A SOJOURN IN THE SYNTHESIS AND BIOACTIVITY OF DIINDOLYLALKANES

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Abstract- The different synthetic routes to diindolylalkanes (DIAs), an important class of synthetic and natural products, their merits and demerits and the properties of the bioactive DIAs have been presented in this review which is the first of its kind in this field. The synthesis of the bioactive DIAs (3), streptindole (4), vibrindole A (6), 10 and 11 has also been included in this review.

Introduction:
The origin of diindolylalkanes dates back to 1886 when Emil Fischer reported the formation of 1,1-bis(3′-methyl-2′-indolyl)-1-phenylmethane by heating skatole with benzaldehyde using zinc chloride as catalyst.1 But more than seventy years later, it was demonstrated that no such product is formed under these conditions.2 The first definitive report on the synthesis of a diindolylalkane, however, came from Fischer himself in the following year of its first report.3 This time he prepared 1,1-bis(2′-methyl-3′-indolyl)-1-phenylmethane (1) by heating 2-methylindole with benzaldehyde - an observation which was confirmed later in the aforementioned study.2 Bis(3-indolyl)methane (2), the simplest member of this class, was, however, synthesised much later by the reaction of indole or 3-indolylmagnesium bromide with formaldehyde and by the dimerisation of 3-hydroxymethylindole or its N,O-diacetyl derivative in neutral, alkaline or slightly acidic solution.4-6 Since the original report, the synthesis of many diindolylalkanes, henceforth abbreviated as DIAs, has been reported, which stemmed mainly from studies of the reactions of indole and its derivatives. But the year 1977 marked the beginning of a new era in this
field when three toxic indolic metabolites were isolated from the fungus, *Balansia epichloe*, a parasite to pasture grasses which were known to elicit ergot-type syndrome in cattle grazing on these infected grasses.\(^7\) One of these compounds was 3,3-bis(3′-indolyl)propane-1,2-diol (3), the first DIA reported from a natural source. Interestingly, both lysergic acid diethylamide (LSD, the most important ergot alkaloid) and 3 are indole derivatives, were isolated from similar fungi and cause similar biological responses in their consumers - human beings for LSD and cattle for 3.

![Chemical structure of DIAs](attachment:image.png)

A number of DIAs have since been reported to be isolated from terrestrial and marine natural sources, *viz.* parasitic bacteria, tunicates and sponges,\(^8-12\) and some of these possess significant biological activities. Expectedly, since the first report of the occurrence of a DIA in nature, there has been a surge in the synthesis of DIAs, occurring naturally or not. In view of the continuous reports of the isolation of DIAs from natural sources, their biological properties and the absence of any collective discussion on this class of compounds, we present herein an overview of the various synthetic avenues to DIAs, including those of the naturally occurring ones, briefly touching upon the sources and structures of the latter and the bioactivities of both natural and synthetic DIAs. Bis(3-indolyl)methane (2) and its derivatives have been discussed only marginally in this review, since their synthesis is well documented.\(^13,14\) Also, only one instance of diindolylalkanes substituted at different sites of the alkane by the two indole nuclei has been discussed, because all naturally occurring and most of the synthetic DIAs, symmetrical or not, contain an alkane backbone substituted at the same site by the two indolyl moieties.

The structures of the naturally occurring DIAs have been depicted below. Of these, six are 3,3′-DIAs (3-6, 10, 11), two are 2,3′-DIAs (7, 8) and the rest is a 3,4′-DIA (9). Additionally, a diindolyl-piperazine,\(^9\) a diindolylindolone\(^10\) and three tris-indoles\(^11,12\) have been reported from natural sources, but these are outside the purview of this article. The structures of many, but not all, synthetic DIAs have been shown later in this article during discussion on their syntheses.

