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## Potential Anticancer Agents. 17. Analogues of Methotrexate with a Tripeptide Side Chain

Dan Carol Suster,<sup>1</sup> EutaŃa Tărnăuceanu, Georgeta Botez, Vasile Dobre, and Ion Niculescu-Duvăz\*

Department of Cytostatics, Oncological Institute, Bucharest, Romania. Received October 6, 1977

Nine tripeptide analogues of methotrexate were synthesized from 2,4-diamino-6-(chloromethyl)pteridine. Only *N*-[*N*-[4-[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]glycyl-DL-aspartic acid (**1a**) showed moderate activity against L1210 murine leukemia (ILS = 69%) and W 256 carcinosarcoma (TGI = 55%).

We recently reported the synthesis of new methotrexate analogues, in which the terminal glutamic acid moiety was replaced by other amino acids.<sup>2a</sup> There is considerable evidence in the literature which points to the importance of the terminal glutamyl residue for biological activity.<sup>2b-6</sup> It is known, also, that the triglutamyl derivative of folic acid exhibits some antitumor activity, whereas folic acid itself is completely ineffective.<sup>7</sup> For these reasons, it was of interest to prepare peptide analogues of methotrexate (MTX), in which the terminal glutamyl moiety remains intact. Since most of the tested homo- and heteropolymeric analogues of MTX have been shown to be ineffective against L1210 murine leukemia, as well as against microorganisms<sup>8-10</sup> (except MTX-immunoglobulin and MTX-albumin covalent complexes<sup>11-13</sup>), we chose to limit ourselves to the synthesis of tripeptide analogues of general structure **1** (see Table I), in which X is a supplementary amino acid.

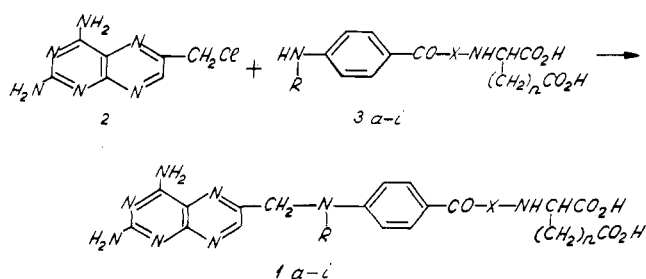
**Synthesis.** Condensation of 2,4-diamino-6-(chloromethyl)pteridine (**2**)<sup>14,15</sup> with tripeptides **3**, in water at pH 7.5, afforded methotrexate analogues **1a-i** (Scheme I). Purification was accomplished readily by column chromatography on cellulose or Sephadex G-10. The physical constants for these new derivatives are given in Table II. The synthesis of tripeptides **3a-i** was achieved as shown in Scheme II. The 4-(*N*-carbobenzyloxy-*N*-methylamino)benzoylamino acids **4** were prepared as previously described,<sup>2a</sup> purified carefully, and condensed with diethyl glutamate or diethyl aspartate<sup>2a,16,17</sup> in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) in order to obtain the protected tripeptides **5a-i**. Saponification of the ester groups yielded the free acids **6a-i** which, on catalytic hydrogenolysis, gave the tripeptides **3a-i**. The physical constants for the new intermediates **3**, **5**, and **6** are listed in Table III.

**Biological Data.** The antitumor effectiveness of the new methotrexate analogues **1a-i** was evaluated against L1210 mouse leukemia and W 256 rat carcinosarcoma. The data given in Table IV indicate that the insertion of an extra amino acid between the aminobenzoyl and glu-

Table I. New Tripeptide Analogues of Methotrexate

compd	R	X	n
<b>1a</b>	H	Gly	1
<b>1b</b>	H	Gly	2
<b>1c</b>	CH <sub>3</sub>	Gly	1
<b>1d</b>	CH <sub>3</sub>	Gly	2
<b>1e</b>	CH <sub>3</sub>	DL-Ala	2
<b>1f</b>	CH <sub>3</sub>	Sar	2
<b>1g</b>	CH <sub>3</sub>	L-Leu	2
<b>1h</b>	CH <sub>3</sub>	L-Phe	1
<b>1i</b>	CH <sub>3</sub>	L-Phe	2

Scheme I



tamic acid moieties may lead to compounds with borderline activity against the L1210 tumor. One compound, the glycylaspartate analogue **1a**, exhibited moderate activity against both tumors.

