20, 96928-72-2; **20** free acid, 96928-73-3; **21**, 96928-74-4; **21** free acid, 96928-75-5; **22**, 96948-40-2; **22** free acid, 96928-76-6; **23**, 96914-93-1; **23** free acid, 96914-94-2; **24**, 96914-95-3; **24** free acid, 96914-96-4; **25**, 676-98-2; **26**, 96914-97-5; **27**, 96914-98-6; **27** free acid, 96914-99-7; C_6H_5COCl, 98-88-4; $C_6H_5CH_2COCl$, 103-80-0; $P(OEt)_3$, 122-52-1; PheMetOMe·HCl, 40290-65-1; $NaP(O)(OBzl)_2$, 72305-26-1; PheLeuOMe·HCl, 38155-45-2; PheLeuOBzl·HCl, 73994-87-3; BocPheMetOMe, 40290-63-9; BocPheLeuOMe, 64152-76-7; BocPheLeuOBzl, 74193-68-3; CbzTyr(OBzl)GlyOMe, 16677-35-3; CbzTyr(OBzl)-D-AlaOMe, 65806-45-3; CbzTyr-(OBzl)Gly, 51952-34-2; CbzTyr(OBzl)-D-Ala, 96915-00-3; $PhCH_2CH_2COCl$, 645-45-4; dibenzyl phosphite, 17176-77-1; 3-hydroxypropanenitrile, 109-78-4; E.C. 3.4.24.11, 82707-54-8; E.C. 3.4.15.1, 9015-82-1.

N-(Aminoalkyl)imide Antineoplastic Agents. Synthesis and Biological Activity

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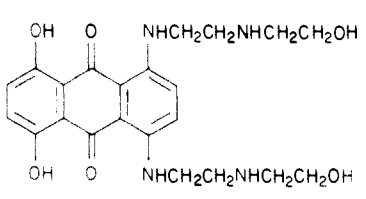
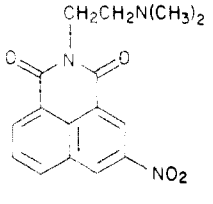
The similarity of the side-chain characteristics of 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-anthraquinone (DHAQ), discovered by us in 1978, and those of the N-substituted imides of 3-nitro-1,8-naphthalic acid, discovered by other investigators recently, led us to conduct a systematic study on the *N*-(aminoalkyl)-substituted derivatives of a variety of imides. Areas of study included (a) selection of the ring system, (b) modification of the side chain, (c) substitution on certain chosen ring systems, and (d) combinations of the aforementioned variants. Preliminary biological activity screening indicated that *N*-(dialkylaminoethyl)imides of the 3,6-dinitro- and 3,6-diamino-1,8-naphthalic acid system possessed prominent antileukemia and antimelanoma activity in both in vitro and in vivo experimental tumor systems.

Since the discovery of the outstanding anticancer activity of 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)-amino]ethyl]amino]anthraquinone, DHAQ (1), in 1978,[1-3] we have been interested in introducing its side-chain characteristics to other ring systems[4,5] as well as in the modification of the side chain.[1,5-8] It was found that the basic nitrogen atom in the middle of the side chain of DHAQ is of vital importance to its antineoplastic activity since replacement of this atom by a sulfur,[1] a carbon,[1,5] or an oxygen atom[8] resulted in a total loss of activity. Modification of the terminal chain substituents attached to the pertinent nitrogen atom by other nonbulky substituents, on the other hand, still retains the antineoplastic activity. For example, substitution of the 2-[(2-hydroxyethyl)amino]ethylamine side chain by the 2-(dimethylamino)ethylamine side chain of DHAQ does not nullify the original activity,[1] although compounds containing the former side chain seem to be somewhat superior to the latter in the anthraquinone series.[1,4]

It is, therefore, of interest to note the reported antineoplastic activity of Mitonafide (2) and three related



1



2

N-substituted imides of 3-nitro-1,8-naphthalic acid against mouse Ehrlich ascites and rat Yoshida carcinoma as well as in vitro cytotoxicity against the HeLa cells.[9-11] These naphthalimides did not inhibit the protein synthesis but did inhibit DNA and RNA synthesis,[11] bound to the double-helical DNA by intercalation,[12] inhibited the incorporation of DNA precursor into the acid-insoluble fraction of cultured cells,[13] induced DNA strand break, and increased the frequency of sister chromatid exchanges and chromosome aberration.[14]

The reported structure–activity characteristics of the side chains of these naphthalimides bear a striking resemblance to that of our anthraquinone derivatives. For example, these investigators stated[9-11] that (a) the basic nitrogen atom on the side chain is essential to their activity, (b) substitution of the nitrogen atom by an oxygen, a sulfur, or a carbon atom resulted in inactive compounds, and (c) the activity is maximal when the nitrogen atom is separated from the ring nitrogen by two methylene units.

1,8-Naphthalimides are not the only imides that possess antineoplastic activity. Among the N-unsubstituted imides, the inhibitory activity of glutarimide antibiotics such as cycloheximide (**3a**) and Streptovitacin (**3b**) against a number of experimental animal tumors is well-known.[15-19]

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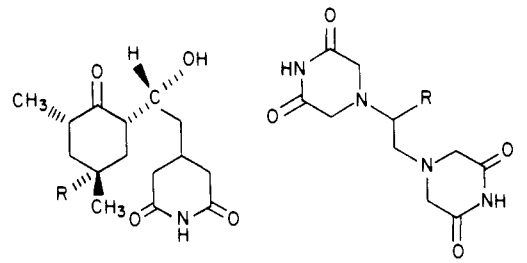
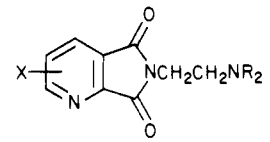


3a, R = H
b, R = OH

4a, R = CH_3
b, R = H



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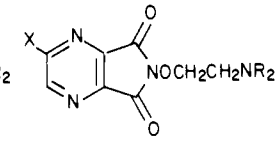

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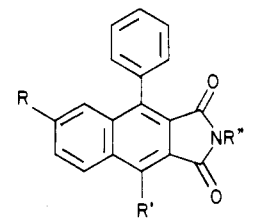

