

TRIFLUOROMETHYLATED PYRIMIDINES STARTING FROM β -TRIFLUOROACETYL-LACTAMS, -LACTONE AND -CYCLANONE

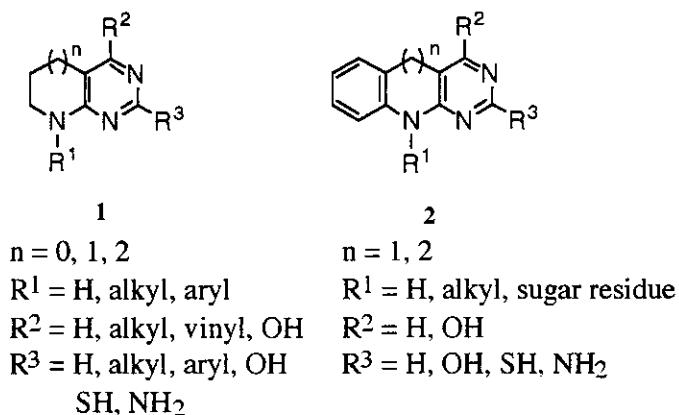
Jean-Philippe Bouillon, Vincent Bouillon, Chantal Wynants, Zdenek Janousek, and Heinz G. Viehe*

Laboratoire de Chimie Organique, Place L. Pasteur 1,
B-1348 Louvain-la-Neuve, Belgium

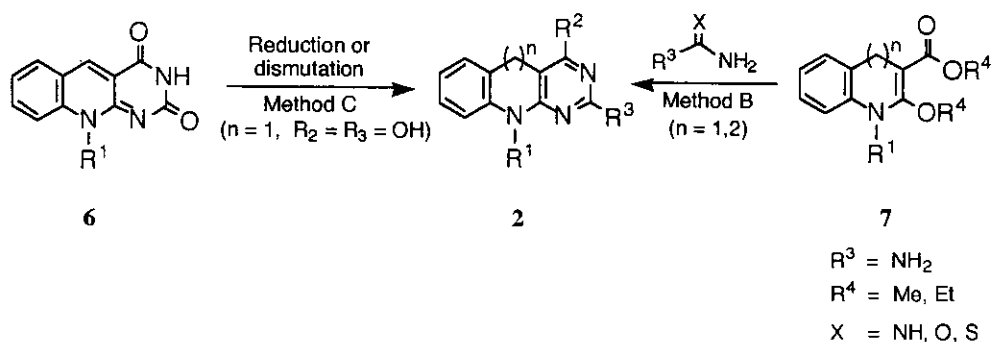
Dedicated to Prof. A. Katritzky on the occasion of his 65th birthday.

Abstract-A synthesis of trifluoromethylated pyrimidines from β -trifluoroacetyl-lactams and -benzolactams is accomplished by reaction with benzamidine as bis-nucleophile. This condensation is also extended to cyclic trifluoromethylated 1,3-diketones and 3-aryl-2-pyrrolidinones.

The synthesis of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines),^{1a} their 5,6-dihydro derivatives^{1a} (**1**) ($n=0$) and the corresponding benzoannulated analogs (**2**) ($n=1$, 5-deazaflavines)^{1b} has been a topic of continuing interest because of their structural similarity with purines and flavines and the interesting biological activities associated with them.



Scheme 1

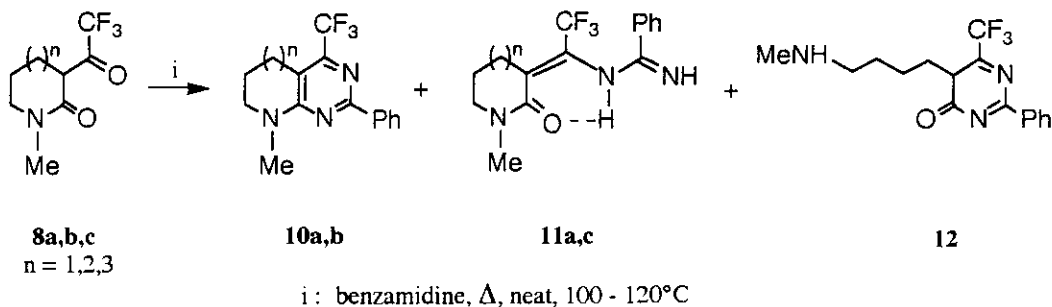


Scheme 3

This shows that the number of methods to access **1** and **2** are quite limited. Furthermore, the starting materials must be highly functionalized which severely limits the scope of these reactions.

Owing to the fact that 3-trifluoroacetyl-lactams (**8**) and -benzolactams (**9**) have become readily available¹⁰ and they cyclize with bis-nucleophiles,¹¹ we have developed a practical one-step synthesis of trifluoromethylated pyrimidines using benzamidine. This condensation was also extended to other cyclic trifluoromethylated 1,3-diketones and 3-aryl-2-pyrrolidinones.

The first attempts to cyclize **8a,b,c** with benzamidine hydrochloride failed but as it turned out, heating neat **8a,b,c** with benzamidine base at 100-120°C for a few hours led to the new [2,3-*d*]pyrimidines (**10a,b**) (Scheme 4, Table 1). Intermediates (**11a,c**) and product (**12**) were also obtained.



Scheme 4

Lactam ^{ref}	n	Conv. (%)	Yield 10 (%) ^a	Yield 11 (%) ^a	Yield 12 (%) ^a
8a ¹⁰	0	49	28	7 ^b	-
8b ¹⁰	1	80	51	-	-
8c ¹⁰	2	100	-	31	41

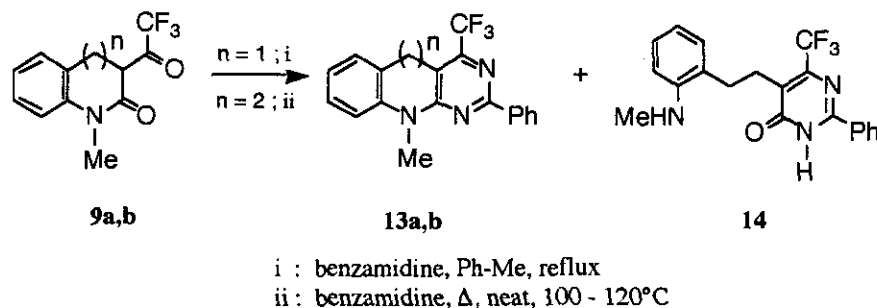
a) chromatography on silica gel (ether/MeOH); b) detected by ¹H and ¹³C nmr

Table 1

These results show that the nature of condensation products depends strongly on the ring size. Also, the non-cyclized *N*-vinyl amidines (**11a,c**) (detected from **8a** and isolated from **8c**) are most probably the reaction intermediates.⁵ Accordingly, **11c** cyclizes into **10c** when heated with POCl₃ (Scheme 6). 3-Trifluoroacetyl- ϵ -caprolactam (**8c**) gave mainly compound (**12**) (41% vs 31% of **11c**). It derives probably from intermediate (**11c**) followed by subsequent ring-opening of the lactam moiety. Nevertheless, it is surprising that no elimination of water occurs which would lead to the formation of pyrimidine (**10c**) as observed for **8a** and **8b** (Scheme 4 - Table 1).

