

4-HYDROXY-2-QUINOLONES

139*. SYNTHESIS, STRUCTURE,

AND ANTIVIRAL ACTIVITY

OF N-R-AMIDES OF 2-HYDROXY-

4-OXO-4H-PYRIDO[1,2-a]PYRIMIDINE-

3-CARBOXYLIC ACIDS

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Dialkylaminoalkylamides of 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acids have been obtained as potential antiviral agents. The special features of the spatial structure of one example of the synthesized compounds have been studied. Results are given of the investigation of cytotoxicity and antiviral activity in relation to type 1 herpes virus and coronavirus.

Keywords: amides, 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidines, herpes, coronavirus, antiviral activity, X-ray structural analysis.

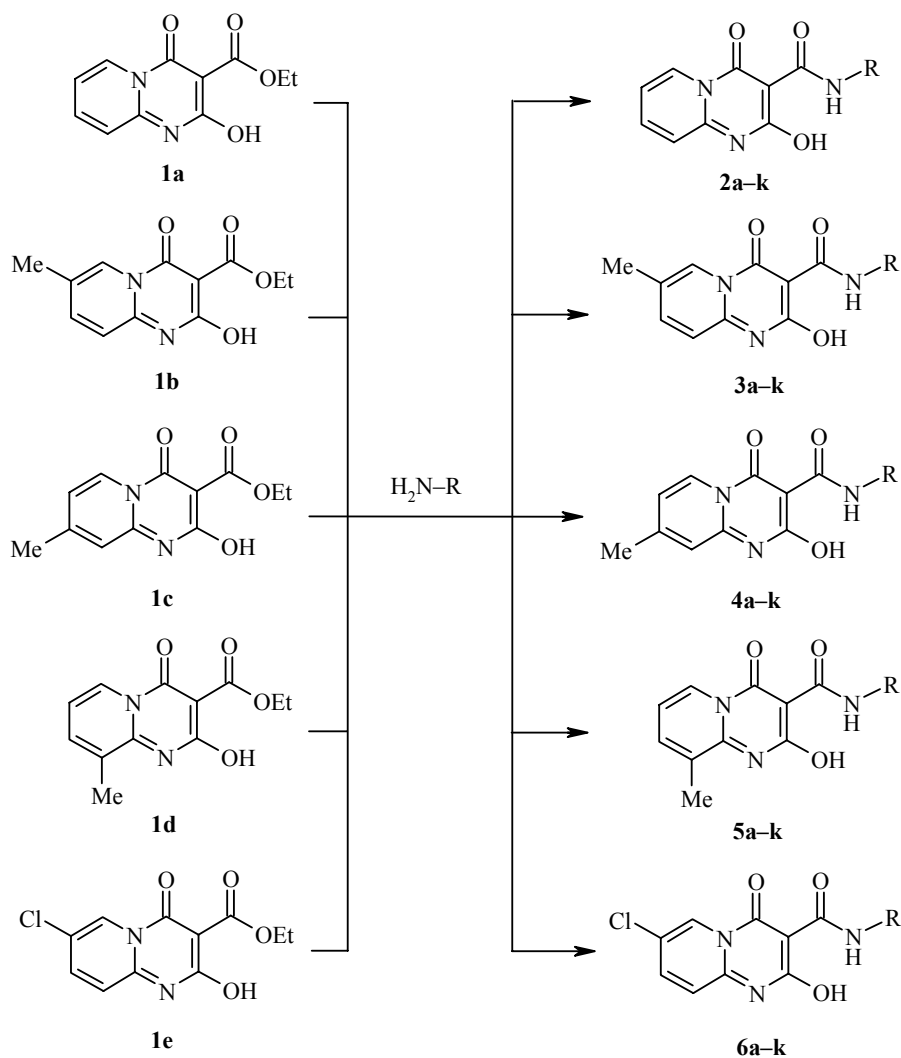
Virology occupies an important place in the medicine of the third millennium in the conviction of many scientists. The basis for this is the fact that the stimulus of ~80% of human infectious diseases is of a viral nature. In the future the role of viruses will grow even more and they will predominate over bacterial infections. With each day more proof accumulates of the participation of viruses in the development of a series of serious illnesses, which previously were neither etiologically nor pathogenetically linked with them, viz. myocardial infarction, atherosclerosis, pyelonephritis, cancer, diabetes, and many others [2]. But there is a virus which causes the greatest worry to doctors, depending on the lack of knowledge frequently applied to the usual simple cold and, at the same time, yields only to influenza by the level of mortality. This is herpes, a very widely distributed virus in the human population, it is considered that its carriers are 99% of the population of the earth. Herpes viruses are able to strike practically all organs and systems of the human organism, and display various symptoms and illnesses. At the present time 8 antigenic serotypes of the herpes virus are known. The most widespread, and consequently also most dangerous, are herpes viruses of types 1 and 2, causing diseases of the skin, mucous membrane, genitals, eyes, and also aseptic meningitis, and pneumonia [3-6]. The remaining types of herpes are not encountered so frequently, but are no less dangerous. For example, herpes type 3 is an inducer

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of all known eruptions (chicken-pox) [7]. In adults it also causes shingles, manifested by discharges on the stomach and chest and accompanied by pains comparable with oncologies. The Epstein-Barr virus (type 4) is the cause of infectious mononucleosis [8]. Cytomegalovirus, little studied at present, herpes type 5, affects the nervous system and human internal organs [9, 10]. An etiological link, not without basis, is proposed for herpes type 6 and encephalitis [7, 11], and for type 7 with chronic fatigue syndrome [7, 9, 10], called in mass information media "the plague of the 21st century". Kaposi sarcoma, associated with HIV infection and AIDS, is also caused by herpes virus, but of type 8 [6, 12].

Proceeding from this, control of the widespread and numerous herpes-viral illnesses is one of the most important problems of contemporary medical science. And although the list of chemical preparations effecting suppression of various stages of reproduction of herpes virus is fairly broad [13], their medicinal and prophylactic effectiveness does not satisfy practical public health at all. For this reason the epidemic spread of herpes virus infections in the world is steadily continuing, and the search for antiherpetic agents with a different mechanism of action has not lost its urgency.



2-6 a R = 2-dimethylaminoethyl, **b** R = 2-ethylaminoethyl, **c** R = 2-(2-hydroxyethylamino)ethyl,
d R = 2-diethylaminoethyl, **e** R = 3-dimethylaminopropyl, **f** R = 3-diethylaminopropyl,
g R = 1-ethylpyrrolidin-2-ylmethyl, **h** R = 2-piperazin-1-ylethyl, **i** R = 2-morpholin-4-yl-ethyl,
j R = 3-morpholin-4-yl-propyl, **k** R = 3-piperidin-1-yl-propyl

TABLE 1. Characteristics of N-R-amides of 2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acids **2-6**