### Experimental Section

Melting points were taken on a Boetius apparatus and are uncorrected. Ultraviolet spectra were determined with CF<sub>4</sub> Optica Milano and Spekord UV-vis Carl Zeiss Jena spectrophotometers, and infrared spectra were run on an UR-10 Carl Zeiss Jena spectrophotometer.

**Ethyl 4-(*N*-Carbobenzyloxyamino)- and 4-(*N*-Carbobenzyloxy-*N*-methylamino)benzoyl Dipeptides **5a-i**.** Diethyl glu-

Table II. Analytical Data for the New Methotrexate Analogues

compd	formula	mp, °C	UV data, <sup>a</sup> λ <sub>max</sub> , nm (log ε)	analyses
1a	C <sub>20</sub> H <sub>21</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	300	240 sh (4.22), 290 (4.24)	C, H, N
1b	C <sub>21</sub> H <sub>23</sub> N <sub>9</sub> O <sub>6</sub> ·H <sub>2</sub> O	~210	246 (4.34), 295 (4.37)	C, H, N
1c	C <sub>21</sub> H <sub>23</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	310	240 (4.31), 308 (4.35)	C, H, N
1d	C <sub>22</sub> H <sub>25</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	240	244 (4.38), 310 (4.38)	C, H, N
1e	C <sub>23</sub> H <sub>27</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	195-197	245 (4.25), 309 (4.31)	H, N; C <sup>c</sup>
1f	C <sub>23</sub> H <sub>27</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	186-188	246 (4.21), 290 (4.03)	C, H, N
1g	C <sub>26</sub> H <sub>23</sub> N <sub>9</sub> O <sub>6</sub>	185-187	245 (4.21), 308 (4.23)	C, H, N
1h	C <sub>28</sub> H <sub>29</sub> N <sub>9</sub> O <sub>6</sub> ·2H <sub>2</sub> O	~220	245 (4.22), 310 (4.29)	C, H; N <sup>d</sup>
1i	C <sub>29</sub> H <sub>31</sub> N <sub>9</sub> O <sub>6</sub> ·H <sub>2</sub> O	230-235 <sup>b</sup>	258 (4.45), 302 (4.45)	C, H, N

<sup>a</sup> Determined in 0.1 N HCl solution. <sup>b</sup> With decomposition. <sup>c</sup> C: calcd, 49.20; found, 50.23. <sup>d</sup> N: calcd, 20.22; found, 19.50.

Table III. Analytical Data for Intermediate Peptides

*3 α-i*

*5 α-l (R<sub>1</sub> = OC<sub>2</sub>H<sub>5</sub>), 6 α-l (R<sub>1</sub> = OH)*

