39–40°, and then poured onto solid agar plates. The compounds to be tested were dissolved in the appropriate amount of Me_2CO and aliquots (0.1 ml) of these solutions were placed on paper disks. The disks were dried and placed on the prepared agar plate which was then incubated at 37° for 24–48 hr.

Acknowledgments. We wish to thank Dr. Peter F. Heinstein for advice and aid on the antibacterial testing which we performed, Dr. K. E. Price for the antibacterial testing performed at Bristol Laboratories, and Dr. Harry B. Wood, Jr., of the National Cancer Institute for the antitumor testing. This investigation was supported by a National Defense Education Act Fellowship (T. R. W.).

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Synthetic Sweeteners. 3. Aspartyl Dipeptide Esters from L- and D-Alkylglycines

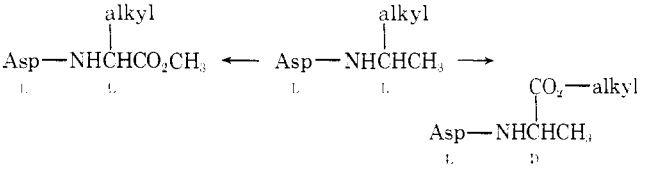
Robert H. Mazur,* Judith A. Reuter, Kenneth A. Swiatek, and James M. Schlatter

Chemical Research Department, Searle Laboratories, Division of G. D. Searle Company, Skokie, Illinois 60076. *Received May 29, 1973*

L-Asp-L-Nle-OMe and L-Asp-D-Ala-O(*i*-Pr) are representatives of new series of sweet dipeptides. In the first case, sweetness is obtained with certain side chains of four to six carbons in the C-terminal amino acid and, in the second, with side chains of one to three carbons.

Following the initial discovery of the very pleasant and potent sweet taste of L-aspartyl-L-phenylalanine methyl ester,[1] an intensive investigation of structure–activity relationships was begun. It became clear that L-aspartic acid was essential for sweetness but that considerable latitude was possible in the other part of the molecule. To summarize very briefly, we found that the C-terminal amino acid could be progressively simplified without great loss in sweetness potency. For example, the carbomethoxy group was replaced by methyl or the phenyl by cyclohexyl. Both these changes could be combined to give an amide which was still sweet. The latter result suggested that aliphatic amides of L-aspartic acid might be sweet and this was confirmed.[2] In addition, the methyl ester was always the most potent ester and all the sweet taste resided in the LL isomer for both dipeptides and amides. Table I gives one example of each of the above modifications.

The present work was prompted by two questions. One, could we go from methyl back to carbomethoxy and use unnatural amino acids with long aliphatic side chains and two, could methylene groups in an aliphatic side chain be replaced by carboxyl leading to dipeptide esters of D-amino acids? It was already known that L-Asp-L-Leu-OMe and L-Asp-D-Phe-OMe were bitter so that an affirmative answer to these questions did not seem highly probable.



The methyl esters of L-norleucine, DL-2-amino-5-methylhexanoic acid,[3] DL-2-aminoheptanoic acid,[4] and DL-2-aminooctanoic acid were synthesized and coupled with *N*-carbobenzoxy-L-aspartic acid α-*p*-nitrophenyl ester β-benzyl ester.[5] The resulting protected dipeptides were hydrogenated to give the required dipeptide methyl esters. Physical properties and yields are shown in the tables. It was found that L-Asp-L-Nle-OMe was moderately sweet (40 times sucrose) in contrast to the bitter isomeric L-Asp-L-Leu-OMe. Furthermore, the higher homologs were all sweet with somewhat increased potency. These latter compounds were tasted as a mixture of LL and LD diastereoisomers so that the potency of the taste-bearing isomer could be double the observed value. Based on previous work and on the results with L-Nle, we assume that the sweet taste is associated with the LL isomer but this has not been actually proved.

The first D-amino acid studied was D-alanine. Synthesis of the methyl ester and conversion to L-aspartyl-D-alanine methyl ester followed usual procedures. This compound had a pleasant sweet taste with a potency of 25 times sucrose. Other esters (C_2–C_5) were prepared; maximum sweetness occurred at *n*-propyl (Table II). In subsequent work, isopropyl rather than *n*-propyl esters were used because it was expected that the former would be more stable, thus possibly avoiding the formation of diketopiperazines.