The above heterocyclisation could not be extended either to acetamidine or to *S*-methylthiourea.

In order to define the scope of the heterocyclisation and in view of interesting biological activities of benzolactams,^{1e,12} we have studied the behaviour of benzoannulated lactams (**9a,b**). 3,4-Dihydro-2*H*-quinolin-2-one (**9a**) affords a fair yield of the expected product (**13a**), whereas benzocaprolactam (**9b**) gives predominantly the ring-opening compound (**14**) (Scheme 5, Table 2).



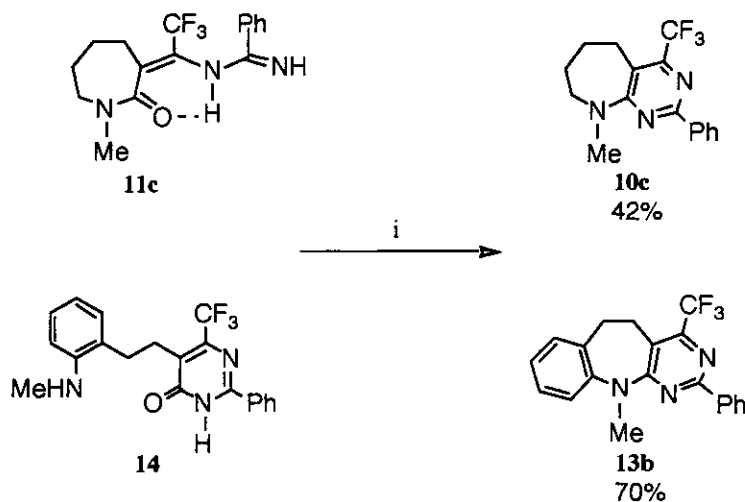
Scheme 5

Benzolactam ^{ref}	n	Conv. (%)	Yield 13 (%) ^a	Yield 14 (%) ^a
9a ¹⁰	1	100	60	-
9b ¹⁰	2	92	12	35

a) chromatography on silica gel (pet. ether/ether)

Table 2

The condensation of amidines followed by ring-opening has already been noticed in the cases of 3-benzoyl-3,4-dihydro-1-thiacoumarin^{13a} and 7*H*-furo-[3,2-*g*]-benzopyranes.^{13b} Similarly to **11c**, **14** is converted to **13b** by treatment with POCl₃ (Scheme 6).

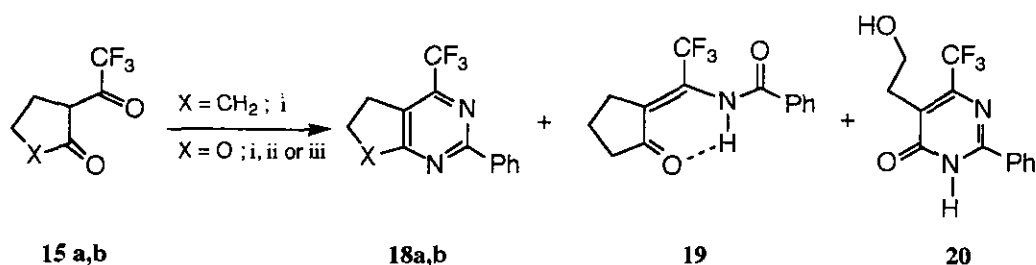


i : POCl₃ excess, reflux, 1 h

Scheme 6

Next we have examined the heterocyclisation with benzamidine and trifluoroacetyl-cyclopentanone (**15a**), -butyrolactone (**15b**) and 3-aryl-2-pyrrolidinones (**17a,b**). Although **15a** and **15b** are known,^{14a,b} we developed an improved procedure of their preparation.¹⁰

As we found, **15a** affords modest yields of pyrimidine (**18a**) and benzamidoenamine (**19**) whereas lactone (**16**) undergoes partly or entirely a ring-opening leading to 2-hydroxy-ethylpyrimidinone (**20**) (Scheme 7, Table 3).



i : benzamidine, cat APTS, Ph-Me, reflux
 ii : benzamidine, Δ , neat, 100 - 140 °C
 iii : 1) EtONa, EtOH, 25°C ; 2) benzamidine, EtOH, reflux

Scheme 7

Substrat ^{ref}	X	Method ^{a)}	Yield 18 (%)	Yield 19 (%)	Yield 20 (%)
15a ^{14a}	CH ₂	i	34	18	-
15b ^{14b}	O	i	19	-	18
		ii	19	-	35
		iii	-	-	25

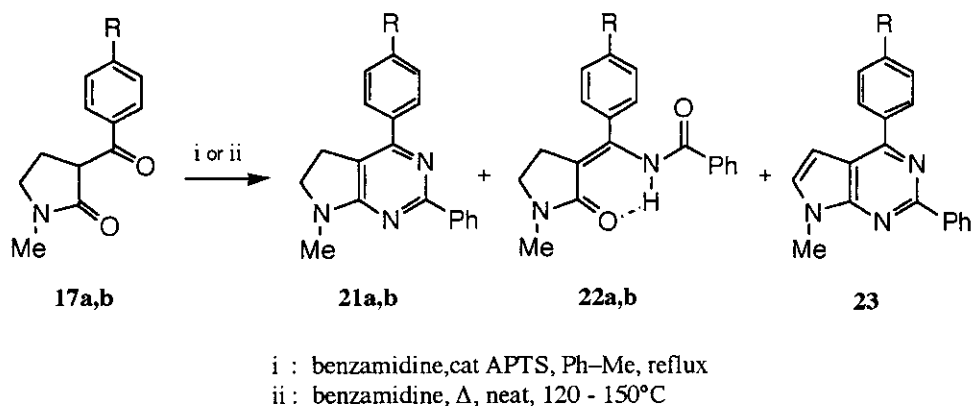
a) Chromatography on silica gel (pet. ether/ether)

Table 3

It should be noted that heterocyclisations with 3-acyllactones generally proceed with ring-opening of the lactone moiety.^{15,16a,b} Accordingly, **18b** should be formed *via* 2-hydroxyethylpyrimidine (**20**) which is the only product when the lactone ring is opened using sodium ethoxide (Table 3, method iii). Similar sequences are frequently used in heterocyclic chemistry.^{15,17} Compound (**20**) has an enolisable amide function and under favourable experimental conditions (Scheme 7, Table 3 : method i or ii), recyclisation leads to a small amount (19 %) of **18b**. This process, however little efficient, takes place under mild conditions. Generally, cyclodehydration into pyrimidines takes place only when concentrated H₂SO₄, POCl₃ or SOCl₂ is applied.^{18a-c}

We have also studied the heterocyclisation of 3-aroyle-2-pyrrolidinones (**17a,b**). Although the product (**17a**) has already been described in the literature,¹⁹ we synthesized the precursors (**17a,b**) using a Claisen condensation.²⁰ Their cyclisation proceeds in complete

analogy with **8,9,15a,b** to give pyrrolo[2,3-*d*]pyrimidines but the yields of **21a,b** and **23** are very low (Scheme 8, Table 4). Even when starting materials are heated without solvent for a few hours the conversion is lower than 50 %.