compd	R	X	n	formula	mp, °C	UV data, <sup>a</sup> λ <sub>max</sub> , nm (log ε)	analyses
3a	H	Gly	1	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	122-125 <sup>b</sup>	285 (3.89)	C, H, N
3b	H	Gly	2	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	138-140 <sup>b</sup>	285 (3.32)	C, H, N
3c	CH <sub>3</sub>	Gly	1	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub>	127-130 <sup>b</sup>	302 (3.75)	C, H, N
3d	CH <sub>3</sub>	Gly	2	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	102-105 <sup>b</sup>	300 (3.99)	C, H, N
3e	CH <sub>3</sub>	DL-Ala	2	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	134-136 <sup>b</sup>	302 (3.50)	C, H, N
3f	CH <sub>3</sub>	Sar	2	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> O <sub>6</sub>	85-88 <sup>b</sup>	382 (4.09)	C, H, N
3g	CH <sub>3</sub>	L-Leu	2	C <sub>19</sub> H <sub>27</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	165-168 <sup>b</sup>	300 (3.67)	C, H, N
3h	CH <sub>3</sub>	L-Phe	1	C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O <sub>6</sub>	132 <sup>b</sup>	302 (4.03)	C, H, N
3i	CH <sub>3</sub>	L-Phe	2	C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> O <sub>6</sub> ·H <sub>2</sub> O	106 <sup>b</sup>	302 (3.81)	C, H, N
5a	H	Gly	1	C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>8</sub>	139-140	268 (4.48) <sup>c</sup>	C, H, N
5b	H	Gly	2	C <sub>26</sub> H <sub>31</sub> N <sub>3</sub> O <sub>8</sub>	68	268 (4.53) <sup>c</sup>	C, H, N
5c	CH <sub>3</sub>	Gly	1	C <sub>26</sub> H <sub>31</sub> N <sub>3</sub> O <sub>8</sub>		262 (4.16)	C, H, N
5d	CH <sub>3</sub>	Gly	2	C <sub>27</sub> H <sub>33</sub> N <sub>3</sub> O <sub>8</sub>		261 (4.09)	C, H, N
5e	CH <sub>3</sub>	DL-Ala	2	C <sub>28</sub> H <sub>35</sub> N <sub>3</sub> O <sub>8</sub>		260 (4.12)	C, H, N
5f	CH <sub>3</sub>	Sar	2	C <sub>28</sub> H <sub>35</sub> N <sub>3</sub> O <sub>8</sub>		250 (4.01)	C, H, N
5g	CH <sub>3</sub>	L-Leu	2	C <sub>31</sub> H <sub>41</sub> N <sub>3</sub> O <sub>8</sub>	72-74	259 (4.13)	C, H, N
5h	CH <sub>3</sub>	L-Phe	1	C <sub>33</sub> H <sub>37</sub> N <sub>3</sub> O <sub>8</sub>	93-94	251 (4.10)	C, H, N
5i	CH <sub>3</sub>	L-Phe	2	C <sub>34</sub> H <sub>39</sub> N <sub>3</sub> O <sub>8</sub>	102-104	260 (4.11)	C, H, N
6a	H	Gly	1	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> O <sub>8</sub>	198-200	268 (4.39) <sup>c</sup>	C, H, N
6b	H	Gly	2	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>8</sub> ·H <sub>2</sub> O	170.5-172	266 (4.37)	C, H, N
6c	CH <sub>3</sub>	Gly	1	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>8</sub>	161-163	260 (4.08)	C, H, N
6d	CH <sub>3</sub>	Gly	2	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>8</sub> ·H <sub>2</sub> O	89-91	260 (4.11)	C, H, N
6e	CH <sub>3</sub>	DL-Ala	2	C <sub>24</sub> H <sub>27</sub> N <sub>3</sub> O <sub>8</sub>	81-82	260 (4.11)	C, H, N
6f	CH <sub>3</sub>	Sar	2	C <sub>24</sub> H <sub>27</sub> N <sub>3</sub> O <sub>8</sub>	137-139	249 (4.02)	C, H, N
6g	CH <sub>3</sub>	L-Leu	2	C <sub>27</sub> H <sub>35</sub> N <sub>3</sub> O <sub>8</sub> ·H <sub>2</sub> O	108-110	262 (4.16)	C, H, N
6h	CH <sub>3</sub>	L-Phe	1	C <sub>29</sub> H <sub>29</sub> N <sub>3</sub> O <sub>8</sub> ·H <sub>2</sub> O	168-171	261 (4.12)	C, H, N
6i	CH <sub>3</sub>	L-Phe	2	C <sub>30</sub> H <sub>31</sub> N <sub>3</sub> O <sub>8</sub>	90-92	261 (4.12)	C, H, N

<sup>a</sup> In MeOH, when not otherwise noted. <sup>b</sup> No definite melting point. <sup>c</sup> In EtOH.

