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Microreactor Technology: Continuous Synthesis of 1*H*-Isochromeno[3,4-*d*]imidazol-5-ones

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Abstract:

A synthetic method was evaluated to form 1*H*-isochromeno[3,4-*d*]imidazol-5-ones *via* ring closure starting from 3-amino-4-(arylamino)-1*H*-isochromen-1-ones. The method was implemented and optimized in a microreactor environment. It was possible to synthesize these compounds in a continuous mode with an output up to 2.2 g/h.

Introduction

During the last decades, microreactor technology has gained an enormous interest in both academic research and within (mostly) the pharmaceutical industry.[1] Extensive research is performed to develop new types of microreactors,[1b,2] but also the application of this technology has been investigated thoroughly. Applications such as protein crystallization,[3] azo-pigment formation,[4] production of peptides,[5] DNA amplification[6] and DNA purification[7] in microstructured devices are well-known. Also a lot of research is done to apply this continuous technology in organic synthesis processes,[8] such as total syntheses[9] and multicomponent reactions.[10] An important advantage of this technology arises where reactions can be successfully accelerated.[11] Owing to the structure of the microreactor (with capillaries in the range of 100 μm), the mixing rate is extremely high, and the temperature profile is very narrow due to a greater surface-to-volume ratio, compared to those in a batch vessel. Due to the design of the subsequent capillary system, back-mixing is minimized and the reaction time is narrowly controlled. As a consequence, switching from batch to continuous processing is beneficial while still using similar conditions minimizing the expensive and time-consuming process of scaling-up. Instead, the principle of numbering-up can be applied.[12] This means that the number of reactors is increased instead of the volume of the reactor. In such a microenvironment setup it is also possible to perform safely hazardous reactions and reactions using toxic reagents.[10a,13]

Following our recent research about the formation of 3,4-diamino-1*H*-isochromen-1-ones **7** under microreactor conditions with in situ formation of hydrogen cyanide,[10a] a ring closure of the vicinal amino groups was evaluated in order to attach an imidazole core to the molecule. Until now, this basic skeleton was only once detected in a side reaction for the production of 3*H*-indeno[2,1-*d*]imidazol-8-ones **5** (Scheme 1).[14] Some related compounds, which contain the chromenone instead of the isochromenone structure, are known to have a biological activity as phosphodiesterase inhibitors for the treatment of allergic or immunity-associated diseases[15] and as central nervous system depressants.[16]

Imidazoles are also very important in view of their potential to form ionic liquids after quaternisation of the nitrogen atom.[17]

Results and Discussion

In this study, the CYTOS College System, a microreactor manufactured by CPC - Cellular Process Chemistry Systems GmbH, was used.[18] This device consists of a stacked plate

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(1) (a) Brivio, M.; Verboom, W.; Reinhoudt, D. N. *Lab Chip* **2006**, *6*, 329. (b) Doku, G. N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron* **2005**, *61*, 2733. (c) de Mello, A.; Wootton, R. *Lab Chip* **2002**, *2*, 7N.

(2) Hong, C.; Choi, J.; Ahn, C. *Lab Chip* **2004**, *4*, 109.

(3) Zheng, B.; Roach, L. S.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2003**, *125*, 11170.

(4) Dietz, E.; Weber, J.; Schnaitmann, D.; Wille, C.; Unverdorben, L. U.S. Patent 6,582,508, 2003.

(5) Flögel, O.; Codée, J. D. C.; Seebach, D.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7000.

(6) Cheng, J.; Hsieh, C.; Chuang, Y.; Hsieh, J. *Analyst* **2005**, *130*, 931.

(7) Lehmann, U.; Vandevyver, C.; Parashar, V. K.; Gijs, M. A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3062.

(8) (a) Watts, P.; Wiles, C. *Chem. Commun.* **2007**, 443. (b) Geyer, K.; Codée, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434. (c) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236. (d) Snyder, D. A.; Noti, C.; Seeberger, P. H.; Schael, F.; Bieber, T.; Rimmel, G.; Ehrfeld, W. *Helv. Chim. Acta* **2005**, *88*, 1.

(9) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427.

(10) (a) Acke, D. R. J.; Stevens, C. V. *Green Chem.* **2007**, *9*, 386. (b) Acke, D. R. J.; Stevens, C. V. *Org. Process Res. Dev.* **2006**, *10*, 417. (c) Van Meenen, E.; Moonen, K.; Acke, D. R. J.; Stevens, C. V. *Arkivoc* **2006**, *i*, 31. (d) Acke, D. R. J.; Orru, R. V. A.; Stevens, C. V. *QSAR Combi. Sci.* **2006**, *25*, 474.

(11) (a) Wensink, H.; Benito-Lopez, F.; Hermes, D. C.; Verboom, W.; Gardeniers, H. J. G. E.; Reinhoudt, D. N.; van den Berg, A. *Lab Chip* **2005**, *5*, 280. (b) Kawazumi, H.; Kanno, K.; Fujii, M.; Yamaguchi, Y.; Maeda, H. Mechanism of Reaction Efficiency Enhancement in Microchannels by Spectroscopic Visualization and Numerical Simulation. In *Abstract Book of the 1st European Chemistry Congress - EuCheMS 2006*; 2006, 245.

(12) (a) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440. (b) Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652.

(13) (a) Ducry, L.; Roberge, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7972. (b) Zhang, X.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455. (c) Ferstl, W. F.; Schwarzer, M. S.; Loebbecke, S. L. *Chem. Ing. Tech.* **2004**, *76*, 1326. (d) Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, 2827. (e) Dummann, G.; Quittmann, U.; Gröschel, L.; Agar, D. W.; Wörz, O.; Morgenschweis, K. *Catal. Today* **2003**, *79*, 433.

(14) Hemmerling, H.; Merschenz-Quack, A.; Wunderlich, H. *Z. Naturforsch. (B)* **2004**, *59*, 1143.

(15) Eggenweiler, M.; Rochus, J.; Wolf, M.; Gassen, M.; Poeschke, O. PCT Int. Appl. WO 01/29049, 2001; *Chem. Abstr.* **2001**, *134*, 331619.

(16) Savel'ev, V. L.; Pryanishnikova, N. T.; Zagorevskii, V. A.; Chernyakova, I. V.; Artamonova, O. S.; Shavyrina, V. V.; Malysheva, L. I. *Khim.-Farm. Zh.* **1983**, *17*, 697; *Chem. Abstr.* **1983**, *99*, 158325.