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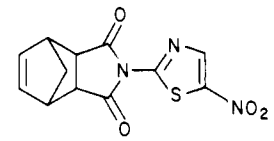

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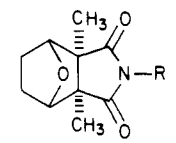


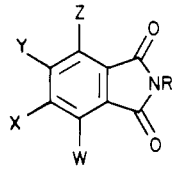
9

ICRF-159 (**4a**) and ICRF-154 (**4b**) demonstrated activity against acute lymphocytic leukemia and lymphoma.[20-24] Several quinolinic acid imides (**5**)[25] and related pyrazine derivatives (**6**)[26] as well as imides of 1-substituted 4-arylnaphthalene-2,3-dicarboxylic acids of type **7**[27] were reported to have antitumor activity. A 3,6-*endo*-methylene-4-cyclohexene-1,2-dicarboximide derivative **8** was reported to show considerable activity against Lewis lung carcinoma.[28] Derivatives of cantharidine of type **9** (R = OH, CH_3, $CH_2CH{=}CH_2$) were found to be effective against ascites mouse liver carcinoma and ascites reticulosarcoma.[29]

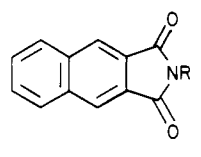
On the basis of the preceding information and the low solubility of Mitonafide and related compounds, a systematic study on the *N*-(aminoalkyl)-substituted derivatives of a variety of imides were designed and synthesized. Our areas of study include (a) variation of the ring system, (b) modification of the side chain, (c) substitution on certain chosen ring systems, and (d) combination of the aforementioned variants.

Chemistry

Variation of the Ring System. Treatment of *N,N*-(dimethylamino)ethylamine with an appropriate acid anhydride followed by ring cyclization of the intermediate carboxylic acid amide yielded the desired N-substituted imides. These include the phthalimides (**10**), 2,3-



10a: W, X, Y, Z = H
b: W = NO_2; X, Y, Z = H
c: X = NO_2; W, Y, Z = H
d: X = Cl; W, Y, Z = H
e: W, X, Y, Z = Cl
f: W, X, Y, Z = Br



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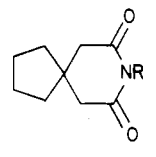

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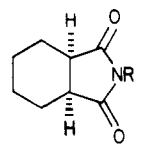

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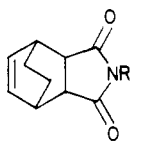

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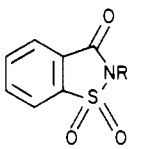

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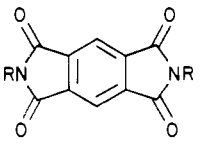

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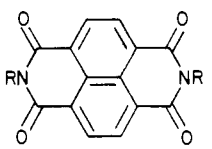

17

R = $(CH_2)_2N(CH_3)_2$

naphthalimide (**11**), 3,3-tetramethyleneglutarimide (**12**), *cis*-1,2-cyclohexanedicarboximide (**13**), *endo*-bicyclo-[2.2.2]oct-5-ene-2,3-dicarboximide (**14**), sulfobenzimide (**15**), 1,2:4,5-benzenetetracarboximide (**16**), and 1,8:4,5-naphthalenetetracarboximides (**17**).

Modification of the Side Chain. Treatment of various substituted (alkylamino)ethylamines with 3-nitro-1,8-naphthalic anhydride in refluxing toluene yielded the desired cyclized products. Most of the target compounds were isolated as their hydrochloride salts for better solubility in water. (For a structure–activity relationship comparison, hydrochloride salts of several known imide derivatives were also prepared.) For the preparation of compound **19e**, which contains the 2-[(2-hydroxyethyl)-amino]ethyl side chain, 2-propanol was used as the reaction solvent since cyclization of the intermediate **18e** in toluene led to extensive decomposition.

Ring-Substituted 1,8-Naphthalimides Containing the 2-(Dimethylamino)ethyl Side Chain. 1,8-Naphthalic anhydrides with the ring substitutions 3-OH,[30,31] 3-SO_3H,[31] 4-Cl,[30] 4-Br-3-OH,[31] 3,6-$(NO_2)_2$,[32,33] and 3,6-$(SO_3H)_2$[34] were all prepared from 1,8-naphthalic anhydride by literature procedures. 4,5-Dichloro-1,8-naphthalic anhydride was prepared by chromic oxidation of 5,6-dichloroacenaphthene.[35] Treatment of these an-

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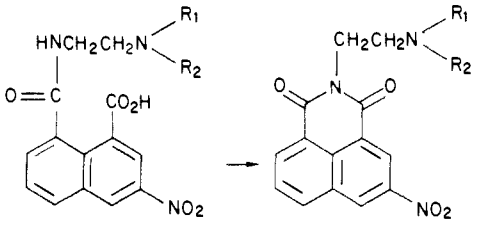
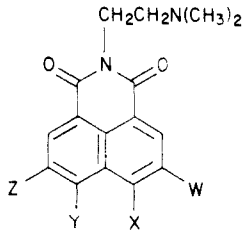


18 19

a. R_1 = H, R_2 = CH_3 · HCl
b. R_1 = H, R_2 = C_2H_5 · HCl
c. R_1, R_2 = CH_3 · HCl
d. R_1, R_2 = C_2H_5 · HCl
e. R_1 = H, R_2 = $(CH_2)_2OH$
f. R_1 + R_2 = $(CH_2)_4$ · HCl
g. R_1 + R_2 = $(CH_2)_5$ · HCl
h. R_1 + R_2 = $(CH_2)_2O(CH_2)_2$ · HCl
i. R_1 + R_2 = $(CH_2)_2NH(CH_2)_2$ · HCl

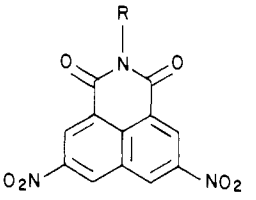
hydrides with [2-(dimethylamino)ethyl]amine under the aforementioned reaction conditions gave the desired target compounds **20a–f**. The ring-unsubstituted compound **20g**



