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Synthesis of new 1-carbamoyl-5-fluorouracil conjugates, derived from omeprazole and cimetidine

Gilles Quéléver[1,2]*, Georges Sturtz[1]

[1] *Laboratoire de Chimie Hétéro-Organique, Faculté des Sciences et Techniques, 6, avenue Le Gorgeu, BP 809, 29285 Brest;*
[2] *Laboratoire de Chimie Bromatologique, Faculté des Sciences de Luminy, Case 901, 13288 Marseille Cedex 9, France*

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Summary — New 1-carbamoyl-5-fluorouracil conjugates which consist of a combination of 5-fluorouracil and anti-ulcer derivatives were designed in order to investigate their antitumor activity toward gastric carcinoma. The synthesis of these new analogs was achieved using a coupling reaction between 1-chloroformyl-5-fluorouracil and 1-(ω-aminoalkyl) derivatives of well-known anti-ulcer compounds, ie, omeprazole and cimetidine.

5-fluorouracil / 1-carbamoyl-5-fluorouracil / omeprazole / cimetidine

Résumé — Synthèse de nouveaux conjugués 1-carbamoyl-5-fluoro-uracile, dérivés de l'oméprazole et de la cimétidine. De nouveaux conjugués 1-carbamoyl-5-fluoro-uracile, dérivés du 5-fluoro-uracile et d'agents anti-ulcéreux, sont décrits afin d'étudier leur activité antitumorale vis-à-vis du cancer gastrique. La synthèse de ces nouveaux analogues a été réalisée selon la réaction de couplage entre le 1-chloroformyl-5-fluoro-uracile et des dérivés 1-(ω-aminoalkyl) de composés antiulcéreux bien connus, c'est-à-dire l'oméprazole et la cimétidine.

5-fluoro-uracile / 1-carbamoyl-5-fluoro-uracile / oméprazole / cimétidine

Introduction

During the two last decades, we have studied the synthesis and the biological activity toward bone carcinoma of gem-bisphosphonic acid analogues of anticancer drugs such as Methotrexate [1, 2] and Doxorubicin [3]. Our studies were carried out on 5-fluorouracil (**1**, 5-FU), a clinically important antitumor agent [4], in view to design active drugs toward gastrointestinal cancer.

This compound is far from possessing optimal delivery properties such as bioavailability [5] or tumor affinity [4]. Moreover, the main toxic effects of 5-FU are exerted on rapidly dividing tissues, primarily the gastrointestinal mucosa [6]. In order to improve the delivery characteristics of 5-FU and to reduce its associated toxic side effects, a promising approach could be to synthesize new 5-FU analogues bearing a pharmacophore known for its high gastrointestinal affinity. The pharmacophores which have been chosen for this purpose are the well-known anti-ulcer omeprazole and cimetidine. In this perspective, it can be hoped that the administered molecular combination would release 5-FU which could make its own antitumor contribution surimposed on the gastrointestinal effect of omeprazole or cimetidine. In this paper, we report the synthesis of 5-FU omeprazole **2** [7, 8] and 5-FU cimetidine **3** [9, 10] conjugates as synthetic target compounds.

The rationale for envisaging 5-FU anti-ulcer mixed molecules stems from an attempt to investigate their clinical pharmacokinetics (absorption, distribution) and toxicity.

Chemistry

Carbamoylation of 5-FU has been extensively studied [11]. This reaction is usually achieved following three general methods [11]:

(i) reaction of 5-FU with isocyanate,

(ii) reaction of 5-FU with carbamoyl chloride,

(iii) reaction of 1-chloroformyl-5-FU with amine.

In a first attempt, we have investigated the possibility of linking the 5-FU carbamoyl intermediate **4** (m) to the pharmacophores omeprazole or cimetidine through direct condensation in the presence of Et_3N. Since this latter condensation failed, conjugation of 5-FU to omeprazole and cimetidine was achieved

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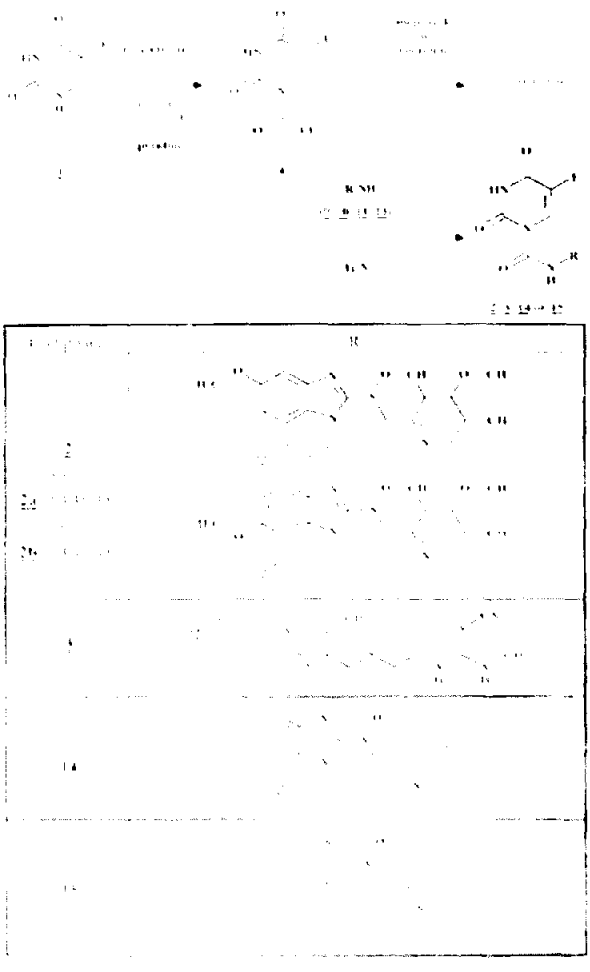
through the use of an alkyl spacer bearing a terminal primary amine group (scheme 1). For this purpose, omeprazole 1-aminoalkyl **11** and cimetidine 1-aminoalkyl **13** intermediates were synthesized according to the following sequences summarized on schemes 2 and 3.



