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ORIGINAL RESEARCH

N-Alkylation of 4-Trichloromethylpyrimidinones: Synthesis of Some New and Interesting Modified Nucleoside Analogues

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Abstract: The N^1-alkylation of 4-(trichloromethyl)pyrimidin-2(1*H*)-one, 4-methoxy-4-(trichloromethyl)-3,4-dihydropyrimidin-2(1*H*)-one, and 5-bromo-4-methoxy-4-(trichloromethyl)-3,4-dihydropyrimidin-2(1*H*)-one with selected alkylating agents such as 2-chloroacetamide, diethyl 2-bromomalonate, and 5-bromo-1,1,1-trichloro-4-methoxypent-3-en-2-one, is presented. Further reactions of 1-[5,5,5-trichloro-2-methoxy-4-oxo-penten-2-yl]4-trichloromethyl-pyrimidin-2(1*H*)-one with primary amines and aminoalcohols furnished a series of unexpected new acyclic nucleoside analogues.

Keywords: *N*-alkylation, nucleoside analogues, enones, trihalogenated heterocycles

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Introduction

Pyrimidines have a long history of biological activity and utilization in fields ranging from pharmaceutics to agriculture.[1–3] The N^1-alkylation of pyrimidines is one way of functionalizing the pyrimidine ring to achieve important physical and bioactive properties. For example, *N*-alkylated nucleic acid bases are widely known for being the most effective antiviral[4–7] and antitumoral agents,[8] as well as for exhibiting anti-inflammatory[9] and herbicidal activity.[10,11] In addition, *N*-alkylated pyrimidines, obtained by alkylating agents such as diazoalkanes[12] alkylhalides[13–15] and alkylsulfates, among others,[16] are important compounds for mutagenic and carcinogenic studies in living systems. Additionally, a series of N^1-(4-substituted-benzyl)-pyrimidines was identified as potent and selective inhibitors of the thymidine monophosphate kinase of *Micobacterium tuberculosis* (TMPKmt), making them a promising target for the development of new anti-tubercular agents.[17] Furthermore, a series of N^1-acetamide uracils, analogues to the compounds obtained in this study, exhibited immunosuppressant antigen conjugates.[18,19]

The introduction of a trifluoromethyl group into bioactive molecules often increases their therapeutic efficiency due to an increase in lipophilicity.[20,21] Thus, pyrimidines bearing a trifluoromethyl group have demonstrated a variety of activities such as herbicidal,[22–27] insecticidal,[28,29] acaricidal,[30] fungicidal,[30] antitumoral,[31] and antiviral,[32] just to mention a few. Trichloromethyl substituted heterocycles have been the subject of fewer studies. However, recent investigations have shown that, in some cases, trichloromethyl-containing heterocycles are more active than the corresponding trifluoromethyl-substituted analogues. For example, NTPDase inhibitory effects in synaptosomes from rat cerebral cortex,[33] antinociceptive effects in mice,[34] and hypothermic and antipyretic effects[35] have been reported.

As part of our ongoing program to develop new methods and molecular scaffolds that aggregate both novelty and potential for biological activity, this study aims to perform N^1-alkylation of 4-trichloromethylpyrimidin-2(1*H*)-ones and two other related dihydropyrimidin-2(1*H*)-ones with selected alkylating agents. In a previous study, it was found that 1-(5,5,5-trichloro-2-methoxy-4-oxopent-2-en-1-yl)-4-trichloromethyl-pyrimidin-2(1*H*)-one (**7**) exhibited a potent cyclin-dependent kinase inhibition.[36] However, the low solubility of this compound made further studies difficult. Thus, as an extension of that study[37] we now synthesize a series of derivatives of compound **7** in order to generate new compounds with increased solubility and potential for biological activity.

Results and Discussion

This study was carried out in three parts: in the first, we examined the *N*-alkylation reaction of 4-trichloromethylpyrimidin-2(1*H*)-one (**1**)[22] with the alkylating agents **2**–**4** (Fig. 1).

Using the reaction conditions reported in Figure 1, pyrimidinone **1** reacted with all three alkylating agents furnishing the respective N^1-alkylated products **5**, **6**, and **7** in 60, 95, and 60% yields, respectively. In fact, compound **7** had already been obtained in a previous work.[37] Curiously, using the same conditions, pyrimidines **1** failed to react with 5-bromo-1,1,1-trifluoro-4-methoxypent-3-en-2-one (a trifluoromethylated analogue of enone **4**).

In the second part of this study, we examined the *N*-alkylation reaction of some dihydro-derivatives of 4-trichloromethylpyrimidin-2(1*H*)-one (**1**) according to Figure 2. The dihydropyrimidinone **8** was obtained from the reaction of pyrimidinone **1** by refluxing the latter in methanol for six hours.[39] The *N*-alkylation reaction of dihydropyrimidinone **8** with all three alkylating agents

