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# Synthesis of N,N'-diarylalkanediamides and their antimycobacterial and antialgal activity

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**Abstract:** A set of N,N'-diarylalkanediamides was synthesised. The compounds were tested for their antimycobacterial and antialgal activity. The antimycobacterial activity of N,N'-diarylalkanediamides depends on the lipophilicity of the respective acid. Antimycobacterially active substances were found only in the series of N,N'-diarylethanediamides and N,N'-diarylbutanediamides. Other compounds (derivatives of pentane-, hexane-, octane- and nonanediamide) were inactive against various strains of mycobacteria. The compounds inhibited growth and chlorophyll production in *Chlorella vulgaris*. Their relatively low antialgal activity is caused by their low aqueous solubility, and hence by a restricted passage of the inhibitor through the hydrophilic regions of thylakoid membranes.

**Keywords:** N,N'-diarylalkanediamides, antimycobacterial activity, antialgal activity.

## Introduction

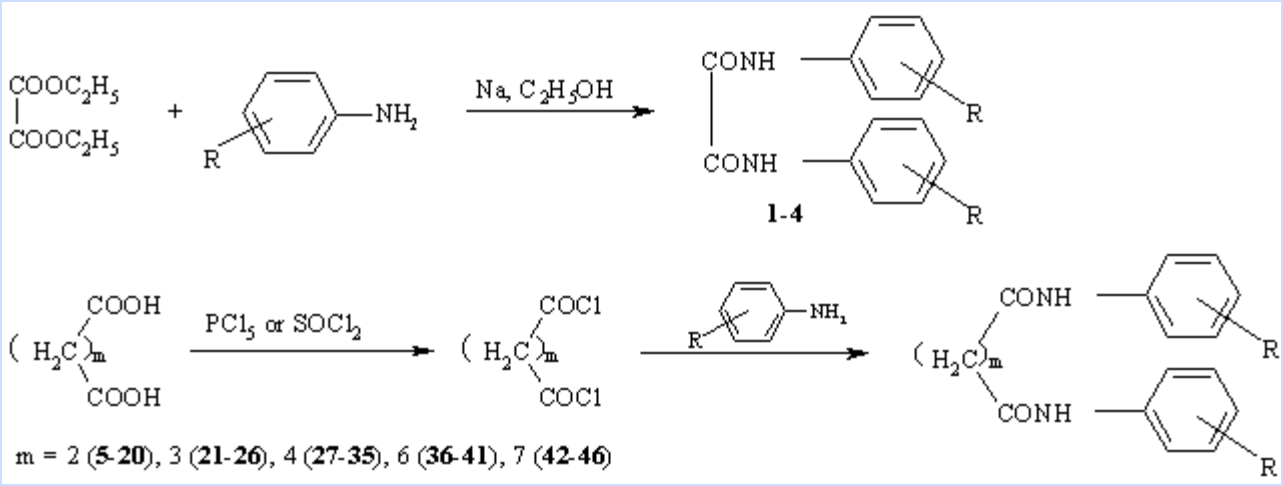
As the end of the 20$^{th}$ century witnesses a sharp rise in the incidence of mycobacterial infections, the development of new antimycobacterial drugs is presently of utmost importance and should proceed at a rapid pace. When exploring a possible link between antituberculous activity and the ability to form chelates with heavy metals, we prepared a set of N,N'-diarylethane- and -propanediamides, which were evaluated *in vitro* against *Mycobacterium tuberculosis*, and some of them showed significant activity [1]. Other authors have described various kinds of biological activity of alkanediamide derivatives as well. For example, some 2-methylcarbonylbutanediamides are active against *M. tuberculosis* [2], 2,3-diarylpentanediamides display activity against Gram-positive bacteria [3], and N,N'-substituted 2-halobutanediamides act as herbicides [4]. Raynes et al. studied the influence of the length of the connecting chain on the antimalarial activity of bisquinolines; the derivative of butanediamide was the most efficient one [5]. In our

previous study [6] we found that N,N'-bis(3,4-dichlorophenyl)butanediamide effectively inhibited oxygen evolution rate (OER) in spinach chloroplasts and that this compounds interacted with the pigment-protein complexes in photosystem 2. The increase of the length of the connecting chain in the series of N,N'-bis(3,4-dichlorophenyl)alkanediamides led to the decrease of OER-inhibiting activity in spinach chloroplast [7]. The decrease in biological activity with increasing lipophilicity of the compounds is probably linked to their lowered aqueous solubility, and hence to a restricted passage of the inhibitor through the hydrophilic regions of thylakoid membranes.