Scheme 8

pyrrolidinone ^{ref}	R	Method	Conv. (%)	Yield 21 (%)	Yield 22 (%)	Yield 23 (%)
17a ²⁰	H	i a)	19	5	8	-
		ii a)	90 ^b	-	-	-
17b ²⁰	CF ₃	i c)	18	-	-	5
		ii a)	48	7 ^d	13 ^d	-

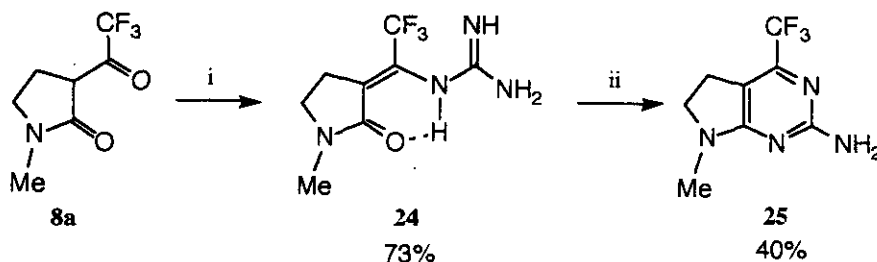
a) chromatography on silica gel (ether/MeOH); b) fragmentation; c) chromatography on silica gel (pet. ether/ether); d) detected by ¹H and ¹⁹F nmr but not isolated

Table 4

Non-cyclic *N*-benzoylenamides (**22a,b**) are also present and two new features are observed. Namely, **21b** oxidizes spontaneously to 7-deazapurine (**23**) (Table 4 : R = CF₃, method i) and a fragmentation to 3-(phenylaminomethylene) pyrrolidone accompanies the process (Table 4 : R = H, method ii). Similar observations have been done during condensations of 3-trifluoroacetylactams with various nucleophiles.²¹

In order to extend the reaction to other 1,3-bis-nucleophiles we also tried guanidine which was prepared from its carbonate and sodium ethoxide. Its treatment with **8a** leads to

guanidyl enamine (**24**). This compound is isolated in a good yield and can be cyclized to **25** using POCl_3 (Scheme 9).



i : 1) EtONa, EtOH, 25°C ; 2) guanidine carbonate, EtOH, reflux
 ii : POCl_3 excess, reflux, 1 h

Scheme 9

In conclusion, we have prepared a series of new trifluoromethylated pyrimidines in one step *via* an original procedure. Several reaction intermediates could be isolated, characterized and in some cases (**11c**, **14** and **24**) cyclized into pyrimidines upon treatment with phosphorus oxychloride. The cyclization with guanidines (Scheme 9) could be extended to other β -trifluoroacetyl-lactams and -benzolactams.

EXPERIMENTAL

Mp were taken using a Dr. Tottoli apparatus and are uncorrected. Ir and mass spectra were measured on a Perkin-Elmer 1710 and A Finnigan Mat TSQ 70 apparatus, respectively. The ^1H , ^{13}C and ^{19}F nmr spectra were run on a Bruker AM 500 spectrometer at 500.13 MHz (^1H) and 125.77 MHz (^{13}C) or with Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^1H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), using 5 mm probes. The TMS signal was taken as an internal reference for the ^1H and ^{13}C spectra, while CFCl_3 was used as an internal reference for the ^{19}F spectra. Most of the ^{13}C nmr spectra were obtained from proton coupled or proton noise decoupled spectra. For molecules (**14**) and (**21a**), unambiguous assignments were obtained by use of the two-dimensional ^1H - ^{13}C heteronuclear chemical shift correlation spectroscopy.^{22,23} For the ^1J connectivities, we have assumed an average one bond carbon-proton coupling constant of

about 135 Hz (fixed delays durations : $\Delta_1 = 1/2 (^1J_{CH}) = 3.6$ Msec; $\Delta_2 = 1/4 (^1J_{CH}) = 1.8$ Msec). For the long-range 1H - ^{13}C connectivities, we have chosen averaged ^{13}C - 1H coupling constant of about 12.5 Hz (fixed delays : $\Delta_1 = 1/2 (^nJ_{CH}) = 40$ Msec; $\Delta_2 = 1/4 (^nJ_{CH}) = 20$ Msec. The two-dimensional data matrix were submitted to a Lorentz-Gauss transformation^{22,23} in the t_1 dimension and to a sinusoidal multiplication^{22,23} in the t_2 dimension prior to Fourier transformation ("power" spectrum calculation in all cases). We have also used the double-quantum filtered correlation spectroscopy (DQF-COSY)²²⁻²⁴ to verify or to assign some of the 1H resonances. The DQF-COSY experiments have been acquired using the TPPI (Time-Proportional Phase Incrementation)^{22,23,25} and transformed in the phase-sensitive mode.^{22,23,25} Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz.

Free benzamidine base was obtained from the commercial hydrochloride using 1N NaOH in CH_2Cl_2 and drying over $MgSO_4$.

General Procedure for Pyrimidines (10a,b; 13b; 18b and 21b.) A stirred liquid mixture of 1,3-dicarbonyl compound (**8a-c**, **9b**, **15b** or **17b** - 10 mmol, 1 eq.) and an excess of benzamidine (2-4 eq.) is heated up to 100-150°C during 4-10 hours. Ether and some methanol are added to the cooled product. The solution is washed twice with brine, dried over $MgSO_4$ and evaporated. The resulting oil is purified on silica gel to give the above mentioned products and also the by-products (**11a,c**; **12**; **14** and **20**).