| Compound | Empirical formula | Found, % | | | mp, °C | Yield, % |
|-----------|---|---------------|-------------|--------------|---------|----------|
| | | Calculated, % | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2a | C ₁₃ H ₁₆ N ₄ O ₃ | <u>56.63</u> | <u>5.95</u> | <u>20.38</u> | 161-163 | 84 |
| | | 56.51 | 5.84 | 20.28 | | |
| 2b | C ₁₃ H ₁₆ N ₄ O ₃ | <u>56.65</u> | <u>5.97</u> | <u>20.19</u> | 196-198 | 80 |
| | | 56.51 | 5.84 | 20.28 | | |
| 2c | C ₁₃ H ₁₆ N ₄ O ₄ | <u>53.34</u> | <u>5.60</u> | <u>19.11</u> | 187-189 | 78 |
| | | 53.42 | 5.52 | 19.17 | | |
| 2d | C ₁₅ H ₂₀ N ₄ O ₃ | <u>59.32</u> | <u>6.53</u> | <u>18.54</u> | 99-101 | 83 |
| | | 59.20 | 6.62 | 18.41 | | |
| 2e | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.80</u> | <u>6.36</u> | <u>19.44</u> | 125-127 | 81 |
| | | 57.92 | 6.25 | 19.30 | | |
| 2f | C ₁₆ H ₂₂ N ₄ O ₃ | <u>60.49</u> | <u>7.08</u> | <u>17.72</u> | 114-116 | 77 |
| | | 60.36 | 6.97 | 17.60 | | |
| 2g | C ₁₆ H ₂₀ N ₄ O ₃ | <u>60.67</u> | <u>6.30</u> | <u>17.62</u> | 110-112 | 79 |
| | | 60.75 | 6.37 | 17.71 | | |
| 2h | C ₁₅ H ₁₉ N ₅ O ₃ | <u>56.65</u> | <u>6.13</u> | <u>22.16</u> | 228-230 | 86 |
| | | 56.77 | 6.03 | 22.07 | | |
| 2i | C ₁₅ H ₁₈ N ₄ O ₄ | <u>56.51</u> | <u>5.64</u> | <u>17.52</u> | 107-109 | 82 |
| | | 56.60 | 5.70 | 17.60 | | |
| 2j | C ₁₆ H ₂₀ N ₄ O ₄ | <u>57.93</u> | <u>6.16</u> | <u>16.99</u> | 104-106 | 78 |
| | | 57.82 | 6.07 | 16.86 | | |
| 2k | C ₁₇ H ₂₂ N ₄ O ₃ | <u>61.88</u> | <u>6.64</u> | <u>17.07</u> | 120-122 | 75 |
| | | 61.80 | 6.71 | 16.96 | | |
| 3a | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.98</u> | <u>6.34</u> | <u>19.21</u> | 150-152 | 82 |
| | | 57.92 | 6.25 | 19.30 | | |
| 3b | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.81</u> | <u>6.17</u> | <u>19.22</u> | 173-175 | 80 |
| | | 57.92 | 6.25 | 19.30 | | |
| 3c | C ₁₄ H ₁₈ N ₄ O ₄ | <u>54.78</u> | <u>5.83</u> | <u>18.38</u> | 180-182 | 76 |
| | | 54.89 | 5.92 | 18.29 | | |
| 3d | C ₁₆ H ₂₂ N ₄ O ₃ | <u>60.44</u> | <u>7.11</u> | <u>17.53</u> | 119-121 | 82 |
| | | 60.36 | 6.97 | 17.60 | | |
| 3e | C ₁₅ H ₂₀ N ₄ O ₃ | <u>59.13</u> | <u>6.70</u> | <u>18.49</u> | 124-126 | 78 |
| | | 59.20 | 6.62 | 18.41 | | |
| 3f | C ₁₇ H ₂₄ N ₄ O ₃ | <u>61.34</u> | <u>7.19</u> | <u>16.77</u> | 117-119 | 73 |
| | | 61.43 | 7.28 | 16.85 | | |
| 3g | C ₁₇ H ₂₂ N ₄ O ₃ | <u>61.87</u> | <u>6.65</u> | <u>16.86</u> | 101-103 | 76 |
| | | 61.80 | 6.71 | 16.96 | | |
| 3h | C ₁₆ H ₂₁ N ₅ O ₃ | <u>58.10</u> | <u>6.48</u> | <u>21.22</u> | 232-234 | 85 |
| | | 57.99 | 6.39 | 21.13 | | |
| 3i | C ₁₆ H ₂₀ N ₄ O ₄ | <u>57.93</u> | <u>6.15</u> | <u>16.94</u> | 144-146 | 80 |
| | | 57.82 | 6.07 | 16.86 | | |
| 3j | C ₁₇ H ₂₂ N ₄ O ₄ | <u>58.88</u> | <u>6.31</u> | <u>16.05</u> | 135-137 | 77 |
| | | 58.95 | 6.40 | 16.17 | | |
| 3k | C ₁₈ H ₂₄ N ₄ O ₃ | <u>62.85</u> | <u>7.10</u> | <u>16.36</u> | 108-110 | 72 |
| | | 62.77 | 7.02 | 16.27 | | |
| 4a | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.81</u> | <u>6.16</u> | <u>19.22</u> | 191-193 | 83 |
| | | 57.92 | 6.25 | 19.30 | | |
| 4b | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.80</u> | <u>6.35</u> | <u>19.26</u> | 140-142 | 81 |
| | | 57.92 | 6.25 | 19.30 | | |
| 4c | C ₁₄ H ₁₈ N ₄ O ₄ | <u>54.77</u> | <u>5.84</u> | <u>18.38</u> | 182-184 | 75 |
| | | 54.89 | 5.92 | 18.29 | | |
| 4d | C ₁₆ H ₂₂ N ₄ O ₃ | <u>60.43</u> | <u>6.90</u> | <u>17.51</u> | 137-139 | 80 |
| | | 60.36 | 6.97 | 17.60 | | |
| 4e | C ₁₅ H ₂₀ N ₄ O ₃ | <u>59.11</u> | <u>6.54</u> | <u>18.34</u> | 125-127 | 77 |
| | | 59.20 | 6.62 | 18.41 | | |
| 4f | C ₁₇ H ₂₄ N ₄ O ₃ | <u>61.52</u> | <u>7.22</u> | <u>16.77</u> | 111-113 | 72 |
| | | 61.43 | 7.28 | 16.85 | | |
| 4g | C ₁₇ H ₂₂ N ₄ O ₃ | <u>61.71</u> | <u>6.63</u> | <u>16.85</u> | 135-137 | 82 |
| | | 61.80 | 6.71 | 16.96 | | |
| 4h | C ₁₆ H ₂₁ N ₅ O ₃ | <u>58.08</u> | <u>6.48</u> | <u>21.20</u> | 222-224 | 87 |
| | | 57.99 | 6.39 | 21.13 | | |

TABLE 1. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-----------|---|--------------|-------------|--------------|---------|----|
| 4i | C ₁₆ H ₂₀ N ₄ O ₄ | <u>57.87</u> | <u>6.15</u> | <u>16.94</u> | 163-165 | 83 |
| | | 57.82 | 6.07 | 16.86 | | |
| 4j | C ₁₇ H ₂₂ N ₄ O ₄ | <u>58.83</u> | <u>6.33</u> | <u>16.08</u> | 158-160 | 80 |
| | | 58.95 | 6.40 | 16.17 | | |
| 4k | C ₁₈ H ₂₄ N ₄ O ₃ | <u>62.86</u> | <u>7.10</u> | <u>16.35</u> | 124-126 | 78 |
| | | 62.77 | 7.02 | 16.27 | | |
| 5a | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.82</u> | <u>6.17</u> | <u>19.24</u> | 113-115 | 85 |
| | | 57.92 | 6.25 | 19.30 | | |
| 5b | C ₁₄ H ₁₈ N ₄ O ₃ | <u>57.97</u> | <u>6.30</u> | <u>19.36</u> | 177-179 | 86 |
| | | 57.92 | 6.25 | 19.30 | | |
| 5c | C ₁₄ H ₁₈ N ₄ O ₄ | <u>54.95</u> | <u>5.98</u> | <u>18.38</u> | 190-192 | 79 |
| | | 54.89 | 5.92 | 18.29 | | |
| 5d | C ₁₆ H ₂₂ N ₄ O ₃ | <u>60.44</u> | <u>6.90</u> | <u>17.51</u> | 84-86 | 82 |
| | | 60.36 | 6.97 | 17.60 | | |
| 5e | C ₁₅ H ₂₀ N ₄ O ₃ | <u>59.12</u> | <u>6.55</u> | <u>18.54</u> | 87-89 | 76 |
| | | 59.20 | 6.62 | 18.41 | | |
| 5f | C ₁₇ H ₂₄ N ₄ O ₃ | <u>61.53</u> | <u>7.37</u> | <u>16.93</u> | 103-105 | 74 |
| | | 61.43 | 7.28 | 16.85 | | |
| 5g | C ₁₇ H ₂₂ N ₄ O ₃ | <u>61.92</u> | <u>6.64</u> | <u>16.87</u> | 91-93 | 83 |
| | | 61.80 | 6.71 | 16.96 | | |
| 5h | C ₁₆ H ₂₁ N ₅ O ₃ | <u>57.90</u> | <u>6.27</u> | <u>21.19</u> | 245-247 | 88 |
| | | 57.99 | 6.39 | 21.13 | | |
| 5i | C ₁₆ H ₂₀ N ₄ O ₄ | <u>57.74</u> | <u>6.15</u> | <u>16.77</u> | 152-154 | 81 |
| | | 57.82 | 6.07 | 16.86 | | |
| 5j | C ₁₇ H ₂₂ N ₄ O ₄ | <u>59.07</u> | <u>6.48</u> | <u>16.28</u> | 121-123 | 75 |
| | | 58.95 | 6.40 | 16.17 | | |
| 5k | C ₁₈ H ₂₄ N ₄ O ₃ | <u>62.70</u> | <u>7.05</u> | <u>16.23</u> | 115-117 | 73 |
| | | 62.77 | 7.02 | 16.27 | | |
| 6a | C ₁₃ H ₁₅ ClN ₄ O ₃ | <u>50.17</u> | <u>4.78</u> | <u>17.94</u> | 133-135 | 92 |
| | | 50.25 | 4.87 | 18.03 | | |
| 6b | C ₁₃ H ₁₅ ClN ₄ O ₃ | <u>50.15</u> | <u>4.98</u> | <u>18.12</u> | 182-184 | 85 |
| | | 50.25 | 4.87 | 18.03 | | |
| 6c | C ₁₃ H ₁₅ ClN ₄ O ₄ | <u>47.87</u> | <u>4.72</u> | <u>17.21</u> | 196-198 | 82 |
| | | 47.79 | 4.63 | 17.15 | | |
| 6d | C ₁₅ H ₁₉ ClN ₄ O ₃ | <u>53.10</u> | <u>5.56</u> | <u>16.47</u> | 130-132 | 86 |
| | | 53.18 | 5.65 | 16.54 | | |
| 6e | C ₁₄ H ₁₇ ClN ₄ O ₃ | <u>51.86</u> | <u>5.35</u> | <u>17.33</u> | 125-127 | 80 |
| | | 51.78 | 5.28 | 17.25 | | |
| 6f | C ₁₆ H ₂₁ ClN ₄ O ₃ | <u>54.38</u> | <u>5.92</u> | <u>15.98</u> | 114-116 | 76 |
| | | 54.47 | 6.00 | 15.88 | | |
| 6g | C ₁₆ H ₁₉ ClN ₄ O ₃ | <u>54.67</u> | <u>5.37</u> | <u>15.86</u> | 136-138 | 84 |
| | | 54.78 | 5.46 | 15.97 | | |
| 6h | C ₁₅ H ₁₈ ClN ₅ O ₃ | <u>51.32</u> | <u>5.25</u> | <u>19.84</u> | 251-253 | 90 |
| | | 51.21 | 5.16 | 19.91 | | |
| 6i | C ₁₅ H ₁₇ ClN ₄ O ₄ | <u>51.17</u> | <u>4.95</u> | <u>15.76</u> | 157-159 | 84 |
| | | 51.07 | 4.86 | 15.88 | | |
| 6j | C ₁₆ H ₁₉ ClN ₄ O ₄ | <u>52.47</u> | <u>5.14</u> | <u>15.18</u> | 140-142 | 80 |
| | | 52.39 | 5.22 | 15.27 | | |
| 6k | C ₁₇ H ₂₁ ClN ₄ O ₃ | <u>55.88</u> | <u>5.73</u> | <u>15.42</u> | 121-123 | 77 |
| | | 55.97 | 5.80 | 15.36 | | |