L-Aspartyl dipeptide isopropyl esters were obtained from D-2-aminobutyric acid, D-valine, DL-norvaline, D-alloisoleucine, D-leucine, and D-norleucine. Physical properties of intermediates and final products are shown in the tables. It seems that a small, compact alkyl side chain (CH_3, C_2H_5, i-C_3H_7) is required for high potency, a not unreasonable result since the group is substituting on a receptor site for a methoxycarbonyl group in the LL series.

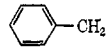
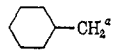
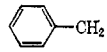
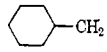
The problem of explaining the diversity of structure giving a sweet taste has challenged a number of investigators but has as yet no completely satisfactory solution. In-

genious proposals based on the assumption of a single complex receptor site have been made by Shallenberger[6] and more recently by Kier.[7] Of special interest in the present work is the observation that space-filling properties are more important than charge properties. One would not have predicted, based on usually accepted active site concepts, that an important ester function could be replaced by an alkyl group and vice versa without major change in biological activity.

Table III attempts to illustrate the relative steric requirements for sweetness in these two series. The basic structure seems to be an α-amide of L-aspartic acid in which the amide nitrogen is attached to an asymmetric carbon bearing two groups of dissimilar size. The exact chemical nature of these groups is not of critical importance. When the groups are of similar size no sweetness results. When the groups are sufficiently different sterically, one of the diastereoisomers will be sweet. The requirement of a particular absolute configuration follows from the fact that the receptor site is asymmetric. The first line of Table III shows that amino acid methyl esters with alkyl side chains do not give sweet derivatives until the receptor site sees a straight chain of at least four carbon atoms. The absolute configuration which fits the receptor site is called L for historical reasons. On the other hand, if an alkylamino acid isopropyl ester is used, a side chain of four carbons is too close in size to the ester for sweetness and really appreciable potency is only reached when the alkyl group consists of a straight chain of one or two carbons. Our system of nomenclature calls the active isomer D even though the receptor site has not changed. We are trying to apply the structure-activity information gained in this work to the design of analogs of peptide hormones.

Synthetic methods were the usual ones for preparations of amino acid derivatives and peptides. A typical example of each reaction is described in the Experimental Section with data for the various compounds given in Tables IV–VI. A very convenient modification of the *p*-nitrophenyl ester coupling reaction was discovered. The reactants were combined in ether from which the desired dipeptide separated in pure form free of starting materials and *p*-nitrophenol.

Table I. Taste of L-Asp-L-NHCHR$_1$R$_2$

R_1	R_2	Potency[b]
	CO_2CH_3	150
	CO_2CH_3	225
	CH_3	50
	CH_3	50
$CH_3(CH_2)_3CHCH_3$	CH_3	50

[a]J. M. Schlatter, U. S. Patent pending. [b]Times sucrose.

Table II. Taste of L-Asp-D-Ala-OR

R	Potency[a]	R	Potency[a]
Me	25	*i*-Pr	125
Et	80	*n*-Bu	10
n-Pr	170	*n*-Am	6

[a]Times sucrose.

Experimental Section

Melting points were determined in open capillaries in a stirred bath and are uncorrected. Optical rotations were measured at room temperature at approximately 1% concentration. Analyses were done under the direction of E. Zielinski; where analyses are indicated only by symbols of the elements, analytical results were within 0.4% of theoretical values. The crude products were dried overnight at 60° and 0.1 mm; in only a few cases as detailed in the footnotes was it necessary to crystallize the compound to ob-

Table III. Taste of Dipeptide Esters, L-Asp-NHCH(R_1)CO_2R_2

	R_1									
	Me	Et	*i*-Pr	*n*-Pr	*sec*-Bu	*i*-Bu	*n*-Bu	*i*-Am	*n*-Am	*n*-Hex
R_2 = Me L series	0[a]		0[a]		0[a]	0[a]	40[b]	80[c]	50[c]	70[c]
R_2 = *i*-Pr D series	125	170	170	17[c]	4[d]	0	0			

[a]Reference 1. [b]Numbers represent the sweetness potency of the compound as a multiple of sucrose. [c]DL-Amino acid used. [d]D-Allo isomer used.