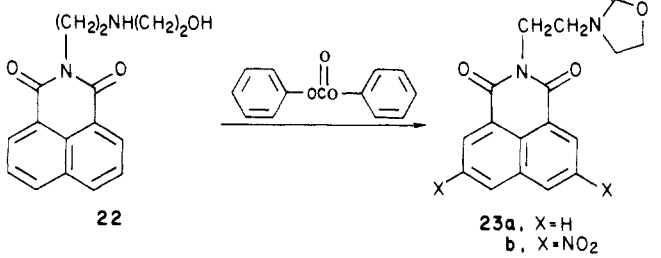
20a: W = OH; X, Y, Z = H
b: X = Cl; W, Y, Z = H
c: W = OH; X = Br; Y, Z = H
d: W, Z = OH; X, Y = H
e: X, Y = Cl; W, Z = H
f: W, Z = NO_2; X, Y = H
g: W, X, Y, Z = H
h: X = OCH_3; W, Y, Z = H
i: X = OH; W, Y, Z = H
j: X, Y = OCH_3; W, Z = H
k: X, Y = OH; W, Z = H
l: W = NH_2; X, Y, Z = H
m: W, Z = NH_2; X, Y = H

was also prepared for a comparison of activity with the substituted analogues. Other target compounds **20h–m** were prepared by converting the ring-substituted functional groups of substituted naphthalimides. Thus, the 4-methoxy derivative **20h** was prepared by treating the 4-chloro compound **20b**, and the 4-hydroxy derivative **20i** was obtained from **20h** by the treatment with hydroiodic acid. In a similar manner, the dimethoxy (**20j**) and the dihydroxy (**20k**) derivatives were prepared from the corresponding dichloro compound **20e**. The amino derivatives **20l** and **20m** were prepared by the reduction of the corresponding nitro compounds.

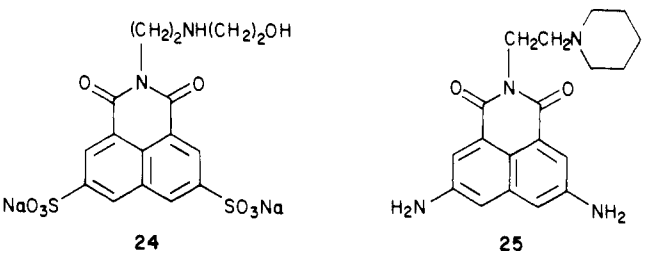
Combined Modifications. The initial screening results of the dinitro compound **20f** encouraged us to prepare additional derivatives **21a–f** of 3,6-dinitro-1,8-naphthalimide. The *N*-[2-[(2-hydroxyethyl)amino]ethyl] derivative **21f** was originally planned to be synthesized from *N*-[2-[(2-hydroxyethyl)amino]ethyl]-1,8-naphthalimide (**22**) via the oxazolidinone intermediates **23a** and **23b** in order to prevent the possible attack of the [(2-hydroxyethyl)amino]ethyl side chain under the nitration conditions. However, the dinitrated oxazolidinone compound **23b** failed to yield the desired **21f** by a variety of agents commonly used for the opening of the oxazolidinone ring. Compound **21f** was eventually obtained by



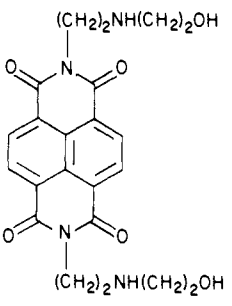
21a, R = $(CH_2)_2N(C_2H_5)_2$
b, R = $(CH_2)_3N(CH_3)_2$
c, R = $(CH_2)_2N(CH_2)_4$
d, R = $(CH_2)_2N(CH_2)_5$
e, R = $(CH_2)_2N$–O
f, R = $(CH_2)_2NH(CH_2)_2OH$
g, R =
h, R =
i, R =



22 **23a**, X = H; **b**, X = NO_2



24 **25**



26

direct and careful nitration of **22**. The dinitronaphthalimides containing a thiazole (**21g,h**) or a thiadiazole ring (**21i**) were prepared on the basis of the claims that compound **8** as well as the thiazole derivative of 1,8-naphthalimide showed considerable activity against Lewis lung carcinoma.[28] For a comparison of structure and activity, the *N*-[2-[(2-hydroxyethyl)amino]ethyl] derivative of the 3,6-disulfonaphthalimide **24**, the 2-(1-piperidinyl)-ethyl derivative of the 3,6-diaminonaphthalimide **25**, and the bis[[(2-hydroxyethyl)amino]ethyl] analogue of **17** (compound **26**) were also prepared.

Although both the 3-nitro- and the 3,6-dinitronaphthalimide derivatives show similar ultraviolet absorption peaks at 268–273 and 330–340 nm, a characteristic infrared absorption peak at 780 cm^{-1} can be readily used to distinguish these compounds. The strong 780-cm^{-1} absorption peak (out-of-plane bending or deformation

(35) Kasai, T.; Himeno, K. *Kogyo Kagaku Zasshi* **1969**, *72*, 1128.

vibration) indicates the presence of three adjacent aromatic hydrogen atoms. This peak is a unique signal for either ring-unsubstituted or monosubstituted naphthalimides. Disappearance of this peak from the IR spectrum, therefore, indicates the dinitro substitution on both rings. Furthermore, the NMR spectra of 3,6-dinitro derivatives show two singlets at δ 9.22 and 9.75 and again substantiate the assigned structure. The 3,6-diamino derivatives show a characteristic UV absorption peak at 430–450 nm. Their IR spectra also show the disappearance of the nitro peak at 1540 cm^{-1}.

Biological Activity

N-(Aminoalkyl)imides and related compounds were screened against P388 leukemia and B16 melanoma in vivo and against L1210 leukemia and human colon adenocarcinoma in vitro. The results are provided in Table I. In general, there is a good correlation between dose potency in in vivo and in vitro activity. The following is a summary of the structure–activity relationship.