Table IV. Anticancer Activity of Methotrexate Analogues

compd	LD <sub>50</sub> <sup>a</sup>		L1210 <sup>b</sup>		W 256 <sup>c</sup>	
	mg/kg	mmol/kg	dose (mg/kg) × no. of admin <sup>f</sup>	ILS, <sup>d</sup> %	dose (mg/kg) × no. of admin <sup>f</sup>	TGI, <sup>e</sup> %
1a	200	0.38	40 × 10	69	60 × 14	55
1b	400	0.78	33 × 6	14	18 × 13	30
1c	500	0.94	100 × 8	40	100 × 13	41
1d	830	1.52	100 × 8	0		
1e	500	0.89	50 × 6	19		
1f	1000	1.78	100 × 6	0		
1g	500	0.88	50 × 8	0		
1h	1000	1.61	100 × 7	0		
1i	500	0.81	50 × 10	25		

<sup>a</sup> A single dose in normal Wistar rats: J. Cornfield and N. Mantel, *J. Am. Stat. Assoc.*, **45**, 181 (1950). <sup>b</sup> In BDF<sub>1</sub> bearing mice: R. H. Adamson, S. T. Yancew, M. Ben, T. L. Loo, and D. P. Rall, *Arch. Int. Pharmacodyn. Ther.*, **153**, 87 (1965); treatment was begun 24 h after ip inoculation of 10<sup>6</sup> leukemic cells. <sup>c</sup> Walker 256 carcinosarcoma in rats; treatment was begun 7 days after tumor transplantation. <sup>d</sup> % ILS = (T/C - 1) × 100. <sup>e</sup> % TGI = (1 - T/C) × 100. <sup>f</sup> Daily administration in an aqueous solution, pH 8.0-8.4.

tamate hydrochloride (36 g, 0.15 mol), or the corresponding amount of diethyl aspartate hydrochloride, was stirred in AcOEt (360 mL) and treated with triethylamine (37 mL). The reaction

mixture was stirred at room temperature overnight, the deposited solid was filtered, and the filtrate was evaporated to dryness under vacuum to obtain the diethyl glutamate (or aspartate) as a free

Scheme II

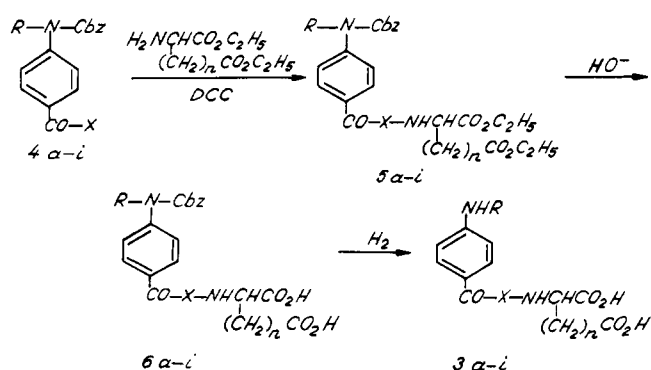


Table V. Solvent Used in the Reaction between Diethyl Glutamate (Diethyl Aspartate) and Protected Amino Acids in the Presence of DCC

compd	solvent
4a,b	AcOEt
4g-i	AcOEt
4c,d	AcOEt-DMF (2:1)
4e	THF-DMF (8:1)
4f	THF-DMF (23:1)

base. The product was added directly to a stirred solution of the desired 4-(N-carbobenzoxyamino)- or 4-(N-carbobenzoxy-N-methylamino)benzoylamino acid (0.1 mol) in an appropriate solvent (Table V), and the mixture was filtered. DCC (22.7 g, 0.11 mol) was added to the filtrate at 0 °C, and the reaction mixture was stirred continuously for 1 h at this temperature and for 96 h at room temperature. The *N,N*-dicyclohexylurea precipitate was filtered and washed with the same solvent that was used in the reaction, and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in AcOEt, and the solution was washed with 2 N HCl for 1-2 h (in order to hydrolyze the nonreacted DCC) and then rinsed successively with  $H_2O$ ,  $NaHCO_3$  solution, and  $H_2O$ . Drying ( $Na_2SO_4$ ) and evaporation to dryness afforded the crude 4-(N-carbobenzoxyamino)- or 4-(N-carbobenzoxy-N-methylamino)benzoyl dipeptide ethyl esters. Purification was achieved by (1) dissolution in AcOEt, followed by the same treatment as described above, and precipitation from concentrated solution with petroleum ether or (2) column chromatography ( $Al_2O_3$ , MeOH). The yields obtained by this procedure ranged between 80 and 85%.