Scheme 1 Synthesis of 1-11 compounds of omeprazole omeprazole and cimetidine analogs

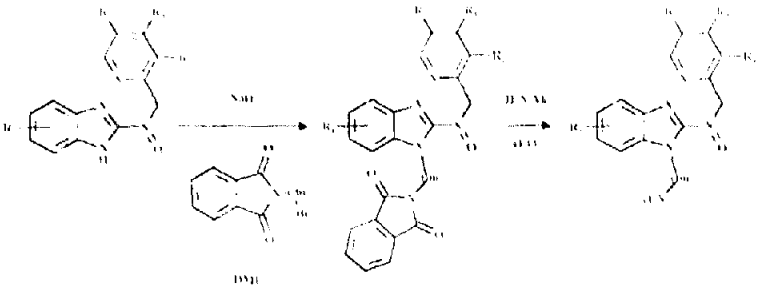
Synthesis of omeprazole **11** *and derivatives*

The intermediate **5** known as omeprazole sulfone used as an omeprazole model was obtained in a two-step synthesis as already reported [12]. N-alkylation of **5** was achieved by condensation of N-bromoalkylphthalimide in DMF using sodium hydride as base (4 h, at 60 °C or 110 °C respectively (scheme 2)). Due to the thermal decomposition of **5**, the resulting coupling products **6** and **7** were isolated in moderate yields respectively 58 % and 42 %. The same reaction with omeprazole **5** failed when it was carried out at room temperature.

Since omeprazole and its analogues are thermally sensitive, the reaction for omeprazole N-alkylation was successfully carried out in 80 % yield, at room temperature to avoid this decomposition. In addition, omeprazole is present as two tautomeric forms **8**. The desired N-propylphthalimide omeprazole **8** was obtained as a mixture of two isomeric compounds **8a** (5-methoxybenzimidazole) and **8b** (6-methoxybenzimidazole) as NMR determined molecular ratios **8a**/**8b** = 65/35. Removal of the phthalimide protecting group was achieved according to Wolfbeis *et al.* [13] by aminolysis using an excess of aqueous methylamine solution. The crude free amine derivatives **9**, **10** and **11** as a mixture of **11a** and **11b** were pure enough to be directly used for the next step (scheme 1).

Synthesis of cimetidine **13** *and derivatives*

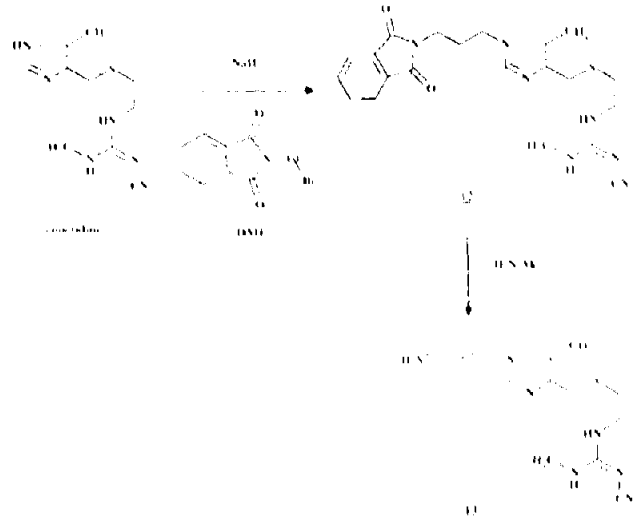
1-Aminoalkylcimetidines were obtained through the following sequence. To a solution of cimetidine (1 eq) treated with NaH (1 eq) in DMF at 0 °C was added N-(bromoalkyl)phthalimide (1 eq). The mixture was heated 2 hours at 110 °C. The desired compounds were obtained after purification in 60 % yields. It should be noted that only N-propylphthalimide **12** which synthesis is described on scheme 3, and N-methylphthalimide derivatives were obtained. Under the same conditions, N-bromomethylphthalimide condensation failed. ^{1}H and ^{13}C NMR analysis showed that the N$_3$ position of the histidine ring of cimetidine was preferentially alkylated by N-(bromoalkyl)phthalimide. Removal of the phthalimide protecting group was performed by aminolysis as already described. Unfortunately, removal of the protecting group of the N-methylphthalimide derivative led to cimetidine by an N-deammonomethylation reaction or retro-Mannich reaction.