Table IV. Amino Acid Ester Hydrochlorides, $H_2NCH(R_1)CO_2R_2 \cdot HCl$

No.	R_1	R_2	Config	Yield, %	Mp, °C	$[\alpha]_D$, deg	Formula[g]
1[a]	Me	Me	D	95	105–110[e]		$C_4H_9NO_2 \cdot HCl$
2[b]	Me	Et	D	94	75–78.5		$C_5H_{11}NO_2 \cdot HCl$
3	Me	*n*-Pr	D	98	91–97.5	0, H[f]	$C_6H_{13}NO_2 \cdot HCl$
4	Me	*i*-Pr	D	98	85–89.5	−2, H	$C_6H_{13}NO_2 \cdot HCl$
5	Me	*n*-Bu	D	94[d]	93–94	0, W	$C_7H_{15}NO_2 \cdot TsOH$
6	Me	*n*-Am	D	94[d]	83–84	+2, W	$C_8H_{17}NO_2 \cdot TsOH$
7	Et	*i*-Pr	D	95	172–179	−10, H	$C_7H_{15}NO_2 \cdot HCl$
8	*n*-Pr	*i*-Pr	DL	94	92–94.5		$C_8H_{17}NO_2 \cdot HCl$
9	*i*-Pr	*i*-Pr	D	79	120–122	−8, M	$C_8H_{17}NO_2 \cdot HCl$
10	*n*-Bu	Me	L	93	136–139	+14, H	$C_7H_{15}NO_2 \cdot HCl$
11	*n*-Bu	*i*-Pr	D	97	130–136	−4, H	$C_9H_{19}NO_2 \cdot HCl$
12	*i*-Bu	*i*-Pr	D	97	140–142	−13, M	$C_9H_{19}NO_2 \cdot HCl$
13	*sec*-Bu	*i*-Pr	D[c]	69	113–123	−11, H	$C_9H_{19}NO_2 \cdot HCl$
14	*n*-Am	Me	DL	94	85–88		$C_8H_{17}NO_2 \cdot HCl$
15	*i*-Am	Me	DL	86	133–135		$C_8H_{17}NO_2 \cdot HCl$
16	*n*-Hex	Me	DL	96	95–96		$C_9H_{19}NO_2 \cdot HCl$

[a]M. Zaoral, J. Kolc, F. Korenczki, V. P. Cherneckii, and F. Sorm, *Collect. Czech. Chem. Commun.*, **32**, 843 (1967); mp 109–111°. [b]E. Klieger and H. Gibian, *Justus Liebigs Ann. Chem.*, **649**, 183 (1961); mp 76–78°. [c]Allo isomer. [d]The *p*-toluenesulfonate was prepared. [e]Most compounds crystallized from Et_2O containing varying amounts of the esterifying alcohol left from incomplete stripping. In the case of **5**, **6**, **9**, and **12** Skellysolve B was used instead of Et_2O. [f]H, 1 *N* HCl; M, MeOH; W, H_2O. [g]All compounds were analyzed for C, H, and N.

Table V. Protected Dipeptide Esters, Z-L-Asp(OBzl)-NHCH(R_1)CO_2R_2

No.	R_1	R_2	Config	Yield, %	Mp, °C	$[\alpha]_D$, deg	Formula[a]
17	Me	Me	D	78, A[b]	113–114[c]	−5, D[d]	$C_{23}H_{26}N_2O_7$
18	Me	Et	D	86, A	107–108.5	−7, D	$C_{24}H_{28}N_2O_7$
19	Me	*n*-Pr	D	78, A	94.5	−10, D	$C_{25}H_{30}N_2O_7$
20	Me	*i*-Pr	D	78, A	104.5–105	−8, D	$C_{25}H_{30}N_2O_7$
21	Me	*n*-Bu	D	91, A	67–68	+1, M	$C_{26}H_{32}N_2O_7$
22	Me	*n*-Am	D	90, A	59.5–60.5	+3, M	$C_{27}H_{34}N_2O_7$
23	Et	*i*-Pr	D	72, A	90–91	−7, D	$C_{26}H_{32}N_2O_7$
24	*n*-Pr	*i*-Pr	DL	88, A	77–80	−8, D	$C_{27}H_{34}N_2O_7$
25	*i*-Pr	*i*-Pr	D	98, M	80–82	−7, M	$C_{27}H_{34}N_2O_7$
26	*n*-Bu	Me	L	80, A	85.5–86.5	−11, D	$C_{26}H_{32}N_2O_7$
27	*n*-Bu	*i*-Pr	D	93, A	73–78	−4, D	$C_{28}H_{36}N_2O_7$
28	*i*-Bu	*i*-Pr	D	91, A	85–86	+6, M	$C_{28}H_{36}N_2O_7$
29	*sec*-Bu	*i*-Pr	D[a]	92, A	63–65	−13, D	$C_{28}H_{36}N_2O_7$
30	*n*-Am	Me	DL	94, A	70–73	−6, D	$C_{27}H_{34}N_2O_7$
31	*i*-Am	Me	DL	80, M	69–72	−8, M	$C_{27}H_{34}N_2O_7$
32	*n*-Hex	Me	DL	94, A	73–78	−5, D	$C_{28}H_{36}N_2O_7$