This study is focused on the synthesis of a large set of N,N'-diarylalkanediamides and on the study of antimycobaterial and antialgal activity of these compounds.

**Results and Discussion**

N,N'-diarylalkanediamides, with the exception of N,N'-diarylethanediamides, were prepared from the corresponding anilines by treatment with the appropriate acyl chlorides in pyridine at 0°C. The reaction mixtures were allowed to stand at room temperature, and after 24 hours they were poured into water. The products were filtered off, washed with water and crystallized from ethanol. The acyl chlorides were prepared from the corresponding acids by the reaction with phosphorus pentachloride (succinyl chloride) or thionyl chloride (all other acyl chlorides). N,N'-diarylethanediamides were prepared from diethyl oxalate by the reaction with the corresponding aniline in the presence of sodium ethanolate. All syntheses are outlined in Scheme 1. The characteristic data of compounds **1--46** are given in Table 1 and Table 2.




**Scheme 1**

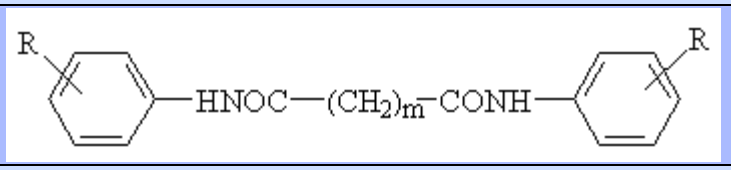
Compounds **1--46** were tested for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *M. avium*, *M. fortuitum* and *M. kansasii*. We found that the antimycobacterial activity of N,N'-diarylalkanediamides depends on the lipophilicity of the respective acid. Active substances were found only in the series of N,N'-diarylethanediamides and N,N'-diarylbutanediamides, but the antimycobacterial activity was mostly low. The MIC values of the active compounds are given in Table 3. All derivatives of pentane-, hexane-, octane- and nonanediamide were inactive against the above mycobacteria strains.

The inhibition of chlorophyll production in statically cultivated algae *Chlorella vulgaris* by selected derivatives was investigated at a constant inhibitor concentration of 75 μmol $dm^{-3}$. The antialgal activity of the compounds was generally low, and the observed inhibition of algal chlorophyll production varied in the range of 14.2 (**10**) to 57.9 % (**40**) (Table 4 and Table 5). The antialgal activity of N,N'-diarylbutanediamides was relatively low, varying in the range of 14.2 (**10**) to 43.6 % (**15**) (Table 5). The most effective inhibitor from the series of N,N'-diarylalkanediamides

was N,N'-bis(4-methoxyphenyl)octanediamide (**40**), causing 57.9 % inhibition of chlorophyll production (Table 4). Antialgal activity of substituted N,N'-diarylalkanediamides with the same substituent R was proportional to the number of methylene groups in the connecting chain of the molecule (m = 2 -- 4, 6, 7) for derivatives with R = H and 4-Cl, respectively. For derivatives with R = 4-$CH_3$, 4-$OCH_3$ and 3,4-$Cl_2$, a quasi-parabolic dependence of the inhibitory activity on m was found, with maximum inhibition for N,N'-diaryloctanediamides (m = 6; R = 4-$CH_3$ (**39**) and 4-$OCH_3$ (**40**)) and N,N'-bis(3,4-dichlorophenyl)hexanediamide (m = 4; **31**). The relatively low biological activity of the compounds is probably a consequence of their low aqueous solubility, and hence a restricted passage of the inhibitor through the hydrophilic regions of thylakoid membranes. An efficient inhibition of photosynthetic electron transport in spinach chloroplasts by N,N'-bis(3,4-dichlorophenyl)butanediamide has been observed previously [6,7].