5	6 a–c	9 a–c
R_1, R_2, R_3, R_4 = H	7 a–c	10 a–c
omeprazole*	8 a–c	11 a–c
R_1 = 5- and/or 6-CH_3O	as in stage of 8a–8b	as in stage of 11a–11b
R_2, R_4 = CH_3; R_3 = CH_3O		

* in solution omeprazole exists as two tautomeric forms [8]

Scheme 2. Synthesis of *N*-(ω-aminoalkyl) derivatives of timoprazole and omeprazole.



Scheme 3. Synthesis of *N*-(3-aminopropyl) derivative of cimetidine.

5-FU omeprazole and 5-FU cimetidine conjugates

5-Fluorouracil treated below 5 °C with trichloromethyl chloroformate in the presence of activated charcoal in pyridine gave the chloroformyl derivative **4** (scheme 1). The latter was condensed with the free (ω-aminoalkyl) derivatives of timoprazole, **9** and **10**, omeprazole, **11**, or cimetidine, **13**, using Et_3N as base. The desired compounds **2**, **14** and **15** were obtained in 27%, 34% and 34% yields respectively and fully characterized. Compound **3**, derivative from cimetidine, was fully characterized but due to its instability, we were unable to purify and isolate this compound. At present, antitumoral activity and gastrointestinal affinity of these new drugs **2**, **14** and **15** are under investigation.

Experimental section

The primary chemicals used were commercial products (Actos Chimica, Sigma-Aldrich). *N,N*-dimethylformamide was dried on P_2O_5 before distillation and pyridine was dried on a molecular sieve of 4 Å. The purity of the products and the reaction progress were monitored on TLC plates ($60F_{254}$, Merck). Liquid chromatography was carried out on a silica gel column (Merck 60, 70–230 mesh). TLC revelations were carried out with a UV lamp (254 nm) or with reagents such as iodine and ninhydrine. Melting points were determined

on a Kofler hot-stage apparatus. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 300 or Bruker DRX 400 spectrometers. The chemical shifts are reported in ppm using TMS as tetramethylsilane) in organic solvents ($CDCl_3$) as reference. Coupling constants J are reported in Hertz (Hz).

2-[(2-Pyridylmethyl)thio]-1H-benzimidazole

2-Mercaptobenzimidazole (4.58 g, 30.5 mmol, 1 eq) treated with NaOH (1.22 g, 30.5 mmol, 1 eq) gave 2-mercaptobenzimidazole sodium salt. The latter was dissolved in ethyl alcohol and 2-chloromethylpyridine hydrochloride (5 g, 30.5 mmol, 1 eq) and Na_2CO_3 (3.23 g, 30.5 mmol, 1 eq) in 10 mL of water–ethyl alcohol solution was added. The reaction mixture was refluxed for 1.5 hours. The solvents were removed under reduced pressure and the residue dissolved in CH_2Cl_2 (100 mL). The organic solution was washed with H_2O (2 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue crystallized from EtOAc. Yield 92%. TLC (EtOAc) R_f = 0.30. Mp = 106–108 °C.

^1H NMR ($CDCl_3$) δ: 4.40 (s, 2H, CH_2), 7.35 (m, 7H, $4H_{4-7}$ + $3H_{3'-5'}$), 8.50 (d, 1H, $H_{6'}$, ^3J = 3.8 Hz).

^{13}C NMR ($CDCl_3$) δ: 37.76 (CH_2), 114.07 (C_4), 121.77 ($C_{3'}$), 122.51 ($C_{5'}$), 123.30 (C_5), 137.36 ($C_{4'}$), 139.33 (C_{3a}, C_7), 148.60 ($C_{2'}$), 150.60 ($C_{6'}$), 157.14 (C_2).

Anal ($C_{14}H_{13}N_3S$) C, H, N.

2-[(2-Pyridylmethyl)sulfinyl]-1H-benzimidazole **5**

A solution of mCPBA (7.27 g, 42.2 mmol, 1.5 eq) in CH_2Cl_2 (20 mL) was added at −10 °C to a solution of the previous sulfide (6.27 g, 28.1 mmol, 1 eq) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at −10 °C for 15 min and 1 hour at room temperature. A solution of triethylamine (4.27 g, 42.2 mmol, 1.5 eq) in CH_2Cl_2 was added and the organic layer was washed with a 2% Na_2CO_3 aqueous solution and then with a 2% $Na_2S_2O_3$ aqueous solution. The organic layer was dried over $MgSO_4$ and concentrated. The residue was crystallized from EtOAc to give a white solid. Yield 86%. TLC (EtOAc) R_f = 0.32. Mp = 162–164 °C. Stable decomposition.