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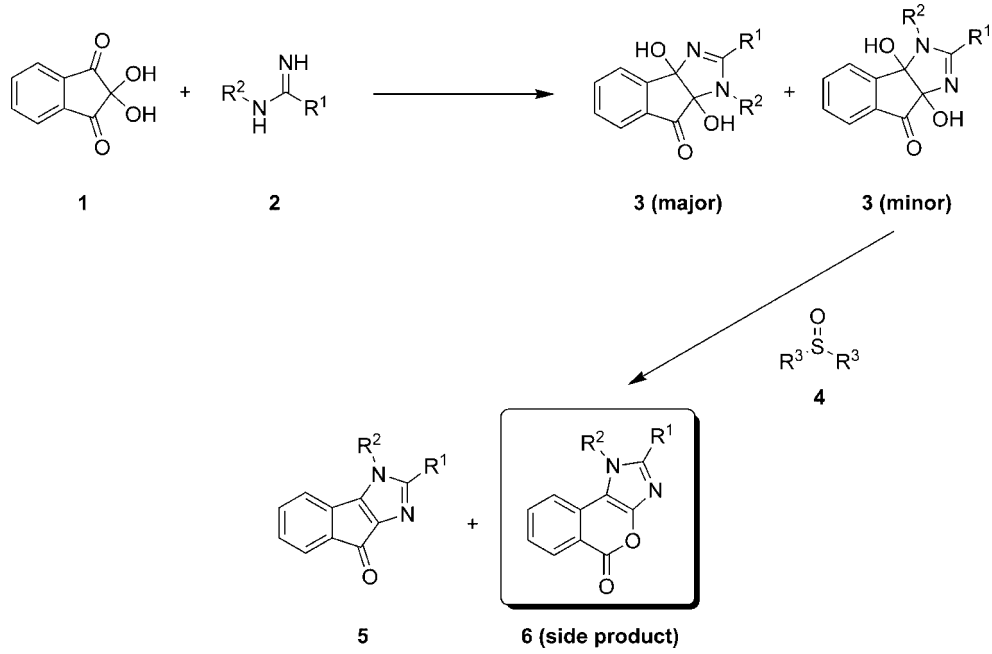
Scheme 1. **Formation of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones 6 as a side product**[14]



Scheme 2. **Formation of 1*H*-isochromeno[3,4-*d*]-imidazol-5-ones 6**

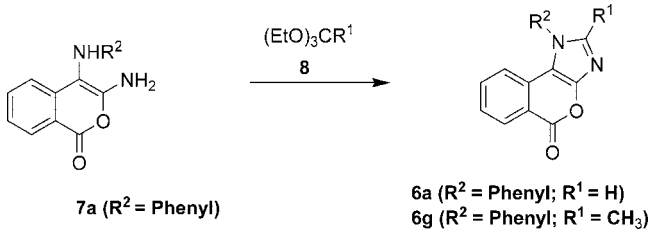


Table 1. **Ring closure to 1*H*-isochromeno[3,4-d]-imidazol-5-ones 6 under batch conditions**

entry	orthoester	conditions	reaction time (h)	yield (%)
1	$(EtO)_3CH$	A[a]	3	quantitative
2	$(EtO)_3CH$	B[b]	0.5	quantitative
3	$(EtO)_3CH$	C[c]	2	97
4	$(EtO)_3CCH_3$	A	6	intermediate **9g**
5	$(EtO)_3CCH_3$	B	2.5	intermediate **9g**
6	$(EtO)_3CCH_3$	C	2	96

[a] A: 1 mmol of compound **7a** and 0.1 mmol of *p*-toluenesulfonic acid monohydrate (*p*-TsOH) were added to 10 mL of the orthoester **8a** or **8b** at 22°C.[19a] [b] B: 1 mmol of compound **7a** and 1 mmol of 12.1 N HCl were added to 5 mL of the orthoester **8a** or **8b** at 22°C.[19a] [c] C: 1 mmol of compound **7a**, 0.5 mmol of trifluoroacetic acid (TFA) and 5 mmol of the orthoester **8a** or **8b** were added to 10 mL of dichloromethane at 22°C.[19b]

microreactor and a residence time unit (RTU), which consists of an isolated tube to increase the reaction time. The microreactor itself has a mixing zone and a reaction zone. Pumping of the reagents through the system is pressure driven.

After the microreactor synthesis and the isolation of the starting 3-amino-4-(arykamino)-1*H*-isochromen-1-one, **7** (R^2 = phenyl for **7a**),[10a] a subsequent microreactor modification was envisaged to decorate the scaffold *via* the synthesis of a physiologically interesting imidazole moiety.

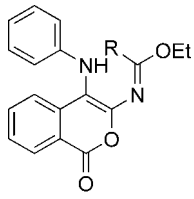
The initial part of the research consisted of the search for compatible reaction conditions for the ring closure in the microreactor. Scheme 2 displays the ring closure using orthoesters. A set of different reaction conditions based on known ring closures to imidazole structures[19] was evaluated in batch to find suitable parameters for the implementation to microreactor conditions. Table 1 summarizes the results of the optimization of the reaction.

In these initial batch studies, three different acids, either in catalytic or in equimolar amounts, were tested to obtain the ring-closed product. In the case of ethyl orthoformate $(EtO)_3CH$ **8a**, a catalytic amount of *p*-TsOH was enough to push the reaction to completion (entry 1). An analogous procedure with HCl (entry 2) yielded the end product also in quantitative amount, but much faster. In both these procedures, the orthoester was used as a solvent. In the case where trifluoroacetic acid (TFA) was used as the acid catalyst (entry 3), almost quantitative yields were obtained. In this reaction setup, dichloromethane was utilised as solvent. However, all these batch procedures showed solubility problems of the starting compound, which needed to be overcome to prevent clogging of the microchannels before testing under microreactor conditions. When dichloromethane was used as solvent, it was possible to dissolve the 3-amino-4-phenylamino-1*H*-isochromen-1-one **7a** only in small amounts (less than 0.1 M). In case when the orthoester itself served as solvent, even worse results were obtained. Since this concentration is too low to perform a continuous reaction with a reasonable output, other solvents were tested. It appeared that only DMF and related solvents were suitable to dissolve larger amounts of the starting compound. If ethyl orthoacetate

(17) (a) Forsyth, S. A.; Pringle, J. M.; MacFarlane, D. R. *Aust. J. Chem.* **2004**, *57*, 113. (b) Marsh, K. N.; Boxall, J. A.; Lichtenthaler, R. *Fluid Phase Equilib.* **2004**, *219*, 93. (c) Headley, A. D.; Bukuo, N. *Aldrichimica Acta* **2007**, *40*, 107.

