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Protein-Binding Polyhedral Boranes. 1

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The development of neutral polyhedral boranes with protein-incorporating functions offers the opportunity of binding these structures to tumor antibodies. This research has led to the synthesis of such boron compounds. Their low incorporation level into proteins indicates the need for water-solubilizing groups in order to increase the number of boron atoms which may be attached to the antibody carrier. This work is a prelude to any clinical trials of this chemoradiotherapeutic procedure.

Clinical failures in the treatment of malignant tumors by neutron capture therapy have stemmed largely from an inability to localize a neutron absorber, such as boron-10, uniformly throughout the neoplasm.[1-3] This major deficiency results in part from the inadequate biochemical information regarding differences between normal and malignant tissues and the inability to utilize the available knowledge to fabricate tumor-seeking boron compounds. However, there is evolving information in the field of tumor immunology and immunochemistry that has a direct bearing on this problem. The capacity of the host, both animal and man, to recognize the malignant process by antibody elaboration against such cells presages a capability to deliver specific nuclides selectively to the tumor. A key requirement is an ability to incorporate such substances into proteins as models for tumor antibodies.

The possible use of ^{10}B antibodies for neutron capture therapy has been suggested[4] and more recently preliminary steps in this direction have been undertaken.[5,6] The types of boron compounds which would be suitable are those which contain a high percentage of boron since it is this boron percentage which will determine the effectiveness of this chemoradiotherapeutic procedure. Two basic types of boron compounds meet this requirement: (1) carboranes and (2) polyhedral boranes. Since ^{10}B is the only isotope of boron which is useful for neutron capture, a major consideration when approaching this research problem must be the ease of synthesizing these boron hydride species from ^{10}B-enriched starting materials. Since ^{10}B-enriched polyhedral boranes can be more easily synthesized and in higher yields from $^{10}BF_3$ etherate than the corresponding carboranes, most of this research effort has involved the readily synthesizable $B_{10}H_{10}^{2-}$ and $B_{12}H_{12}^{2-}$ anions. These anions per se have been shown to be strongly bound by ionic forces to proteins. Such a property might readily obscure and prevent selective tumor localization *via* the boron-bound antibody, since ionically bound compounds may be readily exchanged with other blood proteins. In order to obviate the protein binding by ionic species, the synthesis of neutral polyhedral boranes containing protein-incorporating functions was undertaken. These functional groups would permit covalent incorporation into proteins. An important binding requirement is that this must occur without conformational alterations since such changes may render the antibody unsuitable as a carrier entity. For these reasons mild conditions for the incorporation of these boron compounds into proteins are essential. Such procedures are well established in protein chemistry utilizing certain functional moieties. Among these are carboxyl groups, aromatic amines, and isothiocyanates. Such entities were chosen for the studies reported here.

Results and Discussion

Synthetic Chemistry. Bis(dimethylsulfido)octahydrodecarborane, $B_{10}H_8[S(CH_3)_2]_2$,[7] and the corresponding dodecaborane, $B_{12}H_{10}[S(CH_3)_2]_2$,[8] can be readily synthesized in suitable yield from their respective anions. Reaction of either 1,10- or 1,6-$B_{10}H_8[S(CH_3)_2]_2$ with potassium phthalimide at elevated temperatures results in the removal of one methyl group to form the corresponding anionic species **1**.[7] This anion has been shown to be quite

$$(CH_3)_2SB_{10}H_8S(CH_3)_2 \xrightarrow[\text{phthalimide}]{\text{potassium}} K^+[(CH_3)_2SB_{10}H_8SCH_3]^- \quad \mathbf{1}$$

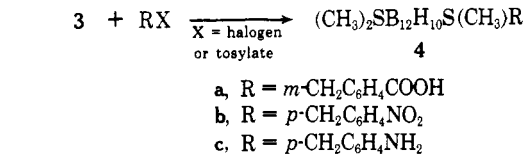
nucleophilic, displacing both alkyl and benzylic halides and tosylates. This displacement reaction has led to the synthesis of type **2** compounds containing various functional groups.