In a continuation of investigations on the search for new biologically active substances among the derivatives of 4-hydroxyquinolin-2-ones and heterocyclic systems related to them, the present communication is devoted to N-R-amides of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **2-6**. These compounds were chosen by us as subjects of investigation, on the basis of a preliminary prognosis carried out with the PASS [14] program, showing a fairly high, not less than 60%, probability of them displaying antiherpes properties. Solubility in water is an important characteristic of a potential antiviral agent, substantially facilitating its study. In view of that, we limited the circle of substances being investigated to dialkylaminoalkylamides, since if necessary they may always be readily converted into water-soluble quaternary ammonium salts with mineral acids.

TABLE 2. ¹H NMR Spectra of the Synthesized Compounds

| Com- pound | Chemical shifts, δ , ppm (<i>J</i> , Hz) | | | | | | | | | |
|---------------|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--|-------------|--------------------------|--|--|
| | NH (1H) | H arom. | | | | | H-9 (1H) | Other functional groups* | | |
| | | H-6 (1H) | H-7 (1H) | H-8 (1H) | H-8 (1H) | H-9 (1H) | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | | | | |
| 2a | 9.65 (t, <i>J</i> = 5.0) | 8.92 (d, <i>J</i> = 7.1) | 7.33 (t, <i>J</i> = 7.0) | 8.05 (t, <i>J</i> = 7.8) | 7.50 (d, <i>J</i> = 8.7) | 3.45 (2H, q, <i>J</i> = 5.8, NHCH ₂); 2.44 (2H, t, <i>J</i> = 6.2, NHCH ₂ CH ₂); 2.19 (6H, s, 2CH ₃) | | | | |
| 2b | 9.73 (t, <i>J</i> = 5.1) | 8.85 (d, <i>J</i> = 7.2) | 7.25 (t, <i>J</i> = 6.9) | 7.97 (t, <i>J</i> = 7.8) | 7.42 (d, <i>J</i> = 8.7) | 3.44 (2H, q, <i>J</i> = 4.7, CONHCH ₂); 2.78 (2H, t, <i>J</i> = 6.0, CONHCH ₂ CH ₂); 2.64 (2H, q, <i>J</i> = 6.9, NHCH ₂ CH ₃); 1.05 (3H, t, <i>J</i> = 7.0, NHCH ₂ CH ₃) | | | | |
| 2c | 9.70 (t, <i>J</i> = 5.1) | 8.87 (d, <i>J</i> = 7.0) | 7.29 (t, <i>J</i> = 7.0) | 8.01 (t, <i>J</i> = 7.9) | 7.46 (d, <i>J</i> = 8.8) | 3.46 (4H, m, CONHCH ₂ + CH ₂ O); 2.78 (2H, t, <i>J</i> = 6.1, CONHCH ₂ CH ₂); 2.66 (2H, t, <i>J</i> = 5.8, CH ₂ CH ₂ OH) | | | | |
| 2d | 9.69 (t, <i>J</i> = 5.2) | 8.92 (d, <i>J</i> = 7.3) | 7.32 (t, <i>J</i> = 7.0) | 8.04 (t, <i>J</i> = 7.8) | 7.50 (d, <i>J</i> = 9.0) | 3.41 (2H, q, <i>J</i> = 6.1, NHCH ₂); 2.45 (6H, m, CH ₂ N(CH ₂) ₂); 0.97 (6H, t, <i>J</i> = 7.2, 2CH ₃) | | | | |
| 2e | 9.65 (t, <i>J</i> = 5.4) | 8.90 (d, <i>J</i> = 7.1) | 7.33 (t, <i>J</i> = 6.9) | 8.04 (t, <i>J</i> = 7.9) | 7.50 (d, <i>J</i> = 8.8) | 3.40 (2H, q, <i>J</i> = 6.5, NHCH ₂); 2.28 (2H, t, <i>J</i> = 6.9, NHCH ₂ CH ₂ CH ₂); 2.14 (6H, s, 2CH ₃); 1.68 (2H, q, <i>J</i> = 6.8, NHCH ₂ CH ₂ CH ₂ N) | | | | |
| 2f | 9.64 (t, <i>J</i> = 5.4) | 8.90 (d, <i>J</i> = 7.1) | 7.32 (t, <i>J</i> = 6.9) | 8.04 (t, <i>J</i> = 7.8) | 7.49 (d, <i>J</i> = 9.0) | 3.39 (2H, q, <i>J</i> = 6.3, NHCH ₂); 2.43 (6H, m, CH ₂ N(CH ₂) ₂); 1.66 (2H, q, <i>J</i> = 6.8, NHCH ₂ CH ₂ CH ₂ N); 0.94 (6H, t, <i>J</i> = 7.1, 2CH ₃) | | | | |
| 2g | 9.69 (t, <i>J</i> = 5.1) | 8.94 (d, <i>J</i> = 7.0) | 7.32 (t, <i>J</i> = 6.9) | 8.04 (t, <i>J</i> = 7.8) | 7.50 (d, <i>J</i> = 8.8) | 3.61-3.02 (6H, m, NHCH ₂ + NCH ₂ CH ₃ + 5'-CH ₂); 2.82 (1H, q, <i>J</i> = 7.3, 2'-CH); 2.31-1.43 (4H, m, 3',4'-CH ₂); 1.05 (3H, t, <i>J</i> = 7.1, CH ₃) | | | | |
| 2h | 9.83 (t, <i>J</i> = 5.0) | 8.87 (d, <i>J</i> = 7.1) | 7.24 (t, <i>J</i> = 7.0) | 7.97 (t, <i>J</i> = 7.8) | 7.41 (d, <i>J</i> = 9.0) | 3.44 (2H, q, <i>J</i> = 5.9, CONHCH ₂); 2.78 (4H, m, HN(CH ₂) ₂ piperazine); 2.40 (6H, m, CH ₂ N(CH ₂) ₂) | | | | |
| 2i | 9.79 (t, <i>J</i> = 5.3) | 8.89 (d, <i>J</i> = 7.2) | 7.27 (t, <i>J</i> = 6.9) | 8.00 (t, <i>J</i> = 7.7) | 7.45 (d, <i>J</i> = 8.9) | 3.58 (4H, m, CH ₂ OCH ₂); 3.46 (2H, q, <i>J</i> = 5.8, NHCH ₂); 2.42 (6H, m, CH ₂ N(CH ₂) ₂) | | | | |
| 2j | 10.12 (t, <i>J</i> = 5.6) | 8.75 (d, <i>J</i> = 7.3) | 7.04 (t, <i>J</i> = 7.0) | 7.79 (t, <i>J</i> = 7.7) | 7.22 (d, <i>J</i> = 9.0) | 3.54 (4H, m, CH ₂ OCH ₂); 3.30 (2H, q, <i>J</i> = 6.0, NHCH ₂); 2.75 (2H, t, <i>J</i> = 7.0, CH ₂ NH(CH ₂) ₂); 2.29 (4H, m, CH ₂ N(CH ₂) ₂); 1.63 (2H, q, <i>J</i> = 6.5, NHCH ₂ CH ₂ CH ₂ N) | | | | |
| 2k | 9.66 (t, <i>J</i> = 5.2) | 8.89 (d, <i>J</i> = 7.1) | 7.32 (t, <i>J</i> = 7.0) | 8.03 (t, <i>J</i> = 7.8) | 7.48 (d, <i>J</i> = 8.8) | 3.39 (2H, q, <i>J</i> = 6.2, NHCH ₂); 2.30 (6H, m, CH ₂ N(CH ₂) ₂); 1.69 (2H, q, <i>J</i> = 6.9, NHCH ₂ CH ₂ CH ₂); 1.47 (4H, m, 3,5-CH ₂ piperidine); 1.36 (2H, q, <i>J</i> = 4.8, 4-CH ₂ piperidine) | | | | |
| 3a | 9.69 (t, <i>J</i> = 5.3) | 8.75 (s) | — | 7.93 (d, <i>J</i> = 8.9) | 7.44 (d, <i>J</i> = 8.9) | 3.44 (2H, q, <i>J</i> = 5.7, NHCH ₂); 2.43 (2H, t, <i>J</i> = 6.0, NHCH ₂ CH ₂); 2.37 (3H, s, 7-CH ₃); 2.19 (6H, s, 2CH ₃) | | | | |
| 3b | 9.77 (t, <i>J</i> = 5.2) | 8.78 (s) | — | 7.95 (d, <i>J</i> = 8) | 7.46 (d, <i>J</i> = 8.8) | 3.45 (2H, q, <i>J</i> = 5.1, CONHCH ₂); 2.78 (2H, t, <i>J</i> = 5.7, CONHCH ₂ CH ₂); 2.63 (2H, q, <i>J</i> = 7.1, NHCH ₂ CH ₃); 2.36 (3H, s, 7-CH ₃); 1.01 (3H, t, <i>J</i> = 7.1, NHCH ₂ CH ₃) | | | | |