(1) None of the [2-(dimethylamino)ethyl]amino derivatives of phthalic (compounds **10a–f**), 2,3-naphthalic (compound **11**), 3,3-tetramethyleneglutaric (compound **12**), *cis*-1,2-cyclohexanedicarboxylic (compound **13**), *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic (compound **14**), sulfobenzoic (compound **15**), 1,2:4,5-benzenetetracarboxylic (**16**), and 1,8:4,5-naphthalenetetracarboxylic anhydrides (**17**) displayed any in vivo or in vitro activity against the experimental systems tested.

(2) The (dialkylamino)ethyl and 2-(hydroxyamino)ethyl derivatives of ring-*un*substituted 1,8-naphthalic imides (compounds **20g** and **22**) possessed borderline activity against P388 leukemia but were inactive in the in vitro assays.

(3) Ring substitution with a chloro, hydroxy, or a methoxy group at C-4 or C-4 and C-5 positions of *N*-[(alkylamino)ethyl]imides results in compounds with no activity against P388 leukemia. This information, coupled with the negative screening resulting of compounds **17** and **26** (which can be considered as 4,5-disubstituted naphthalimides), signifies the rigid steric requirements of this region to the pertinent binding site in vivo before the antineoplastic action can be exercised.

(4) Antineoplastic activity of a nitro group substituted at C-3 of *N*-[(alkylamino)ethyl]imides has already been indicated.[9-11] It has now been found that substitution at C-3 with electron-donating groups such as NH_2 or OH also furnishes compounds with inhibitory activity against P388 leukemia. The potency of activity is actually increased with ring substitutions at both C-3 and C-6 (compare compounds **20a** vs. **20d**, **20l** vs. **20m**, and **19c** vs. **20f**). The dinitro- and the diamino-substituted compounds **20f**, **21d**, **25**, and **20m** possessed good inhibitory activity at comparatively lower dosages against both P388 leukemia and B16 melanoma.

(5) In accord with the structure–activity relationship observed in another series of compounds,[1] insertion of an additional methylene unit on the side chain between the two nitrogen atoms resulted in a reduction of activity (compare compound **20f** vs. compound **21b**). This observation was in total agreement with a recently reported computer-assisted structure–activity correlation study.[36]

(6) The sodium salt of the 3,6-disulfonaphthalimide derivative **24** was without in vivo or in vitro activity. Perhaps the extreme ionic character of this compound drastically modified the in vivo transport mechanism and failed to deliver it to the desired target site.

Conclusions

Our results indicate that the [2-(substituted amino)ethyl]amino fragment plays a prominent role with regard to the antineoplastic activity when it is attached to proper polycyclic ring systems (such as the anthraquinones or the naphthalimides). The steric requirements of the naphthalimide ring are rather strict, as substitutions at ring positions C-4 and/or C-5 afford only inactive compounds. Substitution at positions C-3 and/or C-6 with either electron-withdrawing groups such as NO_2 or electron-donating groups such as NH_2 or OH yields compounds with increased activity. Perhaps hydrogen-bonding formation or covalent interaction of these groups with pertinent biopolymer sites in vivo assist in the "anchoring" of these molecules to exert proper action. In this regard, groups with extreme ionic character such as SO_3Na cause a deleterious effect to the activity. The present study, along with previously published results, further signifies the importance of the presence of the amino nitrogen atom on the side chain to antineoplastic activity.

Only compounds with established or borderline activity in vivo against leukemia P388 are listed in Table I. Compounds possessing T/C values less than 120 against P388 *and* inactive in vitro tests are not listed, but their molecular formula and melting point (°C) are given as follows: **10a** ($C_{12}H_{14}N_2O_2$·HCl; mp 217–218), **10b** ($C_{12}H_{13}N_3O_4$·HCl; mp 290–291), **10c** ($C_{12}H_{13}N_3O_4$·HCl; mp 256–258), **10d** ($C_{12}H_{13}ClN_2O_2$·HCl; mp 263–264), **10e** ($C_{12}H_{10}Cl_4N_2O_2$·HCl; mp 310–312), **10f** ($C_{12}H_{10}Br_4N_2O_2$·HCl; mp 329–331), **11** ($C_{16}H_{16}N_2O_2$·HCl; mp 305–307), **12** ($C_{13}H_{22}N_2O_2$·HCl; mp 191–193), **13** ($C_{12}H_{20}N_2O_2$·HCl; mp 193–195), **14** ($C_{14}H_{20}N_2O_2$·HCl; mp 281–283), **15** ($C_{11}H_{14}N_2O_3S$·$C_2H_4O_2$; mp 228–230), **16** ($C_{18}H_{22}N_4O_4$·2HCl; mp 335 dec), **20c** ($C_{16}H_{15}BrN_2O_3$; mp 212–214), **20k** ($C_{16}H_{16}N_2O_4$·HI; mp 270–272), **21g** ($C_{15}H_6N_4O_6S$, mp 275–277), **21h** ($C_{18}H_{10}N_4O_8S$; mp 258–260), **23a** ($C_{17}H_{14}N_2O_4$·0.25H_2O; mp 226–228), **24** ($C_{16}H_{14}N_2Na_2O_9S_2$; mp >300), **26** ($C_{22}H_{24}N_4O_6$; mp 202–204). All compounds tested were up to toxic levels. The first dose listed for each compound is the maximum tolerated dose. For the sake of space saving, toxic doses are not listed.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained by those elements were within ±0.4% of the theoretical values.

General Preparation of *N*-(Aminoalkyl)imides. Unless otherwise stated, all imides reported were prepared by the following general procedure. To a stirred solution of 0.05 mol of the proper anhydride in 450 mL of toluene was added dropwise 0.06 mol of the appropriate (alkylamino)alkylamine in 50 mL of toluene in 5 min. The mixture was stirred at room temperature for 60 min and then heated under reflux while connected to a Dean–Stark trap for 2 h. After the theoretical amount of water was removed, the reaction mixture was cooled, washed successively with H_2O (2 × 120 mL), 5% $NaHCO_3$ (2 × 120 mL), and H_2O (2 × 120 mL), and then dried (Na_2SO_4). To the dried filtrate were added 50 mL of methanolic HCl (2.4 mmol/mL of MeOH) and 200 mL of Et_2O. The resulting solid was collected by filtration, washed with Et_2O, and then dried to give the HCl salt of the desired imide derivative. The analytical sample was obtained by recrystallization from a mixture of MeOH (or EtOH) and Et_2O. Yields of these imides were generally high: 75–85%. The following compounds were prepared by this general method and all analyzed correctly for C, H, N: **10a–f**, 11–16, 17[37] **19a–d**, 19f–i, **20a–g**, **21a–e**, **22**, and **24**.