**Tables**

**Table 1.** Experimental data of the compounds




| **Compd.** | Formula (M. w.) | m | R | M. p. (°C) Yield (%) | IR nu(C=O) ($cm^{-1}$) |
|---|---|---|---|---|---|
| **1** | $C_{16}H_{16}N_2O_2$ (268.32) | 0 | 2-$CH_3$ | 212[a] 65.2 | 1668 |
| **2** | $C_{16}H_{16}N_2O_2$ (268.32) | 0 | 3-$CH_3$ | 135--137[a] 59.7 | 1666 |
| **3** | $C_{14}H_{10}N_4O_6$ (330.26) | 0 | 4-$NO_2$ | 357[a] 61.4 | 1706 |
| **4** | $C_{14}H_{10}Br_2N_2O_2$ (398.05) | 0 | 4-Br | 329--331[a] 57.6 | 1666 |
| **5** | $C_{16}H_{14}Br_2N_2O_2$ (426.11) | 2 | 4-Br | 281[a] 92.4 | 1652 |
| **6** | $C_{16}H_{12}Cl_4N_2O_2$ (406.10) | 2 | 3,4-$Cl_2$ | 258--259[b] 93.1[b] | 1659[b] |
| **7** | $C_{16}H_{16}N_2O_2$ (268.32) | 2 | H | 231--233[a] 94.6 | 1663 |
| **8** | $C_{18}H_{20}N_2O_4$ (328.37) | 2 | 4-$OCH_3$ | 256--257[a] 89.5 | 1648 |
| **9** | $C_{16}H_{14}Cl_2N_2O_2$ (337.21) | 2 | 4-Cl | 288--290 90.3 | 1652 |
| **10** | $C_{18}H_{20}N_2O_2$ (296.37) | 2 | 4-$CH_3$ | 273--275 91.4 | 1655 |
| **11** | $C_{16}H_{14}F_2N_2O_2$ (304.30) | 2 | 3-F | 206--207 88.5 | 1663 |
| **12** | $C_{16}H_{14}F_2N_2O_2$ | 2 | 4-F | 244--245 92.2 | 1651 |

| | | | | | |
|---|---|---|---|---|---|
| | $C_{20}H_{24}N_2O_4$ (304.30) | | | 234 | |
| **13** | $C_{16}H_{14}N_4O_6$ (358.31) | 2 | 3-$NO_2$ | 228--230 87.5 | 1675 |
| **14** | $C_{20}H_{24}N_2O_2$ (324.42) | 2 | 3,4-$(CH_3)_2$ | 231--232 85.2 | 1651 |
| **15** | $C_{16}H_{14}Cl_2N_2O_2$ (337.21) | 2 | 3-Cl | 233--235[a] 92.3 | 1668 |
| **16** | $C_{24}H_{32}N_2O_2$ (380.53) | 2 | 4-$C_4H_9$ | 232--234 81.0 | 1659 |
| **17** | $C_{22}H_{28}N_2O_2$ (352.48) | 2 | 4-iso$C_3H_7$ | 234--236 82.5 | 1656 |
| **18** | $C_{24}H_{32}N_2O_2$ (380.53) | 2 | 4-sec$C_4H_9$ | 178--179 80.7 | 1655 |
| **19** | $C_{20}H_{26}N_4O_2$ (354.45) | 2 | 4-$N(CH_3)_2$ | 282.5--283.5[a] 88.4 | 1645 |
| **20** | $C_{18}H_{14}N_4O_2S_2$ (382.45) | 2 | c) | 282--285 91.5 | 1694 |
| **21** | $C_{17}H_{16}Cl_2N_2O_2$ (351,23) | 3 | 4-Cl | 243 69.5 | 1664 |
| **22** | $C_{19}H_{22}N_2O_4$ (342.39) | 3 | 4-$OCH_3$ | 224 62.2 | 1659 |
| **23** | $C_{17}H_{18}N_2O_2$ (282.34) | 3 | H | 225[a] 84.3 | 1673 |
| **24** | $C_{19}H_{22}N_2O_2$ (310.40) | 3 | 4-$CH_3$ | 221[a] 54.4 | 1664 |
| **25** | $C_{17}H_{14}Cl_4N_2O_2$ (420.12) | 3 | 3,4-$Cl_2$ | 267[b] 63.0[b] | 1679[b] |
| **26** | $C_{17}H_{16}Br_2N_2O_2$ (440.13) | 3 | 4-Br | 257[a] 57.5 | 1664 |
| **27** | $C_{20}H_{24}N_2O_2$ (324.42) | 4 | 4-$CH_3$ | 252 67.4 | 1659 |
| **28** | $C_{18}H_{20}N_2O_2$ (296.37) | 4 | H | 238[a] 75.0 | 1660 |
| **29** | $C_{18}H_{18}N_4O_6$ (386.36) | 4 | 3-$NO_2$ | 239 58.3 | 1667 |
| **30** | $C_{18}H_{18}Cl_2N_2O_2$ (365.26) | 4 | 3-Cl | 197 59.8 | 1663 |
| **31** | $C_{18}H_{16}Cl_4N_2O_2$ (434.15) | 4 | 3,4-$Cl_2$ | 277[b] 58.8[b] | 1670[b] |
| **32** | $C_{20}H_{24}N_2O_4$ (356.42) | 4 | 2-$OCH_3$ | 152 40.3 | 1659 |
| | $C_{20}H_{24}N_2O_4$ | | | 234 | |