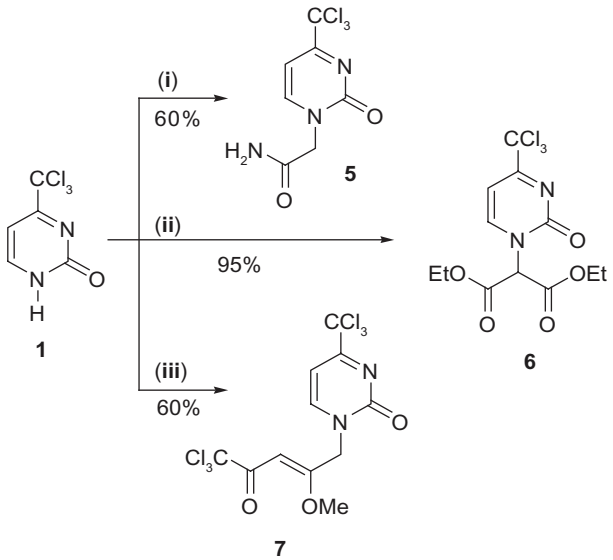

Figure 1. Reagents and conditions: (**i**) 2-chloroacetamide (**2**), K_2CO_3, acetone, r.t., 24 h; (**ii**) diethyl 2-bromomalonate (**3**), K_2CO_3, acetone, r.t., 16 h; (**iii**) 5-bromo-1,1,1-trichloro-4-methoxypent-3-en-2-one (enone **4**), K_2CO_3, acetone, reflux, 16 h.

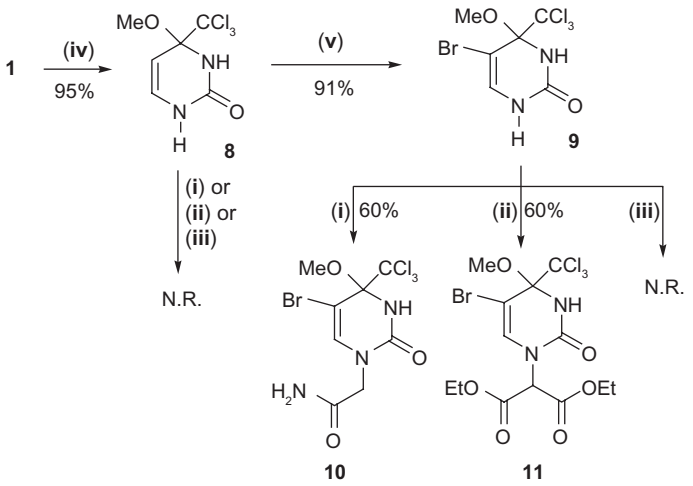

Figure 2. Reagents and conditions: (**i**) 2-chloroacetamide (**2**), K_2CO_3, acetone, reflux, 24 h; (**ii**) diethyl 2-bromomalonate (**3**), K_2CO_3, acetone, reflux, 24 h; (**iii**) enone (**4**), K_2CO_3, acetone, reflux, 24 h; (**iv**) MeOH, reflux, 24 h; (**v**) Br_2, MeOH, reflux, 16 h.

selected for this study failed to give the expected products. Actually, compound **8** was not stable and during the alkylation reaction it was converted back to its precursor **1** and yielding the same products reported in Figure 1. Dihydropyrimidinone **9** was obtained in 91% yield from the bromination of dihydropyrimidinone **8** with bromine in methanol under reflux for 16 hours. The bromine at the 5–position stabilized the dihydropyrimidine, probably by steric effects.[40] Thus compound **9** reacted with alkylating agents **2** and **3** to give the N^1-alkylated products **10** and **11**, respectively, both in 60% yield. However, compound **9** failed to react with the brominated enone **4**. Pyrimidine **9** was submitted to alkylation because it exhibited significant inhibition of ATP and ADP hydrolysis in synaptosomes from rat cerebral cortex.[33]

Table 1 reports the optimized reaction conditions and yields for the synthesis of compounds **5**–**7**, **10** and **11**. For the compounds that were not formed, the conditions included reaction times and an alternate base, sodium hydride.

In the third part of this study, we examined the reaction of **7** with a series of primary amines. Compound **7** exhibited potent cyclin-dependent kinase inhibition, in preliminary assays, however, the very low solubility of **7** made further studies difficult. Reactions of compound **7** with secondary amines were carried out furnishing a series of 1-(2-alkylamine-5,5,5-trichloro-4-oxopent-2-en-1-yl)-4-trichloromethylpyrimidinones in good yields[21] In the same study, the reaction of compound **7** with primary amines rendered a complex mixture of products. In this report, a modified procedure using a large excess (5–10 times) of the primary amines in acetonitrile was carried out and an unexpected result was found. Instead of the Michael addition of the amines followed by the elimination of the alkoxy group, as is usually observed for parent enones,[41–49] the substitution of the CCl_3 group by the primary amines also occurred simultaneously to furnish *N*-alkyl-3-(alkylamino)-4-[2-oxo-4-(trichloromet-hyl)pyrimidin-1(2*H*)-yl]but-2-enamide **12a–g**, according to Figure 3. So far, no evidence of such a double-substitution has been observed for trichloro- or trifluoromethylated enones. Compounds **12a**–**g** were isolated by filtration and the solids were washed with acetonitrile (10 mL) and twice with dichloromethane (10 mL) to remove the excess of amines. The solid products **12a**–**g** showed high purity after drying in a desiccator. Compounds were analyzed by ^1H and ^{13}C NMR and purity was confirmed by HPLC, elemental analysis or HRMS. Representative compounds were also analyzed by 2D-NMR COSY and HMQC experiments.