TABLE 2. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-----------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---|
| 3c | 9.74 (t, <i>J</i> = 5.3) | 8.76 (s) | — | 7.94 (d, <i>J</i> = 8.9) | 7.45 (d, <i>J</i> = 8.9) | 3.42 (4H, m, CONHCH ₂ + CH ₂ O); 2.77 (2H, t, <i>J</i> = 6.3, CONHCH ₂ CH ₂); 2.61 (2H, t, <i>J</i> = 5.9, CH ₂ CH ₂ OH); 2.38 (3H, s, 7-CH ₃) |
| 3d | 9.71 (t, <i>J</i> = 5.2) | 8.75 (s) | — | 7.94 (d, <i>J</i> = 8.8) | 7.44 (d, <i>J</i> = 8.9) | 3.42 (2H, q, <i>J</i> = 6.0, NHCH ₂); 2.59 (6H, m, CH ₂ N(CH ₂) ₂); 2.38 (3H, s, 7-CH ₃); 0.97 (6H, t, <i>J</i> = 7.1, 2CH ₃) |
| 3e | 9.66 (t, <i>J</i> = 5.3) | 8.73 (s) | — | 7.91 (d, <i>J</i> = 9.0) | 7.48 (d, <i>J</i> = 9.0) | 3.40 (2H, q, <i>J</i> = 6.7, NHCH ₂); 2.39 (3H, s, 7-CH ₃); 2.30 (2H, t, <i>J</i> = 6.8, NHCH ₂ CH ₂ CH ₂); 2.18 (6H, s, 2CH ₃); 1.66 (2H, q, <i>J</i> = 6.7, NHCH ₂ CH ₂ CH ₂ N) |
| 3f | 9.62 (t, <i>J</i> = 5.2) | 8.71 (s) | — | 7.90 (d, <i>J</i> = 8.9) | 7.43 (d, <i>J</i> = 8.9) | 3.45 (2H, q, <i>J</i> = 6.5, NHCH ₂); 2.43 (6H, m, CH ₂ N(CH ₂) ₂); 2.35 (3H, s, 7-CH ₃); 1.66 (2H, q, <i>J</i> = 6.6, NHCH ₂ CH ₂ CH ₂ N); 0.99 (6H, t, <i>J</i> = 7.0, 2CH ₃) |
| 3g | 9.73 (t, <i>J</i> = 5.2) | 8.77 (s) | — | 7.94 (d, <i>J</i> = 9.0) | 7.44 (d, <i>J</i> = 9.0) | 3.62–3.03 (6H, m, NHCH ₂ + NCH ₂ CH ₃ + 5'-CH ₂); 2.80 (1H, q, <i>J</i> = 7.5, 2'-CH); 2.38 (3H, s, 7-CH ₃); 2.29–1.45 (4H, m, 3',4'-CH ₂); 1.05 (3H, t, <i>J</i> = 7.3, CH ₃) |
| 3h | 9.87 (t, <i>J</i> = 5.1) | 8.79 (s) | — | 7.97 (d, <i>J</i> = 8.9) | 7.48 (d, <i>J</i> = 8.9) | 3.44 (2H, q, <i>J</i> = 5.7, CONHCH ₂); 2.75 (4H, m, HN(CH ₂) ₂ piperazine); 2.37 (9H, m, CH ₂ N(CH ₂) ₂ + 7-CH ₃) |
| 3i | 9.80 (t, <i>J</i> = 5.2) | 8.76 (s) | — | 7.95 (d, <i>J</i> = 9.0) | 7.46 (d, <i>J</i> = 9.0) | 3.57 (4H, m, CH ₂ OCH ₂); 3.43 (2H, q, <i>J</i> = 5.8, NHCH ₂); 2.44 (6H, m, CH ₂ N(CH ₂) ₂); 2.35 (3H, s, 7-CH ₃) |
| 3j | 9.86 (t, <i>J</i> = 5.5) | 8.79 (s) | — | 7.96 (d, <i>J</i> = 8.9) | 7.47 (d, <i>J</i> = 8.9) | 3.59 (4H, m, CH ₂ OCH ₂); 3.41 (2H, q, <i>J</i> = 6.4, NHCH ₂); 2.38 (3H, s, 7-CH ₃); 2.32 (6H, m, CH ₂ N(CH ₂) ₂); 1.66 (2H, q, <i>J</i> = 6.6, NHCH ₂ CH ₂ CH ₂ N) |
| 3k | 9.72 (t, <i>J</i> = 5.3) | 8.74 (s) | — | 7.94 (d, <i>J</i> = 8.9) | 7.45 (d, <i>J</i> = 8.9) | 3.42 (2H, q, <i>J</i> = 6.4, NHCH ₂); 2.35 (9H, m, CH ₂ N(CH ₂) ₂ + 7-CH ₃); 1.74 (2H, q, <i>J</i> = 6.7, NHCH ₂ CH ₂ CH ₂); 1.40 (6H, m, 3,4,5-CH ₂ piperidine) |
| 4a | 9.61 (t, <i>J</i> = 5.1) | 8.80 (d, <i>J</i> = 7.2) | 7.19 (t, <i>J</i> = 7.2) | — | 7.32 (s) | 3.44 (2H, q, <i>J</i> = 5.6, NHCH ₂); 2.43 (5H, m, NHCH ₂ CH ₂ + 8-CH ₃); 2.18 (6H, s, 2CH ₃) |
| 4b | 9.62 (t, <i>J</i> = 5.2) | 8.78 (d, <i>J</i> = 7.2) | 7.17 (t, <i>J</i> = 7.2) | — | 7.28 (s) | 3.43 (2H, q, <i>J</i> = 5.0, CONHCH ₂); 2.75 (2H, t, <i>J</i> = 5.8, CONHCH ₂ CH ₂); 2.61 (2H, q, <i>J</i> = 7.0, NHCH ₂ CH ₃); 2.43 (3H, s, 8-CH ₃); 1.03 (3H, t, <i>J</i> = 7.1, NHCH ₂ CH ₃) |
| 4c | 9.65 (t, <i>J</i> = 5.1) | 8.80 (d, <i>J</i> = 7.2) | 7.18 (t, <i>J</i> = 7.4) | — | 7.31 (s) | 3.44 (4H, m, CONHCH ₂ + CH ₂ O); 2.75 (2H, t, <i>J</i> = 6.2, CONHCH ₂ CH ₂); 2.63 (2H, t, <i>J</i> = 5.8, CH ₂ CH ₂ OH); 2.45 (3H, s, 8-CH ₃) |
| 4d | 9.60 (t, <i>J</i> = 5.0) | 8.79 (d, <i>J</i> = 7.1) | 7.18 (t, <i>J</i> = 7.3) | — | 7.30 (s) | 3.41 (2H, q, <i>J</i> = 6.1, NHCH ₂); 2.60 (6H, m, CH ₂ N(CH ₂) ₂); 2.45 (3H, s, 8-CH ₃); 0.98 (6H, t, <i>J</i> = 7.2, 2CH ₃) |
| 4e | 9.75 (t, <i>J</i> = 5.2) | 8.84 (d, <i>J</i> = 7.2) | 7.20 (t, <i>J</i> = 7.2) | — | 7.30 (s) | 3.42 (2H, q, <i>J</i> = 6.6, NHCH ₂); 2.46 (3H, s, 8-CH ₃); 2.31 (2H, t, <i>J</i> = 6.8, NHCH ₂ CH ₂ CH ₂); 2.17 (6H, s, 2CH ₃); 1.68 (2H, q, <i>J</i> = 6.7, NHCH ₂ CH ₂ CH ₂ N) |
| 4f | 9.68 (t, <i>J</i> = 5.1) | 8.83 (d, <i>J</i> = 7.1) | 7.18 (t, <i>J</i> = 7.3) | — | 7.33 (s) | 3.43 (2H, q, <i>J</i> = 6.4, NHCH ₂); 2.44 (9H, m, CH ₂ N(CH ₂) ₂ + 8-CH ₃); 1.63 (2H, q, <i>J</i> = 6.7, NHCH ₂ CH ₂ CH ₂ N); 0.97 (6H, t, <i>J</i> = 7.0, 2CH ₃) |