| | | | | | |
|---|---|---|---|---|---|
| **33** | (356.42) | 4 | 4-$OCH_3$ | 64.5 | 1648 |
| **34** | $C_{18}H_{18}Cl_2N_2O_2$ (356.26) | 4 | 4-Cl | 239<br>66.7 | 1656 |
| **35** | $C_{24}H_{28}N_2O_6$ (440.50) | 4 | 4-$COOC_2H_5$ | 217<br>54.0 | 1708, 1693 |
| **36** | $C_{20}H_{20}Cl_4N_2O_2$ (462.20) | 6 | 3,4-$Cl_2$ | 167--168[b]<br>34.6[b] | 1671[b] |
| **37** | $C_{20}H_{22}Cl_2N_2O_2$ (393.31) | 6 | 4-Cl | 197--198<br>81.3 | 1659 |
| **38** | $C_{20}H_{24}N_2O_2$ (324.42) | 6 | H | 186--188[a]<br>57.2 | 1659 |
| **39** | $C_{22}H_{28}N_2O_2$ (352.48) | 6 | 4-$CH_3$ | 224--226[a]<br>54.7 | 1656 |
| **40** | $C_{22}H_{28}N_2O_4$ (384.48) | 6 | 4-$OCH_3$ | 220--221<br>63.2 | 1652 |
| **41** | $C_{20}H_{22}Br_2N_2O_2$ (482.21) | 6 | 4-Br | 253[a]<br>53.6 | 1664 |
| **42** | $C_{21}H_{22}Cl_4N_2O_2$ (476.23) | 7 | 3,4-$Cl_2$ | 170--171[b]<br>52.2[b] | 1680[b] |
| **43** | $C_{21}H_{24}Cl_2N_2O_2$ (407.34) | 7 | 4-Cl | 196--197<br>61.4 | 1660 |
| **44** | $C_{21}H_{26}N_2O_2$ (338.45) | 7 | H | 180--181[a]<br>62.7 | 1671 |
| **45** | $C_{23}H_{30}N_2O_2$ (366.50) | 7 | 4-$CH_3$ | 197--198[a]<br>61.4 | 1662 |
| **46** | $C_{23}H_{30}N_2O_4$ (398.50) | 7 | 4-$OCH_3$ | 194--196<br>43.9 | 1655 |

[a] M. p. values from literature: Compound, value (°C) [ref.]: **1**, 209 [8]; **2**, 133 [8]; **3**, 359 [9]; **4**, 321--322 [10]; **5**, 284 [11]; **7**, 230,5 [12]; **8**, 256 [13]; **15**, 232 [14]; **19**, 277-280 [15]; **23**, 223 [11]; **24**, 218 [11]; **26**, 256 [11]; **28**, 235 [11]; **38**, 186--7 [16]; **39**, 219 [11]; **41**, 248 [11]; **44**, 186--7 [16]; **45**, 198 [11].

[b] The data of compounds **6**, **25**, **31**, **36** and **42** were taken from [7].

[c] The compounds is N,N'-bis(2-benzothiazolyl)butanediamide.