Table 1. Optimized reaction conditions and yields for the synthesis of compounds **5–7, 10,** and **11.**

Entry	Pyrimi-dinone	Alkylating agent	Reaction conditions[a]	Yield (%)[b]	Product
1	**1**	**3**	A	**60**	**5**
2	**1**	**3**	B	**95**	**6**
3	**1**	**4**	C	**60**	**7**
4	**9**	**2**	D	**60**	**10**
5	**9**	**3**	D	**60**	**11**

[a]Reaction conditions: A = K_2CO_3, acetone, r.t., 24 h; B = K_2CO_3, acetone, r.t., 16 h; C = K_2CO_3, acetone, reflux, 16 h; D = K_2CO_3, acetone, reflux, 24 h. [b]Yields of isolated products.

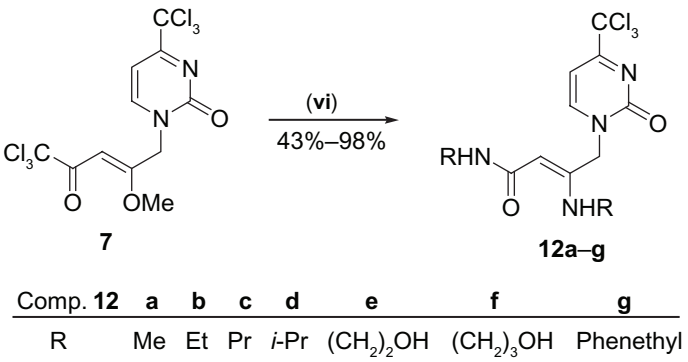

Figure 3. Reagents and conditions: (**vi**) RNH_2, (5–10 equiv.), ACN, r.t., 1.4–24 h.

Table 2 shows the optimized reaction conditions and yields for the synthesis of compounds **12a**–**g**.

The retention time of compounds **12b–g** was determined by liquid chromatography (HPLC) as described in the experimental part. All products were eluted on a C-18 column with a methanol–water gradient of 40 to 100% of methanol for 10 minutes and kept at 100% of methanol for 5 minutes. Products **12b–g** eluted with retention times of 8.17, 11.43, 10.81, 3.08, 4.37, and 12.44, respectively, while compound **12a** did not elute under this condition. One can observe that the hydroxyl–alkyl derivatives **12e** and **12f** are the most soluble products and can also be considered nucleoside analogues.

Conclusion

In conclusion, we have shown that 4-trichloromethyl-pyrimidin-1*H*-2-one(**1**)reactedpositivelywithallthree alkylating agent used in this work. The 4-methoxy-4-trichloromethyl-3,4-dihydropyrimidin-2(1*H*)-one (**8**) failed to furnish alkylated products, however, bromination at the 5-position of compound **8** resulted in a more stable compound (**9**) that was accessible to alkylation with 2-chloroacetamide and diethyl 2-bromomalonate, but failed to react with enone **4**. In addition, compound **7** underwent an unexpected double addition substitution of the methoxy and the CCl_3 groups by reaction with primary amines, furnishing a series of new enamides **12a–g**, in moderate yields.

Experimental

Unless otherwise indicated, all commercial reagents and solvents were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using Silica Gel plates GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. The CHN microanalyses were performed on a PerkinElmer 2400 elemental analyzer from the Department of Chemistry at the Universidade de São Paulo (USP), São Paulo, SP, Brazil. High resolution mass spectra were recorded on ESI-mode. ^1H and ^{13}C NMR were recorded on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in DMSO–d_6 or $CDCl_3$, using TMS as the internal reference. HPLC spectra were recorded on a HP 1100 chromatograph equipped with UV/Vis DAD, reverse phase C-18 column (100 mm × 2.1 mm, 5 μm). Compounds were eluted in a methanol-water gradient (1 mL/min.) from 40% to 100% of methanol for 10 min. and kept at 100% of methanol for 5 min.

Table 2. Optimized conditions for the synthesis of compounds **12a–g**.

Entry	Amine	Ratio 7:amine[a]	Time (h)	Yield (%)[b]	Product
1	$MeNH_2$	1:10	5.0	50	**12a**
2	$EtNH_2$	1:5	1.4	51	**12b**
3	$PrNH_2$	1:5	3.3	48	**12c**
4	*i*-$PrNH_2$	1:5	3.3	45	**12d**
5	HO-$(CH_2)_2$-NH_2	1:10	24.0	45	**12e**
6	HO-$(CH_2)_3$-NH_2	1:5	5.3	43	**12f**
7	C_6H_5-$(CH_2)_2$-NH_2	1:5	4.0	98	**12g**

[a]Reaction condition: acetonitrile, stirring at room temperature.
[b]Yields of isolated products.

Typical procedure for the synthesis of compound 5–7, 10, and 11

To a mixture of pyrimidinones **1**, **8**, and **9** (2.0 mmol) and potassium carbonate (0.27 g, 2.0 mmol) in acetone (see Table 1), was added the alkylating agents (2.0 mmol). Mixtures were stirred at room temperature or under reflux (see Table 1) and followed by TLC until the reaction was completed (16–24 h). The solvent was removed on a rotary evaporator, and water (50 mL) was then added before extracting with ethyl acetate (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated to give the pure products.

2-[2-Oxo-4(trichloromethyl)pyrimidin-1(2*H*)-yl]acetamide (5)

Yield: 60%; white solid; mp 199–200 °C.