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Table I. Antineoplastic and Cytotoxic Activities of *N*-(Aminoalkyl)imides

compd	mol formula	mp, °C	in vivo tests[a] P388, T/C, mg/kg	in vitro tests,[b] M L1210 (met. 2)	in vitro tests,[b] M human colon adenocarcinoma
17	$C_{22}H_{24}N_4O_4$	236–238	125 (6.25) 116 (3.12)		
19a	$C_{15}H_{13}N_3O_4 \cdot HCl$	271–273	177 (12.5) 139 (6.25) 129 (3.12)	2.66×10^{-7}	
19b	$C_{16}H_{15}N_3O_4 \cdot HCl$	277–279	162 (25) 129 (12.5) 123 (6.25)	7.00×10^{-7}	
19c	$C_{16}H_{15}N_3O_4 \cdot HCl$	309–311	164 (6.25) 138 (3.12) 121 (1.56)	1.51×10^{-7}	1.06×10^{-7}
19d	$C_{18}H_{19}N_3O_4 \cdot HCl$	255–257	149 (25) 120 (12.5)	1.37×10^{-6}	
19e	$C_{16}H_{15}N_3O_5 \cdot 0.5H_2O$	119–120	163 (25)[c,d] 151 (12.5) 137 (6.25)		3.88×10^{-7}
19f	$C_{18}H_{17}N_3O_4 \cdot HCl$	315–316	163 (12.5) 149 (6.25) 135 (3.13)	1.59×10^{-7}	
19g	$C_{19}H_{19}N_3O_4 \cdot HCl$	295–296	176 (50) 137 (25) 119 (12.5)	5.90×10^{-7}	
19h	$C_{18}H_{17}N_3O_5 \cdot HCl$	318–320	183 (100) 105 (50)	inactive	
19i	$C_{18}H_{18}N_4O_4 \cdot HCl$	305–307	136 (50) 129 (25) 116 (12.5)	1.38×10^{-6}	
20a	$C_{16}H_{16}N_2O_3$	210–212	142 (200) 115 (100)	1.64×10^{-6}	inactive
20b	$C_{16}H_{15}ClN_2O_2 \cdot HCl$	293–295	120 (100) 121 (50) 105 (25)	1.01×10^{-6}	
20d	$C_{16}H_{16}N_2O_4$	270–272	140 (400) 149 (200) 148 (100) 142 (50) 130 (25) 122 (12.5)	3.54×10^{-6}	inactive
20e	$C_{16}H_{14}Cl_2N_2O_2 \cdot HCl$	302–304	107 (25)	6.99×10^{-7}	
20f	$C_{16}H_{14}N_4O_6 \cdot HCl \cdot 1.5H_2O$	296–298	167 (3.12) 169 (3.00) 155 (1.56) 167 (1.50) 159 (0.75)	3.61×10^{-8}	4.13×10^{-8}
20g	$C_{16}H_{16}N_2O_2 \cdot HCl$	283–284	166 (100) 130 (50) 116 (25)	2.05×10^{-6}	
20h	$C_{17}H_{18}N_2O_3$	248–250	133 (200) 117 (100) 109 (50)	inactive	
20i	$C_{16}H_{16}N_2O_3 \cdot HI$	266–267	120 (400) 112 (200) 107 (100)	inactive	
20j	$C_{18}H_{20}N_2O_4 \cdot 0.5H_2O$	254–255	123 (200) 118 (100) 120 (50) 102 (25)	inactive	
20l	$C_{16}H_{17}N_3O_2$	169–171	177 (16)[d] 144 (8) 142 (4) 135 (2)		
20m	$C_{16}H_{18}N_4O_2 \cdot 3HCl$	295–297	188 (60) 163 (15) 163 (7.5) 125 (3.75)	3.37×10^{-7}	6.77×10^{-7}
21a	$C_{18}H_{18}N_4O_6 \cdot HCl$	252–254	215 (50) 207 (25) 141 (12.5)	3.47×10^{-7}	8.20×10^{-7}
21b	$C_{17}H_{16}N_4O_6 \cdot HCl$	295–297	154 (50) 129 (25) 113 (12.5)	1.42×10^{-6}	1.18×10^{-6}
21c	$C_{18}H_{16}N_4O_6 \cdot HCl$	294–295	136 (3.12) 138 (1.56) 126 (0.78) 117 (0.39)	8.29×10^{-8}	1.72×10^{-7}

Table I (Continued)

compd	mol formula	mp, °C	in vivo tests[a] P388, T/C, mg/kg	in vitro tests,[b] M L1210 (met. 2)	in vitro tests,[b] M human colon adenocarcinoma
21d	$C_{19}H_{18}N_4O_6$·HCl	264–266	247 (50)[d,e] 181 (25) 138 (12.5)	2.87×10^{-7}	5.39×10^{-7}
21e	$C_{18}H_{16}N_4O_7$·HCl	275–276	147 (50)[d] 131 (25) 112 (12.5)	1.13×10^{-6}	7.22×10^{-7}
21f	$C_{16}H_{14}N_4O_7$·0.5H_2SO_4	178–180	132 (240) 123 (120) 123 (60) 118 (30)	4.31×10^{-7}	1.25×10^{-6}
21i	$C_{14}H_5N_5O_6S$·0.25H_2O	178–180	137 (100)[d] 127 (50) 119 (25) 91 (12.5)	inactive	inactive
22	$C_{16}H_{16}N_2O_3$·HCl	278–279	120 (50) 102 (25)	2.05×10^{-6}	
23b	$C_{17}H_{12}N_4O_8$·H_2O	238–240	119 (120) 109 (60)	2.02×10^{-6}	inactive
25	$C_{19}H_{22}N_4O_2$·1.5HCl	258–260	191 (60)[f] 142 (30) 136 (15) 119 (12.5)	1.39×10^{-6}	1.27×10^{-6}