1-Methyl-7-phenyl-5-trifluoromethylpyrrolo[2,3-d]pyrimidine (10a). mp > 240°C. Ir (KBr) : 3062, 3036, 2962, 2938, 2899, 1608, 1576, 1505, 1482, 1379, 1038. Ms (m/z) : 279, 233, 149, 98, 69. 1H Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 2.9-3.0 (m, 2H), 3.08 (s, 3H), 3.57 (t, 2H, $J = 6.0$ Hz), 7.3-7.4 (m, 1H), 7.5-7.6 (m, 1H), 8.26 (dd, 1H, $J = 7.9$ and 2.3 Hz). ^{13}C Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 22.7 (tm, $^4J_F = 2.3$ and $^1J_H = 135.7$ Hz), 39.0, 49.8 (tm, $^1J_H = 141.3$ Hz), 113.7 (sm, $^3J_F = 2.4$ Hz), 122.6 (qs, $^1J_F = 276.6$ Hz), 127.1 (dddd, $^1J_H = 161.5$, $^3J_H = 6.0$, 6.0 and $^2J_H = 1.6$ Hz), 127.6 (ddm, $^1J_H = 160.5$ and $^3J_H = 6.8$ Hz), 128.7 (dt, $^1J_H = 163.8$ and $^3J_H = 6.0$ Hz), 138.9 (st, $^3J_H = 4.4$ Hz), 148.3 (qm, $^2J_F = 28.2$ Hz), 162.0 (sm), 165.2 (sm). ^{19}F Nmr (DMSO- d_6 ; 25°C) : δ -63.5 (s).

3-(1-Benzamidino-2,2,2-trifluoroethylidene)-1-methyl-2-pyrrolidinone (11a). ^1H Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 7.3-7.4 (m, 2H), 7.5-7.6 (m, 2H), 7.6-7.7 (m, 1H). ^{13}C Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 20.9, 43.9, 46.9, 112.7, 127.9 (dm, $^1J_{\text{H}} = 158.8$ Hz), 129.1 (dt, $^1J_{\text{H}} = 160.0$ and $^3J_{\text{H}} = 7.9$ Hz), 129.5 (sm), 131.5 (dm, $^1J_{\text{H}} = 162.8$ Hz), 171.8 (sm), 174.3 (sm). ^{19}F Nmr (DMSO- d_6 ; 25°C) : δ -63.8 (s).

1-Methyl-7-phenyl-5-trifluoromethylpiperidino[2,3-d]pyrimidine (10b). mp 105-107°C. Ir (KBr) : 3054, 3010, 2960, 2942, 2967, 1581, 1553, 1524, 1454, 1175. Ms (m/z) : 293, 264, 121, 105, 77, 51. ^1H Nmr (CDCl_3) : δ 1.99 (qt, 2H, $J = 5.9$ Hz), 2.89 (tm, 2H, $J = 5.8$ Hz), 3.31 (s, 3H), 3.48 (tm, 2H, $J = 5.9$ Hz), 7.4-7.5 (m, 3H), 8.3-8.4 (m, 2H). ^{13}C Nmr (CDCl_3) : δ 19.8 (ttm, $^1J_{\text{H}} = 130.7$ and $^2J_{\text{H}} = 4.1$ Hz), 21.9 (tm, $^4J_{\text{F}} = 2.7$ and $^1J_{\text{H}} = 131.4$ Hz), 36.2 (qt, $^6J_{\text{F}} = 1.5$, $^1J_{\text{H}} = 138.5$ and $^3J_{\text{H}} = 1.7$ Hz), 48.8 (tm, $^1J_{\text{H}} = 139.5$ Hz), 110.1 (stm, $^3J_{\text{F}} = 1.1$ and $^2J_{\text{H}} = 5.9$ Hz), 122.1 (qs, $^1J_{\text{F}} = 276.4$ Hz), 127.7 (ddd, $^1J_{\text{H}} = 163.9$, $^3J_{\text{H}} = 6.6$ and $^2J_{\text{H}} = 2.4$ Hz), 127.9 (dm, $^1J_{\text{H}} = 161.7$ Hz), 130.0 (dtt, $^1J_{\text{H}} = 160.2$, $^3J_{\text{H}} = 7.9$ and $^2J_{\text{H}} = 1.3$ Hz), 137.6 (st, $^3J_{\text{H}} = 4.4$ Hz), 148.6 (qt, $^2J_{\text{F}} = 32.5$ and $^3J_{\text{H}} = 3.0$ Hz), 160.3 (sm), 160.9 (sm). ^{19}F Nmr (CDCl_3) : δ -66.0 (s). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{F}_3$: C, 61.43; H, 4.81; N, 14.33. Found C, 61.18; H, 4.75; N, 14.09.

3-(1-Benzamidino-2,2,2-trifluoroethylidene)-1-methyl-2-caprolactam (11c). mp 195-198°C. Ir (KBr) : 3440-3410, 2954, 2939, 1589, 1574, 1559, 1521, 1506, 1451, 1163. Ms (m/z) : 326, 325, 282, 254, 104, 84, 57, 44. ^1H Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 1.60 (qt, 2H, $J = 7.6$ Hz), 1.73 (qt, 2H, $J = 6.8$ Hz), 2.58 (m, 2H), 2.64 (s, 3H), 2.96 (t, 2H, $J = 6.5$ Hz), 5.3-5.9 (br s, NH_2), 7.3-7.4 (m, 3H), 8.29 (dd, 2H, $J = 6.6$ and 2.1 Hz). ^{13}C Nmr (DMSO- d_6 ; 500 MHz; 30°C) : δ 23.6 (tm, $^4J_{\text{F}} = 2.2$ and $^1J_{\text{H}} = 131.9$ Hz), 25.3 (tm, $^1J_{\text{H}} = 126.3$ Hz), 25.7 (tm, $^1J_{\text{H}} = 126.2$ Hz), 33.8 (qt, $^1J_{\text{H}} = 139.1$ and $^3J_{\text{H}} = 2.2$ Hz), 48.9 (tm, $^1J_{\text{H}} = 138.5$ Hz), 119.8 (sm, $^3J_{\text{F}} = 1.2$ Hz), 122.9 (qs, $^1J_{\text{F}} = 276.6$ Hz), 127.7 (ddd, $^1J_{\text{H}} = 161.2$, $^3J_{\text{H}} = 5.4$ and $^2J_{\text{H}} = 5.4$ Hz), 127.8 (ddm, $^1J_{\text{H}} = 160.7$ and $^3J_{\text{H}} = 6.8$ Hz), 129.3 (dt, $^1J_{\text{H}} = 159.9$ and $^3J_{\text{H}} = 8.0$ Hz), 138.8 (st, $^3J_{\text{H}} = 6.5$ Hz), 148.6 (qt, $^2J_{\text{F}} = 31.0$ and $^3J_{\text{H}} = 4.5$ Hz), 161.6 (sm), 175.0 (st, $^3J_{\text{H}} = 4.8$ Hz). ^{19}F Nmr (DMSO- d_6 ; 25°C) : δ -62.5 (s).