[a]Allo isomer. [b]A, active ester; M, mixed anhydride. [c]Melting points were taken on crude products except that no. **25, 28,** and **31** were crystallized from aqueous *i*-PrOH. [d]D, DMF; M, MeOH. [e]All compounds were analyzed for C, H, and N.

Table VI. Dipeptide Esters, L-Asp-NHCH(R_1)CO_2R_2

No.	R_1	R_2	Config	Yield, %	Mp, °C	$[\alpha]_D$, deg	Formula[c]
33	Me	Me	D	94	150–151[b]	+72, H[d]	$C_8H_{14}N_2O_5$
34	Me	Et	D	54	147–149	+67, H	$C_9H_{16}N_2O_5 \cdot 0.5H_2O$
35	Me	*n*-Pr	D	98	Glass	+58, H	$C_{10}H_{18}N_2O_5 \cdot 0.5H_2O$
36	Me	*i*-Pr	D	78	172–176	+59, H	$C_{10}H_{18}N_2O_5$
37	Me	*n*-Bu	D	88	141–142	+56, W	$C_{11}H_{20}N_2O_5 \cdot 0.75H_2O$
38	Me	*n*-Am	D	83	139–140	+53, W	$C_{12}H_{22}N_2O_5$
39	Et	*i*-Pr	D	90	167–168	+58, H	$C_{11}H_{20}N_2O_5 \cdot 1.25H_2O$
40	*n*-Pr	*i*-Pr	DL	96	149–151	+14, H	$C_{12}H_{22}N_2O_5$
41	*i*-Pr	*i*-Pr	D	100	150–153	+19, M	$C_{12}H_{22}N_2O_5 \cdot 0.5H_2O$
42	*n*-Bu	Me	L	99	248	−14, H	$C_{11}H_{20}N_2O_5 \cdot 0.25H_2O$
43	*n*-Bu	*i*-Pr	D	93	173–175	+48, H	$C_{13}H_{24}N_2O_5$
44	*i*-Bu	*i*-Pr	D	82	167–169	+61, W	$C_{13}H_{24}N_2O_5 \cdot 0.25H_2O$
45	*sec*-Bu	*i*-Pr	D[a]	100	140–143	+39, H	$C_{13}H_{24}N_2O_5$
46	*n*-Am	Me	DL	100	100–103[c]	−12, D	$C_{12}H_{22}N_2O_5$
47	*i*-Am	Me	DL	89	130–133	+3, A	$C_{12}H_{22}N_2O_5 \cdot 0.25H_2O$
48	*n*-Hex	Me	DL	98	85–105	−10, D	$C_{13}H_{24}N_2O_5$

[a]Allo isomer. [b]Melting points were taken on crude products except that no. **36** was crystallized from H_2O. [c]A second mp, 230–240°, was observed. [d]A, HOAc; D, DMF; H, 1 *N* HCl; M, MeOH; W, H_2O. [e]All compounds were analyzed for C, H, and N.

tain a satisfactory analysis. All intermediates and products were essentially homogeneous as determined by tlc on silica. Protected compounds were run in a suitable mixture of MeOH and $CHCl_3$. Deprotected compounds were run in *n*-BuOH–HOAc–H_2O (7:1:2). Spots were detected by the *tert*-butyl hypochlorite-starch iodide method.[8] Protected dipeptides were prepared by the *p*-nitrophenyl ester[9] or mixed anhydride[10] procedure. Hydrogenations were carried out in either 90% HOAc or 75–90% alcohol over 10% by weight of Pd at room temperature and up to 4 atm of pressure. The particular alcohol was selected to correspond to the ester being used. We thank W. M. Selby, J. Serauskas, M. G. Scaros, and E. Saugstad for many hydrogenations.