(18) CPC - Cellular Process Chemistry Systems GmbH: Heiligkreuzweg 90, D-55130 Mainz, Germany, www.cpc-net.com. Schwalbe, T.; Golbig, K.; Hohmann, M.; Georg, P.; Oberbeck, A.; Dittmann, B.; Stasna, J.; Oberbeck, S. (Cellular Process Chemistry Inc., U.S.A.). Eur. Pat. Appl. EP 1 123 734, 2001; *Chem. Abstr.* **2001**, *135*, 154468b.

(19) (a) Rivas, F. M.; Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2002**, *67*, 1708. (b) Chi, Y.; Sun, C. *Synlett* **2000**, 591.



9a (R = H)
9g (R = CH_3)

Figure 1. **Ethyl *N*-(1-oxo-4-phenylamino-1*H*-isochromen-3-yl)acetimidate 9g formed as intermediate.**

$(EtO)_3CCH_3$ **8b** was used as orthoester, only an intermediate product was formed using HCl (entry 4) or *p*-TsOH (entry 5). The cyclization with $(EtO)_3CCH_3$ therefore proved to be more demanding.[19a] It was observed that the reaction did not go to completion, and on the basis of the spectral data it was assumed that ethyl *N*-(1-oxo-4-phenylamino-1*H*-isochromen-3-yl)acetimidate **9g** was isolated as the intermediate (Figure 1). Only in the case of TFA was complete cyclization obtained in excellent yields (entry 6).

To optimize the reaction under microreactor conditions, different parameters were analyzed: solvent, residence time τ (i.e., reaction time), temperature, concentration and the ratio of start product **7**, catalyst and orthoester **8**. The optimization was started based on the reaction conditions of the *p*-TsOH-catalyzed ring closure. Due to the low solubility of the start product **7a**, DMF was the solvent of choice. Table 2 shows the optimization efforts. As can be seen in Table 2, the optimum reaction temperature was 22 °C (entry 2). Both an increase or a decrease of the reaction temperature led to worse results. In the case of 0 °C (entry 1), the final reaction mixture still contained a considerable amount of starting material together with the end product. At higher temperatures (entries 4a−c), no significant conversion was observed after the microreactor unit. Upon passage through the RTU, all starting material was consumed. However, a significant buildup of the intermediate was observed (as high as 40 mol % of the reaction mixture), which resulted in a rather poor conversion into the end product.

Increasing the catalytic amount of *p*-TsOH gave rise to the formation of trace amounts of ethyl *p*-toluenesulfonate (*p*-TsOEt, entries 5 and 6). If the excess of orthoester was increased, similar effects occurred (entries 7 and 8). In the case of a 50:50 solvent mixture (orthoester/DMF, entry 9), incomplete conversion was achieved, and the amount of *p*-TsOEt increased even to 11 mol% of the mixture. The concentration of the starting material was finally doubled to 0.2 M with a similar outcome as entry 2 (entry 10). With a final optimization effort, the residence time τ was reduced to approximately 30 min (entries 11−13). By a further decrease of the reaction time also incomplete conversion was experienced. The optimized conditions were: 0.2 M starting material **7a** in DMF was mixed at 22 °C in the microreactor with a mixture of 0.1 equiv of *p*-TsOH and 5 equiv of $(EtO)_3CH$ **8a** in DMF with a total residence time in the microreactor and RTU of 30 min.

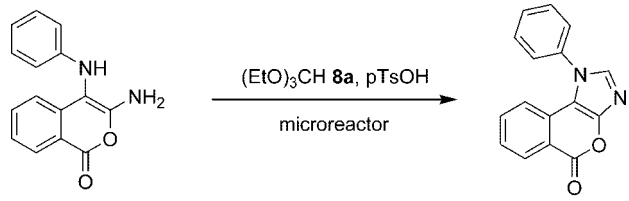
Although complete conversion and reasonable yields were already obtained after the RTU with the initial reaction conditions (entry 2), further optimization was performed in order to achieve a complete conversion after the microreactor unit (i.e., after 3 min of reaction instead of 118 min). The goal to achieve complete conversion after the microreactor was to combine the reaction with a continuous extraction in the RTU, since initial tests with a continuous extraction gave better performance in product recovery. An optimized work-up procedure had to be evaluated, since DMF is difficult to remove from the reaction mixture. Several conditions were tested such as a basic extraction in the presence of $NaHCO_3$ and different acidic work ups (HCl, acetic acid) in batch mode and also *via* a microextraction in basic medium. Under batch conditions, several extraction steps were necessary to remove all DMF in both basic and acid extractions, which resulted in a loss of approximately 20% of the product. The HCl-based extraction gave the best performance in view of DMF removal, while the acetic acid-based extraction was the worst. Since the microreactor used in this study is made of stainless steel, continuous aqueous HCl extraction was impossible; thus, only the basic extraction was tested in the microextraction procedure. This gave a recovery of 97% of the end product, however, with a lower performance in DMF removal.

Comparison of the conversion results after the microreactor and after the RTU showed that in most cases complete conversion was easily obtained in the latter case, which is obvious due to the prolonged reaction time. On the other hand, after the microreactor a mean conversion of only 50% was achieved. The different optimization steps were not successful in order to get to a complete conversion. The best result was obtained in the case of a 25-fold excess of $(EtO)_3CH$ **8a** (81%, entry 8). In all reaction samples taken after the microreactor unit, traces of the intermediate **9a**, *p*-TsOEt or both were detected.

A final attempt to achieve complete conversion at the end of the microreactor was based on successful stopped-flow experiments in previous work.[10b,20] The rationale of this process is to increase the residence time and thus the reaction time, by pausing the pumping at regular time intervals. It is also possible to have longer residence times by using slower flow rates. However, this is not feasible, due to reproducibility problems of the pump flow. Therefore, the stopped-flow technique was introduced. On the basis of the optimized results for the output after the microreactor in Table 2 (which gave a conversion of around 50%, entry 2), it was decided to double the residence time in the microreactor twice: one time to achieve a theoretically 100% conversion and a second time as a safety margin. This led to a flow period of 1 min alternated with a pump stop period of 3 min. Table 3 shows the results of this study. Entry 1 shows that this setup did not result in complete conversion. An increase of the residence time by increasing the stop period (entry 3) gave even a lower conversion. Longer residence times were not examined since it is not efficient from a practical point of view, leading to a low output per time unit. A final attempt was made by increasing the excess of orthoester since this gave better results in the optimization procedure (Table 2, entry 8). In this case, similar results were obtained. Therefore, it was not possible to get complete conversion after the microreactor

(20) (a) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065. (b) Wiles, C.; Watts, P.; Haswell, S. J. *Org. Process Res. Dev.* **2004**, *8*, 28. (c) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62.