TABLE 2. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-----------|--------------------------|-------------------------|-------------------------|-------------------------|----------|---|
| 4g | 9.64 (t, $J = 5.2$) | 8.82 (d, $J = 7.2$) | 7.19 (t, $J = 7.3$) | — | 7.32 (s) | 3.60-3.04 (6H, m, NHCH ₂ + NCH ₂ CH ₃ + 5'-CH ₂); 2.81 (1H, q, $J = 7.3$, 2'-CH); 2.45 (3H, s, 8-CH ₃); 2.30-1.45 (4H, m, 3',4'-CH ₂); 1.04 (3H, t, $J = 7.2$, CH ₃) |
| 4h | 9.69 (t, $J = 5.4$) | 8.79 (d, $J = 7.3$) | 7.16 (t, $J = 7.3$) | — | 7.28 (s) | 3.45 (2H, q, $J = 5.8$, CONHCH ₂); 2.73 (4H, m, HN(CH ₂) ₂ piperazine); 2.44 (3H, s, 8-CH ₃); 2.37 (6H, m, CH ₂ N(CH ₂) ₂) |
| 4i | 9.66 (t, $J = 5.3$) | 8.80 (d, $J = 7.3$) | 7.19 (t, $J = 7.3$) | — | 7.31 (s) | 3.59 (4H, m, CH ₂ OCH ₂); 3.45 (2H, q, $J = 5.7$, NHCH ₂); 2.45 (9H, m, CH ₂ N(CH ₂) ₂ + 8-CH ₃) |
| 4j | 9.60 (t, $J = 5.5$) | 8.79 (d, $J = 7.3$) | 7.21 (t, $J = 7.3$) | — | 7.33 (s) | 3.57 (4H, m, CH ₂ OCH ₂); 3.39 (2H, q, $J = 6.3$, NHCH ₂); 2.45 (3H, s, 8-CH ₃); 2.33 (6H, m, CH ₂ N(CH ₂) ₂); 1.69 (2H, q, $J = 6.7$, NHCH ₂ CH ₂ CH ₂ N) |
| 4k | 9.77 (t, $J = 5.3$) | 8.78 (d, $J = 7.2$) | 7.20 (t, $J = 7.2$) | — | 7.30 (s) | 3.40 (2H, q, $J = 6.3$, NHCH ₂); 2.42 (3H, s, 8-CH ₃); 2.34 (6H, m, CH ₂ N(CH ₂) ₂); 1.71 (2H, q, $J = 6.8$, NHCH ₂ CH ₂ CH ₂); 1.42 (6H, m, 3,4,5-CH ₂ piperidine) |
| 5a | 9.66 (t, $J = 4.8$) | 8.80 (d, $J = 7.0$) | 7.24 (t, $J = 7.0$) | 7.92 (d, $J = 6.7$) | — | 3.45 (2H, q, $J = 5.7$, NHCH ₂); 2.43 (5H, m, NHCH ₂ CH ₂ + 9-CH ₃); 2.20 (6H, s, 2CH ₃) |
| 5b | 9.68 (t, $J = 5.0$) | 8.77 (d, $J = 7.1$) | 7.19 (t, $J = 6.9$) | 7.88 (d, $J = 6.7$) | — | 3.44 (2H, q, $J = 4.9$, CONHCH ₂); 2.76 (2H, t, $J = 6.0$, CONHCH ₂ CH ₂); 2.61 (2H, q, $J = 7.1$, NHCH ₂ CH ₃); 2.41 (3H, s, 9-CH ₃); 1.04 (3H, t, $J = 7.2$, NHCH ₂ CH ₃) |
| 5c | 9.73 (t, $J = 5.0$) | 8.78 (d, $J = 7.2$) | 7.22 (t, $J = 7.0$) | 7.90 (d, $J = 6.8$) | — | 3.47 (4H, m, CONHCH ₂ + CH ₂ O); 2.77 (2H, t, $J = 5.9$, CONHCH ₂ CH ₂); 2.64 (2H, t, $J = 5.7$, CH ₂ CH ₂ OH); 2.40 (3H, s, 9-CH ₃) |
| 5d | 9.70 (t, $J = 5.1$) | 8.81 (d, $J = 7.0$) | 7.24 (t, $J = 7.1$) | 7.93 (d, $J = 6.9$) | — | 3.42 (2H, q, $J = 6.1$, NHCH ₂); 2.59 (6H, m, CH ₂ N(CH ₂) ₂); 2.42 (3H, s, 9-CH ₃); 0.98 (6H, t, $J = 7.1$, 2CH ₃) |
| 5e | 9.98 (t, $J = 5.4$) | 8.72 (d, $J = 7.0$) | 7.06 (t, $J = 6.9$) | 7.77 (d, $J = 6.9$) | — | 3.34 (2H, q, $J = 6.3$, NHCH ₂); 2.36 (3H, s, 9-CH ₃); 2.25 (2H, t, $J = 6.7$, NHCH ₂ CH ₂ CH ₂); 2.11 (6H, s, 2CH ₃); 1.62 (2H, q, $J = 7.0$, NHCH ₂ CH ₂ CH ₂ N) |
| 5f | 9.85 (t, $J = 5.2$) | 8.76 (d, $J = 7.0$) | 7.11 (t, $J = 7.0$) | 7.79 (d, $J = 6.9$) | — | 3.36 (2H, q, $J = 6.4$, NHCH ₂); 2.44 (6H, m, CH ₂ N(CH ₂) ₂); 2.37 (3H, s, 9-CH ₃); 1.61 (2H, q, $J = 6.9$, NHCH ₂ CH ₂ CH ₂ N); 0.96 (6H, t, $J = 7.2$, 2CH ₃) |
| 5g | 9.71 (t, $J = 5.2$) | 8.82 (d, $J = 7.2$) | 7.23 (t, $J = 7.0$) | 7.92 (d, $J = 7.0$) | — | 3.62-3.04 (6H, m, NHCH ₂ + NCH ₂ CH ₃ + 5'-CH ₂); 2.80 (1H, q, $J = 7.2$, 2'-CH); 2.41 (3H, s, 9-CH ₃); 2.33-1.45 (4H, m, 3',4'-CH ₂); 1.05 (3H, t, $J = 7.2$, CH ₃) |
| 5h | 9.84 (t, $J = 5.1$) | 8.77 (d, $J = 7.2$) | 7.17 (t, $J = 7.1$) | 7.87 (d, $J = 7.0$) | — | 3.45 (2H, q, $J = 5.7$, CONHCH ₂); 2.75 (4H, m, HN(CH ₂) ₂ piperazine); 2.38 (9H, m, CH ₂ N(CH ₂) ₂ + 9-CH ₃) |
| 5i | 9.71 (t, $J = 5.4$) | 8.81 (d, $J = 7.0$) | 7.25 (t, $J = 7.1$) | 7.93 (d, $J = 7.0$) | — | 3.59 (4H, m, CH ₂ OCH ₂); 3.48 (2H, q, $J = 5.9$, NHCH ₂); 2.41 (9H, m, CH ₂ N(CH ₂) ₂ + 9-CH ₃) |
| 5j | 10.18 (t, $J = 5.6$) | 8.64 (d, $J = 7.2$) | 6.93 (t, $J = 6.9$) | 7.65 (d, $J = 6.9$) | — | 3.54 (4H, m, CH ₂ OCH ₂); 3.29 (2H, q, $J = 6.2$, NHCH ₂); 2.71 (2H, t, $J = 7.0$, CH ₂ NH(CH ₂) ₂); 2.30 (7H, m, CH ₂ N(CH ₂) ₂ + 9-CH ₃); 1.62 (2H, q, $J = 6.7$, NHCH ₂ CH ₂ CH ₂ N) |