The compounds reported here were tasted by two or three untrained individuals and threshold potencies determined. Solutions of the unknown were made up at concentration increments of 20–33%; for example, 0.006, 0.008, 0.010, 0.012, 0.015, 0.020, 0.025, and 0.033% for high to medium potency compounds and 0.05, 0.06, 0.08, 0.10, 0.12, 0.15, 0.20, 0.25, and 0.33% for medium to low potency compounds. By tasting up and down a series it was possible to determine reproducibly the concentration which just produced a sweet taste. Assuming a threshold concentration of sucrose of 1%, a typical value for untrained tasters, the potency of the test compound was calculated by simply taking the reciprocal of its threshold concentration. Agreement among the tasters was quite good, never varying by more than one concentration increment. The resulting difference in potency might have been eliminated by determining individual sucrose thresholds before each test. In cases where subsequent careful taste panel evaluations were carried out, the screening potencies were approximately confirmed.

D-Ala-O(*i*-Pr)·HCl. Isopropyl alcohol (1200 ml) was cooled to −20° and 43.6 ml (0.6 mol) of thionyl chloride added with stirring followed by 44.5 g (0.5 mol) of D-alanine. The solution was heated 24 hr at reflux, most of the solvent stripped off, and the residue dissolved in 800 ml of Et_2O. The product crystallized on standing: yield 82 g (98%); mp 85–89.5°. *Anal.* ($C_6H_{13}NO_2 \cdot HCl$) C, H, Cl, N.

Z-L-Asp(OBzl)-D-Ala-O(*i*-Pr). D-Alanine isopropyl ester hydrochloride (9.20 g, 55 mmol) was suspended in 25 ml of CH_2Cl_2 and shaken with 10 ml of 5 *M* K_2CO_3. The CH_2Cl_2 was decanted and the aqueous slush shaken with 25 ml of fresh CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and stripped to dryness at 40°. Z-L-Asp(OBzl)-ONP (23.9 g, 50 mmol) was melted on the steam bath and dissolved in 250 ml of Et_2O. The above amino ester in a little Et_2O was added and the solution allowed to stand 24 hr at 5°. The product was filtered and washed with a large volume of cold Et_2O: yield 18.3 g (78%); mp 104.5–105°. *Anal.* ($C_{25}H_{30}N_2O_7$) C, H, N.

L-Asp-D-Ala-O(*i*-Pr). Protected dipeptide (37.4 g, 79 mmol) was dissolved in 375 ml of 75% isopropyl alcohol and hydrogenated over 3.7 g of Pd at room temperature and 60 psi until hydrogen uptake was complete. After removal of the catalyst, the solvents were stripped off and the residue was crystallized from 50 ml of H_2O: yield 15.2 g (78%); mp 172–176° dec. *Anal.* ($C_{10}H_{18}N_2O_5$) C, H, N.

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Chemotherapeutic Nitroheterocycles. Antischistosomal Properties of Nitrofurylvinyl and Nitrothienylvinyl Heterocycles

D. W. Henry,* V. H. Brown, M. Cory, J. G. Johansson,

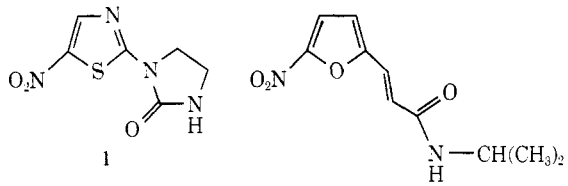
Department of Bio-organic Chemistry, Stanford Research Institute, Menlo Park, California 94025

and E. Bueding

Department of Pathobiology, School of Hygiene and Public Health, and Department of Pharmacology and Experimental Therapeutics, School of Medicine, The Johns Hopkins University, Baltimore, Maryland 21205. *Received May 29, 1973*