^1H NMR (200 MHz, DMSO-d_6): δ = 4.59 (s, 2H, CH_2), 7.05 (d, 1*H*, *J* = 6.6 Hz, H–5), 8.40 (d, 1*H*, *J* = 6.6 Hz, H–6), 7.38 and 7.78 (br s, 2H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.1, 95.4, 98.1, 154.0, 154.3, 167.5, 170.4.

Anal. Calcd for $C_7H_6Cl_3N_3O_2$ (270.50): C, 31.08; H, 2.24; N, 15.53. Found: C, 31.13; H, 2.18; N, 15.41.

Diethyl 2-[2-Oxo-4-(trichloromethyl)pyrimidin-1(2*H*)-yl]malonate (6)

Yield 95%; brown oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 (t, 6H, *J* = 7.0 Hz, 2 CH_3), 4.33 (m, 4H, 2 CH_2), 6.53 (s, 1*H*, CH), 6.97 (d, 1*H*, *J* = 7.4 Hz, H–5), 8.15 (d, 1*H*, *J* = 7.2 Hz, H–6).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.3, 62.4, 63.7, 95.0, 99.1, 153.2, 153.3, 163.3, 171.4.

Anal. Calcd for $C_{12}H_{13}Cl_3N_2O_5$ (371.50): C, 39.79; H, 3.53; N, 7.54. Found: C, 39.76; H, 3.61; N, 7.51.

5-Bromo-4-trichloromethyl-4-methoxy-3,4-dihydropyrimidin-2(1*H*)-one (9)

To a solution of pyrimidine **8** (0.245 g, 1.0 mmol) in methanol (10 mL), bromine (0.28 g 1.7 mmol) was added and the mixture was refluxed for 16 hours. The reaction mixture was concentrated and product **9** precipitated, isolated by filtration and recrystallized from methanol to give compound **9** in 91% yield; mp 198–200 °C.

^1H NMR (200 MHz, DMSO-d_6): δ = 3.29 (s, 3H, OMe), 7.11 (d, 1*H*, *J* = 5.4 Hz, CH), 8.25 (br s, 1*H*, NH), 9.58 (br d, 1*H*, *J* = 5.4 Hz, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 51.9, 86.1, 93.5, 105.8, 135.6, 151.3.

Anal. Calcd for $C_6H_6BrCl_3N_2O_2$ (324.39): C, 22.22; H, 1.86; N, 8.64. Found: C, 22.35; H, 1.92; N, 8.67.

2-(5-Bromo-4-methoxy-2-oxo-4-(trichloromethyl)-3,4-dihydropyrimidin-1(2*H*)-yl) acetamide (10)

Yield: 60%; white solid; mp 210–212 °C.

^1H NMR (200 MHz, DMSO-d_6): δ = 3.89 (s, 3H, OMe), 4.39 (s, 1*H*, CH_2), 7.27 and 7.65 (br s, 2H, NH_2), 8.34 (s, 1*H*, H–6).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 50.8, 54.9, 85.3, 97.6, 150.1, 154.0, 166.4, 168.2.

Anal. Calcd for $C_8H_9BrCl_3N_3O_3$ (381.4): C, 25.19; H, 2.38; N, 11.02. Found: C, 25.08; H, 2.16; N, 11.00.

Diethyl 2-[5-bromo-4-methoxy-2-oxo-4-(trichloromethyl)-3,4-dihydropyri-midin-1(2*H*)-yl] malonate (11)

Yield: 60%, brown oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, 6H, *J* = 7.2 Hz, 2 CH_3), 4.05 (s, 3H, OMe), 4.31 (m, 4H, 2 CH_2), 6.39 (s, 1*H*, CH), 7.95 (s, 1*H*, H–6).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.7, 55.4, 62.1, 62.7, 86.7, 97.1, 148.7, 153.3, 163.7, 166.8.

Anal. Calcd for $C_{13}H_{16}BrCl_3N_2O_6$ (482.4): C, 25.19; H, 2.38; N, 11.02. Found: C, 25.08; H, 2.16; N, 11.00.

Typical procedure for the synthesis of compounds 12a–g

To a mixture of **7** (0.86 g, 2 mmol) and acetonitrile was added an excess of primary amines (10–20 mmol). The mixture was stirred at room temperature and followed by TLC until the reaction was completed (see Table 2). The resulting mixture was filtered, washed with acetonitrile (1 × 10 mL) and dichloromethane (2 × 10 mL) and dried in a desiccator under vacuum. Products **12a–g** were obtained in high purity from this procedure.

***N*-Methyl-3(methylamino)-4-[2-oxo-(trichloromethyl)-pyrimidin-1(2*H*)-yl]-but-2-enamide (12a)**

Yield: 50%; light yellow solid comprised by *E*- and *Z*-isomers; mp 263–267 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.48–2.78 (m, 6H, 2 CH_3), 4.03 and 4.54 (s, 1*H*, CH), 4.44 and 5.05 (s, 2H, CH_2), 5.70 (d, 1*H*, *J* = 7.6 Hz, H–5), 5.72 (d, 1*H*, *J* = 7.2 Hz, H–5), 6.02 (br s, 1*H*, NH), 7.06 (br s, 1*H*, NH), 7.28 (br s, 1*H*, NH), 7.35 (d, 1*H*, *J* = 7.6 Hz, H–6), 7.63 (br s, 1*H*, NH), 7.68 (d, 1*H*, *J* = 7.2 Hz, H–6), 8.77 (br s, 1*H*, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.8, 25.3, 26.8, 28.5, 45.3, 47.1, 83.6, 86.8, 94.5, 94.7, 144.1, 144.2, 153.9, 155.4, 156.2, 157.3, 163.1, 168.2, 170.2.