**4-(N-Carbobenzoxyamino)- and 4-(N-Carbobenzoxy-N-methylamino)benzoyl Dipeptides 6a-i.** To a solution of intermediates 5a-i (0.1 mol) in MeOH (450 mL) was added 1 N NaOH (225 mL), while maintaining the temperature below +5 °C. The reaction was allowed to proceed for 1 h at 0 °C and then at room temperature. The end of the reaction was determined by TLC (Kieselgel F<sub>254</sub>, 9.5:0.5:0.5  $CHCl_3$ -AcOH- $H_2O$ ). The reaction mixture was filtered and diluted to 2 L ( $H_2O$ ), and the pH was adjusted to 2.0 with 6 N HCl to obtain the 4-(N-carbobenzoxyamino)- or 4-(N-carbobenzoxy-N-methylamino)benzoyl dipeptides as solid or oily residues which crystallized on standing. The crude tripeptide acids were dissolved in  $H_2O$  at pH 7.0 (1 N NaOH) and stirred with charcoal for several hours. Filtration and addition of 6 N HCl until the pH was 2.0 gave a solid which was recrystallized from AcOEt-petroleum ether (bp 45-60 °C) in order to obtain good yields (80-90%) of the pure tripeptide.

**4-Amino- and 4-(N-Methylamino)benzoyl Dipeptides 3a-i.** A 10% (w/v) solution of 4-(N-carbobenzoxyamino)- or 4-(N-

carbobenzoxy-N-methylamino)benzoyl dipeptide in MeOH was subjected to catalytic hydrogenolysis (over 10% Pd/C) at room temperature and atmospheric pressure. After the completion of the reaction, the catalyst was filtered and the filtrate evaporated to dryness under vacuum to obtain pure tripeptides (yields ca. 90%).

**4-[N-(2,4-Diamino-6-pteridiny)]methylamino]benzoyl- and 4-[N-(2,4-Diamino-6-pteridiny)]methyl]-N-methylamino]benzoyl Dipeptides 1a-i.** An aqueous solution containing the desired tripeptide 3a-i (0.1 mol) was adjusted to pH 7.5 with solid  $NaHCO_3$  and heated to 45 °C, while adding finely powdered 2,4-diamino-6-(chloromethyl)pteridine (25 g, 0.12 mol) during 1-2 h. The reaction mixture was stirred at 45 °C for 24 h, the pH being maintained at 7.5 with occasional addition of solid  $NaHCO_3$ . The hot solution was filtered, the pH of the filtrate adjusted to 4.0, and the solution kept overnight at 4 °C. The solid was filtered and washed successively with cold  $H_2O$ ,  $Me_2CO$ , and  $Et_2O$  to obtain the tripeptide analogues. Final purification of compounds 1a-i was achieved by column chromatography on cellulose (cellulose-product, 50:1), using 0.1 M  $Na_2HPO_4$ , pH 7.0 (HCl), as the eluant. Compounds 1a,b required additional chromatography on a Sephadex G-10 column using  $H_2O$  as the eluant. The chromatographic fractions were checked by paper chromatography [Whatman No. 1, descending, 0.1 M  $Na_2HPO_4$  buffer (pH 7.0)] and acidified to pH 3.5-4.0 (AcOH). With the exception of compounds 1a,b, pure products were obtained, after chromatography through a single column, with a consistent overall yield of 8-12%.

## References and Notes

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