$$(CH_3)_4N[(CH_3)_2SB_{10}H_8SCH_3] \xrightarrow[\text{where X = halogen or tosylate}]{RX} (CH_3)_2SB_{10}H_8S(CH_3)R \quad \mathbf{2}$$

a, R = $-CH_2CH_2COOH$
b, R = p-$CH_2C_6H_4NO_2$
c, R = $-(CH_2)_5COOH$
d, R = m-$CH_2C_6H_4COOH$
e, R = p-$CH_2C_6H_4NH_2$
f, R = p-$CH_2C_6H_4NCS$
g, R = $-CH_2CH{=}CH_2$

A similar reaction scheme has been applied to the synthesis of functionally substituted $B_{12}H_{10}R_2$ species.[8] In this case, separation of the isomeric dimethylsulfidodecahydrododecaboranes was not carried out as in the B_{10} species. The entire isomeric mixture was used in the synthesis of compounds **3** and **4**.

$$B_{12}H_{10}[S(CH_3)_2]_2 \xrightarrow[\text{phthalimide}]{\text{potassium}} K^+[(CH_3)_2SB_{12}H_{10}SCH_3]^- \quad \mathbf{3}$$

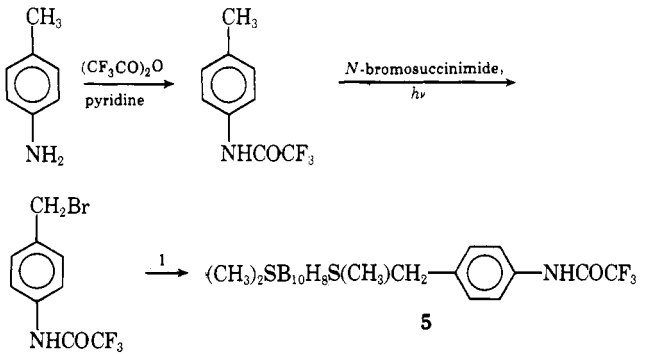


4

a, R = *m*-$CH_2C_6H_4COOH$
b, R = *p*-$CH_2C_6H_4NO_2$
c, R = *p*-$CH_2C_6H_4NH_2$

Work is currently underway to separate the various isomers. However, from water solubility considerations, the mixture of isomers may offer a distinct advantage. A more soluble boron entity may be essential in maximizing the number of polyhedral groups which can be incorporated into an antibody while still maintaining water solubility of the boron-protein conjugate. A comparison of the isomerically pure octahydrodecaboranes with the dodecahydrodecaborane mixture seems to confirm the latter's increased aqueous solubility.

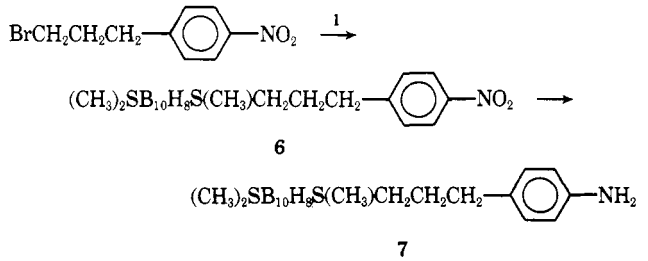
The synthesis carried out involved basically high-yield reactions. However, the reduction of the nitro compounds **2b** and **4b** gave unpredictable yields by both chemical and catalytic procedures. In these reactions, in addition to amines, decomposition products were obtained which can be attributed to benzyl–sulfur cleavage compounds as well as the alteration of polyhedral cage. In order to avoid the need for such a reduction step, the following sequence was employed.



5

Attempts to deblock the amide **5** under basic conditions resulted unexpectedly in a quantitative yield of **1**. It was considered that the result could be attributed to the fact that the benzyl–S linkage is a reactive one under basic conditions. Acidic hydrolysis, however, did result in a reasonable yield of **1e**.

In view of the lability of the benzylic group and its possible contribution to the difficulties experienced in the reduction procedures, we undertook the synthesis of **6**. In this structure, the boron cage is insulated from the phenyl moiety by three methylene groups. This compound has been synthesized and facilely reduced to the corresponding amine in 90% yield. The sequence used is shown below.