5-(4-Methylaminobutyl)-2-phenyl-6-trifluoromethylpyrimidin-5H-(4)-one (12). mp 91-92°C. Ir (KBr) : 3205, 3072, 3056, 2976, 2938, 1618, 1588, 1570, 1519, 1450, 1122. Ms (m/z) : 325, 256, 254, 103, 77, 69. ^1H Nmr (CDCl_3) : δ 1.6-1.9 (m, 4H), 2.5-2.8 (m, 4H), 2.90 (s, 3H), 3.7-4.0 (m, 2H), 7.0-7.3 (m, 3H), 8.1-8.2 (d, 2H, $J = 7.7$ Hz). ^{13}C Nmr (CDCl_3) : δ 22.0 (tm, $^4J_{\text{F}} = 2.0$ and $^1J_{\text{H}} = 131.8$ Hz), 22.5 (tm, $^1J_{\text{H}} = 125.7$ Hz), 27.0 (tm, $^1J_{\text{H}} = 125.8$ Hz), 39.5 (dm, $^1J_{\text{H}} = 136.8$ Hz), 50.0 (qt, $^6J_{\text{F}} = 2.0$, $^1J_{\text{H}} = 140.5$ and $^3J_{\text{H}} = 2.0$ Hz), 52.2 (tm, $^1J_{\text{H}} = 138.1$ Hz), 122.7 (qs, $^1J_{\text{F}} = 276.6$ Hz), 127.2 (dm, $^1J_{\text{H}} = 161.2$ Hz), 128.4 (dm, $^1J_{\text{H}} = 160.4$ Hz), 129.2 (sm), 131.3 (dm, $^1J_{\text{H}} = 160.1$ Hz), 149.6 (qm, $^2J_{\text{F}} = 29.2$ Hz), 161.9 (sm), 165.1 (sm). ^{19}F Nmr (CDCl_3) : δ -64.7 (s).

11H-5,6-Dihydro-2-phenyl-11-methyl-4-trifluoromethylpyrimido[4,5-b]benzo[f]azepine (13b). mp 110-112°C. Ir (KBr) : 3068, 2977, 2944, 2928, 1555, 1533, 1497, 1480, 1436, 1412, 1390, 1224. Ms (m/z) : 356, 355, 341, 340, 286, 103, 91, 77. ^1H Nmr (CDCl_3) : δ 3.0-3.5 (m, 4H), 3.73 (s, 3H), 7.1-7.3 (m, 4H), 7.4-7.5 (m, 3H), 8.4-8.6 (m, 2H). ^{13}C Nmr (CDCl_3) : δ 28.6 (tm, $^5J_{\text{F}} = 1.3$ and $^1J_{\text{H}} = 128.6$ Hz), 29.1 (tm, $^4J_{\text{F}} = 2.9$ and $^1J_{\text{H}} = 132.2$ Hz), 39.6 (qs, $^1J_{\text{H}} = 139.8$ Hz), 113.8 (sm, $^3J_{\text{F}} = 2.6$ Hz), 120.6 (qs, $^1J_{\text{F}} = 276.9$ Hz), 121.1 (ddd, $^1J_{\text{H}} = 158.9$, $^3J_{\text{H}} = 7.1$ and $^2J_{\text{H}} = 1.4$ Hz), 123.9 (dm, $^1J_{\text{H}} = 160.1$ Hz), 125.7 (ddd, $^1J_{\text{H}} = 161.0$, $^3J_{\text{H}} = 7.3$ and $^2J_{\text{H}} = 1.8$ Hz), 126.4 (dm, $^1J_{\text{H}} = 161.7$ Hz), 126.5 (dm, $^1J_{\text{H}} = 162.0$ Hz), 126.9, 129.2 (dtm, $^1J_{\text{H}} = 161.8$ and $^3J_{\text{H}} = 7.6$ Hz), 135.4 (sm), 135.6 (sm), 143.4 (sm), 151.0 (qm, $^2J_{\text{F}} = 31.1$ Hz), 158.0 (sm), 159.8 (sm). ^{19}F Nmr (CDCl_3) : δ -66.2 (s).

5-(o-Methylaminophenylethyl)-2-phenyl-6-trifluoromethylpyrimidin-4-one (14). mp 241-242°C. Ir (KBr) : 3458, 3066, 3013, 2935, 1660, 1606, 1585, 1560, 1512, 1204. Ms (m/z) : 374, 373, 253, 210, 120, 91, 77. ^1H Nmr ($\text{DMSO}-d_6$; 500 MHz; 40°C) : δ 2.5-2.6 (m, 2H), 2.7-2.8 (m, 2H), 2.81 (s, 3H), 4.0-7.0 (br s, NH_2), 6.5-6.6 (m, 2H), 6.96 (dd, 1H, $J = 7.5$ and 1.3 Hz), 7.07 (ddd, 1H, $J = 7.7$, 7.7 and 1.4 Hz), 7.54 (dd, 2H, $J = 7.8$ and 6.5 Hz), 7.60 (tt, 1H, $J = 7.2$ and 1.0 Hz), 8.14 (d, 2H, $J = 7.3$ Hz). ^{13}C Nmr ($\text{DMSO}-d_6$; 500 MHz; 40°C) : δ 24.6 (tm, $^1J_{\text{H}} = 128.5$ Hz), 29.88 (tm, $^1J_{\text{H}} = 124.2$ Hz), 29.95 (qs, $^1J_{\text{H}} = 134.8$ Hz), 108.9 (dd, $^1J_{\text{H}} = 155.6$ and $^3J_{\text{H}} = 7.8$ Hz), 115.4 (dd, $^1J_{\text{H}} = 160.4$ and $^3J_{\text{H}} = 7.7$ Hz), 119.5 (qs, $^1J_{\text{F}} = 276.5$ Hz), 124.0 (sm), 125.7 (sm), 127.3 (ddd, $^1J_{\text{H}} = 156.9$, $^3J_{\text{H}} = 7.6$ and

$^2J_H = 1.1$ Hz), 127.7 (ddd, $^1J_H = 161.5$, $^3J_H = 7.3$ and 5.7 Hz), 128.3 (ddtd, $^1J_H = 154.1$, $^3J_H = 8.0$, 5.2 and $^2J_H = 2.0$ Hz), 128.6 (dd, $^1J_H = 162.5$ and $^3J_H = 7.6$ Hz), 131.3 (st, $^3J_H = 7.7$ Hz), 132.0 (dt, $^1J_H = 162.1$ and $^3J_H = 7.5$ Hz), 146.7 (qt, $^2J_F = 32.3$ and $^3J_H = 4.4$ Hz), 147.1 (sm), 155.3 (sm), 164.2 (st, $^3J_H = 5.5$ Hz). ^{19}F Nmr (DMSO- d_6): δ -65.2 (s). Anal. Calcd for $C_{20}H_{18}N_3OF_3$: C, 64.34; H, 4.86; N, 11.25. Found C, 63.95; H, 4.78; N, 11.22.