**Table 2.** $^1$H NMR spectroscopic data and elemental analyses of selected compounds

| **Compd.** | $^1$H NMR delta (ppm) | % Calc.<br>% Found | | |
|---|---|---|---|---|
| | | C | H | N |
| **9** | 2.63 (s, 4H), 7.35--7.28 (m, 4H), 7.63--7.56 (m, 4H), 10.14 (s, 2H) | 56.99<br>57.24 | 4.18<br>4.15 | 8.31<br>8.38 |

| | | | | |
|---|---|---|---|---|
| **10** | 2.21 (s, 6H), 2.60 (s, 4H), 7.11--7.03 (m, 4H), 7.48--7.40 (m, 4H), 9.89 (s, 2H) | 72.95<br>72.87 | 6.80<br>6.79 | 9.45<br>9.59 |
| **11** | 2.65 (s, 4H), 6.88--6.78 (m, 2H), 7.36--7.22 (m, 4H), 7.62--7.53 (m, 2H), 10.23 (s, 2H) | 63.15<br>62.88 | 4.64<br>4.49 | 9.21<br>9.02 |
| **12** | 2.62 (s, 4H), 7.15--7.05 (m, 4H), 7.63--7.53 (m, 4H), 10.05 (s, 2H) | 63.15<br>62.78 | 4.64<br>4,50 | 9.21<br>9.13 |
| **13** | 2.72 (s, 4H), 7.57 (t, J=8.2 Hz, 2H), 7.90--7.82 (m, 4H), 8.63 (t, J=2.1 Hz, 2H), 10.53 (s, 2H) | 53.63<br>53.22 | 3,94<br>3,96 | 15.64<br>15.78 |
| **14** | 2.12 (s, 6H), 2.14 (s, 6H), 2.58 (bs, 4H), 6.99 (d, J=8.2 Hz, 2H), 7.27 (dd, J=8.2, J=2.1 Hz, 2H), 7.34 (d, J=2.1Hz, 2H), 9.80 (s, 2H) | 74.05<br>73.84 | 7,46<br>7,37 | 8.63<br>8.77 |
| **16** | 0.85 (t, J=7.3 Hz, 6H), 1.33--1.18 (m, 4H), 1.55--1.42 (m, 4H), 2.52--2.45 (signal overlaped by solvent, 4H), 2.60 (s, 4H), 7.11--7.03 (m, 4H), 7.50--7.42 (m, 4H), 9.90 (s, 2H | 75.75<br>76.07 | 8.48<br>8.16 | 7.36<br>7.47 |
| **17** | 1.13 (d, J=6.9, 12H), 2.60 (s, 4H), 2.85--2.73 (m, 2H), 7.16--7.08 (m, 4H), 7.50--7.42 (m, 4H), 9.89 (s, 2H) | 74.97<br>74.93 | 8.01<br>8.03 | 7.97<br>7.97 |
| **18** | 0.72 (t, J=7.1 Hz, 6H), 1.13 (d, J=7.1 Hz, 6H), 1.57--1.40 (m, 2H), 2.60 (s, 4H), 7.11--7.05 (m, 4H), 7.50--7.44 (m, 4H), 9.91 (s, 2H) | 75.75<br>75.80 | 8.48<br>8.48 | 7.36<br>7.28 |
| **20** | 2.88 (s, 4H), 7.32--7.23 (m, 2H), 7.46--7.37 (m, 2H), 7.76--7.69 (m, 2H), 7.97--7.90 (m, 2H) | 56.53<br>56.55 | 3.69<br>3.87 | 14.65<br>14.88 |
| **21** | 1.95--1.81 (m, 2H), 2.36 (t, J=7.4 Hz, 4H), 7.35--7.29 (m, 4H), 7.64--7.57 (m, 4H), 10.05 (s, 2H) | 58.13<br>58.13 | 4.59<br>4.59 | 7.98<br>7.98 |