(*Z*)-*N*-Ethyl-3(ethylamino)-4-[2-oxo-(trichloromethyl)-pyrimidin-1(2*H*)-yl]-but-2-enamide (12b)

Yield: 51%; white solid; mp 223–225 °C.

^{1}*H* NMR (400 MHz, DMSO-d_6): δ = 1.09 (t, 3H, *J* = 7.2 Hz, CH_3), 1.25 (t, 3H, *J* = 7.2 Hz, CH_3), 3.29 (q, 2H, *J* = 6.0 Hz, CH_2), 3.49 (q, 2H, *J* = 6.0 Hz, CH_2), 4.77 (s, 2H, CH_2), 5.24 (s, 1*H*, CH); 5.76 (d, 1*H*, *J* = 7.2 Hz, H–5), 7.53 (d, 1*H*, *J* = 7.2 Hz, H–6), 7.78 (br s, 1*H*, NH), 10.17 (br s, 1*H*, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 14.0, 14.7, 47.7, 80.5, 94.9, 97.0, 144.5, 155.4, 163.6, 168.7, 178.5.

HRMS (ESI) m/z calcd for $C_{13}H_{17}Cl_3N_4O_2$ $[M+H]^+$ 367.0495 Found: 367.0443.

(*Z*)-4-[2-Oxo-4-(trichloromethyl)pyrimidin-1-(2*H*)-yl]-*N*-propyl-3-(propylamino)but-2-enamide (12c)

Yield: 48%; white solid; mp 155–157 °C.

^{1}*H* NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, 3H, *J* = 7.2 Hz, CH_3), 0.95 (t, 3H, *J* = 7.2 Hz, CH_3), 1.51 (sext, 2H, *J* = 6.0 Hz, CH_2), 1.64 (sext, 2H, *J* = 7.6, CH_2), 3.21 (q, 2H, *J* = 6.0 Hz, CH_2), 3.43 (q, 2H, *J* = 6.0 Hz, CH_2), 4.74 (s, 2H, CH_2), 5.26 (s, 1*H*, CH), 5.78 (d, 1*H*, *J* = 7.4 Hz, H–5), 7.52 (d, 1*H*, *J* = 7.4 Hz, H–6), 7.77 (br s, 1*H*, NH), 10.56 (br s, 1*H*, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 10.9, 11.3, 21.7, 23.3, 41.4, 44.4, 47.7, 80.7, 94.9, 96.9, 144.4, 155.3, 163.8, 169.0, 178.5.

HRMS (ESI) m/z calcd for $C_{15}H_{21}Cl_3N_4O_2$ $[M+H]^+$ 395.0808 Found: 395.0763.

(*Z*)-*N*-Isopropyl-3-(isopropylamino)-4-[2-oxo-(trichloromethyl)-pyrimidin-1(2*H*)-yl]-but-2-enamide (12d)

Yield: 45%; white solid; mp 237–240 °C.

^{1}*H* NMR (400 MHz, DMSO-d_6): δ = 1.11 (d, 6H, *J* = 6.0 Hz, CH_3), 1.27 (d, 6H, *J* = 6.4 Hz, CH_3), 4.04–4.13 (m, 2H, *J* = 6.4 Hz, CH), 4.77 (s, 2H, CH_2), 5.24 (s, 1*H*, CH), 5.74 (d, 1*H*, *J* = 7.2 Hz, H–5), 7.54 (d, 1*H*, *J* = 7.2 Hz, H–6), 7.64 (d, 1*H*, *J* = 7.6 Hz, NH), 10.53 (d, 1*H*, *J* = 8.8 Hz, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.9, 23.0, 41.2, 45.1, 47.6, 80.5, 96.9, 144.5, 155.4, 162.9, 167.9, 178.6.

HRMS (ESI) m/z calcd for $C_{15}H_{21}Cl_3N_4O_2$ $[M+H]^+$ 395.0808 Found: 395.0760.

(*Z*)-*N*-(2-Hydroxyethyl)-3-(2-hydroxyethyl-amino)-4-[2-oxo-4-(trichloro-methyl)-pyrimidin-1-(2*H*)-yl]but-2-enamide (12e)

Yield: 45%; white solid; mp 168–171 °C.

^{1}*H* NMR (400 MHz, DMSO-d_6): δ = 3.48–3.52 (m, 4H, 2 CH_2), 3.54–3.56 (m, 2H, CH_2), 3.61–3.63 (m, 2H, CH_2), 4.75 (s, 2H, CH_2), 4.80 (t, 1*H*, *J* = 4.4 Hz, OH), 5.12 (t, 1*H*, *J* = 4.4 Hz, OH), 5.26 (s, 1*H*, CH), 5.83 (d, 1*H*, J = 7.4 Hz, H–5), 7.52 (d, 1*H*, *J* = 7.4 Hz, H–6), 7.83 (t, 1*H*, *J* = 5.4 Hz, NH), 10.65 (t, 1*H*, *J* = 5.0, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 42.6, 45.3, 48.0, 59.4, 80.7, 95.2, 97.0, 144.6, 155.5, 164.1, 169.0, 178.5.

HRMS (ESI) m/z calcd for $C_{13}H_{17}Cl_3N_4O_4$ $[M+H]^+$ 399.0393 Found: 399.0347.