Sources:
For 4: *Streptococcus faecium* IB 37 (human intestinal bacteria)\(^8\)
For 5: *Didemnum candidum* (a tunicate)\(^9\)
For 6: *Vibrio parahaemolyticus* (marine bacteria)\(^10\)
For 5, 7-9: *Orina* species (sponge)\(^11\)
For 10, 11: *Escherichia coli* (bacteria; indole-supplemented)\(^12\)
A survey of the literature on the synthesis of the naturally occurring DIAs unfolded two important pieces of information. Firstly and interestingly, one DIA, viz. vibrindole A (6) had been synthesised at least thrice much earlier than and once contemporarily with the first report of its isolation from a natural source. Secondly, the DIAs 3-6, 10 and 11 have been synthesised by the reaction of indoles with aldehydes, \(^7,8,15\) \(\alpha\)-ketoacids, \(^12,16\) enoic and ynoic acids and esters, \(^17\) carbon-transfer reagents, \(^18,19\) alcohols \(^20\) and nitrones, \(^21,22\) catalysed mostly by protic or Lewis acids. Thus, five different routes \(^15,17-22\) were successfully employed for the synthesis of vibrindole A (6), four routes \(^8,16,18,19,21,22\) for streptindole (4), and one route each for \(3,7,5,21,22\) 10, \(^12\) and 11, \(^12\) A large number of DIAs, not reported from natural sources, have also been synthesised by many of the aforesaid and similar \(^6,23-36\) routes. A new route involving the aminoalkylation of electron-rich aromatics using preformed iminium salts has recently been reported for the synthesis of DIAs. \(^37\) The various routes have been briefly discussed below in the chronological order of their appearances, mentioning therein, as and when applicable, the synthesis of the naturally occurring DIAs as well.

(1) **Reaction of indoles with aldehydes or ketones**: \(^7,8,13,15,23-27\)

The acid-catalysed reaction of indoles with aldehydes or ketones is the earliest, by far the simplest and the most widely used route to the synthesis of DIAs. The literature abounds in examples of this approach and the work carried out till late sixties is well documented. \(^13,23\) Indole and 3-unsubstituted indoles form 3,3’-DIAs, and 3-substituted indoles result in 2,2’-DIAs. The reactions may generally be represented as follows (Scheme 1).
Through this route were achieved the syntheses of the first reported natural DIA, 3,3-bis(3′-indolyl)propane-1,2-diol (3)\textsuperscript{7} and of the bacterial metabolites streptindole (4)\textsuperscript{8} and vibrindole A (6)\textsuperscript{15} by the reaction of indole with glyceraldehyde, glycolaldehyde acetate and acetaldehyde, respectively (Scheme 2).

An interesting observation on the reaction of indoles with acylpyridines was recorded by Bergman.\textsuperscript{24} Indole itself condensed with 3- and 4-acetylpyridines to furnish the 1,1-bisindolyl-1-pyridyl-ethanes (12). In contrast, 2-alkylindoles reacted with 3- and 4-acetylpyridines to form 1-indolyl-1-pyridylethenes (13) and 1,2-bisindolyl-1-pyridylethanes (14), respectively. Compounds of type 13 were suggested to be the unisolated intermediates in the formation of the products (14). The 1,1-bis(indolyl)-ethanes (12) could be differentiated from the 1,2-bis(indolyl)ethanes (14) by their mass spectra. Thus, in the MS of 12, the base peaks corresponded to the loss of a methyl radical, whereas the MS of 14 recorded dominant peaks, but not base peaks, arising from the loss of an indolylmethylene radical (Scheme 3).

The reaction of indoles with aldehydes and ketones has also been successfully accomplished employing lanthanide triflates as catalysts, usually in aqueous ethanol at room temperature for 12-36 h, to furnish DIAs in 47-99\% yields.\textsuperscript{25} Expectedly, 2,3-diunsubstituted indoles furnished 3,3′-DIAs, whereas 2,2′-DIAs resulted from 3-substituted indoles. Of the various lanthanides used, dysprosium (Dy) was found to
be most effective. Thus, the DIA (15), for example, was obtained in 77% yield from indole and acetophenone using dysprosium triflate as catalyst (Scheme 4).

It may be noted that the reaction of indole-3-acetic acid (IAA) with n-hexanal followed different courses with different solvents. In chloroform, the product was the 2,2'-DIA (16), as against the ethylated 2-substituted IAA (17), formed in aqueous ethanol (Scheme 5).

Recently indium trichloride has been demonstrated to effectively catalyse the reaction of indole itself with substituted benzaldehydes (five substrates) and Schiff bases (also five substrates) in acetonitrile solution at room temperature to furnish bis(3'-indolyl)methanes (18) as the only products in good yields (Scheme 6).