^1H NMR ($CDCl_3$) δ: 4.65 (AB, 2H, CH_2, J_{gem} = 14.3 Hz), 7.35 (m, 7H, $4H_{4-7}$ + $3H_{3'-5'}$), 8.40 (d, 1H, $H_{6'}$, ^3J = 5.0 Hz).

^{13}C NMR ($CDCl_3$) δ: 62.51 (CH_2), 109.50 (C_4), 123.19 ($C_{3'}$), 123.65 ($C_{5'}$), 125.11 (C_5), 136.73 ($C_{4'}$), 139.50 (C_{3a}, C_7), 149.80 ($C_{6'}$), 149.87 ($C_{2'}$), 152.08 (C_2).

Anal ($C_{13}H_{11}N_3OS$) C, H, N.

N-[2-[1-[2-[(2-Pyridylmethyl)sulfinyl]benzimidazolyl]]ethyl]phthalimide **6**

To a suspension of NaH (0.27 g, 11.3 mmol, 1.1 eq) in 20 mL of anhydrous DMF under nitrogen atmosphere was added a solution of **5** (2.66 g, 10.3 mmol, 1 eq) in anhydrous DMF (10 mL). After complete dissolution, a solution of *N*-(2-bromoethyl)phthalimide (2.87 g, 11.3 mmol, 1.1 eq) in anhydrous DMF (10 mL) was added. The reaction mixture was stirred at 60 °C for 24 hours and poured into 100 mL of brine. After extraction with $CHCl_3$ (3 × 50 mL), the organic layers were dried over $MgSO_4$ to give after the solvent evaporation the title compound **6**. This compound was purified on a silica gel column using EtOAc as eluent. Yield 58%. TLC (EtOAc) R_f = 0.36. Mp = 141–146 °C.

^1H NMR ($CDCl_3$) δ: 4.20 (t, 2H, CH_2 NPhth), 4.65 (t, 2H, CH_2 Nbenzimidazolyl), 5.05 (s, 2H, CH_2), 7.45 (m, 11H, $4H_{4-7}$ + $3H_{3'-5'}$ + $4H_{Phth}$), 8.52 (d, 1H, $H_{6'}$, ^3J = 3.0 Hz).

^{13}C NMR ($CDCl_3$) δ: 37.82 (CH_2 NPhth), 42.39 (CH_2-Nbenzimidazolyl), 62.27 (CH_2), 109.35 (C_4), 121.02 ($C_{3'}$), 123.07 (C_6), 123.21 (C_5 + C_{Phth}), 124.49 (C_7), 125.23 ($C_{5'}$), 131.52 (C_{Phth}), 134.00 (C_{Phth}), 136.05 ($C_{4'}$), 136.65 ($C_{3'}$), 142.01 (C_{3a}), 150.03 ($C_{6'}$), 150.66 ($C_{2'}$), 151.10 (C_2), 167.71 (C=O_{Phth}).

Anal ($C_{23}H_{18}N_4O_4S$) C, H, N.

N-[3-[1-[2-[[(2-Pyridyl)methyl]sulfinyl]]benzimidazolyl]propyl]phthalimide **7**

The title compound was prepared in 42% yield (3.86 g) from **5** (5.32 g, 20.7 mmol) according to the previous process using a reaction time of 2 hours at 110 °C. TLC (EtOAc) R_f = 0.34. Mp = 126–128 °C.

^1H NMR ($CDCl_3$) δ: 2.13 (m, 2H, PhthN CH_2-CH_2-CH_2-Nbenzimidazolyl), 3.69 (t, 2H, CH_2-NPhth), 4.33 (m, 2H, CH_2 Nbenzimidazolyl, J_{gem} = 13.7 Hz), 4.79 (AB, 2H, CH_2, J_{gem} = 12.9 Hz), 7.19 (m, 2H, $H_{5'}$ + $H_{5''}$), 7.57 (m, 9H, $4H_{4-7}$ + $H_{4'}$ + $4H_{Phth}$), 8.45 (ddd, 1H, $H_{6''}$, ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 1.1 Hz).

^{13}C NMR ($CDCl_3$) δ: 29.16 (PhthN CH_2 CH_2 CH_2 Nbenzimidazolyl), 35.29 (CH_2-NPhth), 42.19 (CH_2-Nbenzimidazolyl), 61.69 (CH_2), 109.95 (C_4), 121.13 ($C_{3'}$), 123.05 (C_6), 123.25 (C_{Phth}), 123.43 (C_5), 124.89 ($C_{5'}$), 125.48 ($C_{5''}$), 131.83 (C_{Phth}), 134.01 (C_{Phth}), 135.52 ($C_{4'}$), 136.72 ($C_{3''}$), 142.20 (C_{3a}), 149.90 ($C_{4''}$), 150.39 ($C_{2''}$), 151.00 (C_2), 168.07 (C=O_{Phth}).

Anal ($C_{24}H_{20}N_4O_4S$) C, H, N.