(Z)-*N*-(3-Hydroxypropyl)-3-(3-hydroxypropyl-amino)-4-[2-oxo-4-(trichloromethyl)-pyrimidin-1 (2*H*)-yl]but-2-enamide (12f)

Yield: 43%; brown solid; mp 150–152 °C.

^{1}*H* NMR (400 MHz, DMSO-d_6): δ = 1.63 (qui, 2H, *J* = 6.8 Hz, CH_2), 1.77 (qui, 2H, *J* = 6.4 Hz, CH_2), 3.30–3.45 (m, 6H, 3 CH_2), 3.50–3.55 (m, 2H, CH_2), 4.57 (t, 1*H*, *J* = 5.6 Hz, OH), 4.75 (s, 2H, CH_2), 5.23 (s, 1*H*, CH), 5.78 (d, 1*H*, *J* = 7.2 Hz, H–5), 7.52 (d, 1*H*, *J* = 7.2 Hz, H–6), 7.78 (t, 1*H*, *J* = 5.6 Hz, NH), 10.58 (t, 1*H*, *J* = 6.0 Hz, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 31.8, 31.9, 36.8, 40.3, 47.7, 57.9, 58.2, 80.5, 94.9, 99.4, 144.5, 155.3, 163.4, 168.8, 178.4.

HRMS (ESI) m/z calcd for $C_{15}H_{21}Cl_3N_4O_4$ $[M+H]^+$ 427.0706 Found: 427.0670.

(*Z*)-4-[2-Oxo-4-(trichloromethyl)pyrimidin-1 (2*H*)-yl]-*N*-phenethyl-3-(phenethyl-amino)but-2-enamide (12g)

Yield: 98%; white solid; mp 140–143 °C.

^{1}*H* NMR (200 MHz, DMSO-d_6): δ = 2.82 (t, 2H, *J* = 7.0 Hz, 2 CH_2), 2.95 (t, 2H, *J* = 7.0 Hz, 2 CH_2), 3.48 (2H, CH_2, underneth the water signal), 3.68–3.78 (m, 2H, CH_2), 4.75 (s, 2H, CH_2), 5.25 (s, 1*H*, CH), 5.77 (d, 1*H*, *J* = 7.2 Hz, H–5), 7.20–7.35 (m, 10H, 2 Ph), 7.47 (d, 1*H*, *J* = 7.4 Hz, H–6), 7.88 (br s, 1*H*, NH), 10.47 (br s, 1*H*, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 34.2, 35.0, 41.2, 44.3, 47.8, 81.04; 95.1, 95.4, 96.95, 126.2, 126.5, 128.3–128.8 138.0, 139.3, 144.5, 155.4, 163.9, 168.7, 178.7.

HRMS (ESI) m/z calcd for $C_{25}H_{25}Cl_3N_4O_2$ $[M+H]^+$ 519.1121 Found: 519.1080.