| **22** | 1.93--1.81 (m, 2H), 2.31 (t, J=7.4 Hz, 4H), 3.69 (s, 6H), 6.89--6.79 (m, 4H), 7.53--7.43 (m, 4H), 9.76 (s, 2H) | 66.65<br>66.93 | 6.48<br>6.45 | 8.18<br>8.24 |
| **27** | 1.63--1.55 (m, 4H),2.21 (s, 6H), 2.33--2.24 (m, 4H), 7.10--7.03 (m, 4H), 7.48--7.41 (m, 4H), 9.79 (s, 2H) | 74.05<br>74.21 | 7.46<br>7.52 | 8.63<br>8.66 |
| **29** | 1.70--1.60 (m, 4H), 2.43--2.33 (m, 4H), 7.57 (t, J=8.1, 2H), 7.91--7.83 (m, 4H), 8.63 (t, J=2.1 Hz, 2H), 10.41 (s, 2H) | 55.96<br>55.80 | 4.70<br>4.73 | 14.50<br>14.67 |
| **30** | 1.65--1.55 (m, 4H), 2.38--2.27 (m, 4H), 7.10--7.03 (m, 2H), 7.30 (t, J=8.1, 2H), 7.45--7.38 (m, 2H), 7.80 (t, J=1.9, 2H), 10.09 (s, 2H) | 59.19<br>59.14 | 4.97<br>4.97 | 7.67<br>7.90 |
| **32** | 1.65--1.54 (m, 4H), 2.44--2.33 (m, 4H), 3.79 (s, 6H), 6.93--6.82 (m, 2H), 7.10--6.96 (m, 4H), 7.97--7.84 (m, 2H), 9.03 (s, 2H) | 67.40<br>67.49 | 6.79<br>6.68 | 7.86<br>7.79 |
| **33** | 1.64--1.52 (m, 4H), 2.33--2.20 (m, 4H), 3.69 (s, 6H), 6.89--6.79 (m, 4H), 7.52--7.42 (m, 4H), 9.74 (s, 2H) | 67.40<br>67.62 | 6.79<br>6.78 | 7.86<br>7.88 |
| **34** | 1.65--1.55 (m, 4H), 2.37--2.26 (m, 4H), 7.35--7.29 (m, 4H), 7.63--7.56 (m, 4H), 10.03 (s, 2H) | 59.19<br>58.91 | 4.97<br>4.82 | 7.67<br>7.79 |
| **35** | 1.28 (t, J=7.1 Hz, 6H), 1.68--1.57 (m, 4H), 2.42--2.31 (m, 4H), 4.25 (q, J=14.2, J=7.1 Hz, 4H), 7.74--7.67 (m, 4H), 7.91--7.84 (m, 4H), 10.25 (s, 2H) | 65.44<br>65.70 | 6.41<br>6.33 | 6.36<br>6.17 |
| **37** | 1.36--1.25 (m, 4H), 1.64--1.49 (m, 4H), 2.27 (t, J=7.4, 4H), 7.35--7.27 (m, 4H), 7.63--7.55 (m, 4H), 10.00 (s, 2H) | 61.11<br>61.08 | 5.60<br>5.64 | 7.12<br>7.12 |
| **40** | 1.34--1.24 (m, 4H), 1.64--1.48 (m, 4H), 2.24 (t, J=7.4, 4H), 3.68 (s, 6H), 6.87--6.79 (m, 4H), 7.50--7.42 (m, 4H), 9.72 (s, 2H) | 68.78<br>68.60 | 7.24<br>7.15 | 7.29<br>7.19 |
| **43** | 1.32--1.22 (m, 6H), 1.63--1.48 (m, 4H), 2.27 (t, J=7.3 Hz, 4H), 7.34--7.28 (m, 4H), 7.62--7.55 (m, 4H), 10.00 (s, 2H) | 61.92<br>62.06 | 5.94<br>5.85 | 6.88<br>6.99 |
| **46** | 1.35--1.20 (m, 6H), 1.63--1.47 (m, 4H), 2.23 (t, J=7.3 Hz, 4H), 3.68 (s, 6H), 6.88--6.80 (m, 4H), 7.50--7.42 (m, 4H), 9.71 (s, 2H) | 69.32<br>69.61 | 7.59<br>7.73 | 7.03<br>7.07 |