5,6-Dihydro-4-trifluoromethylfurano[2,3- d]pyrimidine (18b). mp $182^\circ C$. Ir (KBr): 3032, 2986, 2935, 1614, 1597, 1574, 1483, 1456, 1443, 1431, 1396, 1388, 1139, 973. Ms (m/z): 267, 266, 247, 216, 197, 170, 140, 115, 103, 77, 69. 1H Nmr ($CDCl_3$): δ 3.49 (t, 2H, $J = 8.5$ Hz), 4.81 (t, 2H, $J = 8.6$ Hz), 7.4-7.6 (m, 3H), 8.45 (dm, 2H, $J = 7.7$ Hz). ^{13}C Nmr (DMSO- d_6 ; 500 MHz; $40^\circ C$): δ 25.3 (t, $^1J_H = 138.8$ Hz), 71.1 (t, $^1J_H = 155.5$ Hz), 115.8 (sm), 120.9 (qs, $^1J_F = 274.4$ Hz), 127.7 (ddd, $^1J_H = 161.0$, $^3J_H = 7.3$ and 5.7 Hz), 128.6 (dd, $^1J_H = 161.5$ and $^3J_H = 6.9$ Hz), 131.2 (dt, $^1J_H = 161.2$ and $^3J_H = 7.6$ Hz), 135.6 (st, $^3J_H = 7.0$ Hz), 148.1 (qt, $^2J_F = 35.8$ and $^3J_H = 2.2$ Hz), 163.6 (sm), 177.1 (stt, $^3J_H = 2.8$ and 2.7 Hz). ^{19}F Nmr (DMSO- d_6): δ -66.7 (s).

5-(2-Hydroxyethyl)-2-phenyl-6-trifluoromethylpyrimidin-4-one (20). mp $223^\circ C$. Ir (KBr): 3371, 3175, 3079, 3056, 2962, 2952, 1654, 1605, 1578, 1557, 1402. 1H Nmr (DMSO- d_6): δ 2.78 (td, 2H, $J = 7.2$ and 1.6 Hz), 3.52 (t, 2H, $J = 7.2$ Hz), 7.33 (br s, NH or OH), 7.43 (t, 1H, $J = 7.8$ Hz), 7.52 (dd, 2H, $J = 7.7$ and 7.6 Hz), 7.94 (br s, OH or NH), 8.11 (dd, 2H, $J = 7.8$ and 1.6 Hz). ^{13}C Nmr (DMSO- d_6): δ 29.0 (tm, $^1J_H = 130.2$ and $^4J_F = 1.9$ Hz), 59.4 (ttt, $^1J_H = 142.5$, $^2J_H = 6.2$ and 1.5 Hz), 122.1 (qs, $^1J_F = 276.7$ Hz), 122.3 (sm, $^3J_F = 0.9$ Hz), 127.8 (dm, $^1J_H = 161.7$ Hz), 128.7 (ddd, $^1J_H = 162.0$, $^3J_H = 7.2$ and $^2J_H = 1.7$ Hz), 131.7 (dt, $^1J_H = 161.5$ and $^3J_H = 7.5$ Hz), 132.9 (st, $^3J_H = 7.4$ Hz), 147.8 (qt, $^2J_F = 31.8$ and $^3J_H = 4.7$ Hz), 156.7 (stq, $^3J_H = 3.7$ and $^4J_F = 1.2$ Hz), 165.8 (st, $^3J_H = 5.2$ Hz). ^{19}F Nmr (CD_3OD): δ -64.1 (s).

General Procedure for Pyrimidines (13a; 18a,b; 21a and 23). A solution of 1,3-dicarbonyl compound (**9a**; **15a,b**; **17a** or **17b**) (10 mmol, 1 eq.), benzamidine (10-30 mmol, 1-3 eq.) and a catalytic amount of *p*-toluenesulfonic acid is refluxed during 10-20

hours. The solution is then cooled, diluted with ether and washed with water. The aqueous phase is saturated with NaCl and extracted twice with ether. The combined organic phase is washed with brine, dried over MgSO_4 and evaporated. A chromatography on silica gel gives pyrimidines (**13a**; **18a,b**; **21a** or **23**). By-products (**19**; **20** and **22a**) are also isolated and characterized.

*1-Methyl-2-phenyl-4-trifluoromethyltetrahydropyrimido[4,5-*b*]quinoline (13a).* mp 172-173°C. Ir (KBr) : 3072, 3041, 2970, 2930, 1603, 1587, 1574, 1551, 1482, 1444, 1417, 1397, 1179. Ms (m/z) : 342, 341, 340, 322, 272, 217, 123, 103, 77. ^1H Nmr (CDCl_3) : δ 3.70 (s, 3H), 4.24 (s, 2H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H), 7.4-7.5 (m, 3H), 8.4-8.5 (m, 2H). ^{13}C Nmr (CDCl_3) : δ 26.6 (tm, $^4J_{\text{F}} = 2.7$ and $^1J_{\text{H}} = 133.3$ Hz), 30.9 (qs, $^6J_{\text{F}} = 2.2$ and $^1J_{\text{H}} = 139.7$ Hz), 110.0 (st, $^3J_{\text{F}} = 1.3$ and $^2J_{\text{H}} = 6.9$ Hz), 113.8 (ddm, $^1J_{\text{H}} = 159.9$ and $^3J_{\text{H}} = 7.9$ Hz), 121.0 (sm), 121.9 (qs, $^1J_{\text{F}} = 276.6$ Hz), 123.0 (ddd, $^1J_{\text{H}} = 162.8$, $^3J_{\text{H}} = 7.1$ and $^2J_{\text{H}} = 1.1$ Hz), 127.8 (m), 128.1 (m), 128.6 (m), 130.8 (dt, $^1J_{\text{H}} = 162.3$ and $^3J_{\text{H}} = 7.5$ Hz), 137.0 (sm), 139.7 (sm), 150.5 (qm, $^2J_{\text{F}} = 32.9$ Hz), 159.7 (sm), 161.5 (sm). ^{19}F Nmr (CDCl_3) : δ -66.6 (s). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{F}_3$: C, 66.85; H, 4.13; N, 12.31. Found C, 66.13; H, 3.95; N, 12.28.