N-[3-[1-[5-(6)-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]]benzimidazolyl]propyl]-phthalimide **8a** *and* **8b**

Similar reaction of omeprazole (2.66 g, 7.4 mmol) with *N*-(3-bromopropyl)phthalimide with a reaction time of 4 hours at room temperature gave a mixture of the title compounds **8a** and **8b**. Yield (89%). The ratio of compounds **8a** and **8b** was determined by ^1H NMR: **8a**/**8b** = 65/35. TLC (EtOAc) R_{f1} = 0.27 and R_{f2} = 0.23.

^1H NMR ($CDCl_3$) **8a**, δ: 2.20 (s, 3H, CH_3 in position 4'), 2.25 (s, 3H, CH_3 in position 5'), 2.30 (m, 2H, PhthN CH_2 CH_2-CH_2 Nbenzimidazolyl), 3.69 (s, 3H, CH_3Opyridyl), 3.82 (t, 2H, PhthN CH_2), 3.84 (s, 3H, 5-CH_3Obenzimidazolyl), 4.12 (m, 2H, CH_2-Nbenzimidazolyl, J_{gem} = 14.7 Hz), 4.33 (AB, 2H, CH_2, J_{gem} = 13.6 Hz), 6.76 (d, 1H, H_4, ^4J = 2.3 Hz), 6.91 (dd, 1H, H_6, ^3J = 8.9 Hz, ^4J = 2.3 Hz), 7.64 (d, 1H, H_7, ^3J = 8.9 Hz), 7.78 (m, 4H, H_{Phth}), 8.10 (s, 1H, $H_{6'}$).

8b, δ: 2.20 (s, 3H, CH_3 in position 3'), 2.25 (s, 3H, CH_3 in position 5'), 2.28 (m, 2H, PhthN CH_2 CH_2 CH_2 Nbenzimidazolyl), 3.69 (s, 3H, CH_3Opyridyl), 3.79 (t, 2H, PhthN CH_2), 3.83 (s, 3H, 6-CH_3Obenzimidazolyl), 4.13 (m, 2H, CH_2 Nbenzimidazolyl, J_{gem} = 14.7 Hz), 4.91 (AB, 2H, CH_2, J_{gem} = 13.6 Hz), 6.97 (dd, 1H, H_5, ^3J = 8.8 Hz, ^4J = 2.4 Hz), 7.22 (d, 1H, H_7, ^4J = 2.4 Hz), 7.24 (d, 1H, H_4, ^3J = 8.8 Hz), 7.78 (m, 4H, H_{Phth}), 8.10 (s, 1H, $H_{6'}$).

^{13}C NMR ($CDCl_3$) **8a**, δ: 11.56 (CH_3 in position 3'), 13.31 (CH_3 in position 5'), 29.04 (PhthN CH_2 CH_2 CH_2 Nbenzimidazolyl), 35.57 (PhthN CH_2), 42.35 (CH_2 Nbenzimidazolyl), 55.79 (5-CH_3Obenzimidazolyl), 59.11 (CH_2), 59.96 (CH_3Opyridyl), 92.55 (C_4), 113.63 (C_7), 121.89 (C_4), 123.37 (C_{Phth}), 126.03 (C_5), 126.79 (C_6), 131.92 (C_{Phth}), 134.13 (C_{Phth}), 136.29 (C_{3a}), 136.84 ($C_{5'}$), 149.47 ($C_{6'}$), 149.71 ($C_{4'}$), 150.91 (C_2), 157.99 (C_7), 164.19 ($C_{2'}$), 168.21 (C=O_{Phth}).

8b: δ: 11.56 (CH_3 in position 3'), 13.31 (CH_3 in position 5'), 29.06 (PhthN-CH_2-CH_2-CH_2-Nbenzimidazolyl), 35.54 (PhthN-CH_2), 42.58 (CH_2 Nbenzimidazolyl), 55.76 (6-CH_3Obenzimidazolyl), 59.17 (CH_2), 59.95 (CH_3Opyridyl), 102.35 (C_5), 110.54 (C_7), 115.89 (C_4), 123.41 (C_{Phth}), 126.05 ($C_{5'}$), 126.79 ($C_{4'}$), 130.21 (C_{7a}), 131.96 (C_{Phth}), 134.09 (C_{Phth}), 143.20 (C_{3a}), 149.49 ($C_{6'}$), 149.72 ($C_{2'}$), 152.04 (C_2), 156.89 (C_6), 164.21 ($C_{4'}$), 168.18 (C=O_{Phth}).

Anal ($C_{28}H_{28}N_4O_5S$) C, H, N.

N-[1-[3-[N$_1$-[5-Methyl-4-[1-[2-[N-(N-cyano)-N-methyl]guanidinyl]ethyl]sulfide]methyl]-imidazolyl]propyl]phthalimide **12**

The title compound was prepared in 67% yield (0.37 g) from cimetidine (0.32 g, 1.3 mmol) and *N*-(3-bromopropyl)phthalimide according to the previous reaction with a reaction time of 2 hours at 110 °C. TLC (EtOAc) R_f = 0.05, (EtOAc/MeOH, 10:1) R_f = 0.24. Mp = 144 °C.