6

7

Protein Binding. Successful synthesis of these neutral species, **2** and **4**, prompted research directed toward their covalent attachment to proteins. The results of these incorporation studies using **2** are summarized in Table I. Compounds **2a**, **2d**, **2e**, and **2f** were bound to bovine serum albumin (BSA) using standard coupling procedures. Even though the number of polyhedral borane cages per protein molecules was not as great as required for tumor cell destruction,† this achievement encouraged attempted incorporation into the more pertinent human gamma globulin fraction (HGG). This protein category was used as a model system for antibodies in view of their similar physicochemical properties. Unfortunately, protein precipitation occurred upon incorporation of **2e** and **2f** to HGG. This result indicated the high water insolubility of this protein–boron conjugate even with the incorporation of a very limited number of polyhedral borane groups. Obviously, such boron compounds lacked any clinical utility and pointed to the need for the development of a second generation of such neutral polyhedral boranes containing both water-solubilizing and protein-incorporating moieties. The synthesis of such compounds is now well underway and will be the topic of a future communication.

Table I. Protein Binding Results

Compd	μg of boron/ml	μg of protein/ml	No. of polyhedral boron groups per protein molecule
2e	10	1560	4
2b	7.3	1055	4
2a	2.8	<30	>60
2d	0.7	<30	>60

In conclusion then, this present work has demonstrated the feasibility of synthesizing in high yields neutral polyhedral boranes capable of being incorporated into proteins. Though clinically useful substances have not been prepared, this research clearly indicated a direction in the synthesis of those more desirable compounds.

Experimental Section

Apparatus and Materials. All melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and all reported compounds were with ±0.4% of theoretical values. Elements which were analyzed are shown in Table II. Ir spectra were determined in a Perkin-Elmer 127 Infracord spectrometer and proton nmr data were obtained on a Varian T-60 instrument. Boron[9] and protein[10] analyses in the conjugates were carried out by known procedures. *p*-(3-Bromopropyl)nitrobenzene was synthesized using an established method.[11]

Dimethylsulfidomethylaralkyloctahydrodecaborane and Dimethylsulfidomethylaralkylsulfidodecahydrododecaborane [$B_{10}H_8S(CH_3)S(CH_3)R$ and $B_{12}H_{10}S(CH_3)S(CH_3)R$]. The procedures for the synthesis of the compounds reported in Table II are similar. In a typical reaction 300–500 mg (1–1.6 mmol) of the demethylated boron hydride **1** or **3** was dissolved in 30–50 ml of dry DMF. A stiochiometric amount of the halide or tosylate was added and the reaction was stirred for 4–12 hr. The solution was then filtered to remove the tetramethylammonium salt and the solvent of the filtrate was removed under reduced pressure. The resulting solid mixture was then extracted with either methylene chloride or acetone and filtered to remove any remaining salt. The filtrate was evaporated to dryness and the compound was recrystallized from an appropriate solvent as shown in Table II.

Dimethylsulfidomethyl *p*-Aminobenzylsulfidooctahydrodecaborane [1,10-$B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NH_2$]. Procedure A. 1,10-$B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NO_2$ (500 mg, 1.38 mmol) was suspended in 40 ml of methanol. PtO_2 (100 mg) was added and the compound was reduced in a Parr apparatus under 50

† Personal communication from Dr. F. C. Dohan, Jr., Neurosurgical Service of the Massachusetts General Hospital. It has been estimated that 200 boron atoms per protein molecule may be necessary for useful chemoradiotherapy.