**Table 3.** Antimycobacterial activity of the active compounds expressed as MIC (μmol $dm^{-3}$). (m = number of methylene groups in the connecting chain of the compounds)

| Compd. | m | R | MIC (μmol $dm^{-3}$) | | | |
|---|---|---|---|---|---|---|
| | | | *M. tuberculosis* | *M. avium* | *M. kansasii* | *M. fortuitum* |
| **3** | 0 | 4-$NO_2$ | 37 | --[a] | --[a] | --[a] |
| **4** | 0 | 4-Br | 4.1 | --[a] | --[a] | --[a] |
| **6** | 2 | 3,4-$Cl_2$ | 250 | 250 | 500 | 500 |
| **7** | 2 | H | 500 | 500 | 500 | 500 |
| **12** | 2 | 4-F | 250 | 1000 | 1000 | 1000 |
| **14** | 2 | 3,4-$(CH_3)_2$ | 500 | >1000 | >1000 | >1000 |
| **15** | 2 | 3-Cl | 500 | >1000 | >1000 | >1000 |
| **16** | 2 | 4-$C_4H_9$ | 500 | 63 | >1000 | >1000 |
| **17** | 2 | 4-iso$C_3H_7$ | >1000 | 63 | >1000 | >1000 |
| **18** | 2 | 4-sec$C_4H_9$ | 500 | 63 | >1000 | >1000 |

a) not tested

**Table 4.** Inhibition of chlorophyll production in *Chlorella vulgaris* by N,N'-diarylalkanediamides (m = number of methylene groups in the connecting chain of the compounds; concentrations of compounds were constant, 75 μmol $dm^{-3}$)

| m | **Compound** % of inhibition | | | | |
|---|---|---|---|---|---|
| | H | 4-$CH_3$ | 4-$OCH_3$ | 4-Cl | 3,4-$Cl_2$ |
| 2 | **7** 22.8 | **10** 14.2 | **8** 30.8 | **9** 33.2 | **6** 19.8 |
| 3 | **23** 41.8 | **24** 26.2 | **22** 41.6 | **21** 34.3 | **25** 28.7 |
| 4 | **28** 41.0 | **27** 37.7 | **33** 46.0 | **34** 41.4 | **31** 33.5 |
| 6 | **38** 44.2 | **39** 41.4 | **40** 57.9 | **37** 45.4 | **36** 22.6 |
| 7 | **44** 48.5 | **45** 37.9 | **46** 53.9 | **43** 45.5 | **42** 15.1 |

**Table 5.** Inhibition of chlorophyll production in *Chlorella vulgaris* by N,N'-diarylbutanediamides (m = 2; concentrations of compounds were constant, 75 μmol $dm^{-3}$)

| Compound | R | % of inhibition | Compound | R | % of inhibition |
|---|---|---|---|---|---|
| **7** | H | 22.8 | **5** | 4-Br | 27.1 |
| **11** | 3-F | 25.2 | **17** | 4-iso$C_3H_7$ | 36.5 |
| **15** | 3-Cl | 43.6 | **16** | 4-$C_4H_9$ | 32.6 |
| **13** | 3-$NO_2$ | 25.4 | **18** | 4-sec$C_4H_9$ | 36.5 |
| **12** | 4-F | 35.4 | **19** | 4-$N(CH_3)_2$ | 28.8 |
| **9** | 4-Cl | 33.2 | **6** | 3,4-$Cl_2$ | 19.8 |
| **10** | 4-$CH_3$ | 14.2 | **14** | 3,4-$(CH_3)_2$ | 26.7 |
| **8** | 4-$OCH_3$ | 30.8 | | | |

**Experimental**

*General*

The melting points were determined on a Kofler block and are uncorrected. The samples for elemental analysis and biological tests were dried over $P_2O_5$ at 61 °C and 66 Pa for 24 h. Elemental analyses were performed on a C,H,N,S analyzer (FISONS AE 1110, Milano). The IR spectra were measured in KBr on a Nicolet Impact 400 apparatus. The purity of the compounds was checked by TLC. TLC was performed using petroleum ether : ethyl acetate (1:1), and chloroform : aceton (9:1) as the mobile phases. $^1$H NMR spectra of new compounds were recorded for DMSO-$d_6$ solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer (operating at 300 MHz). Chemical shifts were recorded as delta values in parts per million (ppm), and were indirectly referenced to tetramethylsilane via the solvent signal (2.49 for $^1$H).

*Synthesis of acyl chlorides*

*Succinyl choride*
Phosphorus pentachloride (328 mmol) was added to a finely powdered succinic acid (400 mmol), and the mixture was heated at 120°C for 5 hours. Phosphorus oxychloride was then distilled off, and the crude product was purified by vacuum distillation (yield 74.5 %, b. p. 104-105 °C / 3.33 kPa, lit. [17] b. p. 103--104 °C / 3.33 kPa).