[a] These in vivo antineoplastic data are the results of screening performed under the auspices of the Screening Operations Section, Drug Evaluation Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. Ascites fluid implanted in BDF_1 mice. Route of drug administration and site of tumor inoculation: ip. Treatment schedule: q1d × 5. For the general screening procedure and data interpretation, cf.: Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.*, Part 3 **1972**, *3*, 1. "Screening Data Summary Interpretation and Outline of Current Screen", Instruction Booklet 14; Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute: Bethesda, MD, 1977. [b] These in vitro cytotoxic data are the results of testing performed at Warner-Lambert/Parke-Davis Co. at Ann Arbor, MI, by J. Besserer and Joan Shillis. Criteria for significant cytotoxic activity is 50% inhibition at a concentration of less than 10^{-6} M. [c] Against B-16 melanoma: T/C 216, 219, 174, 142 and 112 at 25, 12.5, 6.25, 3.13, and 1.56 mg/kg, respectively. [d] Treatment schedule: q1d × 9. [e] Against B-16 melanoma: T/C 156, 133, and 114 at 25, 12.5, and 6.25, respectively. [f] Against L-1210 leukemia: T/C 145, 125, and 119 at 50, 25, and 12.5 mg/kg, respectively.

***N*-[2-[(2-Hydroxyethyl)amino]ethyl]-3-nitro-1,8-naphthalimide (19e).** To a stirred solution of 20.2 g (0.2 mol) of 2-[(2-aminoethyl)amino]ethanol in 100 mL of 2-PrOH was slowly added 12.2 g (0.05 mol) of 3-nitro-1,8-naphthalenedicarboxylic acid anhydride in 15 min. The mixture was stirred for 2 h after the addition, and the resulting solid was collected by filtration. It was washed with 2-PrOH and dried to give 15.3 g of a crude product. Recrystallization from a mixture of 2-PrOH and H_2O gave 3.5 g (21% yield) of **19e** as tan-beige plates, mp 119–120 °C. Anal. ($C_{16}H_{15}N_3O_5$·0.5H_2O) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-4-methoxy-1,8-naphthalimide Hydrochloride (20h).** A mixture of 6.8 g (0.02 mol) of *N*-[2-(dimethylamino)ethyl]-4-chloro-1,8-naphthalimide hydrochloride and 3.5 g (0.06 mol) of $NaOCH_3$ in 180 mL of MeOH was heated in an autoclave at 150 °C for 18 h. The reaction mixture was cooled and filtered. The salt was washed with MeOH (2 × 20 mL). To the combined washings and filtrate was added, with stirring, 36 mL of methanolic HCl (2.3 mmol HCl/mL of MeOH) followed by 600 mL of Et_2O. After standing overnight, the solid product was collected by filtration, washed well with Et_2O, and dried to give 8.3 g of a crude white solid, mp 244–246 °C. Recrystallization from a mixture of 350 mL of EtOH and 150 mL of Et_2O gave 4.2 g (62.7% yield) of purified **20h**, mp 248–250 °C. UV: λ_{max}^{MeOH} 206 nm (log ε 4.14), 220 (4.08), 244 (4.37), 368 (4.00). Anal. ($C_{17}H_{18}N_2O_3$·HCl) C, H, N.

The corresponding 4,5-dimethoxy derivative **20j** was prepared from the 4,5-dichloro compound **20e** by essentially the same procedure (except that a 5 times excess of $NaOCH_3$ was used) in 38% yield; mp 254–255 °C. Anal. ($C_{18}H_{20}N_2O_4$·0.5H_2O) C, H, N.

***N*-[2-(Dimethylamino)ethyl]-4-hydroxy-1,8-naphthalimide Hydroiodide (20i).** A mixture of 1 g (0.0029 mol) of **20h** in 6 mL of Ac_2O and 4 mL of 47% HI was heated at 165–167 °C for 10 h. To the cooled reaction mixture was added 80 mL of Et_2O. The solid formed was collected by filtration, washed with Et_2O, and dried to give 0.83 g (62.7% yield) of the product, mp 264–266 °C. It gave a positive $FeCl_3$ test. The NMR spectrum of the product showed the absence of the OCH_3 group. An analytical sample was prepared by recrystallizing 0.3 g of the product from a mixture of EtOH and petroleum ether (bp 35–60 °C) to give 60 mg of white crystals, mp 266–267 °C. UV: λ_{max}^{MeOH} 204 nm (log ε 4.46), 220 (4.51), 242 (4.49), 378 (4.09), 450 (3.62). Anal. ($C_{16}H_{16}N_2O_3$·HI) C, H, N.

The corresponding 4,5-dihydroxy derivative **20k** was prepared in a similar manner from the 4,5-dimethoxy compound **20j** in 95% yield, mp 270–272 °C. Anal. ($C_{16}H_{16}N_2O_4$·HI) C, H, N.

3,6-Diamino-*N*-[2-(dimethylamino)ethyl]-1,8-naphthalimide (20m). Method A (Chemical Reduction). A mixture of 2 g (5 mmol) of **20f**, 5.9 g (5 mmol) of 20-mesh tin metal in 60 mL of H_2O, and 20 mL of concentrated HCl was heated at 90–100 °C for 2 h with stirring. After cooling, the insoluble solid was removed by filtration and washed with 2 × 30 mL of hot H_2O. The combined filtrate and washings were evaporated to dryness. The resulting residue was extracted with hot MeOH (8 × 50 mL). The MeOH extracts were evaporated to dryness, and the residue was triturated with 50 mL of Et_2O and filtered and the solid washed with Et_2O. The resulting hygroscopic solid was recrystallized from 150 mL of EtOH to give 0.4 g of the tin complex of the HCl salt of the diamino compound, mp 190–193 °C. An additional 0.5 g of product was obtained by concentration of the mother liquor. The total yield was 30%. UV: λ_{max}^{MeOH} 250 nm (log ε 4.66), 273 (4.31), 435 (4.09). Anal. ($C_{16}H_{18}N_4O_2$·$SnCl_2$·3HCl) C, H, N.