*2-Phenyl-6-trifluoromethylcyclopenta[*d*]pyrimidine (18a).* mp 106-107°C. Ir (KBr) : 2981, 2966, 2931, 2909, 1595, 1575, 1558, 1457, 1422, 1387, 1186. Ms (m/z) : 265, 264, 245, 236, 216, 195, 169, 104, 103, 77, 69. ^1H Nmr (CDCl_3 ; 500 MHz) : δ 2.22 (qt, 2H, $J = 7.7$ Hz), 3.13 (dd, 2H, $J = 8.1$ and 7.7 Hz), 3.17 (tq, 2H, $J = 7.5$ and $^5J_{\text{F}} = 1.8$ Hz), 7.4-7.5 (m, 3H), 8.47 (dm, 2H, $J = 7.1$ Hz). ^{13}C Nmr (CDCl_3) : δ 22.0 (ttt, $^1J_{\text{H}} = 132.4$, $^2J_{\text{H}} = 3.2$ and 3.2 Hz), 28.3 (tm, $^4J_{\text{F}} = 1.6$ and $^1J_{\text{H}} = 133.1$ Hz), 34.1 (ttt, $^1J_{\text{H}} = 132.2$, $^2J_{\text{H}} = 5.6$ and $^3J_{\text{H}} = 2.8$ Hz), 121.5 (qs, $^1J_{\text{F}} = 275.5$ Hz), 128.3 (ddd, $^1J_{\text{H}} = 161.0$, $^3J_{\text{H}} = 7.2$ and $^2J_{\text{H}} = 2.4$ Hz), 128.5 (ddd, $^1J_{\text{H}} = 160.7$, $^3J_{\text{H}} = 7.0$ and $^2J_{\text{H}} = 2.2$ Hz), 129.3 (sm, $^3J_{\text{F}} = 1.4$ Hz), 130.9 (dt, $^1J_{\text{H}} = 160.4$ and $^3J_{\text{H}} = 7.7$ Hz), 136.7 (st, $^3J_{\text{H}} = 7.0$ Hz), 150.0 (qm, $^2J_{\text{F}} = 36.1$ Hz), 163.5 (sm), 179.2 (sm). ^{19}F Nmr (CDCl_3) : δ -68.6 (s). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{F}_3$: C, 63.63; H, 4.20; N, 10.60. Found C, 63.84; H, 4.41; N, 10.53.

2-(1-Benzamido-2,2,2-trifluoroethylidene)cyclopentanone (19). mp 161-162°C. Ir (KBr) 3266, 2973, 1722, 1695, 1672, 1602, 1585, 1538, 1509, 1490, 1365, 1120. Ms (m/z) : 284, 283, 263, 214, 163, 106, 105, 77. ^1H Nmr (CD_3OD) : δ 2.0-3.0 (m, 6H), 7.5-7.7 (m, 3H), 7.90 (dd, 2H, $J = 7.1$ and 1.5 Hz). ^{13}C Nmr ($\text{DMSO}-d_6$) : δ 22.0 (ttt, $^1J_{\text{H}} = 132.0$, $^2J_{\text{H}} = 3.3$ and 3.3 Hz), 31.1 (tm, $^1J_{\text{H}} = 132.0$ Hz), 35.7 (tt, $^1J_{\text{H}} = 133.4$ and $^2J_{\text{H}} = 3.0$ Hz), 122.4 (qd, $^1J_{\text{F}} = 271.8$ and $J_{\text{H}} = 4.5$ Hz), 125.4 (qm, $^2J_{\text{F}} = 32.6$ Hz), 128.6 (dm, $^1J_{\text{H}} = 162.3$ Hz), 128.7 (dm, $^1J_{\text{H}} = 163.3$ Hz), 132.0 (st, $^3J_{\text{H}} = 7.6$ Hz), 133.3 (dtt, $^1J_{\text{H}} = 162.3$, $^3J_{\text{H}} = 7.6$ and $^2J_{\text{H}} = 1.2$ Hz), 144.6 (sm, $^3J_{\text{F}} = 4.3$ Hz), 166.3 (sm), 168.4 (sm). ^{19}F Nmr (CD_3OD) : δ -63.4 (s).

1-Methyl-5,7-diphenylpyrrolo[2,3-d]pyrimidine (21a). mp 172-173°C. Ir (KBr) : 3072, 2912, 2869, 1601, 1567, 1537, 1492, 1449, 1411, 1378, 1251. Ms (m/z) : 288, 287, 286, 248, 183, 140, 104, 98, 77, 44. ^1H Nmr ($\text{DMSO}-d_6$; 500 MHz; 35°C) : δ 3.03 (s, 3H), 3.31 (t, 2H, $J = 8.3$ Hz), 3.63 (t, 2H, $J = 8.3$ Hz), 7.4-7.5 (m, 4H), 7.52 (ddd, 2H, $J = 7.7$, 7.7 and 1.5 Hz), 8.03 (dd, 2H, $J = 7.6$ and 1.5 Hz), 8.44 (dd, 2H, $J = 7.5$ and 1.7 Hz). ^{13}C Nmr ($\text{DMSO}-d_6$; 500 MHz; 35°C) : δ 25.3 (tm, $^1J_{\text{H}} = 135.4$ Hz), 30.9 (qs, $^1J_{\text{H}} = 137.5$ Hz), 50.5 (ttq, $^1J_{\text{H}} = 142.9$, $^2J_{\text{H}} = 3.2$ and $^3J_{\text{H}} = 3.2$ Hz), 114.6 (stt, $J_{\text{H}} = 2.4$ and 1.8 Hz), 127.5 (dddd, $^1J_{\text{H}} = 159.8$, $^3J_{\text{H}} = 7.2$, 7.2 and $^2J_{\text{H}} = 1.8$ Hz), 127.7 (ddd, $^1J_{\text{H}} = 159.5$, $^3J_{\text{H}} = 6.8$ and 6.8 Hz), 128.1 (ddd, $^1J_{\text{H}} = 160.9$, $^3J_{\text{H}} = 7.5$ and $^2J_{\text{H}} = 1.1$ Hz), 128.4 (dd, $^1J_{\text{H}} = 160.5$ and $^3J_{\text{H}} = 7.5$ Hz), 129.1 (dt, $^1J_{\text{H}} = 160.9$ and $^3J_{\text{H}} = 7.5$ Hz), 129.8 (dt, $^1J_{\text{H}} = 160.5$ and $^3J_{\text{H}} = 7.9$ Hz), 137.7 (st, $^3J_{\text{H}} = 7.4$ Hz), 138.3 (st, $^3J_{\text{H}} = 6.1$ Hz), 152.9 (sm), 161.7 (sdd, $^3J_{\text{H}} = 3.9$ and 3.3 Hz), 168.3 (sm). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3$: C, 79.41; H, 5.96; N, 14.62. Found C, 79.17; H, 5.82; N, 14.60.

3-(1-Benzamido-1-phenylmethylene)-1-methyl-2-pyrrolidinone (22a). mp > 240°C. Ir (KBr) : 3300-3100, 3057, 2931, 2883, 1685, 1651, 1598, 1520, 1498, 1485, 1466, 1444, 1404, 1291. Ms (m/z) : 307, 306, 201, 105, 86, 84, 77. ^1H Nmr (CDCl_3) : δ 2.66 (t, 2H, $J = 7.4$ Hz), 2.97 (s, 3H), 3.40 (t, 2H, $J = 7.3$ Hz), 7.3-7.5 (m, 8H), 8.00 (dd, 2H, $J = 7.8$ and 1.5 Hz), 12.3 (br s, NH). ^{13}C Nmr (CDCl_3) : δ 22.6 (tdd, $^1J_{\text{H}} = 135.4$, $^2J_{\text{H}} = 6.0$ and 6.0 Hz), 29.8 (qt, $^1J_{\text{H}} = 138.5$ and $^3J_{\text{H}} = 3.0$ Hz), 46.8 (tm, $^1J_{\text{H}} = 142.5$ Hz), 111.3 (sm), 127.2 (dm, $^1J_{\text{H}} = 160.5$ Hz), 127.5 (dm, $^1J_{\text{H}} = 159.9$ Hz), 128.0 (ddd, $^1J_{\text{H}} = 159.8$, $^3J_{\text{H}} = 6.6$ and

$^2J_H = 2.7$ Hz), 128.1 (dm, $^1J_H = 160.6$ Hz), 128.5 (dm, $^1J_H = 160.5$ Hz), 131.7 (dt, $^1J_H = 160.4$ and $^3J_H = 7.8$ Hz), 134.0 (sm), 135.8 (sm), 142.7 (sm), 164.0 (sm), 170.5 (sm).