In more recent times, an Indian group has developed a highly efficient synthesis of 3,3'-diindolylalkanes (19) by the reaction of mainly indole (using 2-methylindole only once) with more than a dozen of aldehydes, mainly araldehydes, and a few ketones using lithium perchlorate in ether or acetonitrile (Scheme 7). Essentially neutral reaction conditions and work-ups were employed, and the products were obtained in high yields.
(2) Reaction of indolyl Grignard reagents with aldehydes and ketones.\(^6\)\(^{28-32}\)

A simple variant of the first route is the reaction of 3-indolylmagnesium bromide or iodide with aldehydes or ketones, leading to symmetrical DIAs (20).\(^{28-31}\) The reaction carried out so far may be represented as follows (Scheme 8).

Bis(3-indolyl)methane was also prepared by the reaction of 3-indolylmagnesium iodide with paraformaldehyde (Scheme 9).\(^6\)

Subsequently, the first synthesis of a 2,2-bis(3′-indolyl)ethylamine, viz. (21), albeit in ‘a small amount’, was achieved by the reaction of 3-indolylmagnesium iodide with benzamidoacetaldehyde (Scheme 10).\(^{32}\)

(3) Reaction of indoles with N,N-dialkylaminoalkyl aldehydes and their diethyl acetals.\(^{33}\)

In mid-60’s, a French group\(^{33}\) dealt with the preparation of a large number of 2,2-bis(3′-indolyl)ethylamines (22) and 3,3-bis(3′-indolyl)propylamines (23) and a few dialkylaminoalkyl 2,2-bis(3′-indolyl)acetates (24, 25) for comparing their pharmacological properties with those of their diaryl analogues.

The major route to the synthesis of nearly thirty bis(indolyl)alkylamines (22) was the acid-catalysed condensation of indoles with N,N-dialkylaminoalkyl aldehydes or their diethyl acetals, as shown below (Scheme 11).\(^{33}\)
The bis(3′-indolyl)ethylamines (23) were also prepared by the reduction of the corresponding acetamides (Scheme 12).\(^{33}\)

![Scheme 12](image1)

The same report also described the preparation of a third group of DIAs, viz. the bis(3′-indolyl)acetates (24) and (25) either by the reaction of bis(indolyl)acetic acid with 1-chloro-2-diethylaminoethane, leading to 24, or by the transesterification of ethyl bis(indolyl)acetate with dialkylaminoethanol or -propanol, leading to 25 (Scheme 13).\(^{33}\)

![Scheme 13](image2)

Of the synthetic compounds reported in this publication,\(^{33}\) three bis(indolyl)ethylamines and two bis(indolyl)propylamines exhibited significant bioactivities, which have been discussed later.

4) Reaction of indoles with \(\alpha\)-ketoacids:\(^{12,16,33-37}\)

The first report on the reaction of indole with an \(\alpha\)-ketoacid was that with glyoxylic acid, catalyzed by sulfuric acid, when 3,3′-diindolylacetic acid (DIAA) was reported to be formed in high yield.\(^{33}\) However, its molecular formula, derived from elemental analysis, was the only evidence put forward in support of the proposed structure (Scheme 14).

![Scheme 14](image3)

It is noteworthy that Greenberg had earlier suggested that the product of reaction between indole and sodium 3-glyoxylate could possibly be diindolylacetic acid.\(^{34,35}\) Galston, who was a party to the Greenberg’s work,\(^{34}\) subsequently studied the reaction of indole with sodium glyoxylate, which furnished sodium 3-indolylglycolate (26a) and DIAA (Scheme 15).\(^{36}\) DIAA showed an auxin-like property, which has been discussed later.
Still later, this reaction was thoroughly studied at different pHs, from which it transpired that the pH of the medium was the predominant factor in controlling the course of the reaction. Thus, at basic pH (<9), the reaction furnished the 3- and 1-substituted monomeric indoles (26a) and (28a) and the dimeric indoles (27a) and (29a), all of which were isolated and identified as their methyl esters (26b-29b) (Scheme 16).