Table II. Analytical Data

Compd	Formula (analyses)	Mp, °C	Ir, cm^{-1}	Nmr[a]	Crystn solvent	% yield
2b	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2C_6H_4NO_2$ (C, H, B, S)	253–256	1302 (w), 2500 (s), 1705 (m), 1600 (m), 1518 (s), 1415 (s), 1340 (s), 1330 (s)	8.2 (m, 4 H), 4.9 (d, 2 H), 3.05 (s, 6 H), 3.0 (s, 3 H)	Acetone–H_2O	83
2d	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2C_6H_4COOH$ (C, H, B, S)	224–228	3000 (m), 2525 (s), 1690 (s), 1430 (s), 1300 (s), 1010 (m), 780 (m), 740 (m), 700 (m)	8 (m, 4 H), 4.9 (d, 2 H), 3.15 (s, 6 H), 3.05 (s, 3 H)	Acetic acid–H_2O	75
2a	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2CH_2COOH$ (C, H, B, S)	144–146	2950 (m), 2525 (s), 1710 (s), 1430 (s), 1265 (m), 1050 (w), 1010 (m)	4.75 (m, 2 H), 3.05 (m, 12 H)	Acetic acid–H_2O	80
2c	$(CH_3)_2SB_{10}H_8S(CH_3)(CH_2)_5COOH$ (C, H, S)	137–140	2925 (w), 2940 (s), 1700 (s), 1420 (m), 1330 (w), 98 (w)	3.5 (t, 2 H), 3.05 (s, 9 H), 2.3 (m, 4 H), 1.7 (t, 4 H)	Acetic acid–H_2O	80
2g	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2CH{=}CH_2$ (C, H, S)	134–137	3010 (w), 2500 (s), 1470 (m), 1050 (w), 1000 (m), 950 (m), 940 (m), 88 (w)	5.6 (m, 3 H), 4.2 (m, 2 H), 3.0 (s, 6 H), 2.9 (s, 3 H)	Acetone–H_2O	72
4b	$(CH_3)_2SB_{12}H_{10}S(CH_3)CH_2C_6H_4NO_2$ (C, H, N, S)	189–192	3000 (w), 2925 (w), 2500 (w), 1700 (m), 1600 (m), 1520 (s), 1180 (m), 1110 (m), 1040 (m), 965 (s)	8 (m, 4 H), 4.4 (d, 2 H), 2.6 (s, 9 H)	Acetone–H_2O	85
4a	$(CH_3)_2SB_{12}H_{10}S(CH_3)CH_2C_6H_4COOH$ (C, H, N, S)	189–192	3000 (w), 2925 (w), 1660 (s), 1585 (w), 1565 (w), 1400 (s), 1290 (m), 1270 (m), 985 (w), 950 (m)	8 (m, 2 H), 7.7 (m, 2 H), 4.4 (d, 2 H), 2.6 (s, 6 H), 2.5 (s, 3 H)	Acetone–H_2O	70
6	$(CH_3)_2SB_{10}H_8S(CH_3)(CH_2)_3C_6H_4N_2$ (C, H, N, S)	196–199	3025 (w), 2940 (w), 2510 (s), 1600 (m), 1525 (s), 1475 (m), 1360 (s), 1125 (m), 1010 (m)	8.4 (d, 2 H), 7.8 (d, 2 H), 3.7 (t, 2 H), 3.2 (s, 9 H)	Acetone–H_2O	96
7	$(CH_3)_2SB_{10}H_8S(CH_3)(CH_2)_3C_6H_4NH_2$ (C, H, N, S, procedure B)	162–165	3400 (w), 3325 (w), 3000 (w), 2930 (w), 2500 (s), 1620 (s), 1515 (s), 1410 (s), 1280 (m), 1190 (m), 1015 (m), 970 (m)	7.0 (d, 2 H), 6.6 (d, 2 H), 3.4 (t, 2 H), 3.1 (s, 9 H), 2.6 (m, 9 H)	CH_2Cl_2–hexane	90
2e	$(CH_3)_2SB_{10}H_8S(CH_3)_2CH_2C_6H_4NH_2$ (C, H, N, B, S, procedures A and B)	171–173	3350 (w), 3200 (w), 2450 (s), 1610 (s), 1490 (m), 1400 (m), 1270 (m), 1160 (m), 1020 (m), 970 (m), 820 (m)	7.4 (d, 2 H), 6.8 (d, 2 H), 4.5 (d, 2 H), 3.1 (s, 6 H), 2.8 (s, 3 H)	CH_2Cl_2–hexane	30–90
5	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2C_6H_4NHCOCF_3$ (C, H, N, S, F)	234–236	3250 (w), 3200 (w), 3010 (m), 2950 (m), 2500 (s), 1720 (s), 1660 (s), 1610 (m), 1560 (m), 1520 (m), 1420 (m), 1260 (m), 1220 (m), 1160 (m)	10.5 (s, 1 H), 7.85 (s, 2 H), 7.8 (s, 2 H), 4.8 (q, 2 H), 3.1 (s, 6 H), 2.9 (s, 3 H)	CH_2Cl_2–hexane	76
2f	$(CH_3)_2SB_{10}H_8S(CH_3)CH_2C_6H_4NCS$ (C, H, N, S)	206–208	2520 (s), 2150 (s), 1510 (m), 1425 (m), 1000 (m)	7.4 (m, 4 H), 4.7 (q, 2 H), 3.1 (s, 6 H), 2.9 (s, 3 H)	$CHCl_3$–hexane	89

