6.95 (1H, t, *J*=7.75 Hz, ArH), 7.19 (1H, d, *J*=7.96 Hz, ArH), 7.33 (1H, d, ArH, *J*=7.55 Hz, ArH), 10.61 (1H, br s, NH); ^{13}C (δ, DMSO-d_6): 8.9 (CH_3), 11.8 (CH_3), 105.5 (C_0), 110.7 (CH), 117.8 (CH), 118.5 (CH), 120 (CH), 129.5 (C_0), 131.8 (C_0), 135.7 (C_0).146 (M^++1, 11), 145 (M^+, 100), 130 (38), 144 (22).

*4.3.3. 1,2,3,4-Tetrahydro-1H-carbazole (**5**)*[17]. The reaction was carried out in accordance with general procedure for batch synthesis (4.3) using cyclohexanone **11** and phenylhydrazine **7** to give the title compound **5** as an off-white solid, mp 118–119 °C (lit.,[16] 116–118 °C); δ_H 1.70–1.81 (4H, m, 2×CH_2). 2.55 (2H, t, *J*=5.6 Hz, CH_2), 2.63 (2H, t, *J*=2.6 Hz, CH_2), 6.85 (1H, t, *J*=7.3 Hz, ArH), 6.91 (1H, t, *J*=7.5 Hz), 7.17 (1H, d, *J*=7.1 Hz, ArH), 7.26 (1H, d, *J*=7.1 Hz, ArH), 10.56 (1H, br s, NH); δ_C 21.2 (CH_2), 23.3 (CH_2), 23.5 (CH_2), 23.6 (CH_2), 108.6 (C_0), 111.1 (C_0), 117.6 (CH), 118.5 (CH), 120.5 (CH), 127.9 (C_0), 134.9 (C_0), 136.2 (C_0); 172 (M^++1, 13), 171 (M^+, 64), 143 (100).

*4.3.4. 1,2,3,4-Tetrahydrocyclopenta[b]indole (**15**)*[17]. The reaction was carried out in accordance with general procedure for batch synthesis (4.3) using cyclopentanone **12** and phenylhydrazine **7** to give the title compound **15** as a white solid, mp 104–105 °C (lit.,[16] 107 °C); δ_H 2.43 (2H, p, *J*=7.0 Hz, CH_2), 2.70 (2H, t, *J*=7.0 Hz, CH_2), 2.79 (2H, t, *J*=7.1 Hz, CH_2), 6.89 (1H, t, *J*=7.3 Hz, ArH), 6.94 (1H, t, *J*=7.4 Hz, ArH), 7.24 (1H, d, *J*=7.1 Hz, ArH), 7.27 (1H, d, *J*=7.1 Hz, ArH), 10.76 (1H, br s, NH); δ_C 24.59 (CH_2), 25.83 (CH_2), 28.85 (CH_2), 112.11 (CH), 118.04 (C_0) 118.34 (CH), 118.97 (CH), 120.10 (CH), 124.72 (C_0), 141.55 (C_0), 144.73 (C_0); 157 (M^+, 74), 156 (100), 130 (41), 77 (36).

*4.3.5. Ethyl 1H-indole-2-carboxylate (**16**)*[18]. The reaction was carried out in accordance with general procedure for batch synthesis (4.3) using ethyl pyruvate **13** and phenylhydrazine **7** to give the title compound **16** as a cream coloured solid, mp 122–123 °C (lit.,[19] 125 °C); δ_H 1.34 (3H, t, *J*=7.1 Hz, CH_3), 4.33 (2H, q, *J*=7.1 Hz, CH_2), 7.07 (1H, t, *J*=8.0 Hz, ArH), 7.13–7.14 (1H, m, ArH), 7.25 (1H, t, *J*=8.3 Hz, ArH), 7.45 (1H, d, *J*=8.2 Hz, ArH), 7.65 (1H, d, *J*=8.0 Hz, ArH), 11.87 (1H br s, NH); δ_C 14.87 (CH_3), 60.98 (O–CH_2), 108.23 (CH), 113.14 (CH), 120.72 (CH), 122.62 (CH), 125.18 (CH), 127.29 (C_0), 127.91 (C_0), 137.93 (C_0) 161.89 (C_0); 190 (M^++1, 9), 189 (M^+, 68), 143 (100), 115 (33).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.005.

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