^{1}H NMR ($CDCl_3$) δ: 2.15 (m, 2H, PhthN-CH_2-CH_2-CH_2-Nimidazolyl), 2.17 (s, 3H, CH_3-imidazolyl), 2.60 (t, 2H, S-CH_2-CH_2-NH), 2.92 (d, 3H, NH-CH_3), 3.47 (m, 2H, S-CH_2-CH_2-NH), 3.59 (s, 2H, S-CH_2-imidazolyl), 3.74 (t, 2H, PhthN-CH_2-CH_2), 3.91 (t, 2H, CH_2-CH_2 Nimidazolyl), 6.20 (broad s, 2H, N*H*), 7.49 (s, 1H, N-C*H*=N), 7.80 (m, 4H, H_{Phth}).

^{13}C NMR ($CDCl_3$) δ: 8.44 (CH_3-imidazolyl), 26.48 (S-CH_2-imidazolyl), 28.46 (NH-CH_3), 29.20 (PhthN-CH_2-CH_2-CH_2-Nimidazolyl), 29.93 (S-CH_2-CH_2-NH), 35.14 (PhthN-CH_2-CH_2), 41.68 (S-CH_2-CH_2-NH), 42.87 (CH_2-CH_2 Nimidazolyl), 119.10 (*C*N), 123.47 (N-*C*(CH$_3$)=C + C_{Phth}), 131.79 (C_{Phth}), 134.36 (C_{Phth}), 135.35 (N-*C*(CH_2-S)=C), 135.38 (N-*C*H=N), 160.54 (NH-*C*(=N)NH), 168.34 (C=O_{Phth}).

Anal ($C_{21}H_{25}N_7O_2S$) C, H, N.

1-[1-[2-[1-[2-[(2-Pyridyl)methyl]sulfinyl]]benzimidazolyl]ethyl]carbamoyl-5-fluorouracil **14**

An excess of 40% aqueous methylamine was added to a suspension of **6** (2.41 g, 5.7 mmol) in water (20 mL). The reaction mixture was stirred 24 hours at room temperature, extracted with $CHCl_3$ (3 × 50 mL) and dried over $MgSO_4$. The organic layers were concentrated under reduced pressure. The crude amine was used without purification for the next step.

To a 0 °C solution of 5-fluorouracil **1** (0.74 g, 5.7 mmol, 1 eq) in the presence of 10 mg of activated charcoal in freshly distilled pyridine (20 mL) was added 0.75 eq of diphosgene (0.45 mL, 1.3 mmol). The reaction mixture was stirred at this temperature for 1 hour and the excess phosgene was expelled with a nitrogen flush. The previous $CHCl_3$ solution of amine with triethylamine was added at 5 °C. This mixture was stirred 1 hour below 10 °C and 2 hours at room temperature. The solution was filtered and concentrated under reduced pressure to give an oily solid. The residue gave the desired compound after chromatography using EtOAc as eluent. Yield 31%. TLC (EtOAc) R_f = 0.11. Mp = 179 °C, with decomposition.

^{1}H NMR (DMSO-d^6) δ: 3.70 (m, 2H, NH-CH_2-CH_2 Nbenzimidazolyl, J_{gem} = 13.9 Hz), 4.61 (m, 2H, NH-CH_2-CH_2 Nbenzimidazolyl, J_{gem} = 14.8 Hz), 4.84 (AB, 2H, CH_2, J_{gem} = 13.4 Hz), 7.38 (m, 4H, H_4 + H_6 + $H_{4'}$ + $H_{5'}$), 7.78 (m, 3H, H_5 + H_7 + $H_{3'}$), 8.30 (d, 1H, CF=C*H*, ^3J = 7.5 Hz), 8.44 (ddd, 1H, $H_{6'}$, ^3J = 4.3 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz), 9.27 (t, 1H, C(=O)-N*H*-CH_2, ^3J = 5.9 Hz), 12.22 (broad s, 1H, C(=O)-N*H*-C(=O)).

^{13}C NMR (DMSO-d^6) δ: 40.94 (NH-CH_2-CH_2 Nbenzimidazolyl), 43.36 (NH-CH_2-CH_2-Nbenzimidazolyl), 60.95 (CH_2), 111.52 ($C_{6'}$), 120.50 (C_4), 122.83 (CF=*C*H, ^2J = 38.0 Hz), 123.25 (C_6), 123.33 (C_5), 124.47 (C_7), 125.78 ($C_{5'}$), 135.58 (C_{7a}), 137.10 ($C_{3'}$), 140.66 (*C*F, ^1J = 233.6 Hz), 141.71 (C_{3a}), 149.58 ($C_{4'}$), 149.89 (N-*C*(=O)-NH-CH_2), 150.05 (N-*C*(=O)-NH-C(=O)), 151.27 (C_2), 152.81 ($C_{2'}$), 156.95 (NH-*C*(=O)-CF, ^2J = 27.0 Hz).