[a] See ref 3.

lbs/in.^{2} of hydrogen for 12 hr. The solution was then filtered and the solid was washed with CH_2Cl_2. The CH_2Cl_2 solution was combined with the original methanol solution and the solvent was removed under reduced pressure. The resulting solid was then dissolved in CH_2Cl_2, filtered, and crystallized from CH_2Cl_2–hexane to give the desired product in 30% yield (mp 171–173°).

Procedure B. In a 250-ml three-neck flask equipped with a mechanical stirrer and reflux condenser 500 mg (1.38 mmol) of 1,10-$B_{10}H_8S(CH_3)_2SCH_3)CH_2C_6H_4NO_2$ was dissolved in 100 ml of benzene. The solution was heated to reflux. After 30 min, 5 g of activated iron was added and the mixture allowed to reflux for another 30 min at which time 1 ml of water was added. Water was added periodically over 7 hr to a total of 10 ml. The solution was then cooled and filtered. The solids were washed repeatedly with hot benzene and these fractions were combined and the solvent was removed. The resulting product was dissolved in CH_2Cl_2 and recrystallized from CH_2Cl_2–hexane. This compound was identical in all respects with the one obtained in procedure A. The yields ranged from 50 to 90%.

***p*-Trifluoroacetotoluidide.** *p*-Toluidine (4 g, 37.3 mol) was dissolved in 10 ml of dry pyridine and the solution was cooled to 0°. A slight excess of trifluoroacetic anhydride was added slowly and the solution was stirred for 2 hr. The pyridine was removed under reduced pressure and the solid was crystallized from hot hexane to give the desired product: mp 105–107°; yield 90%.

4-Bromomethyltrifluoroacetanilide. 4-Methyltrifluoroacetanilide (2 g, 9.85 mmol) was dissolved in 75 ml of CCl_4. A stoichiometric amount of *N*-bromosuccinimide was added and the solu-

tion was refluxed. The reaction was irradiated with a 75-W floodlamp for 2.5 hr. The solution was then cooled to room temperature and filtered. The CCl_4 was removed under reduced pressure and the solid dissolved in diethyl ether. The compound was crystallized from Et_2O–hexane (yield 80%): mp 131–135°.

Bis(dimethylsulfido)decahydrododecaborane $[B_{12}H_{10}[S(CH_3)_2]_2]$. The procedure for the synthesis of $B_{12}H_{10}[S(CH_3)_2]_2$ was a modification of the procedure given to us by Kaczmarczyk.[8] In a typical reaction 3 g (15.9 mmol) of $Na_2B_{12}H_{12}$ was dissolved in 20 ml of warm DMSO in a 100-ml round-bottom flask equipped with a reflux condenser and N_2 inlet. Acetic anhydride (20 ml) was added slowly. When all of the acetic anhydride had been added the temperature of the reaction was raised to 90°. At this point an exothermic reaction took place and the temperature of the solution rose to 140–150°. After the exothermic reaction had stopped the flask was cooled to room temperature. The reaction mixture was then poured into 300 ml of H_2O containing 4 g of NaCl. If the product precipitated out as a solid, it was removed by filtration and crystallized from EtOH–H_2O. Many times the product precipitated as an oil. In this case the aqueous mixture was extracted with several portions of CH_2Cl_2. The CH_2Cl_2 fractions were collected, the solvent was removed, and the product crystallized from EtOH–H_2O (mp 220–235°) in 60% yield.