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References

1. Charvet AS, Camplo M, Faury P, et al. Inhibition of human immunodeficiency virus type 1 replication by phosphonoformate- and phosphonoacetate-2',3'-dideoxy-3'-thiacytidine conjugates. *J Med Chem*. 1994;37:2216–23.
2. Soudeyns H, Yao Q, Belleau B, et al. Anti-human immunodeficiency virus type 1 activity and in vitro toxicity of 2'-deoxy-3'-thiacytidine (BCH-189), a novel heterocyclic nucleoside analog. *Antimicrob Agents Chemother*. 1991;35:1386–90.
3. Schinazi R, Chu C, Peck A, et al. Activities of the four optical isomers of 2',3'-dideoxy-3'-thiacytidine (BCH-189) against human immunodeficiency virus type 1 in human lymphocytes. *Antimicrob Agents Chemother*. 1992;36:672–6.
4. Amblard F, Nolan SP, Schinazi RF, Agrofoglio LA. Efficient synthesis of various acycloalkenul derivatives of pyrimidines using cross-metathesis and Pd(0) methodologies. *Tetrahedron*. 2005;61:537–44.
5. Maruenda H, Johnson F. Design and synthesis of novel inhibitors of HIV-1 reverse transcriptase. *J Med Chem*. 1995;38:2145–51.
6. Faul MM, Huff BE, Dunlap SE, et al. *Tetrahedron*. 1997;53:8085–104.
7. Bronson JJ, Ghazzouli I, Hitchcock MJM, Webb RR, Martin JC. Synthesis and antiviral activity of the nucleotide analogue (*S*)-1-[3-hydroxy-2-(phosp honylmethoxy)propyl]cystosine. *J Med Chem*. 1989;32:1457–63.
8. Hattori H, Nozawa E, Iino T, et al. Nucleosides and nucleotides. 175. Structural requirements of the sugar moiety for the antitumor activities of new nucleoside antimetabolites, 1-(3-C-ethynyl-*β*-D-*ribo*-pentofuranosyl)cytosine and -uracil. *J Med Chem*. 1998;41:2892–902.
9. Senda S, Hirota K, Banno K. Pyrimidine derivatives and related compounds. 15. Synthesis and anlgetic and anti-inflammatory activities of 1,3-substituted 5-amino-6-methyluracil derivatives. *J Med Chem*. 1972;15:471–6.
10. Tice CM, Bryman LM, Roemmele RC. 2-Phenyl-quinazoline derivs for selective pre and post emergence weed control. *Eur Pat Appl*. 1994;EP 733622 [*Chem Abstr.* 1996;125:275903s].
11. Tice CM New 4-imino or amino: pyrimidine derivs. useful as herbicides, prepd. e.g. from *N*-alkyl-amidine and beta-keto-ester. *US Pat*. 1994;US 5300477 [*Chem Abstr.* 1994;122:31543w].
12. Wong JL, Fuchs DS. Reactivities and electronic aspects of nucleic acid heterocycles. II. Diazomethane methylation of uracil and its methyl derivatives. *J Org Chem*. 1971;36:848–50.
13. Danel K, Larsen E, Pedersen BE, Vestergaard BF, Nielsen, C. Synthesis and potent anti-HIV-1 activity of novel 6-benzyluracil analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. *J Med Chem*. 1996;39:2427–31.
14. Jane DE, Hoo K, Kamboj R, Deverill M, Bleakman D, Mandelzys A. Synthesis of willardiine and 6-azawillardiine analogs: pharmacological characterization on cloned homomeric human AMPA and kainite receptor subtypes. *J Med Chem*. 1997;40:3645–50.
15. Ogilvie KK, Beaucage SL. Facile alkylation of purines, pyrimidines, nucleosides and nucleotides using tetrabutylammonium fluoride. *Tetrahedron Lett*. 1978;19:1663–6.
16. Yamauchi K, Kinoshita M. *N*-alkylation of thymine and uracil with trialkyl phosphates. *J Chem Soc Perkin Trans 1*. 1973:391–2.
17. Gasse C, Douguet D, Huteau V, Marchal G, Munier-Lehmann H, Pochet S. Substituted benzyl-purimidines targeting thymidine monophosphate kinase of *Micobacterium tuberculosis*: synthesis and in vitro anti-mycobacterial activity. *Bioorg Med Chem*. 2008;16:6075–85.
18. Pischel H, Holy A, Wagner G. Immunosuppressant antigen conjugates. XXI. Synthesis of conjugates of 5-halouracils with proteins using activated esters. *Collect Czech Chem Commun*. 1979;44:1634–41.
19. Pischel H, Holy A, Wagner G. Immunosuppressant antigen conjugates. XXI. Synthesis of conjugates of 1-(carboxymethyl)cytosine and 1-95-O-carboxymethyl-β-D-arabinofuranosyl)cytosine with proteins. *Collect Czech Chem Commun*. 1979;44:3023–32.
20. Lin P, Jiang J. Synthesis of monotrifluoromethyl-substituted saturated cycles. *Tetrahedron*. 2000;56:3635–71.
21. Welch JT. Advanced in the preparation of biologically active organofluorine compounds. *Tetrahedron*. 1987;43:3123–97.
22. Pees K, Liers P, Karla C. 7-Amino-azolo (1,5-A)-pyrimidine derivs: useful as fungicides especially against Pyricularia grisea f.sp. oryzea and Rhizoctonia solani. *Eur Pat Appl*. 1998;EP 834513 [*Chem Abstr.* 1998;128:257444a].
23. Drewes MW, Andree R, Dollinger M. New imino:alkoxy-phenyl:uracil derivatives—used as herbicides for pre- and post-emergence selective weed control in crops and as defoliants and desiccants. *PCT Int Appl*. 1999, WO 9854155. [*Chem Abstr.* 1999;130:38393w].
24. Tice CM. New 2-aryl-3-substd-4-(thio)oxo-pyrimidine derivs—useful as herbicides, prepd. e.g. from N-alkyl-amidine and beta-keto ester. *Eur Pat Appl*. 1994;EP 579424 [*Chem Abstr.* 1994;121:280638n].
25. Wenger J, Winternitz P, Zeller J. 3-Aryl-uracil derivs.—are effective against weeds, act as dessicants, and facilitate harvesting of cotton, potato or rape. *Ger Offen*. 1993;DE 4237920 [*Chem Abstr.* 1993;119:180808b].
26. Tice CM, Musco VA, Roemmele RC, Warner HL. New 2-aryl-pyrimidine(s)—useful as broad spectrum herbicides. *US Pat*. 1998; US5726124 [*Chem Abstr.* 1998;128:227320q].
27. Sato J, Kawamura Y, Fukuda K, Ito K, Kita H. 3-[4-(phenylmethoxy)phenyl]-1-substituted-6-haloalkyl-uracil herbicides. *Jpn Kokai Tokkyo Koho*. 1992; JP 04178373 [*Chem Abstr.* 1993;118:59721u].
28. Perrior TR, Tapolkzay DJ, Whittle A. New 1-(4-tri:fluoromethyl-phenyl)-4-substd-pyrimidine-6-one derivs—useful as insecticides esp. for controlling cockroaches and house flies. *J Eur Pat Appl*. 1989;EP338686 [*Chem Abstr.* 1990;112:179009r].
29. Ishii S, Akimoto K, Nakayama K, et al. Preparation of 6-phenylpyrimidine derivatives as pesticides. *Jpn Kokai Tokkyo Koho*. 1993 JP0543555 [*Chem Abstr* 1993;119:180804x].
30. Inoue Y, Kobayashi T, Masu A, Asahina K. Preparation of 2-(alkylthio)-6-amino-5-(trifluoromethyl)-4(3*H*)-pyrimidinone derivatives as insecticides or agrochemical fungicides. *Jpn Kokai Tokkyo Koho*. 1991;JP03197467 [*Chem Abstr.* 1991;115:280054p].
31. Kawauchi K, Fukazawa N, Ishibashi D. Preparation of 3-propargyl-α,α,α-trifluorothimidines as antitumors. *Jpn Kokai Tokkyo Koho*. 1994. JP06172377 [*Chem Abstr.* 1995;123:33585f].
32. Magnus NA, Confalone PN, Storace L. A new asymmetric 1,4-addition method: application to the synthesis of the HIV non-nucleoside reverse transcriptase inhibitor DPC 961. *Tetrahedron Lett*. 2000;41:3015–9.
33. Cechin SR, Schetinger MRC, Zanatta N, et al. Inhibitory effect of novel pyrimidines on ATP and ADP hydrolysis in synaptosomes from rat cerebral cortex. *Chem Res Toxicol*. 2003;16:1433–9.
34. Godoy MCM, Fighera MR, Souza FR, et al. α_2-Adrenoceptors and 5-HT receptors mediate antinociceptive effect of new pyrazolines, but not of dipyrone. *Eur J Pharmacol*. 2004;496:93–7.
35. Souza FR, Souza VT, Ratzlaff V, et al. Hypotermic and antipyretic effect of 3-methyl- and 3-phenyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-pyrazole-1-carboxamides. *Eur J Pharmacol*. 2002;451:141–7.
36. Unpublished Results.
37. Zanatta N, Flores DC, Amaral SS, Bonacorso HG, Martins MAP, Flores A. FC. Design and synthesis of novel trichloromethylated *N*-azolylmethyl-1*H*-pyrimidin-2-ones and related *N*-methylenaminones. *Synlett*. 2005;3079–82.
38. Pacholski IL, Blanco I, Zanatta N, Martins MAP. 4-Alkoxy-1,1,1-trihalo-3-alken-2-ones as building blocks for trihalomethylated heterocycles. Synthesis of 4-trihalomethyl-2-pyrimidinones. *J Braz Chem Soc*. 1991;2:118–20.
39. Martins MAP, Zanatta N, Pacholski IL, et al. Molecular structure of heterocycles: NMR spectroscopy, x-ray diffraction, and semiempirical MO calculations of 5-bromo-4,6-dimethoxy-4-trichloromethyl-hexahydropyrimidin-2-one. *Spectroscopy Lett*. 1998;31:1125–39.
40. Zanatta N, Faoro D, Fernandes Lda S, et al. Comparative study of the chemoselectivity and yields of the synthesis of *N*-alkyl-4-(trhalomethyl)-1*H*-pyrimidin-2-ones. *Eur J Org Chem*. 2008:5832–8.