Method B (Catalytic Reduction). A mixture of 2 g (5 mmol) of **20f** and 350 mg of 10% Pd–C in 120 mL of H_2O was hydrogenated at room temperature under 40 psi of H_2. The theoretical amount of H_2 was absorbed after 1 h. To the mixture was added 3 mL of concentrated HCl. The mixture was filtered, and the filtrate was evaporated under reduced pressure to dryness. The residue was triturated with 30 mL of EtOH, and the solid was collected by filtration. It was washed with Et_2O (5 × 10 mL) and dried to give 2.1 g (95% yield) of the diamino compound. Recrystallization from 150 mL of MeOH gave 0.7 g (31.7% yield) of the purified product, mp 295–297 °C. UV: λ_{max}^{MeOH} 250 nm (log ε 4.57), 275 (4.25), 430 (3.96) 445 (3.68). Anal. ($C_{16}H_{18}N_4O_2$·3HCl) C, H, N.

The corresponding piperidinylethyl derivative **25** was prepared in a similar manner from the dinitro compound **21d**, mp 258–260 °C (69% yield). UV: λ_{max}^{MeOH} 250 nm (log ϵ 4.51), 275 (4.19), 430 (3.96), 445 (3.93). Anal. ($C_{19}H_{22}N_4O_2 \cdot 1.5HCl$) C, H, N. Mass spectrum: m/e 338 (M^+).

3,6-Dinitro-*N*-[2-[(2-hydroxyethyl)amino]ethyl]-1,8-naphthalimide Hemisulfate (21f). A mixture of 5.9 g (0.02 mol) of **22** in 28 mL of concentrated H_2SO_4 was stirred for 3 h in an ice bath until a solution was formed. To the solution was added 10 mL of 70% HNO_3 in 30 min. The temperature throughout the addition was kept below 20 °C. The mixture was stirred at 45–50 °C for 1 h and then poured onto 150 g of crushed ice with vigorous stirring. It was then carefully neutralized with 83 g (0.6 mol) of K_2CO_3 in 300 mL of H_2O. The resulting brown precipitate was collected by filtration, washed with H_2O (3 × 20 mL), and dried to give a crude solid product that contained much inorganic salt. The solid was boiled with 200 mL of dimethylacetamide, the insoluble salts were removed by filtration, and to the filtrate was added a solution of 60 mL of concentrated HCl in 300 mL of H_2O. After overnight cooling, the crystallized product was collected by filtration, washed with H_2O, and dried to give 3 g (35.5% yield) of **21f**, mp 178–180 °C. UV: λ_{max}^{MeOH} 208 nm (log ϵ 4.47), 240 (4.37), 273 (4.43), 335 (3.97). Anal. ($C_{16}H_{14}N_4O_7 \cdot 0.5H_2SO_4$) C, H, N.

3,6-Dinitro-*N*-(2-thiazolyl)-1,8-naphthalimide (21g). A mixture of 2.9 g (0.01 mol) of 3,6-dinitro-1,8-naphthalic anhydride and 200 mL of toluene was azeotropically refluxed for 2 h. The solution was cooled to room temperature. To this was added a hot, filtered solution of 1.5 g (0.015 mol) of 2-aminothiazole dissolved in 100 mL of hot toluene (the filtering funnel was rinsed with 50 mL of hot toluene and added to the reaction mixture). The resulting mixture was stirred at room temperature for 10 min and then azeotropically refluxed for 1 h (0.25 mL of H_2O was collected). The reaction mixture was cooled overnight; the separated crystalline product was collected by filtration, washed with Et_2O (2 × 20 mL), and dried to give 2.9 g of the product, mp 274–276 °C. The mother liquor was washed successively with H_2O (3 × 30 mL), 5% $NaHCO_3$ (2 × 25 mL), and H_2O (3 × 30 mL), dried (Na_2SO_4), and evaporated to yield another 0.4 g of the product, mp 275–277 °C (total yield was 89%). An analytical sample was obtained by recrystallization from toluene as light yellow crystals, mp 275–277 °C. UV: λ_{max}^{MeOH} 206 nm (log ϵ 4.49), 267 (4.65), 320 (3.97), 332 (3.99). Anal. ($C_{15}H_6N_4O_6S$) C, H, N.

Compounds **21h** (mp 258–260 °C) and **21i** (mp 178–180 °C) were prepared in a similar manner from the appropriate heterocyclic compounds. Anal. for **21h** ($C_{18}H_{10}N_4O_8S$) C, H, N. For **21i** ($C_{14}H_5N_5O_6S \cdot 0.25H_2O$) C, H, N.

[2-(2-Oxo-3-oxazolidinyl)ethyl]-1*H*-benz[*d*,*e*]isoquinoline-1,3(2*H*)-dione (23a). A mixture of 1.42 g (0.005 mol) of *N*-[2-[(2-hydroxyethyl)amino]ethyl]-1,8-naphthalimide (**22**) and 4.5 g (0.02 mol) of diphenyl carbonate was heated at 180–190 °C for 30 min. The resulting clear brown solution was cooled and, with stirring, was diluted with 50 mL of Et_2O. The solid that formed was collected by filtration, washed with ether, and dried to give 1.2 g (77.4% yield) of the cyclized product, mp 225–228 °C. An analytical sample was prepared by recrystallizing 0.35 g of the solid from 100 mL of EtOH. The purified compound, 0.25 g, was isolated as white needles, mp 226–228 °C. λ_{max}^{MeOH} 215 nm (log ϵ 4.32), 235 (4.62), 335 (4.13), 345 (4.11). Anal. ($C_{17}H_{14}N_2O_4 \cdot 0.25H_2O$) C, H, N.