Anal ($C_{20}H_{17}FN_6O_4S$) C, H, N.

1-[1-[3-[1-[2-[[(2-Pyridyl)methyl]sulfinyl]benzimidazolyl]propyl]]carbamoyl-5-fluoro-uracil **15**

A similar reaction from **7** gave the desired compound **15** as a white solid in 34% yield (0.34 g). TLC (EtOAc) R_f = 0.08. Mp = 174 °C, with decomposition.

^{1}H NMR (DMSO-d^6) δ: 2.00 (m, 2H, NH-CH_2-CH_2-CH_2-Nbenzimidazolyl), 3.28 (m, 2H, NH-CH_2-CH_2), 4.46 (m, 2H, CH_2-CH_2-Nbenzimidazolyl), 4.92 (AB, CH_2, J_{gem} = 13.1 Hz), 7.35 (m, 4H, H_4 + H_6 + $H_{4'}$ + $H_{5'}$), 7.75 (m, 3H, H_5 + H_7 + $H_{3'}$), 8.33 (d, 1H, CF=C*H*, ^3J = 7.5 Hz), 8.48 (ddd, 1H, $H_{6'}$, ^3J = 4.8 Hz, ^4J = 1.7 Hz, ^5J = 0.8 Hz), 9.45 (t, 1H, C(=O)-N*H*-CH_2, ^3J = 5.7 Hz), 12.27 (broad s, 1H, C(=O)-N*H*-C(=O)).

^{13}C NMR (DMSO-d^6) δ: 29.30 (NH-CH_2-CH_2-CH_2 Nbenzimidazolyl), 38.05 (N*H*-CH_2-CH_2), 41.65 (CH_2-CH_2-Nbenzimidazolyl), 60.44 (CH_2), 111.30 ($C_{6'}$), 120.37 (C_4), 122.89 (CF=*C*H, ^2J = 37.5 Hz), 123.06 (C_6), 123.14 (C_5), 124.38 (C_7), 125.45 ($C_{5'}$), 135.39 (C_{7a}), 136.91 ($C_{3'}$), 140.49 (*C*F, ^1J = 233.9 Hz), 141.55 (C_{3a}), 149.52 (N-*C*(=O)-NH-CH_2-$C_{3'}$), 149.91 (N-*C*(=O)-NH-C(=O)), 151.03 (C_2), 152.07 ($C_{2'}$), 156.89 (NH-*C*(=O)-CF, ^2J = 27.2 Hz).

Anal ($C_{21}H_{18}FN_6O_4S$) C, H, N.

1-[1-[3-[1-[5-(6)-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]]benzimidazolyl]propyl]]-carbamoyl-5-fluorouracil **2a** *and* **2b**

The mixture of compounds **2a** and **2b** was prepared with a similar two-step reaction from the mixture **11a/11b**. The ratio of **2a/2b** was determined by ^{1}H NMR: **2a/2b** = 60:40. Yield 27%. TLC (EtOAc) $R_{f\,a\ and\ b}$ = 0.07.

^{1}H NMR ($CDCl_3$) **2a**: δ: 2.19 (s, 3H, CH_3 in position 3'), 2.18 (m, 2H, NH-CH_2-CH_2-CH_2-Nbenzimidazolyl), 2.31 (s, 3H, CH_3 in position 5'), 3.41 (m, 2H, NH-CH_2-CH_2), 3.72 (s, 3H, $CH_3O_{pyridyl}$), 3.86 (s, 3H, 5-CH_3Obenzimidazolyl), 4.42 (m, 2H, CH_2-CH_2 Nbenzimidazolyl, J_{gem} = 14.5 Hz), 5.08 (s, 2H, CH_2), 6.78 (d, 1H, H_4, ^4J = 2.3 Hz), 6.93 (dd, 1H, H_6, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.04 (d, 1H, H_7, ^3J = 9.0 Hz), 8.18 (s, 1H, $H_{6'}$), 8.25 (d, 1H, CF=C*H*, ^3J = 6.7 Hz), 9.17 (t, 1H, C(=O)-N*H*-CH_2, ^3J = 6.3 Hz), 10.90 (broad s, 1H, C(=O)-N*H*-C(=O)).

2b: δ: 2.19 (s, 3H, CH_3 in position 3'), 2.18 (m, 2H, NH-CH_2-CH_2-CH_2-Nbenzimidazolyl), 2.31 (s, 3H, CH_3 in position 5'), 3.41 (m, 2H, NH-CH_2-CH_2), 3.72 (s, 3H, CH_3Opyridyl), 3.82 (s, 3H, 6-CH_3Obenzimidazolyl), 4.42 (m, 2H, CH_2-CH_2-Nbenzimidazolyl, J_{gem} = 14.5 Hz), 5.08 (s, 2H, CH_2), 7.00 (dd, 1H, H_5, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.20 (d, 1H, H_7, ^4J = 2.3 Hz), 7.28 (d, 1H, H_4, ^3J = 9.0 Hz), 8.18 (s, 1H, $H_{6'}$), 8.22 (d, 1H, CF=C*H*, ^3J = 6.7 Hz), 9.13 (t, 1H, C(=O)-N*H*-CH_2, ^3J = 6.3 Hz), 10.90 (broad s, 1H, C(=O)-N*H*-C(=O)).