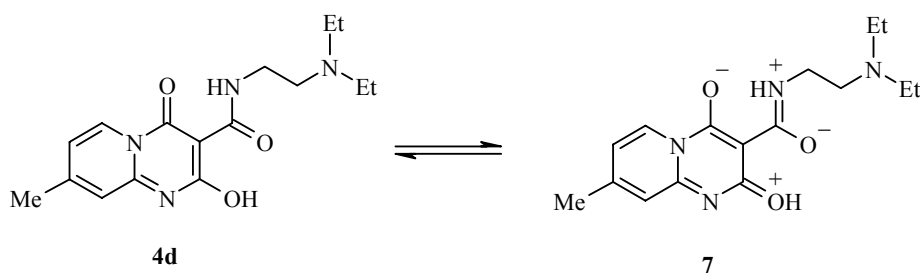
TABLE 2. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-----------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--|
| 5k | 9.84 (t, $J = 5.3$) | 8.73 (d, $J = 7.1$) | 7.12 (t, $J = 7.0$) | 7.78 (d, $J = 6.9$) | — | 3.42 (2H, q, $J = 6.3$, NHCH ₂); 2.43 (3H, s, 9-CH ₃); 2.34 (6H, m, CH ₂ N(CH ₂) ₂); 1.72 (2H, q, $J = 6.7$, NHCH ₂ CH ₂ CH ₃); 1.40 (6H, m, 3,4,5-CH ₂ piperidine) |
| 6a | 9.60 (t, $J = 5.2$) | 8.87 (d, $J = 2.4$) | — | 8.08 (d, $J = 9.5$) | 7.49 (d, $J = 9.5$) | 3.45 (2H, q, $J = 5.9$, NHCH ₂); 2.43 (2H, t, $J = 6.1$, NHCH ₂ CH ₂); 2.21 (6H, s, 2CH ₃) |
| 6b | 9.58 (t, $J = 5.3$) | 8.89 (d, $J = 2.6$) | — | 8.11 (d, $J = 9.4$) | 7.47 (d, $J = 9.4$) | 3.43 (2H, q, $J = 4.6$, CONHCH ₂); 2.80 (2H, t, $J = 6.1$, CONHCH ₂ CH ₂); 2.63 (2H, q, $J = 6.8$, NHCH ₂ CH ₃); 1.03 (3H, t, $J = 7.0$, NHCH ₂ CH ₃) |
| 6c | 9.63 (t, $J = 5.2$) | 8.90 (d, $J = 2.6$) | — | 8.13 (d, $J = 9.4$) | 7.49 (d, $J = 9.4$) | 3.44 (4H, m, CONHCH ₂ + CH ₂ O); 2.79 (2H, t, $J = 6.0$, CONHCH ₂ CH ₂); 2.64 (2H, t, $J = 5.9$, CH ₂ CH ₂ OH) |
| 6d | 9.65 (t, $J = 5.1$) | 8.93 (d, $J = 2.4$) | — | 8.08 (d, $J = 9.5$) | 7.51 (d, $J = 9.5$) | 3.42 (2H, q, $J = 6.1$, NHCH ₂); 2.41 (6H, m, CH ₂ N(CH ₂) ₂); 0.98 (6H, t, $J = 7.0$, 2CH ₃) |
| 6e | 9.61 (t, $J = 5.2$) | 8.88 (d, $J = 2.5$) | — | 8.06 (d, $J = 9.5$) | 7.48 (d, $J = 9.5$) | 3.43 (2H, q, $J = 6.4$, NHCH ₂); 2.28 (2H, t, $J = 6.7$, NHCH ₂ CH ₂ CH ₂); 2.17 (6H, s, 2CH ₃); 1.66 (2H, q, $J = 6.6$, NHCH ₂ CH ₂ CH ₂ N) |
| 6f | 9.66 (t, $J = 5.3$) | 8.91 (d, $J = 2.5$) | — | 8.10 (d, $J = 9.4$) | 7.52 (d, $J = 9.4$) | 3.40 (2H, q, $J = 6.4$, NHCH ₂); 2.45 (6H, m, CH ₂ N(CH ₂) ₂); 1.65 (2H, q, $J = 6.7$, NHCH ₂ CH ₂ CH ₂ N); 0.96 (6H, t, $J = 7.0$, 2CH ₃) |
| 6g | 9.59 (t, $J = 5.2$) | 8.90 (d, $J = 2.4$) | — | 8.05 (d, $J = 9.5$) | 7.49 (d, $J = 9.5$) | 3.63-3.07 (6H, m, NHCH ₂ + NCH ₂ CH ₃ + 5'-CH ₃); 2.84 (1H, q, $J = 7.1$, 2'-CH); 2.30-1.44 (4H, m, 3',4'-CH ₂); 1.02 (3H, t, $J = 7.0$, CH ₃) |
| 6h | 9.64 (t, $J = 5.2$) | 8.86 (d, $J = 2.4$) | — | 8.10 (d, $J = 9.4$) | 7.47 (d, $J = 9.4$) | 3.41 (2H, q, $J = 6.0$, CONHCH ₂); 2.80 (4H, m, HN(CH ₂) ₂ piperazine); 2.42 (6H, m, CH ₂ N(CH ₂) ₂) |
| 6i | 9.66 (t, $J = 5.3$) | 8.84 (d, $J = 2.3$) | — | 8.07 (d, $J = 9.3$) | 7.49 (d, $J = 9.3$) | 3.55 (4H, m, CH ₂ OCH ₂); 3.48 (2H, q, $J = 5.9$, NHCH ₂); 2.41 (6H, m, CH ₂ N(CH ₂) ₂) |
| 6j | 9.72 (t, $J = 5.4$) | 8.87 (d, $J = 2.3$) | — | 8.09 (d, $J = 9.4$) | 7.50 (d, $J = 9.4$) | 3.52 (4H, m, CH ₂ OCH ₂); 3.34 (2H, q, $J = 5.9$, NHCH ₂); 2.31 (6H, m, CH ₂ N(CH ₂) ₂); 1.65 (2H, q, $J = 6.6$, NHCH ₂ CH ₂ CH ₂ N) |
| 6k | 9.70 (t, $J = 5.3$) | 8.86 (d, $J = 2.4$) | — | 8.11 (d, $J = 9.4$) | 7.49 (d, $J = 9.4$) | 3.40 (2H, q, $J = 6.1$, NHCH ₂); 2.34 (6H, m, CH ₂ N(CH ₂) ₂); 1.67 (2H, q, $J = 6.7$, NHCH ₂ CH ₂ CH ₂); 1.45 (6H, m, 3,4,5-CH ₂ piperidine) |

* Signals of protons of hydroxyl and secondary amino groups are not shown in the spectra because of rapid deuterium exchange.

The desired compounds **2-6** (Table 1) were obtained by amidation of the ethyl esters of the corresponding 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **1a-e** with an excess of dialkylaminoalkylamine in boiling ethanol. They were all colorless crystalline substances, readily soluble in alcohols and practically insoluble in ether. The moderate solubility of dialkylaminoalkylamides **2-6** in water enabled a study of their antiviral properties to be carried out without conversion into salts.

The structures of all the synthesized substances were confirmed by ¹H NMR spectra (Table 2). The structure of one of the compounds, amide **4d**, was investigated in a more detailed manner by X-ray structural analysis (Fig. 1, Tables 3 and 4). It was established that all the non-hydrogen atoms of its pyridinopyrimidine bicycle and also the O₍₁₎, C₍₉₎, O₍₃₎, N₍₃₎, C₍₁₀₎, O₍₂₎, and C₍₁₆₎ atoms lie in one plane with a precision of 0.02 Å, which is probably caused by the presence of two strong intramolecular hydrogen bonds: O₍₁₎-H₍₁₀₎···O₍₃₎ (H···O 1.56 Å, O-H···O 158°) and N₍₃₎-H_(3N)···O₍₂₎ (H···O 1.95 Å, N-H···O 136°). The formation of the indicated hydrogen bonds leads to a significant redistribution of electron density in the pyrimidone fragment. The C₍₆₎-C₍₇₎ 1.412(2), C₍₈₎-O₍₁₎ 1.324(2), and C₍₉₎-N₍₃₎ 1.328(2) Å bonds are shortened compared with average values [15] of 1.455, 1.333, and 1.339 Å, respectively, but the O₍₂₎-C₍₆₎ 1.237(2), (1.210 Å), C₍₇₎-C₍₈₎ 1.410(2) (1.326 Å), and O₍₃₎-C₍₉₎ 1.260(2) (1.210 Å) are lengthened. Such a redistribution of electron density permits the structure of amide **4d** in the crystal to be represented as a superposition of the resonance structures **4d** ↔ **7** with a predominant contribution by the 2-hydroxy-4-oxo form **4d**, while the initial ethyl esters of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **1a-e** were established previously by us in the bipolar 2,4-dioxo form with the proton on the nitrogen atom in position 1 [16].