5,8-Dinitro[2-(2-oxo-3-oxazolidinyl)ethyl]-1*H*-benz[*d*,*e*]isoquinoline-1,3(2*H*)-dione (23b). To 9 g (0.029 mol) of powdered **23a** stirred rapidly in an ice bath was added dropwise 30 mL of concentrated H_2SO_4. Stirring was continued until all solids dissolved (ca. 40 min, the entire operation was conducted in the absence of moisture). To the resulting solution kept at 0–5 °C was added dropwise 10 mL of 70% HNO_3 (9.8 g, 0.155 mol). After the addition was complete, which took 45 min, the solution was stirred in the ice bath for 3 h and at room temperature for 15 min and then was poured into 400 mL of ice water with vigorous stirring. The resulting solid was collected by filtration, washed with H_2O (3 × 5 mL), and dried at room temperature. It was suspended and stirred twice in Et_2O (2 × 100 mL) and the ethereal solution discarded. The crude product, mp 110–115 °C, which still contained many impurities including the mononitro derivatives, was purified as follows: It was boiled with 100 mL of EtOH. Most of the impurities dissolved in this fraction of EtOH and were removed by filtration. The insoluble portion, which contained mostly the desired product, was recrystallized from 500 mL of EtOH to give 6.4 g (53.1% yield) of **23b**, mp 238–240 °C. UV: λ_{max}^{MeOH} 206 nm (log ϵ 4.37), 269 (4.55), 330 (3.88). Anal. ($C_{17}H_{12}N_4O_8 \cdot H_2O$) C, H, N.

***N*,*N*'-Bis[2-[(2-hydroxyethyl)amino]ethyl]-1,4:5,8-naphthalenetetracarboximide (26).** To a stirred solution of 12.5 g (0.047 mol) of 1,4,5,8-naphthalenetetracarboxylic acid anhydride in 135 mL of 2-PrOH was added 19.5 g (0.187 mole of 2-[(2-aminoethyl)amino]ethanol. The mixture was refluxed with stirring for 14 h and cooled. The resulting solid product was collected by filtration, washed with anhydrous Et_2O, and dried to give 15 g of light brown powder, mp 195–197 °C. Recrystallization from aqueous EtOH gave 6.6 g (32.3% yield) of purified material, mp 202–204 °C. Anal. ($C_{22}H_{24}N_4O_6$) C, H, N.

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Registry No. **10a**, 20320-52-9; **10a** (anhydride), 85-44-9; **10b**, 96807-36-2; **10b** (anhydride), 641-70-3; **10c**, 96807-37-3; **10c** (anhydride), 5466-84-2; **10d**, 96807-38-4; **10d** (anhydride), 118-45-6; **10e**, 91346-02-0; **10e** (anhydride), 117-08-8; **10f**, 96825-34-2; **10f** (anhydride), 632-79-1; **11**, 96807-39-5; **11** (anhydride), 716-39-2; **12**, 96729-86-1; **12** (anhydride), 5662-95-3; **13**, 96807-40-8; **13** (anhydride), 13149-00-3; **14**, 96893-71-9; **14** (anhydride), 24327-08-0; **15**, 92491-53-7; **15** (anhydride), 81-08-3; **16**, 96825-35-3; **16** (anhydride), 89-32-7; **17**, 22291-04-9; **17** (anhydride), 81-30-1; **19** (anhydride), 3027-38-1; **19a**, 79070-62-5; **19a**·HCl, 96807-41-9; **19b**, 96807-69-1; **19b**·HCl, 96807-42-0; **19c**, 54824-17-8; **19c**·HCl, 96807-43-1; **19d**, 54824-18-9; **19d**·HCl, 96807-44-2; **19e**, 96807-45-3; **19f**, 54824-20-3; **19f**·HCl, 96807-46-4; **19g**, 54824-19-0; **19g**·HCl, 96807-47-5; **19h**, 69408-75-9; **19h**·HCl, 96807-48-6; **19i**, 96807-70-4; **19i**·HCl, 96807-49-7; **20a**, 69408-95-3; **20a** (anhydride), 23204-36-6; **20b**, 96807-71-5; **20b**·HCl, 96807-50-0; **20b** (anhydride), 4053-08-1; **20c**, 96807-51-1; **20c** (anhydride), 25994-06-3; **20d**, 96807-52-2; **20d** (anhydride), 23204-37-7; **20e**, 96807-72-6; **20e**·HCl, 96807-53-3; **20e** (anhydride), 7267-14-3; **20f**, 94985-14-5; **20f**·HCl, 94985-13-4; **20f** (anhydride), 3807-80-5; **20g**, 79070-66-9; **20g**·HCl, 96807-54-4; **20g** (anhydride), 81-84-5; **20h**, 36780-21-9; **20h**·HCl, 3029-58-1; **20i**, 88145-19-1; **20i**·HI, 96807-55-5; **20j**, 81451-45-8; **20k**, 96807-56-6; **20l**, 69408-81-7; **20m**, 95097-80-6; **20m**·3HCl, 96807-57-7; **21a**, 94985-18-9; **21a**·HCl, 94985-17-8; **21b**, 96807-73-7; **21b**·HCl, 96807-58-8; **21c**, 94985-16-7; **21c**·HCl, 94985-15-6; **21d**, 94985-25-8; **21d**·HCl, 94985-20-3; **21e**, 94985-21-4; **21e**·HCl, 94985-19-0; **21f**, 96807-74-8; **21f**·$0.5H_2SO_4$, 96825-36-4; **21g**, 96807-59-9; **21h**, 96807-60-2; **21i**, 96807-61-3; **22**, 96807-75-9; **22**·HCl, 96807-67-9; **23a**, 96807-62-4; **23b**, 96807-63-5; **24**, 96807-64-6; **24** (anhydride), 9682-37-5; **25**, 94985-24-7; **25**·HCl, 96807-65-7; **26**, 96807-66-8; $H_2N(CH_2)_2NHCH_3$, 109-81-9; $H_2N(CH_2)_2NHC_2H_5$, 110-72-5; $H_2N(CH_2)_2N(CH_3)_2$, 108-00-9; $H_2N(CH_2)_2N(C_2H_5)_2$, 100-36-7; $H_2N(CH_2)_2NH(CH_2)_2OH$, 111-41-1; $H_2N(CH_2)_2N(CH_2)_4$, 7154-73-6; $H_2N(CH_2)_2N(CH_2)_5$, 27578-60-5; $H_2N(CH_2)_2N(CH_2)_2O(CH_2)_2$, 2038-03-1; $H_2N(CH_2)_2NH(CH_2)_2$, 140-31-8; $H_2N(CH_2)_3N(CH_3)_2$, 109-55-7; 2-thiazolamine, 96-50-4; ethyl 2-amino-4-thiazolecarboxylate, 5398-36-7; 1,3,4-thiadiazole-2-amine, 4005-51-0.