Tetramethylammonium Dimethylsulfidomethylsulfidodecahydrododecaborate $[(CH_3)_4N[(CH_3)_2SB_{12}H_{10}SCH_3]]$. $B_{12}H_{10}[S(CH_3)_2]_2$ (1 g, 3.78 mmol) was dissolved in 50 ml of dry DMF in a 100-ml three-neck flask equipped with a condenser and N_2 inlet. Potassium phthalimide (1 g) was added and the temperature was raised to 100° and maintained there for 3 hr. The solution was then raised to 140° for 1 hr. The flask was cooled and the solution was filtered. After the solvent had been removed, the solid residue was extracted with three 500-ml portions of hot water. Addition of $(CH_3)_4NCl$ to the aqueous solution resulted in the precipitation of $(CH_3)_4N[(CH_3)_2SB_{12}H_{10}SCH_3]$. The product was crystallized from hot water (90% yield).

Conjugation of $B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NH_2$ and Bovine Serum Albumin (BSA). To 33 mg of $B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NH_2$ (**2e**) was added 0.3 ml of a 1 *M* HCl solution in an ice bath. $NaNO_2$ solution (1 mg/ml, 7 ml) was added and the solution was stirred for 1 hr. The mixture was filtered cold (4°) and diluted to 25 ml with 0.1 *M* HCl. This solution was added slowly to 65 mg of BSA in a phosphate buffer (pH 8). The solution tended to become acidic and was maintained at pH 8 with 0.1 *M* NaOH. After stirring for 24 hr at 4°, the mixture was dialyzed exhaustively against isotonic saline and the undialyzed product was analyzed for both boron and protein.

Conjugation of $B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NCS$ and BSA. $B_{10}H_8S(CH_3)_2S(CH_3)CH_2C_6H_4NCS$ (15 mg, **2b**) was dissolved in 10 ml of dioxane. The solution was added slowly to 150 mg of BSA in 30 ml of a CO_3^{2-}/HCO_3^{1-} buffer (pH 9). After the addition, the pH of the solution had dropped to 7 and was adjusted to 9 with Na_2CO_3. The solution was stirred at 0° overnight. The mixture was then filtered and dialyzed in a comparable manner to the above procedure.

Coupling of RCOOH (2a and 2d) with BSA. The desired boron hydride (27 mg) was dissolved in 20 ml of DMF along with 30 mg of BSA and 10 mg of dicyclohexylcarbodiimide (DDC) and stirred in an ice bath for 12 hr. The solution was then diluted with 30 ml of H_2O and dialyzed in a similar manner to the above procedure. The solution was then centrifuged to remove any suspended solids and analyzed for boron and protein content.

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Application of the Sequential Simplex Method in Designing Drug Analogs

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An EVOP sequential simplex optimization method is proposed for the design of drug analogs. The method is based on certain regularities in the structure of compounds having the same biological activity, and it does not require numerical calculation. The Hansch parameters and the biological activities were taken as coordinates in our work. The method has been illustrated by retrospective examples. According to the statistical analysis regarding a less favorable example, the method is superior to an unsystematic choice at a significance level of 0.01%.

In the past decade the Hansch method has become one of the most widespread methods in quantitative structure–activity relationship (QSAR) studies and in drug design. The method has been applied to more than 1500 members of about 150 different sets of compounds.[1]

First the Hammett constants and the partition coefficients were used to correlate the biological activity with the structure.[2] During the past 10 years the application of almost all the linear free energy related parameters has been used in correlations with biological activities of compounds;[1] however, there have been few attempts to use methods other than regression analysis to utilize the correlations between these parameters and the biological activities. As far as we know, there have been three attempts to apply methods other than regression analysis in this field.[3-5]

It is well known that structure–activity correlations for series of compounds can be determined by Hammett-type constants and the Hansch π constant by some simple relationships.[1] So one may expect that biological effects are