It was also demonstrated in this work that (i) the reaction between indole and sodium glyoxylate in nearly neutral aqueous solution afforded 27a, (ii) that between indole and 26a,b at basic pH (<9) furnished 27a, b (iii) the same between 26b and 28b at pH 9 rapidly formed 29b and (iv) increasing pH values raised the ratio of 1- to 3-substitution.37 Streptindole (4), the first genotoxic diindolylethane metabolite isolated from the cultures of human bacteria, was first synthesised by this route in moderate yield (42% from indole) (Scheme 17).16

The two novel bisindoles 2,2-bis(3′-indolyl)propionic acid (10) and 2,2-bis(3′-indolyl)isocaproic acid (11), isolated from indole-supplemented supernatants of E. coli and corynebacteria, were recently synthesised in unspecified yields by the reaction of indole with pyruvic acid and α-ketoisocaproic acid, respectively, following incubation at 37°C in aqueous medium (Scheme 18).12
The author suggested that this type of condensation may also proceed in vivo, thus accounting for the \( \alpha \)-ketoacid toxicity observed in the neurogenic degenerative disorders, known as maple syrup urine disease.\(^{38,39}\)

(5) Reaction of indole with enoic / ynoic acids and esters:\(^{17}\)

Vibrindole A (6), isolated in 1994 from marine bacteria, symbiotic with the ichthyotoxic mucus of the box fish, \textit{Ostracion cubicus}, had been synthesised two decades before its isolation from a natural source by the reaction of indole with propiolic acid or its methyl ester or with 3-(3\(^{\prime}\)-indolyl)acrylic acid, followed by hydrolysis (where applicable) and decarboxylation (Scheme 19).\(^{17}\)

Obviously, all three routes proceeded through the intermediacy of 2,2-bis(3\(^{\prime}\)-indolyl)propionic acid. Vibrindole A showed antibacterial activity, discussed later.

(6) Reaction of indoles with carbon-transfer reagents:\(^{18,19}\)

A recent method described the acid-catalysed condensation of indoles with oxazolidines and tetrahydro-\((2H)\)-1,3-oxazines to furnish a variety of functionalised 3,3\(^{\prime}\)-DIAs in low to good yields.\(^{18,19}\) Mechanistically, the appropriate C-2 carbon units of the oxazolidines and tetrahydrooxazines were transferred by acid-catalysis to indoles (Scheme 20). Tetrahydrooxazines were found to be more efficient than oxazolidines as carbon-transfer reagents.
Both streptinole (4) and vibrindole A (6), the latter even before its isolation from a natural source, were prepared\textsuperscript{18,19} by this method, as shown below (Scheme 21).

The mechanism of the acid-catalysed carbon-transfer reactions, as suggested by the authors, is shown in Scheme 22. However, it should be noted that the initial protonation should occur at the basic nitrogen atom rather than at the oxygen atom.

The authors claimed that this synthesis of streptindole was better than a previous low-yielding (2\%) synthesis\textsuperscript{8} and that the present approach was versatile enough to be considered better than another previous synthesis\textsuperscript{16} which involved survival of the labile indole moiety in all chemical transformations. Strangely, there was no mention of the yield of 4 in this report.\textsuperscript{18,19}

(7) Cyclodextrin-mediated anodic oxidation of indoles and alcohols:\textsuperscript{20}

In a recent novel approach, 1,1-bis(3′-indolyl)alkanes (30) were prepared by the anodic oxidation of indoles and alcohols in presence of 2,6-di-O-methyl-β-cyclodextrin (DMCD) (Scheme 23).\textsuperscript{20}

Experimenting with the formation of vibrindole A (6), the authors observed that DMCD was more efficient than α-, β- or γ-cyclodextrins.\textsuperscript{20} Cyclic voltametry and macro-scale electrolyses showed that these reactions were initiated by the oxidation of substrates (alcohols) with less negative (i.e. higher)
oxidation potentials than those of indoles. Examples of this type of electrochemical oxidation were stated to be rare (see refs. 2a and 2b in ref. 20 above). The presence of a cyclodextrin was found to be essential for the formation of the DIAs, as only a tarry material was obtained in its absence.

(8) Reaction of indoles with nitrones and 3-indolylhydroxylamines:21,22,38,40

The condensation of indoles with activated aromatic nitrones was first studied by an Indian group.40 Indole and 2-methyl/phenylindoles were allowed to react with two phenylnitrones to furnish 1,1-bis(2'-H/methyl/phenyl-3'-indolyl)-1-(phenyl/nitrophenyl)methanes (31), as shown in Scheme 24. 3-Substituted indoles, e.g., skatole was found to be inert to such conditions.