41. Zanatta N, Squizani AMC, Fantinel L, Nachtigall FM, Bonacorso HG, Martins MAP. Application of 4-alkoxy-1,1,1-trifluoro[chloro]alk-3-en-2-ones as selective protecting groups of amino acids. *Synthesis*. 2002:2409–15.
42. Bonacorso HG, Duarte SHG, Zanatta N, Martins MAP. Regiospecific synthesis of 3-alkyl-2-aryl-4-trifluoromethylbenzo[*h*]quinolines by intramolecular cyclization of *N*-(alkyl-1-aryl-3-oxo-4,4,4-trifluorobut-1-en-1-yl)1-naphthylamines. *Synthesis*. 2002:1037–42.
43. Bonacorso HG, Wentz AP, Bittencourt SRT, Marques LML, Zanatta N, Martins MAP. Synthesis of some *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloro(trifluoro)-1-buten-1-yl]-*o*-aminophenols and *o*-phenilenediamines as potential anticancer agents. *Synth Commun*. 2002;32:335–41.
44. Andrew RJ, Mellor JM. Synthesis of trifluoromethylpyrroles and related heterocycles from 4-ethyloxy-1,1,1-trifluorobut-3-ene-2-one. *Tetrahedron*. 2000;56:7267–72.
45. Gorbunova MG, Gerus II, Kukhar VP. Synthesis and properties of β-ethoxyvinyl polyfluoroalkyl ketones. *Synthesis*. 2000;738–42.
46. Zanatta N, Borchhardt DM, Alves SH, et al. Synthesis and antimicrobial activity of new (4,4,4-trihalo-3-oxo-but-1-enyl)-carbamic acid ethyl esters, (4,4,4-trihalo-3-hydrocy-butyl)-carbamic acid ethyl esters, and 2-oxo-6-trihalomethyl-[1,3]oxazinane-3-carboxyxic acid ethyl esters. *Bioorg Med Chem*. 2006;14:3174–84.
47. Zanatta N, Schneider JMFM, Schneider PH, et al. Regiospecific synthesis of 4-alkoxy and 4-amino substituted 2-trifluoromethyl pyrroles. *J Org Chem*. 2006;71:6996–8.
48. Zanatta N, Borchhardt DM, Flores DC, et al. Synthesis and characterization of new trifluoromethyl substituted 3-ethoxycarbonyl- and 3-pyrimidin-2-yl)-(1,2,3)-oxathiazinane-S-Oxide. *J Heterocycl Chem.* 2008;45:335–41.
49. Martins MAP, Guarda EA, Frizzo CP, et al. An ionic liquid as reaction medium for the synthesis of halo-containing β-enaminones at room temperature. *Monatsh Chem*. 2008;139:1321–7.