*Suberyl choride*
Suberic acid (287 mmol) was heated with thionyl chloride (1260 mmol) at 120 °C for 4 hours. After the removal of the excess reagent by distillation, the crude product was purified by distillation at reduced pressure (yield 69.20 %, b. p. 145°C / 1.33 kPa, lit. b. p. [18] 149--150 °C / 1.60 kPa). The same protocol was used for the preparation of the remaining acyl chlorides (yield; b. p.; b. p. [ref]): glutaryl chloride (90.7 %; 104 °C / 2.53 kPa; 100 °C / 2.00 kPa [19]); adipoyl chloride (81.2 %; 130--132 °C / 2.40 kPa; 130--132 °C / 2.40 kPa [20]); azelayl chloride (71.4 %; 162 °C / 1.20 kPa; 165 °C / 1.73 kPa [20]).

*Synthesis of N,N'-diarylalkanediamides*

*N,N'-diarylethanediamides (**1--4**)*
Sodium (1 g) was dissolved in absolute ethanol (100 ml), 3-methylaniline (300 mmol) followed by diethyl oxalate (150 mmol) were added to the solution, and the reaction mixture was heated at reflux for 1 hour. The crude product was filtered off, washed with water, and crystallized from ethanol. The yields, melting points, and IR spectral data of compounds **1--4** are given in Table 1.

*Other N,N'-diarylalkanediamides*

Succinyl chloride (16 mmol) was added dropwise to a stirred solution of 4-methylaniline (32 mmol) in pyridine (20 ml) at 0°C. The reaction mixture was allowed to stand at ambient temperature for 24 hours, and then poured into water (100 ml). The product was filtered off and crystallized from ethanol. The remaining amides were prepared in an analogous fashion. The yields, melting points, IR, and NMR spectral data as well as elemental analyses are summarised in Table 1 and Table 2.

*Biological assays*

*Antimycobacterial activity*
Antimycobacterial evaluation of N,N'-diarylalkanediamides (m = 0, 3, 4, 6, 7) was carried out in a semisynthetic liquid protein-containing Sula medium (IMUNA, Sarisske Michalany), buffered to pH 7.2. The following mycobacterial strains were used: *Mycobacterium tuberculosis* $H_{37}$*Rv*, *M. kansasii PKG8, M. avium No. 80/72* and *M. fortuitum 1021*. The MICs were determined after 14 days of incubation at 37 °C. The compounds were added to the medium in a dimethyl sulfoxide solution. The final concentrations were 1000; 333; 111; 37; 12.3; and 4.1 μmol $dm^{-3}$.

Antimycobacterial activity of butanediamides (m = 2) was determined in Sula semisynthetic medium (SEVAC, Prague). For evaluation of their *in vitro* antimycobacterial activity, the following strains were used: *M. tuberculosis* CNCTC My 1/47, *M. kansasii* CNCTC My 235/80, *M. avium* CNCTC My 80/72 and *M. fortuitum* CNCTC My 187/73 from the National Institute of Public Health, Prague. The compounds were added to the medium in dimethyl sulfoxide solutions. The final concentrations were 1000; 500; 250; 125; 62; 31; 16; 8; 4 μmol $dm^{-3}$. The minimum inhibitory concentrations were determined after incubation at 37 °C for 21 days.

MIC was the lowest concentration of a substance (on the above-stated concentration scale), at which inhibition of the growth of mycobacteria occurred. The compound is considered as active, when its MIC is lower than 1000 μmol $dm^{-3}$.

*Antialgal activity*
The inhibitory effect of selected N,N'-diarylalkanediamides on algal chlorophyll (Chl) production has been investigated in statically cultivated *Chlorella vulgaris* (96 hours; photoperiod 16 h light / 8 h dark; illumination: 5 000 lx; pH = 7.2; Chl content at the beginning of cultivation: 0.5 mg $dm^{-3}$) at room temperature and a constant inhibitor concentration 75 μmol $dm^{-3}$ according to Kralova et al. [21]. Chl content of algal suspensions was determined spectrophotometrically following its extraction into N,N-dimethylformamide according to Inskeep and Bloom [22]. The compounds were dissolved in dimethyl sulfoxide (DMSO) as their solubility in water was insufficient. The antialgal activity was expressed as the percentage of inhibition of the untreated control.

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