This method with a clearly greater potential was later well explored by a French group who thoroughly studied the reaction of indoles with nitrones and 3-indolylhydroxylamines using trimethylsilyl chloride (TMS-Cl) as an activator.21,22 Thus, indoles and substituted indoles reacted with the nitrones of several alkanals and araldehydes to furnish symmetrical bis(3-indolyl)alkanes (32) (Scheme 25).

The metabolites (4, 5 and 6) were prepared in good to moderate yields by this method (Scheme 26).
The most usual procedure of preparing symmetrical 3,3'-DIA is the acid-catalysed reaction of indoles with aldehydes or ketones. In the case of aldehydes, the method suffers from the disadvantages that the products are formed in only moderate yields, an indole dimer is a usual by-product and acid-sensitive aldehydes cannot be used. The present method using nitrones does not suffer from any such problem. When, however, equimolar amounts of indole and nitroene were mixed in presence of two equivalents of anhydrous hydrogen chloride at 0° to -10°C, thirteen 3-indolylhydroxylamines (33) were obtained in moderate to good yields, as shown below (Scheme 27).21,22

The reaction failed in the case of the reaction of indole itself with the nitrones derived from isobutanal and benzaldehyde. Also, in two cases, the reactions were carried out at room temperature. Trifluoroacetic acid in methanol or pyridinium p-toluenesulfonate (PPTS) in toluene was also used in place of anhydrous hydrogen chloride, but in that case the yields were lower and 3,3'-DIA were formed as by-products.22

This synthesis of 3-indolylhydroxylamines (33) led to the first-ever general synthesis of nine unsymmetrical DIA (34) by the reaction of 33 (six substrates) with indoles using conditions as in the case of the reactions with nitrones. It must be emphasized that two symmetrical DIA were also prepared by this method using similarly substituted indoles and indolylhydroxylamines (Scheme 28).21,22

(9) Aminoalkylation of indoles using preformed iminium salt.41

A simple and straightforward route to a variety of Mannich bases has recently been developed using preformed iminium salts derived from aldehydes other than formaldehyde as reagents for the aminoalkylation of, inter alia, indoles.41 In this method, N-methylindole reacted with preformed N-methyl-N-trimethylsilylimminium triflate (34) to furnish the DIA (35) in a better yield (77%) than that reported in its earlier preparation (60%) by the acid-catalysed condensation of N-methylindole with benzaldehyde (Scheme 29).23
We like to conclude our discussion on the synthetic efforts towards DIAs by stating that we have recently developed a new, expeditious, efficient and general synthesis of 2,2-bis(3′-indolyl)nitroethanes (37) by the microwave-assisted Michael reaction of 3-(2′-nitrovinyl)indole (36) with indole and alkylindoles on TLC-grade silica gel surface with and without the use of microwave (Scheme 30). When microwave was used, the reactions were remarkably fast, complete within 10 minutes, and the yields were consistently high. To our knowledge, this is the first microwave-assisted synthesis of DIAs, and that too on a solid surface. Only the product (37) (R=R′=X=H) obtained from indole and 36 was a symmetrical DIA, and the rest were unsymmetrical DIAs. This method constitutes the second general synthesis of unsymmetrical DIAs, the previous one being the TMS-Cl-catalysed condensation of indoles with nitrones or 3-indolylhydroxylamines.

As shown in Scheme 30, the same products (37) were also obtained in comparable yields without taking resort to microwave, i.e., at room temperature but again on TLC-grade silica gel surface. These reactions, however, required considerably longer periods for completion. TLC-Grade silica gel was found to be crucial for the success of the reactions under both sets of conditions. Under either of the conditions, skatole failed to react with 36. Interestingly, the reactions also proceeded in solution, but both symmetrical and unsymmetrical DIAs were produced. The symmetrical DIAs resulted from tandem Michael reaction-elimination-Michael reaction, which also, to our knowledge, has not been documented as yet.

**Biological activity of DIAs:**

The bioactivity of DIAs of synthetic origin appears to have been first reported by the French workers Julia and Tilly way back in 1965. Of the several DIAs prepared by them, the bis(3-indolyl)propylamine lactates (38) and (39) showed strong coronary dilating activity, which was comparable to that of papaverine. These DIAs also displayed long-acting stimulating activity on isolated rabbit heart. The bis(3-indolyl)ethylamine hydrochlorides (40-42) exhibited antagonistic activity on the arterial tension of dogs.
Pertinently, the important coronary dilator (43), a Hoechst product, initiated this piece of synthetic work.\textsuperscript{33} Expectedly, the structurally similar propylamines (38) and (39) showed similar and more potent properties than the diindolylethylamines (40-42).