Table 2. **Optimization of the ring closure of 7a under microreactor conditions[a]**



7a **6a**

				after microreactor		after RTU	
entry	T (°C)	p-TsOH (equiv)	$(EtO)_3CH$ (equiv)	conversion (%)[b]	yield (%)[c]	conversion (%)[b]	yield (%)[c]
				$\tau = 5$ min		$\tau = 118$ min	
1	0	0.1	5	41	24	78	58
2	rt	0.1	5	58	28	100	86
3	50	0.1	5	52	19	100	87
4a	100	0.1	5	0	0	59	38
4b	120	0.1	5	5	3	58	37
4c	140	0.1	5	6	3	71	67
5	rt	0.2	5	52	29	100	78
6	rt	0.5	5	60	28	100	82
7	rt	0.1	10	46	22	100	79
8	rt	0.1	25	81	50	100	76
9	rt	0.1	60	19	14	90	67
10[d]	rt	0.1	5	54	43	100	82
				$\tau = 1.5$ min		$\tau = 59$ min	
11[d]	rt	0.1	5	–	–	100	80
				$\tau = 0.75$ min		$\tau = 29.5$ min	
12[d]	rt	0.1	5	–	–	100	88
				$\tau = 0.5$ min		$\tau = 19.6$ min	
13[d]	rt	0.1	5	–	–	97	43

[a] General conditions: inlet A: 0.1 M of **7** in DMF; inlet B: 0.1 M $(EtO)_3CH$ **8a** (for the runs with 1 equiv of orthoester; 0.2 M for the runs with 2 equiv, ...) and p-TsOH in DMF; residence time after microreactor: 5 min; residence time after RTU: 118 min. [b] Based on the integration signals in the ^1H NMR spectrum. [c] Based on the total mass of end product collected from the rough mixture and the degree of conversion, see Experimental Section. [d] Inlet A: 0.2 M of **7a** in DMF; inlet B: 1 M $(EtO)_3CH$ **8a** and p-TsOH in DMF.

Table 3. **Use of the stopped-flow technique[a] in the optimization of the reaction output at the microreactor outlet**

				after microreactor	
entry	stop − flow (min − min)	residence time (min)	$(EtO)_3CH$ (equiv)	conversion (%)[b]	yield (%)[c]
1	3 − 1	12	5	84	61
2	3 − 1	18	25	87	59
3	5 − 1	18	5	60	35

[a] General conditions: inlet A: 0.2 M of **7a** in DMF; inlet B: $(EtO)_3CH$ **8a** and 0.02 M of p-TsOH in DMF; 22°C; stopped-flow technique. [b] Based on the integration signals in the ^1H NMR spectrum. [c] Based on total mass of end product collected in the rough mixture and degree of conversion, see Experimental Section.

unit, and consequently, an advantageous microextraction procedure could not be established.

Finally, the generality of the optimized conditions was tested. This was accompanied with some additional problems. The results are shown in Table 4. Entries 2 and 4 already indicate that the optimized reaction conditions are not general for all starting materials. However, after elongation of the residence time to approximately 2 h, all the end products without substituent on the 2-position were completely converted to the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **6** (entry 3 and entry 7−9). The only exception was the 3-tolyl-substituted compound **7c** that was only converted in 48% to the end product (entry 5). To investigate whether the lack of generality for the ring closure with triethyl orthoformate was due to a microreactor effect, the synthesis of compounds **6a**−**c** was also conducted in batch mode under identical conditions as in the optimized microreactor procedure (entries 2b−5b). A correlation between the two modes of synthesis seems absent given the discrepancies in conversion and yield, except for compound **6a**. Complete conversion and high yields of derivative **6b** could be obtained after shorter reaction times in batch mode. Formation of compound **6c**, however, was only observed under microreactor conditions.

In the case of more sterically demanding orthoesters, such as triethyl orthoacetate **8b**, trimethyl orthovalerate **8c** and trimethyl orthobenzoate **8d**, it was not possible to obtain a complete conversion at the end of the RTU under the given conditions. Since under batch conditions the reaction to achieve ring closure was faster with TFA (Table 1), it was decided to check these harsher conditions for the reactions that did not proceed or proceeded only partially. It had to be taken into account that there was no known effect of the TFA concentration on the interior of the microreactor unit.[21] In the case of the 3-tolyl-substituted 1*H*-isochromen-1-one **1c**, it was possible to obtain a complete conversion of the reaction (entry 6). For the other substituents, it was only possible to obtain a partial

(21) Oral communication with the manufacturers of the microreactor device learned that there was no knowledge about the effect of TFA on stainless steel 1.4571 (German Standard). It was decided to work under very dry conditions, using fresh DMF.

Table 4. **Optimized conditions[a,b] to produce 1*H*-isochromeno[3,4-*d*]imidazol-5-ones 6**

entry	R^2	R^1	product	conversion (%)[c]	yield (%)[d]	output (g/h)
1[e]	Ph	H	**6a**	100	88	2.21
1b[i]	Ph	H	**6a**	100	91	
2[e]	3-methoxyphenyl	H	**6b**	46	7	0.20[h]
2b[i]	3-methoxyphenyl	H	**6b**	100	86	
3[f]	3-methoxyphenyl	H	**6b**	100	55	0.39
3b[j]	3-methoxyphenyl	H	**6b**	100	96	
4[e]	3-tolyl	H	**6c**	34	8	0.21[h]
4b[i]	3-tolyl	H	**6c**	0	0	
5[f]	3-tolyl	H	**6c**	48	27	0.18[h]
5b[j]	3-tolyl	H	**6c**	0	0	
6[g]	3-tolyl	H	**6c**	100	69	0.46
7[f]	4-tolyl	H	**6d**	100	78	0.52
8[f]	4-methoxyphenyl	H	**6e**	100	75	0.53
9[f]	4-fluorophenyl	H	**6f**	100	92	0.62
10[f]	Ph	CH_3	**6g**	0	0	0
11[g]	Ph	CH_3	**6g**	52	36	0.24[h]
12[g]	Ph	C_4H_9	**6h**	27	18	0.14[h]
13[g]	Ph	Ph	**6i**	2	1	0.01[h]

[a] General microreactor conditions: inlet A: 0.2 M of **7** in DMF; inlet B: acid and 1.0 M of **8** in DMF; 22 °C, sampling at the RTU outlet. See footnotes *e*−*h*. [b] Batch conditions: 0.1 M of **7**, 5 equiv of TsOH and 0.1 equiv of **8** in DMF, 22 °C. See footnotes *i* and *j*. [c] Based on the integration signals in the ^{1}H NMR spectrum. [d] Based on the total mass of end product collected from the rough mixture and the degree of conversion, see Experimental Section. [e] Residence time: 29.5 min, acid: 0.02 M *p*-TsOH. [f] Residence time: 118 min, acid: 0.02 M *p*-TsOH. [g] Residence time: 118 min, acid: 0.1 M TFA. [h] Purification *via* crystallization. [i] Reaction time: 30 min. [j] Reaction time: 120 min.