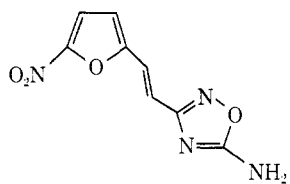
A series of 24 analogs of the experimental antischistosomal agent, 5-amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (**3**), was prepared and evaluated in mice infected with *Schistosoma mansoni*. Although antischistosomal activity was widespread in the series, only four of the compounds showed significant curative properties. Compounds containing 2-imidazolyl (**4**) and 2-pyridyl (**15**) groups gave cure rates around 25% at 400 and 250 mg/kg dose levels, respectively. The 2-thiazolyl (**8**) and 2-pyrimidyl (**18**) derivatives were especially notable, yielding 100% cures at 250 and 200 mg/kg dose levels, respectively.

Schistosomiasis has proven to be one of the most intractable diseases to which man is subject, and as yet no practical and generally effective drugs or methods of control are available.[1,2] Among the many types of drugs that have shown potentially useful antischistosomal activity, the nitroheterocycles have demonstrated unusual promise. Niridazole (**1**) has achieved some clinical use in the treatment of infections with *Schistosoma haematobium* and *Schistosoma mansoni*.[3] Furapromidium (**2**) has been reported to be effective in limited trials against *Schistosoma japonicum*.[1,4,5] More recently, Robinson, *et al.*,[6-9] found another experimental nitrofuran, 5-amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (**3**, SQ 18506), that possesses high activity against *S. mansoni* and *S. japonicum* in mice, hamsters, and monkeys as well as lower host toxicity compared with **1**, **2**, and other related compounds. As part of this study, these authors noted that activity in this class of compounds could be correlated with certain common structural features. One of the required features is a 5-nitrofuran or 5-nitrothiazole nucleus linked through the 2 position to a rigid side chain bearing a low-basicity nitrogen. The nitrogen atom must be located in a specific spatial position relative to the nitroheterocyclic nucleus. In **1** and **2**, the nitrogen atom of the NH moiety in the urea and the amide groups, respectively, fills this role; and in **3**, one of the oxadiazole ring nitrogens occupies the same position.



1

2



3

Further development of the hypothesis by Hulbert, *et al.*,[7] has led to the conclusion that the nature of the side chain connecting the key nitrogen atom to the nitroheterocyclic nucleus is critical. Working with the furanacrylamide system of furapromidium, they found that altering the geometry and/or electronic properties of the system by replacing the vinyl bridge with ethylene or acetylene linkages totally eliminated antischistosomal activity. On the other hand, a variety of acrylamides with varying substituents on the amide nitrogen retained the desired biochemical and chemotherapeutic properties.

Further studies aimed at delineating the limits of the initial structure-activity hypothesis[6] are reported in this paper. Specifically, we have examined the effect of altering the heterocyclic ring system through which the low-basicity nitrogen is introduced into analogs of **3**. In addition, we have examined the antischistosomal properties of the 5-nitro-2-thienyl group as a replacement for the nitrofuran moiety in some of these analogs. Using a carboxamide moiety to replace the vinyl bridge of active compounds was also evaluated.

Chemistry. The 5-nitrofuran-2-vinyl and 5-nitrothiophene-2-vinyl compounds in Table I were prepared by condensation of 5-nitrofurfural or 5-nitrothiophene-2-carboxaldehyde with appropriate methyl-substituted heterocycles in acetic anhydride–acetic acid solvent (method A). For the imidazole (**4** and **5**) and benzimidazole (**26**) compounds, the *N*-acetyl derivatives (**6**, **7**, and **27**) were isolated as intermediates and subsequently hydrolyzed by 6 *N* HCl (method B). The carboxamide analogs **12**, **14**, and **19** were prepared by reaction of 5-nitro-2-furoic acid chloride and the appropriate amino heterocycle (method C). As noted in Table I, several of the compounds were known previously, usually for their antibacterial properties.

Pharmacology. The antischistosomal activity of this group of compounds is characterized by a consistent course of biochemical and morphological events.[6,7,10] Within 2 days following the administration of an active compound to mice infected with *S. mansoni*, the activity of glycogen phosphorylase phosphatase, of the worms, is reduced, along with an associated decrease in glycogen levels. The biochemical changes are observed at low dose levels of active compounds that do not bring about a shift