In the pyridine fragment of amide **4d** a tendency was observed towards the localization of bonds. The bond lengths of C₍₄₎-C₍₅₎ 1.349(2) and C₍₂₎-C₍₃₎ 1.365(2) Å were significantly shortened and the bonds C₍₃₎-C₍₄₎ 1.418(2) and C₍₂₎-C₍₁₎ 1.417(2) Å were lengthened. An analogous effect has also been noted in other pyridopyrimidines [17, 18]. The C₍₁₁₎ atom is found in the *ap*-conformation relative to the C₍₉₎-N₍₃₎ bond (torsion angle C₍₉₎-N₍₃₎-C₍₁₀₎-C₍₁₁₎ 173.8(1)°). The N₍₄₎ atom has a pyramidal configuration (sum of valence angles centred on the nitrogen atom is 332.1°) and is found in the +*sc*-conformation relative to the N₍₃₎-C₍₁₀₎ bond (torsion angle N₍₃₎-C₍₁₀₎-C₍₁₁₎-N₍₄₎ 62.9(2)°). The C₍₁₂₎-C₍₁₃₎ ethyl substituent occupies a position intermediate between -*ac*- and *apr*-conformations, but the C₍₁₄₎-C₍₁₅₎ ethyl substituent is found in the +*sc*-conformation relative to the C₍₁₁₎-C₍₁₀₎ bond (torsion angles C₍₁₂₎-N₍₄₎-C₍₁₁₎-C₍₁₀₎ 155.9(1), C₍₁₄₎-N₍₄₎-C₍₁₁₎-C₍₁₀₎ 80.7(2)°). The C₍₁₃₎ atom has an orientation close to +*sc*, but the C₍₁₅₎ has an orientation close to *ap* relative to the C₍₁₁₎-N₍₄₎ bond (torsion angles C₍₁₁₎-N₍₄₎-C₍₁₂₎-C₍₁₃₎ 75.9(2), C₍₁₁₎-N₍₄₎-C₍₁₄₎-C₍₁₅₎ -160.0(2)°). Such a position of the ethyl groups leads to shortened intramolecular contacts – H_(10b)···C₍₁₄₎ 2.84 (sum of van der Waals radii 2.87 [19]), H_(10b)···H_(14a) 2.18 (2.34), H_(11b)···C₍₁₃₎ 2.63 (2.87), H_(11b)···H_(13c) 2.15 (2.34), H_(12b)···C₍₁₅₎ 2.65 (2.87), H_(12b)···C_(15c) 2.16 (2.34), and H_(14a)···C₍₁₀₎ 2.71 Å (2.87 Å).

The creation of effective and safe antiviral preparations is one of the most complex problems in contemporary pharmaceutical chemistry and medicine. The complexity of this consists of the need to develop substances capable of selectively repressing reproduction of the virus without affecting the active life of the cells of the host organism. Because of this the first step of the biological testing of amides **2-6** was the determination of their cytotoxicity. Cultures of transplanted calf embryo kidney cells (CK) and calf coronary vessels (CCV) were used for this.

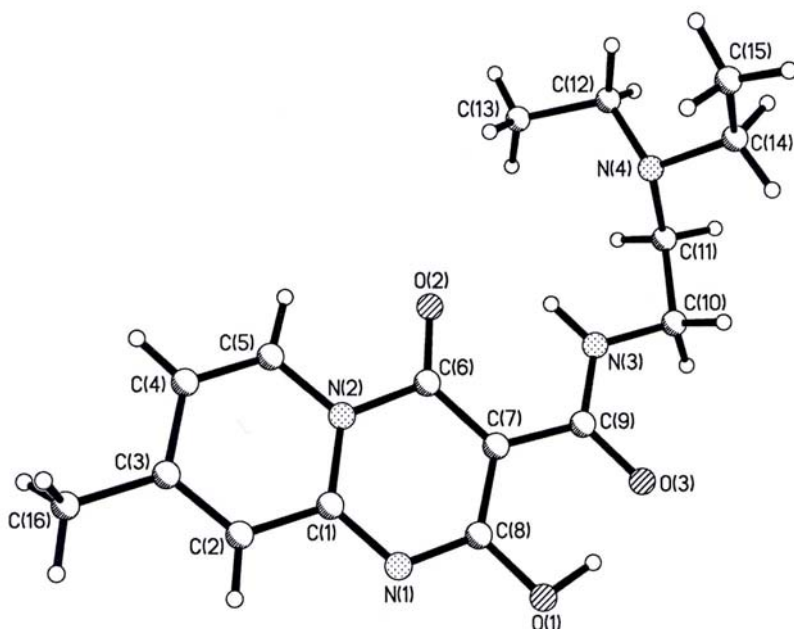


Fig. 1. Structure of the amide **4d** molecule with numbering of atoms.

As it turned out, at a concentration of 0.5% a toxic effect was recorded for the majority of amides **2-6** even on the second day by the appearance of individual degenerated cells on a background of incipient destruction of the cell monolayer. On the fifth day signs of cytotoxic action were intensified even more. Significant destruction of the monolayer of cells was observed by the appearance of conglomerates of degenerated cells (rounded forms with granular cytoplasm) and tearing of them away from the glass surface. In the majority of these cases cytotoxicity was assessed as destruction of the cell monolayer by 50%. And finally, complete degeneration of almost all cells set in after 7-8 days of cultivation. Control cell cultures (CK and CCV) still displayed viability at this time, although the appearance was also observed of individual degenerative cells on a background of incipient destruction of the cell monolayer. It follows from the experiments carried out that at a concentration of 0.5% amides **2-6** show a negative effect on the morphology of cultured CK and CCV cells and due to the expressed toxicity cannot be used for carrying out further investigations.

TABLE 3. Bond Lengths (*l*) in the Structure of Amide **4d**

| Bond | <i>l</i> , Å | Bond | <i>l</i> , Å |
|--------------------------------------|--------------|--------------------------------------|--------------|
| N ₍₁₎ -C ₍₈₎ | 1.327(2) | N ₍₁₎ -C ₍₁₎ | 1.335(2) |
| N ₍₂₎ -C ₍₁₎ | 1.379(2) | N ₍₂₎ -C ₍₅₎ | 1.383(2) |
| N ₍₂₎ -C ₍₆₎ | 1.450(2) | N ₍₃₎ -C ₍₉₎ | 1.328(2) |
| N ₍₃₎ -C ₍₁₀₎ | 1.454(2) | N ₍₄₎ -C ₍₁₁₎ | 1.465(2) |
| N ₍₄₎ -C ₍₁₄₎ | 1.466(2) | N ₍₄₎ -C ₍₁₂₎ | 1.468(2) |
| O ₍₁₎ -C ₍₈₎ | 1.324(2) | O ₍₂₎ -C ₍₆₎ | 1.237(2) |
| O ₍₃₎ -C ₍₉₎ | 1.260(2) | C ₍₁₎ -C ₍₂₎ | 1.417(2) |
| C ₍₂₎ -C ₍₃₎ | 1.365(2) | C ₍₃₎ -C ₍₄₎ | 1.418(2) |
| C ₍₃₎ -C ₍₁₆₎ | 1.496(2) | C ₍₄₎ -C ₍₅₎ | 1.349(2) |
| C ₍₆₎ -C ₍₇₎ | 1.412(2) | C ₍₇₎ -C ₍₈₎ | 1.410(2) |
| C ₍₇₎ -C ₍₉₎ | 1.474(2) | C ₍₁₀₎ -C ₍₁₁₎ | 1.513(2) |
| C ₍₁₂₎ -C ₍₁₃₎ | 1.517(3) | C ₍₁₄₎ -C ₍₁₅₎ | 1.508(3) |

Nonetheless, a concentration of 0.25% of amides **2-6** proved to be less toxic and some of them (for example, **2b,e,f,h**, **4d**, and **5h**) in the first days of observation displayed only insignificant signs of cytotoxic action. More substantial injury of cells and the cell monolayer was noted towards the end of five days. Of all the studied derivatives of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **2-6** only two substances, amides **5d** and **5i**, at a concentration of 0.25% did not in general show a cytotoxic action over a stretch of several days. Only towards the fifth day of observation were the first signs of toxic injury displayed. However towards this time analogous changes were also noted in control cell cultures. On the basis of the investigations carried out it may therefore be stated that one of the main criteria taken into consideration on selecting substances with potential antiviral activity, *viz.* the absence of an effect on the cell of a macroorganism, is fulfilled by 0.25% aqueous solutions of amides **5d** and **5i**, which were passed on to the following stage of screening.

The type 1 herpes simplex virus containing DNA (HSV-1) is one of the most widespread in the *Herpesviridae* family, which led to its selection as the test-virus. The "US" strain used by us was isolated from a patient with clinically expressed form of acute herpes viral infection and was obtained from the virus collection of the D. I. Ivanovskii Institute of Virology of the Russian Academy of Medical Sciences (Moscow, Russia). To restore the infectious activity the strain underwent three passages in cell cultures. The antiherpes activity of amides **5d** and **5i** were studied by the neutralization reaction in cultures of transplanted CK and CCV cells allowing for the cytopathic action displayed by HSV-1.

On the basis of the investigations carried out by us it must be said that the data of computer prognosis on the expediency of testing amide derivatives of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids for the presence of antiviral activity in them was in fact confirmed. Both of the investigated substances proved to be capable of significantly inhibiting the reproduction of HSV-1, amide **5i** by 1.5 log and amide **5d** by 2.2 log. This circumstance enabled the more active compound, the 2-dimethylaminoethylamide of 2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**5d**), to be recommended for further in depth study, including experiments *in vivo*, as a potential antiherpes agent.

Several years ago the whole world was alarmed by the outbreak of a serious respiratory illness, accompanied by high mortality, and called atypical pneumonia or SARS (*severe acute respiratory syndrome*).