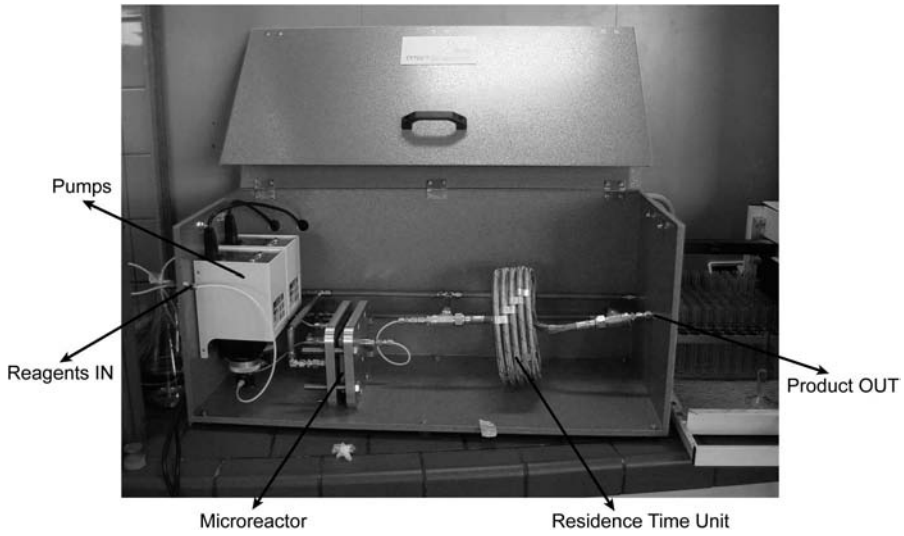


Figure 2. **CYTOS College System.**[18]

conversion (entries 11−13). This was due to the bulky substituent that had to be incorporated which lowered the reaction rate. In the case of complete conversion to the end products, extra purification was not necessary. When only partial conversion was obtained, the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **6** were further purified by crystallization. Using the method optimized in this study, it was possible to produce a library of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones **6** by applying microreactor technology.

Conclusions

Starting from 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, also produced under microreactor conditions, and different orthoesters, a ring-closure method was developed to obtain 1*H*-isochromeno[3,4-*d*]imidazol-5-ones. By optimizing the reaction conditions, it was possible to apply this method under microreactor conditions, leading to a library of compounds with a new 1*H*-isochromeno[3,4-*d*]imidazol-5-one skeleton. Moderate to good yields were obtained, and in the case of complete conversion of the reaction a continuous output of 0.4−2.2 g/h of end product was achieved.

Experimental Section

Material and Methods. The microreactor used in this study is a CYTOS College System[18] (Figure 2). The CYTOS College System microreactor consists of several stacked plates with microstructures in the sub-millimeter range (width approximately 100 μm). The volume of the microreactor itself is 1.2 mL and that of the RTU 45 mL so the total volume (V_{total}) of the system is 46.2 mL. The pumps were calibrated at the desired flow rate. The temperature was controlled using an external circuit (Huber Tango thermostat).

The reagents were used without prior purification before use. ^{1}H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz) and

^{19}F NMR spectra (282 MHz) were recorded on a Jeol Eclipse FT 300 NMR spectrometer. IR spectra were measured with a Perkin-Elmer Spectrum One FT-IR spectrophotometer. Low-resolution mass spectra were recorded on an Agilent 1100 series VL mass spectrometer (ES 70 eV). Elemental analysis was performed with a Perkin-Elmer 2400 series 2 elemental analyzer. Melting points were measured with a Büchi B-540 apparatus and are uncorrected. Crude reaction mixtures were analyzed on LC/MS/UV.

Batch Reactions. *Condition A.* Compound **7a** (0.252 g, 1 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol, 0.1 equiv) were added to the orthoester **8a** or **8b** (10 mL, 60 equiv of **8a** or 55 equiv of **8b**). The mixture was stirred at 22 °C. After completion of the reaction, followed by TLC, the mixture was poured in ethyl acetate (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL). The water phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered, and the solvent was evaporated to obtain the end product.

Condition B. Compound **7a** (0.252 g, 1 mmol, 1 equiv) and HCl (12.1 N, 83 μL, 1 mmol, 1 equiv) were added to the orthoester **8a** or **8b** (5 mL, 30 equiv of **8a** or 27 equiv of **8b**). The mixture was stirred at 22 °C. After completion of the reaction, followed by TLC, the mixture was poured in dichloromethane (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL). The water phase was extracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered, and the solvent was evaporated to obtain the end product.

Condition C. Compound **7a** (0.252 g, 1 mmol, 1 equiv), trifluoroacetic acid (37 μL, 0.5 mmol, 0.5 equiv) and the orthoester **8a** or **8b** (5 mmol, 5 equiv) were added to dichloromethane (10 mL). The mixture was stirred at 22 °C. After completion of the reaction, followed by TLC, the mixture was poured in dichloromethane (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL). The water phase was extracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried with $MgSO_4$. The $MgSO_4$ was filtered, and the solvent was evaporated to obtain the end product.

Optimized Procedure (Table 2, entry 12). 3-Amino-4-(phenylamino)-1*H*-isochromen-1-one **7a** (3.53 g, 14 mmol) was dissolved in *N*,*N*-dimethyl formamide (70 mL) in a measuring cylinder. The other measuring cylinder contained *p*-toluenesulfonic acid monohydrate (0.266 g, 1.4 mmol) and triethyl orthoformate **8a** (10.36 g, 70 mmol) dissolved in *N*,*N*-dimethyl formamide (70 mL). Both solutions were connected to the inlets of the device. Both pumps were adjusted to the same flow rate (r) of 0.8 mL/min/pump to obtain a residence time (τ) of 29.5 min. The flow rate was controlled by measuring the ingoing and outgoing volumes. The residence time was calculated by the formula:

$$\tau = \frac{V_{\text{total}}}{r_{\text{total}}} \quad \text{with} \quad r_{\text{total}} = 1.6 \ \text{mL/min} \tag{1}$$

The temperature of the system was controlled at room temperature, i.e. 22 °C. At the outlet of the RTU, the end product was collected at steady-state conditions, i.e. after 1.6 τ. A sample (10 mL) was collected for work-up. The reaction mixture was quenched with water (20 mL). Extra water (80 mL) was added to the mixture, and this was extracted with dichloromethane (50 mL). The organic phase was subsequently washed with water (100 mL), HCl (0.5 N, 2 × 100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$. After filtration of the drying product, the solvent was evaporated to obtain the end product **6a**.