^{13}C NMR ($CDCl_3$) **2a**: δ: 11.93 (CH_3 in position 3'), 13.54 (CH_3 in position 5'), 28.93 (NH-CH_2-CH_2-CH_2 Nbenzimidazolyl), 38.60 (NH-CH_2-CH_2), 42.42 (CH_2-CH_2 Nbenzimidazolyl), 55.99 (5-CH_3Obenzimidazolyl),

58.05 (CH_2), 60.08 (CH_3Opyridyl), 92.92 (C_5), 113.43 (C_5), 121.71 (C_4), 122.30 (CF=CH, ^2J = 37.5 Hz), 126.33 ($C_{5'}$), 127.45 ($C_{3'}$), 136.23 ($C_{2'}$), 136.63 (C_{3a}), 140.71 (C-F, ^1J = 240.0 Hz), 149.03 ($C_{6'}$), 149.24 (N-C(=O)-NH-CH_2), 149.34 (C_2), 149.79 (N-C(=O)-NH-C(=O)), 150.27 (C_2), 156.45 (NH-C(=O)-CF, ^2J = 27.5 Hz), 157.90 (C_5), 164.33 (C_4).

2b: δ: 11.93 (CH_3 in position 3'), 13.54 (CH_3 in position 5'), 28.93 (NH-CH_2-CH_2-CH_2-Nbenzimidazolyl), 38.60 (NH-CH_2-CH_2), 42.12 (CH_2-CH_2-Nbenzimidazolyl), 55.79 (6-CH_3Obenzimidazolyl), 58.05 (CH_2), 60.08 (CH_3Opyridyl), 101.93 (C_5), 110.74 (C_7), 115.76 (C_4), 122.30 (CF=CH, ^2J = 37.5 Hz), 126.33 ($C_{5'}$), 127.45 ($C_{3'}$), 130.05 (C_{7a}), 140.71 (C-F, ^1J = 240.0 Hz), 142.92 (C_{3a}), 149.03 ($C_{6'}$), 149.24 (N-C(=O)-NH-CH_2), 149.34 ($C_{2'}$), 149.79 (N-C(=O)-NH-C(=O)), 151.23 (C_2), 156.45 (NH-C(=O)-CF, ^2J = 27.5 Hz), 156.79 (C_5), 164.33 (C_4).

Anal ($C_{25}H_{27}FN_6O_6S$) C, H, N.

1-[1-[3-[N1-[5-Methyl-4-[[1-[2-[N-(N-cyano-N-methyl)-guanidinyl]ethyl]]sulfide]methyl]imidazolyl]propyl]]-carbamoyl-5-fluorouracil **3**

The title compound was characterized by ^{1}H and ^{13}C NMR spectroscopy after being prepared by a similar process as previously. TLC (EtOAc/MeOH, 10:1) R_f = 0.03.

^{1}H NMR (DMSO-d^6) δ: 1.90 (m, 2H, NH-CH_2-CH_2-CH_2-Nimidazolyl), 2.13 (s, 3H, CH_3-imidazolyl), 2.55 (t, 2H, S-CH_2-CH_2-NH), 2.69 (d, 3H, NH-CH_3, ^3J = 4.9 Hz), 3.30 (m, 4H, S-CH_2-CH_2-NH + NH-CH_2-CH_2), 3.61 (s, 2H, S-CH_2-imidazolyl), 3.94 (m, 2H, CH_2-CH_2-Nimidazolyl), 7.56 (s, 1H, N-CH=N), 8.37 (d, 1H, CF=CH, ^3J = 7.5 Hz), 9.20 (t, 1H, C(=O)-NH-CH_2, ^3J = 5.1 Hz).

^{13}C NMR (DMSO-d^6) δ: 8.00 (CH_3-imidazolyl), 28.29 (S-CH_2-imidazolyl + NH-CH_3), 29.56 (NH-CH_2-CH_2-CH_2-Nimidazolyl), 31.22 (S-CH_2-CH_2-NH), 37.93 (S-CH_2-CH_2-NH), 40.81 (NH-CH_2-CH_2), 41.73 (CH_2-CH_2-Nimidazolyl), 118.03 (CN), 122.70 (CF=CH, ^2J = 37.6 Hz), 123.17 (N-C(CH$_3$)=C), 133.79 (N-C(CH_2-S)-C), 135.53 (N-CH=N), 140.39 (C-F, ^1J = 233.5 Hz), 149.41 (N-C(=O)-NH-CH_2), 149.92 (N-C(=O)-NH-C(=O)), 156.94 (NH-C(=O)-CF, ^2J = 26.8 Hz), 159.63 (NH-C(=N)NH).

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