TABLE 4. Valence Angles (ω) in the Structure of Amide **4d**

| Angle | ω , deg. | Angle | ω , deg. |
|--|-----------------|--|-----------------|
| C ₍₈₎ -N ₍₁₎ -C ₍₁₎ | 117.7(1) | C ₍₁₎ -N ₍₂₎ -C ₍₅₎ | 120.6(1) |
| C ₍₁₎ -N ₍₂₎ -C ₍₆₎ | 121.5(1) | C ₍₅₎ -N ₍₂₎ -C ₍₆₎ | 117.9(1) |
| C ₍₉₎ -N ₍₃₎ -C ₍₁₀₎ | 121.5(1) | C ₍₁₁₎ -N ₍₄₎ -C ₍₁₄₎ | 109.8(1) |
| C ₍₁₁₎ -N ₍₄₎ -C ₍₁₂₎ | 111.2(1) | C ₍₁₄₎ -N ₍₄₎ -C ₍₁₂₎ | 111.1(1) |
| N ₍₁₎ -C ₍₁₎ -N ₍₂₎ | 122.6(1) | N ₍₁₎ -C ₍₁₎ -C ₍₂₎ | 119.6(1) |
| N ₍₂₎ -C ₍₁₎ -C ₍₂₎ | 117.8(1) | C ₍₃₎ -C ₍₂₎ -C ₍₁₎ | 121.9(2) |
| C ₍₂₎ -C ₍₃₎ -C ₍₄₎ | 118.2(2) | C ₍₂₎ -C ₍₃₎ -C ₍₁₆₎ | 121.6(2) |
| C ₍₄₎ -C ₍₃₎ -C ₍₁₆₎ | 120.2(2) | C ₍₅₎ -C ₍₄₎ -C ₍₃₎ | 120.3(2) |
| C ₍₄₎ -C ₍₅₎ -N ₍₂₎ | 121.2(2) | O ₍₂₎ -C ₍₆₎ -C ₍₇₎ | 128.1(1) |
| O ₍₂₎ -C ₍₆₎ -N ₍₂₎ | 117.5(1) | C ₍₇₎ -C ₍₆₎ -N ₍₂₎ | 114.4(1) |
| C ₍₈₎ -C ₍₇₎ -C ₍₆₎ | 119.0(1) | C ₍₈₎ -C ₍₇₎ -C ₍₉₎ | 119.5(1) |
| C ₍₆₎ -C ₍₇₎ -C ₍₉₎ | 121.5(1) | O ₍₁₎ -C ₍₈₎ -N ₍₁₎ | 115.1(1) |
| O ₍₁₎ -C ₍₈₎ -C ₍₇₎ | 120.0(1) | N ₍₁₎ -C ₍₈₎ -C ₍₇₎ | 124.9(1) |
| O ₍₃₎ -C ₍₉₎ -N ₍₃₎ | 120.6(2) | O ₍₃₎ -C ₍₉₎ -C ₍₇₎ | 120.3(1) |
| N ₍₃₎ -C ₍₉₎ -C ₍₇₎ | 119.1(1) | N ₍₃₎ -C ₍₁₀₎ -C ₍₁₁₎ | 109.3(1) |
| N ₍₄₎ -C ₍₁₁₎ -C ₍₁₀₎ | 112.6(1) | N ₍₄₎ -C ₍₁₂₎ -C ₍₁₃₎ | 112.2(2) |
| N ₍₄₎ -C ₍₁₄₎ -C ₍₁₅₎ | 113.1(2) | | |

The origin of it was coronavirus, one of the most important representatives of the RNA-containing viruses. In spite of the whole intensity of the investigations undertaken, the search for effective anticoronavirus drugs, regrettably, has not yet been crowned with success and is still urgent. Considering that amides **5d** and **5i** displayed antiviral activity in relation to HSV-1, they were tested by us as possible inhibitors of the hemagglutinating activity of coronaviruses.

It was established that amides **5d** and **5i** did not show a significant effect on the viability of coronavirus. Consequently their further investigation in this direction is unpromising.

EXPERIMENTAL

The ^1H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX-200 instrument (200 MHz), solvent was DMSO- d_6 , and internal standard TMS. The ethyl esters of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **1a-e** were obtained by the known procedure of [16].

N-R-Amides of 2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acids 2-6 (General Method). The appropriate amine (0.015 mol) was added to a solution of the corresponding 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid ethyl ester **1** (0.01 mol) in ethyl alcohol (10 ml) and the mixture boiled for 10 h. The reaction mixture was cooled, diluted with ether, and maintained in an ice bath for several hours. The solid amide **2-6** which separated was filtered off, thoroughly washed with ether, and dried.

X-ray Structural Investigation. The crystals of amide **4d** were triclinic (acetone), at 20°C: $a = 5.738(1)$, $b = 7.065(1)$, $c = 21.300(3)$ Å, $\alpha = 83.31(1)^\circ$, $\beta = 84.85(1)^\circ$, $\gamma = 69.61(2)^\circ$, $V = 802.7(2)$ Å³, $M_r = 318.38$, $Z = 2$, space group $P\bar{1}$, $d_{\text{calc}} = 1.317$ g/cm³, $\mu(\text{MoK}\alpha) = 0.093$ mm⁻¹, $F(000) = 340$. Parameters of the unit cell and the intensities of 8254 reflections (3685 independent, $R_{\text{int}} = 0.026$) were measured on a Xcalibur-3 diffractometer (MoK α radiation, CCD detector, graphite monochromator, ω scanning, $2\theta_{\text{max}} = 55^\circ$).

The structure was solved by the direct method with the SHELXTL set of programs [20]. The positions of hydrogen atoms were made apparent from an electron density difference synthesis and were refined isotropically. The structure was refined on F^2 with the full matrix least squares method in an anisotropic approach for non-hydrogen atoms to $wR_2 = 0.127$ for 3576 reflections ($R_1 = 0.051$ at 2688 reflections with $F > 4\sigma(F)$, $S = 1.094$). Full crystallographic information is deposited in the Cambridge Crystal Database, No. CCDC 650595. Interatomic distances and valence angles are given in Tables 3 and 4.

Cytotoxicity Determination. Transplanted cells of calf embryo kidney were incubated in medium 199 with added 10% bovine serum, cells of calf coronary vessels in a medium consisting of equal volumes of Eagle's medium and medium 199 with a 10% content of bovine serum. To prevent possible bacterial contamination of the nutrient media, the antibiotics penicillin and streptomycin were added when carrying out experimental investigations. Both types of cells were cultured in a thermostat at 37°C and a medium pH of 7.2-7.4 for 2 days. After this, growth medium was removed from the test tubes and aqueous solutions (about 0.2 ml) of the amides **2-6** being tested at concentrations of 0.25 and 0.5% and supporting nutrient medium (about 0.8 ml) were introduced to the formed monolayer of cultured cells. The test tubes, about 10 for each specimen at both concentrations, were incubated at 37°C, and observed for 7-8 days. Test tubes with cell cultures without addition of substances being studied served as controls. Cytotoxicity was determined by examining under a microscope at low ($\times 10$) magnification for disturbance of the monolayer and changes in the morphology of cells as to their roundness, shriveling, or tearing away of degenerated cells from the glass surface.

Determination of Antiherpes Activity. To a suspension (0.2 ml) containing HSV-1 at a working dose of 100 CPD_{50/0.2 ml} (cytopathic dose of virus causing disease in 50% of the cell monolayer) was added a 0.25% aqueous solution (0.2 ml) of the compound being studied, and the resulting mixture was incubated at room temperature for 10 min. The obtained mixture (0.2 ml) was introduced into a test tube with a 2-day culture of

cells and then supporting nutrient medium 199 (0.8 ml) containing no serum (antiviral inhibitors possibly present in it) was added. In this way the actual concentration of amides **5d** and **5i** in the tests was 250 µg/ml. Cell cultures, without addition of test virus and cells infected with HSV-1 at the operating dose without the chemical substance being tested, were used as controls. After incubation at 37° C for 7 days the morphological changes of the cell monolayer (cytopathic effect of the virus) were recorded. The virus titer in the presence of test compounds and in the controls was calculated in log CPD₅₀. The criterion of antiviral action was calculated from the presence of differences of virus titer in comparison with control values.

Determination of the Effect on Coronavirus. Strain Kharkov /343/86 was used in the experiments and was obtained from the Institute of Experimental and Clinical Veterinary Medicine (Kharkov, Ukraine) and was checked for viability before carrying out experiments. Study of the antiviral activity of amides **5d** and **5i** in relation to coronavirus was carried out with the hemagglutination inhibition reaction. Equal volumes of a coronavirus suspension in the operating dose (4 hemagglutinating units) and the chemical substance as a 0.25% aqueous solution showing no cytotoxic action were mixed, and after incubation for 30 min at room temperature the degree of inhibition of the hemagglutinating activity of coronavirus was determined. Coronavirus at the indicated operating dose and mouse erythrocytes prepared in physiological solution (pH 7.2) and concentration 1% were used as control.

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