This procedure has been used to obtain the results of Table 2, entry 12. The other results were obtained in the same way, except for minor changes such as concentration, temperature, flow rate ($\sim \tau$), equivalents of reagents and starting 3-amino-4-(arylamino)-1*H*-isochromen-1-one (**7a**: R^2 = phenyl) as stated within the experiments. In the case of incomplete conversions, such as the samples at the microreactor outlet, a ^{1}H NMR spectrum of the crude mixture was recorded. In both starting material **7** and end products **6**, the anisotropic effect of the carbonyl moiety causes a significant downfield shift of the aromatic ortho protons (respectively H-8 and H-6). This results in a shift of both signals out of the rest of the aromatic signals and makes a clear integration possible. The degree of conversion was calculated using the integration of these signals in the ^{1}H NMR spectrum. The yield of the reaction was calculated from the total mass of end product collected and the conversion, using the following formula:

$$\text{yield}\ (\%) = \frac{\text{mass}_{\text{weighed}}}{\text{mass}_{\text{calculated 100\% conversion}}} \times \text{conversion} \tag{2}$$

In the experiments with the stopped-flow, the same conditions were used as in the general microreactor procedure. Samples were taken only at the microreactor outlet. A flow time of 1 min was chosen, and a stop time of 3 or 5 min. With a total volume of 1.2 mL and a flow rate of 0.2 mL/min/pump, this meant the total residence time increased from 5 min to 12 or 18 min.

In Table 4, entries 6, 11, 12 and 13, trifluoroacetic acid (0.5 equiv) was used instead of *p*-toluenesulfonic acid monohydrate (0.1 equiv). As a consequence, fresh DMF was used.[21]

The starting materials were produced according to the methods described in previous work.[10a] The spectra of the starting compounds were in accordance with literature data.[22]

*Compound **6a**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 6.94 (d, J = 8.0 Hz, 1 H, H-9), 7.36 (td, J = 7.6, 1.0 Hz, 1 H, H-7), 7.46−7.56 (m, 4 H, H-2, H-8, H-2′ and H-6′), 7.63−7.68 (m, 3 H, H-3′, H-4′ and H-5′), 8.35 (d, J = 8.0 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 109.0 (C-9b), 119.0 (C-9), 119.2 (C-5a), 126.7 (3 C, C-7, C-2′ and C-6′), 129.7 (C-9a), 130.2 (3 C, C-3′, C-4′ and C-5′), 132.3 (C-6), 134.9 (C-8), 136.3 (C-1′), 136.5 (C-2), 151.4 (C-3a), 161.7 (C═O). IR (KBr): ν_{max} = 3436, 3136, 1729 (C═O), 1718, 1616, 1498, 1470, 1418, 1380, 1316, 1218, 1070, 1037, 1017, 824, 777, 760, 706, 683, 644, 554 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 263 (M + H$^+$). Elem. anal.: calculated for $C_{16}H_{10}N_2O_2$: C, 73.27, H, 3.84, N, 10.68, found: C, 73.24, H, 3.85, N, 10.67. Mp: 221.7−222.4 °C. Yellow crystals. R_f (PE/EA 50:50) = 0.32.

(22) Opatz, T.; Ferenc, D. *Eur. J. Org. Chem.* **2005**, 817.

*Compound **6b**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 3.89 (s, 3 H, OCH_3), 7.00−7.03 (m, 2 H, H-9 and H-2′), 7.09 (ddd, J = 7.7, 1.5, 0.8 Hz, 1 H, H-4′ or H-6′), 7.16 (ddd, J = 8.3, 2.5, 0.8 Hz, 1 H, H-4′ or H-6′), 7.37 (pseudo-td, J = 7.6, 1.2 Hz, 1 H, H-7), 7.48−7.54 (m, 2 H, H-8 and H-5′), 7.55 (s, 1 H, H-2), 8.37 (pseudo-d, J = 7.4 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 55.8 (OCH_3), 109.0 (C-9b), 112.3 (C-2′), 115.9 (C-4′ or C-6′), 118.7 (C-4′ or C-6′), 119.2 (C-9 and C-5a), 126.6 (C-7), 129.7 (C-9a), 130.9 (C-5′), 132.3 (C-6), 134.8 (C-8), 136.4 (C-2), 137.3 (C-1′), 151.3 (C3-a), 160.8 (C-3′), 161.7 (C═O). IR (KBr): ν_{max} = 3089, 1735 (C═O), 1619, 1605, 1494, 1477, 1417, 1377, 1334, 1271, 1222, 1064, 1029, 845, 798, 757, 684 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 293 (M + H$^+$). Elem. anal.: calculated for $C_{17}H_{12}N_2O_3$: C, 69.86, H, 4.14, N, 9.58, found: C, 69.88, H, 4.14, N, 9.57. Mp: 166.6−167.2 °C. Orange-yellow powder. R_f (PE/EA 50:50) = 0.32.

*Compound **6c**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 2.50 (s, 3 H, CH_3), 6.96 (d, J = 8.0 Hz, 1 H, H-9), 7.27−7.53 (m, 6 H, H-7, H-8, H-2′, H-4′, H-5′ and H-6′), 7.54 (s, 1 H, H-2), 8.37 (dd, J = 8.0, 0.8 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 21.5 (CH_3), 109.0 (C-9b), 119.1 (C-9 and C-5a), 123.7 (C-6′), 126.6 (C-7), 127.1 (C-2′), 129.8 (C-9a), 129.9 (C-5′), 130.9 (C-4′), 132.3 (C-6), 134.9 (C-8), 136.2 (C-1′), 136.5 (C-2), 140.6 (C-3′), 151.3 (C-3a), 161.8 (C═O). IR (KBr): ν_{max} = 3126, 1732 (C═O), 1615, 1550, 1494, 1472, 1414, 1378, 1333, 1216, 1068, 1043, 1019, 809, 762, 708, 684, 636 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 277 (M + H$^+$). Elem. anal.: calculated for $C_{17}H_{12}N_2O_2$: C, 73.90, H, 4.38, N, 10.14, found: C, 73.91, H, 4.38, N, 10.13. Mp: 166.4−168.6 °C. Brown orange powder. R_f (PE/EA 70:30) = 0.17.