2-Phenyl-4-(p-trifluoromethylphenyl)-7-methylpyrrolo[2,3-d]pyrimidine (23). mp 172-174°C. Ir (KBr) : 3195, 3057, 3028, 2924, 2855, 1605, 1573, 1541, 1503, 1486, 1350, 1273. Ms (m/z) : 353, 311, 309, 281, 268, 234, 104, 103, 77. 1H Nmr (DMSO- d_6) : δ 6.2-6.3 (m, 1H), 7.2-7.7 (m, 8H), 8.30 (d, 2H, $J = 7.5$ Hz). ^{13}C Nmr (DMSO- d_6) : δ 39.8 (qs, $^1J_H = 140.0$ Hz), 68.4 (dm, $^1J_H = 155.9$ Hz), 126.2 (dm, $^3J_F = 3.5$ and $^1J_H = 158.1$ Hz), 127.0 (sm), 127.5 (ddm, $^1J_H = 160.5$ and $^3J_H = 6.5$ Hz), 128.0, 128.3, 128.5 (ddd, $^1J_H = 160.2$, $^3J_H = 7.4$ and $^2J_H = 1.4$ Hz), 130.1 (sm), 132.1, 133.2 (sm), 137.3 (qm, $^2J_F = 31.2$ Hz), 144.1 (sm), 159.1 (sm), 159.3 (sm). ^{19}F Nmr (DMSO- d_6) : δ -60.5 (s).

3-(1-Guanidino-2,2,2-trifluoroethylidene)-1-methyl-2-pyrrolidinone (24). Guanidine carbonate (0.90 g, 5 mmol, 1 eq.) is added to a stirred mixture of 0.44 g (18 mmol, 3.6 eq.) NaH (60 %) in 20 ml of dry methanol. After 15 min, **8a** (0.98 g, 5 mmol, 1 eq.) in 10 ml of methanol is added and the mixture is refluxed during 12 h. Water (10 ml) is added and the precipitated solid is collected, washed with water and dissolved in boiling methanol. This solution is dried over $MgSO_4$ and evaporated. Yield of **24** : 0.86 g (73 %). The product is used as such for the preparation of **25**.

mp > 220°C. Ir (KBr) : 3419, 3365, 2929, 2887, 1659, 1594, 1507, 1386, 1288. Ms (m/z) : 236, 195, 187, 131, 126, 69, 44. 1H Nmr (DMSO- d_6 ; 500 MHz; 40°C) : δ 2.50 (s, 3H), 2.5-2.7 (m, 2H), 3.2-3.4 (m, 2H and NH_2), 6.9 (br s, NH_2). ^{13}C Nmr (DMSO- d_6 ; 500 MHz; 40°C) : δ 21.0 (tm, $^4J_F = 2.1$ and $^1J_H = 134.6$ Hz), 29.1 (qs, $^1J_H = 137.2$ Hz), 46.9 (tm, $^1J_H = 140.5$ Hz), 92.5 (sm, $^3J_F = 1.9$ Hz), 120.9 (qs, $^1J_F = 286.8$ Hz), 157.2 (qm, $^2J_F = 32.5$ Hz), 157.9 (sm), 173.6 (sm). ^{19}F Nmr (DMSO- d_6 ; 25°C) : δ -70.9 (s).

Cyclization of Intermediates (11c, 14, 24) by means of $POCl_3$. Azapropenylidene lactam (10 mmol, 1 eq.) is refluxed in 30 ml $POCl_3$ for 1 h. The resulting mixture is evaporated, the residue is diluted with ether, washed twice with water and dried over $MgSO_4$. A chromatography on silica gel using ether/methanol (**10c** : 25/75, **25** : 95/5) or pet. ether/ether (**13b** : 30/70) as eluent gives pyrimidines (**10c**, **13b** and **25**), respectively.

7-Amino-1-methyl-5-trifluoromethylpyrrolo[2,3-d]pyrimidine (25). mp > 220°C. Ir (KBr) : 3450, 3026, 2973, 2950, 1593, 1521, 1338, 1135. Ms (m/z) : 219, 218, 150, 122, 83, 69. ^1H Nmr (CD_3OD) : δ 2.99 (s, 3H), 3.0-3.2 (m, 2H), 3.44 (t, 2H, $J = 6.3$ Hz). ^{13}C Nmr (CD_3OD) : δ 24.9 (tt, $^4J_{\text{F}} = 3.3$, $^1J_{\text{H}} = 134.0$ and $^2J_{\text{H}} = 3.0$ Hz), 30.1 (qs, $^6J_{\text{F}} = 1.5$ and $^1J_{\text{H}} = 138.8$ Hz), 45.0 (tm, $^5J_{\text{F}} = 1.5$ and $^1J_{\text{H}} = 141.6$ Hz), 116.5 (sm, $^3J_{\text{F}} = 1.9$ Hz), 120.5 (qt, $^1J_{\text{F}} = 274.1$ and $^4J_{\text{H}} = 3.7$ Hz), 120.6 (qt, $^2J_{\text{F}} = 38.7$ and $^3J_{\text{H}} = 2.0$ Hz), 134.5 (sm), 164.0 (st, $^3J_{\text{H}} = 2.9$ Hz). ^{19}F Nmr (CD_3OD) : δ -65.3 (t, 3F, $J = 3.7$ Hz).

A two-step Synthesis of Pyrimidine (20) (Scheme 7, Table 3, Method iii). 3-Trifluoroacetyl- γ -butyrolactone **16** (0.72 g, 4 mmol, 1 eq.) is added to a stirred solution of 0.10 g (4 mmol, 1 eq.) of Na in 5 ml of ethanol. After 30 min at room temperature (0.49 g, 4 mmol, 1 eq.) of a benzamidine are added portionwise. The solution is refluxed for 3 h, then evaporated and dissolved in 10 ml of water. This mixture is extracted twice with ether and the extract is washed with brine, dried over MgSO_4 and evaporated. Chromatography (silica gel, ether then 95 ether/5 methanol) gives 0.28 g (25 %) of **20**.

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