As hinted at earlier, Greenberg’s original observation in 1968\textsuperscript{35} was verified later in 1969.\textsuperscript{36} 2,2-Bis(3′-indolyl)acetic acid was indeed found to be markedly active, more active than auxin, in promoting extension of 5 mm etiolated pea sections in presence of 2% sucrose. At an optimum concentration of 1.5-5 mg/mL, the section length increased by 120-130% after 16-18 h and by 150-170% after 30 h.

The first reported naturally occurring DIA (3), a fungal metabolite, was found to be toxic to fertile leghorn eggs.\textsuperscript{7} Streptindole (4) was the first bacterial DIA metabolite which showed genotoxicity and DNA-damaging activity which were reparable in \textit{Bacillus subtilis} cells.\textsuperscript{8} In this report, other indolic genotoxic metabolites were suggested to be produced by \textit{Veillonella parvula} ATCC 10790 strain which too is predominant in human faeces.

When stressed or disturbed, the box fish \textit{Ostracion cubicus} (Ostraciidae) secretes an ichthyotoxic mucus from its skin. This white, foamy mucus was cultured in sterile sea water containing SLB agar. Two of the strains isolated from this culture medium were identified as \textit{Vibrio parahaemolyticus} (Vibrionaceae). From the ethyl acetate extract of this culture medium was isolated a DIA, designated vibrindole A (6), in addition to 2,2-bis(3′-indolyl)-3-indolone.\textsuperscript{8} The DIA (6), though prepared since 1963 by several routes, was demonstrated for the first time to exhibit antibacterial activity against \textit{Staphylococcus aureus}, \textit{S. albus} and \textit{B. subtilis}, where gentamycin was used as the standard drug. In \textit{in vitro} antiserotoninergetic activity assays performed on male guinea pig ileum, the sponge metabolites (7, 8) (both 2,3′-DIAs) and (9) (a 3,4′-DIA) showed weak antagonistic activity at low concentrations (IC\textsubscript{50}: 7, 50; 8, 10; 9, 100 \textmu M).

In the somatostatin receptor-neuropeptide Y receptor-binding and human B2 bradykinin receptor-binding assays at a concentration of 5 \textmu g/mL, the DIAs (7) and (8) showed 87% and 91%, 63% and 67%, and 63% and 89% inhibitions, respectively, of the specific ligand binding. These properties were helpful in developing immunochemical studies on these compounds.

It needs to be emphasized that 3,3′-diindolylmethane (DIM) has been gaining increasing importance in recent years because of its potent anti-carcinogenic properties. It is well known that indole-3-carbinol occurs as a glucosinolate in cruciferous vegetables like cabbage and broccoli. This dietary indole has long
been known to modulate carcinogenesis in many animals. In late eighties, it was first pointed out that dietary indoles influence monooxygenase activity through a number of their acid-condensation products generated upon the introduction of these indoles into the stomach. DIM, subsequently identified as the major (40%) conversion product of indole-3-carbinol in stomach was later found to be responsible for the observed in vivo effect of this dietary indole. In subsequent years, DIM was reported to induce hydroxylation of hepatic estradiol and adrosterone, inhibit cytochrome P-450 and detoxification of the hepatocarcinogen aflatoxin B1, cause apoptosis in human breast cancer cells via the activation of estrogen receptor function and act as a potent estrogen in rainbow trout liver. Dihalo-DIMs have recently been reported to significantly inhibit carcinogen-induced rat mammary growth.

CONCLUSION:
It is evident from the aforesaid discussions that diindolylalkanes constitute an emerging class of natural products which are structurally attractive, synthetically challenging and significantly bioactive. Though the synthesis of symmetrical DIAs has been studied in greater details throughout the last century, the synthesis of the unsymmetrical DIAs is still wide open. The development of only two general synthetic avenues to the unsymmetrical DIAs – one in 1997 by a French group and the other by us – bears testimony to this assertion. Besides, broad-spectrum biological screening of both types of DIAs still remains to be done.

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