*Compound **6d**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 2.53 (s, 3 H, CH_3), 6.96 (d, J = 8.0 Hz, 1 H, H-9), 7.34−7.52 (m, 6 H, H-7, H-8, H-2′, H-3′, H-5′ and H-6′), 7.53 (s, 1 H, H-2), 8.38 (pseudo-d, J = 8.0 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 21.5 (CH_3), 109.1 (C-9b), 119.0 (C-9), 119.2 (C-5a), 126.4 (2 C, C-2′ and C-6′), 126.6 (C-7), 129.8 (C-9a), 130.7 (2 C, C-3′ and C-5′), 132.3 (C-6), 133.7 (C-1′), 134.8 (C-8), 136.5 (C-2), 140.5 (C-4′), 151.3 (C-3a), 161.8 (C═O). IR (KBr): ν_{max} = 3117, 1736 (C═O), 1619, 1509, 1476, 1421, 1380, 1334, 1215, 1138, 1067, 1033, 822, 757, 685, 525 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 277 (M + H$^+$). Elem. anal.: calculated for $C_{17}H_{12}N_2O_2$: C, 73.90, H, 4.38, N, 10.14, found: C, 73.90, H, 4.40, N, 10.15. Mp: 170.3−171.4 °C. Pale yellow powder. R_f (PE/EA 70:30) = 0.34.

*Compound **6e**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 3.95 (s, 3 H, OCH_3), 6.93 (d, J = 8.0 Hz, 1 H, H-9), 7.08−7.16 (m, 2 H, H-3′ and H-5′), 7.34−7.40 (m, 1 H, H-7), 7.40−7.44 (m, 2 H, H-2′ and H-6′), 7.46−7.50 (m, 1 H, H-8), 7.52 (s, 1 H, H-2), 8.39 (pseudo-d, J = 8.0 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 55.8 (OCH_3), 109.3 (C-9b), 115.2 (C-3′ and C-5′), 118.9 (C-9), 119.2 (C-5a), 126.6 (C-7), 128.0 (C-2′ and C-6′), 128.9 (C-1′), 129.9 (C-9a), 132.3 (C-6), 134.8 (C-8), 136.7 (C-2), 151.1 (C-3a), 160.8 (C-4′), 161.8 (C═O). IR (KBr): ν_{max} = 3100, 1741 (C═O), 1618, 1550, 1509, 1476, 1413, 1380, 1303, 1261, 1027, 835, 757 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 293 (M + H$^+$). Elem. anal.: calculated for $C_{17}H_{12}N_2O_3$: C, 69.86, H, 4.14, N, 9.58, found: C, 69.83, H, 4.15, N, 9.56. Mp: 169.2−169.4 °C. Pale yellow powder. R_f (PE/EA 70:30) = 0.22.

*Compound **6f**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 6.89 (d, J = 7.7 Hz, 1 H, H-9), 7.31−7.42 (m, 3 H, H-7, H-3′ and H-5′), 7.49−7.55 (m, 4 H, H-2, H-8, H-2′ and H-6′), 8.38 (dd, J = 8.0, 1.1 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 109.2 (C-9b), 117.3 (d, $J_{C,F}$ = 22.9 Hz, C-3′ and C-5′), 118.8 (C-9), 119.2 (C-5a), 126.8 (C-7), 128.7 (d, $J_{C,F}$ = 8.0 Hz, C-2′ and C-6′), 129.5 (C-9a), 132.3 (d, $J_{C,F}$ = 3.4 Hz, C-1′), 132.4 (C-6), 134.9 (C-8), 136.6 (C-2), 151.3 (C-3a), 161.7 (C═O), 163.3 (d, $J_{C,F}$ = 254.2 Hz, C-4′). ^{19}F NMR (282 MHz, $CDCl_3$, 20 °C): δ = −109.3 (septet, J = 4.0 Hz, 1 F). IR (KBr): ν_{max} = 3139, 1717 (C═O), 1618, 1553, 1508, 1418, 1382, 1333, 1300, 1253, 1209, 1159, 1142, 1087, 1065, 1033, 1019, 846, 765, 735, 687, 659, 612, 551 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 281 (M + H$^+$). Elem. anal.: calculated for $C_{16}H_9FN_2O_2$: C, 68.57, H, 3.24, N, 10.00, found: C, 68.59, H, 3.24, N, 10.01. Mp: 223.4−224.8 °C. Orange yellow powder. R_f (PE/EA 50:50) = 0.38.

*Compound **6g**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 2.32 (s, 3 H, CH_3), 6.57 (d, J = 8.2 Hz, 1 H, H-9), 7.27 (td, J = 7.7, 1.1 Hz, 1 H, H-7), 7.39 (td, J = 7.7, 1.4 Hz, 1 H, H-8), 7.44−7.47 (m, 2 H, H-2′ and H-6′), 7.62−7.69 (m, 3 H, H-3′, H-4′ and H-5′), 8.30 (d, J = 8.0 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 13.7 (CH_3), 109.1 (C-9b), 118.0 (C-9), 118.6 (C-5a), 125.8 (C-7), 127.8 (C-2′ and C-6′), 130.1 (C-9a), 130.4 (C-3′, C-4′ and C-5′), 132.2 (C-6), 134.8 (C-8), 136.3 (C-1′), 145.5 (C-2), 150.4 (C-3a), 161.9 (C═O). IR (KBr): ν_{max} = 3573, 3436, 3058, 1734 (C═O), 1622, 1599, 1556, 1499, 1396, 1363, 1317, 1301, 1266, 1213, 1069, 1018, 998, 787, 752, 700, 682, 544, 514 cm^{-1}. LRMS (70 eV, ES$^+$): m/z = 277 (M + H$^+$). Elem. anal.: calculated for $C_{17}H_{12}N_2O_2$: C, 73.90, H, 4.38, N, 10.14, found: C, 73.88, H, 4.40, N, 10.13. Mp: 243.4−244.0 °C. Yellow crystals. R_f (PE/EA 50:50) = 0.26.

*Compound **6h**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 0.85 (t, J = 7.4 Hz, 3 H, CH_3), 1.30 (sextet, J = 7.4 Hz, 2 H, CH_2CH_3), 1.68 (quintet, J = 7.7 Hz, 2 H, $CH_2CH_2CH_3$), 2.57 (t, J = 7.7 Hz, 2 H, CCH_2), 6.50 (d, J = 8.0 Hz, 1 H, H-9), 7.27 (t, J = 7.6 Hz, 1 H, H-7), 7.37 (t, J = 7.6 Hz, 1 H, H-8), 7.42−7.46 (m, 2 H, H-2′ and H-6′), 7.62−7.71 (m, 3 H, H-3′, H-4′ and H-5′), 8.34 (d, J = 8.2 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 13.8 (CH_3), 22.4 (CH_2CH_3), 26.8 (CCH_2), 30.2 ($CH_2CH_2CH_3$), 108.9 (C-9b), 118.0 (C-9), 118.7 (C-5a), 125.7 (C-7), 128.1 (C-2′ and C-6′), 130.2 (C-9a), 130.4 (C-3′, C-4′ and C-5′), 132.2 (C-6), 134.7 (C-8), 136.2 (C-1′), 149.4 (C-2), 150.6 (C-3a), 162.0 (C═O). IR (KBr): ν_{max} = 2957, 2935, 2862, 1721 (C═O), 1620, 1592, 1548, 1486, 1393, 1357, 1263, 1064, 1017, 768, 707, 685. LRMS (70 eV, ES$^+$): m/z = 319 (M + H$^+$). Elem. anal.: calculated for $C_{20}H_{18}N_2O_2$: C, 75.45, H, 5.70, N, 8.80, found: C, 75.48, H, 5.71, N, 8.78. Mp: 140.6−141.7 °C. Pale yellow crystals. R_f (PE/EA 70:30) = 0.24.

*Compound **6i**:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 6.59 (d, J = 8.2 Hz, 1 H, H-9), 7.21−7.70 (m, 12 H, H-7, H-8 and arom. H), 8.38 (d, J = 7.7 Hz, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 110.7 (C-9b), 118.5 (C-9), 119.1 (C-5a), 126.2 (C-7), 128.4 (2 C, arom. CH), 128.6 (2 C, arom.

CH), 128.7 (2 C, arom. CH), 129.1 (C-1″), 129.3 (arom. CH), 130.0 (C-9a), 130.5 (C-3′, C-4′ and C-5′), 132.4 (C-6), 134.8 (C-8), 137.2 (C-1′), 145.8 (C-2), 151.1 (C-3a), 161.7 (C═O). IR (KBr): ν_{max} = 3841, 3737, 3673, 3650, 3568, 1732 (C═O), 1618, 1509, 1494, 1382, 1068, 1024, 755, 694 cm^{-1}. LRMS (70 eV, ES^+): m/z = 339 ($M + H^+$). Elem. anal.: calculated for $C_{22}H_{14}N_2O_2$: C, 78.09, H, 4.17, N, 8.28, found: C, 78.09, H, 4.18, N, 8.26. Mp: 256.7−257.3 °C. Pale pink crystals. R_f (PE/EA 70:30) = 0.39.

Compound ***7f****:* ^{1}H NMR (300 MHz, DMSO, 20 °C): δ = 6.53−6.59 (m, 4 H, H-2′, H-6′ and NH_2), 6.79 (s, 1 H, NH), 6.91 (pseudo-t, J = 8.8 Hz, 2 H, H-3′ and H-5′), 7.03−7.11 (m, 2 H, H-5 and H-7), 7.53 (pseudo-t, J = 7.7 Hz, 1 H, H-6), 7.92 (dd, J = 8.0, 0.8 Hz, 1 H, H-8). ^{13}C NMR (75 MHz, DMSO, 20 °C): δ = 91.3 (C-4), 114.1 (d, $J_{C,F}$ = 6.9 Hz, C-2′ and C-6′), 114.6 (C-8a), 115.9 (d, $J_{C,F}$ = 21.8 Hz, C-3′ and C-5′), 120.1 (C-5), 122.7 (C-7), 129.9 (C-8), 135.5 (C-6), 142.2 (C-4a), 144.9 (C-1′), 155.4 (d, $J_{C,F}$ = 229.0 Hz, C-4′), 156.8 (C-3), 160.9 (C═O). ^{19}F NMR (282 MHz, DMSO, 20 °C): δ = −128.6 (septet, J = 4.0 Hz, 1 F). IR (KBr): ν_{max} = 3474, 3375, 3303, 3158, 1748 (C═O), 1631, 1602, 1547, 1508, 1482, 1351, 1302, 1266, 1220, 1151, 1098, 1026, 982, 822, 760, 678, 507 cm^{-1}. LRMS (70 eV, ES^+): m/z = 271 ($M + H^+$). Elem. anal.: calculated for $C_{15}H_{11}FN_2O_2$: C, 66.66, H, 4.10, N, 10.37, found: C, 66.64, H, 4.10, N, 10.38. Mp: 223.4−224.8 °C. Mp: 191.0−191.3 °C. Yellow powder. R_f (PE/EA 50:50) = 0.52.

Compound ***9g****:* ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 1.24 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.07 (s, 3 H, CH_3), 4.14 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.98 (br s, 1 H, NH), 6.62 (dd, J = 8.4, 1.0 Hz, 2 H, H-2″ and H-6″), 6.79 (t, J = 7.4 Hz, 1 H, H-4″), 7.15 (dd, J = 8.5, 7.4 Hz, 2 H, H-3″ and H-5″), 7.40 (td, J = 7.4, 1.1 Hz, 1 H, H-7′), 7.51−7.54 (m, 1 H, H-5′), 7.63 (td, J = 7.6, 1.1 Hz, 1 H, H-6′), 8.27 (dd, J = 8.0, 0.8 Hz, 1 H, H-8′). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 14.0 (OCH_2CH_3), 19.2 (CH_3), 63.3 (OCH_2CH_3), 106.8 (C-4′), 114.4 (C-2″ and C-6″), 118.8 (C-8′a), 119.1 (C-4″), 122.7 (C-5′), 126.5 (C-7′), 129.3 (C-3″ and C-5″), 130.1 (C-8′), 135.0 (C-6′), 139.2 (C-4′a), 146.9 (C-1″), 150.7 (C-3′), 161.8 (C═O), 167.5 (*C*═N). IR (KBr): ν_{max} = 3324 (NH), 1721, 1706 (C═O and *C*═N), 1639, 1599, 1559, 1495, 1478, 1368, 1283, 1255, 1226, 1161, 1052, 1025, 905, 839, 753, 693 cm^{-1}. LRMS (70 eV, ES^+): m/z = 323 ($M + H^+$), 277 ($M + H^+ -$ EtOH). Elem. anal.: calculated for $C_{19}H_{18}N_2O_3$: C, 70.79, H, 5.63, N, 8.69, found: C, 70.80, H, 5.64, N, 8.69. Mp: 110.9−111.5 °C. Yellow crystals. R_f (PE/EA 70:30) = 0.48.

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