

## Naturally Occurring Isocyano/Isothiocyanato Compounds: Their Pharmacological and SAR Activities

Dmitri O Levitsky<sup>1</sup>, Tatyana A Glorizova<sup>2</sup>, Vladimir V Poroikov<sup>2</sup>, Valery M Dembitsky<sup>3</sup>

<sup>1</sup>CNRS UMR 6204, Biotechnologie, Biocatalyse et Biorégulation, Faculté des Sciences et des Techniques, Université de Nantes Nantes, 44322 Nantes Cedex 03, France.

<sup>2</sup>Institute of Biomedical Chemistry, Moscow 119121, Russia.

<sup>3</sup>Institute for Drug Discovery, P.O. Box 45289, Jerusalem 91451, Israel.

**Corresponding Author:** Valery M. Dembitsky, Institute for Drug Discovery, 8 Ha-Marpe Str, P.O. Box 45289, Jerusalem 91451, Israel, **Tel:** +972-526877444; **Email:** iddrdo@gmx.com

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### ABSTRACT

The present paper describes research on natural isocyano/isothiocyanato compounds isolated from various cyanobacteria and other microorganisms. More than 80 biologically active metabolites show confirmed antibacterial, antitumor, antifungal, and other activities. The structures and reported pharmacological activities of isocyanide/isothiocyanato and thiocyanato compounds are reviewed. Using the SAR (Structure–Activity Relationships) approach realized in computer program PASS, some additional activities were also predicted, which point toward new possible applications for these compounds. According to SAR investigation with PASS, natural isocyano/isothiocyanato compounds primarily show antineoplastic, antiprotozoal, and anti-psoriatic activities. This article emphasizes the role of isocyano/isothiocyanato and thiocyanato metabolites as important leads for drug discovery.

### ABBREVIATIONS

The MIC (minimum inhibitory concentration) is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

Pa and Pi value tells the probability of activity. Pa means probability to be active and Pi means probability to be inactive.

The IC<sub>50</sub> is a measure of how effective a drug is. It indicates how much of a particular drug or other substance is needed to inhibit a given biological process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half.

### INTRODUCTION

Isocyano/isothiocyanato compounds are a rare group of biological active products with limiting occurrence in nature [1,2]. They play an important role in the secondary metabolism of cyanobacteria and other microorganisms [1-6]. More than three and a half thousand strains of cyanobacteria have been studied, resulting in the description of more than one thousand secondary compounds, including more than two hundred alkaloids, and other bioactive metabolites [7-19].

Many of these alkaloids possess diverse pharmacological activities, such as antibacterial, antimalarial, antifouling, and anti-algal activities. These alkaloids apparently function via isocyanide (-N≡C), isothiocyanate (-N=C=S) and/or thiocya-

nate (-S-C≡N) group(s). Isothiocyanates have been identified as preferred active constituents of several cyanobacterial families, and some microorganisms. Isothiocyanates suppress tumor cells growth by generating reactive oxygen species or by inducing cycle arrest leading to apoptosis [20-22].

Compounds containing the isocyano group include notably natural alkaloids, and the first isocyanide, xanthocillin was obtained from fermentation broth of the fungus *Penicillium-notatum* as early as in 1948 [23-25]. Similar metabolites containing a thiocyanate moiety have recently been isolated, and a few thiocyanate alkaloids have recently been discovered [26-28].

Several reviews on naturally occurring isocyano/ isothiocyano/thiocyano natural products and related compounds from both marine and terrestrial sources have been published [1, 6, 24, 29-35].

Using the SAR (*Structure–Activity Relationships*) approach realized in computer program PASS, some additional activities were also predicted, which indicates new possible applications for these compounds. This article emphasizes the role of isocyano/isothiocyanato and thiocyanato compounds as significant sources of leads for drug discovery. The surprising results refine the current understanding of the interplay between the chemical structure and activities.

### Prediction of Novel and Additional Pharmacological Activities

Bearing in mind that the above data on the biological activity of isocyano/isothiocyanato compounds and their analogues characterized only a small part of the possible biological potential in these molecules, we estimated their biological activity spectra using a computer prediction (Table 1). Computer program PASS (*Prediction of Activity Spectra for Substances*) estimates the probable biological activity profiles for compounds based on their structural formulae in MOL file or SD file formats [36-39].

A general list of predictable biological activities consists of over 7,000 terms including pharmaco-therapeutic effects (e.g., antiarrhythmic), biochemical mechanisms (e.g., cyclooxygenase 1 inhibitor), toxicity (e.g., carcinogenic), metabolism (e.g., CYP3A4 inhibition), gene expression regulation (e.g., VEGF expression inhibition), and transporter-related activities (e.g., P-glycoprotein substrate). PASS prediction is based on information of the structure-activity relationships in more than 900,000 compounds with known biological activities. The average prediction accuracy estimated in a leave-one-out cross-validation procedure for the entire PASS training set is approximately 95% [40]. For each activity, Pa and Pi values are calculated and can be interpreted either as the probabilities of a molecule belonging to the classes of active and inactive compounds, respectively, or as the probabilities of the first and second types of errors in prediction.

The robustness of the PASS algorithm has been shown in special experiments with principal compounds from an MDDR database consisting of 18,977 compounds with 124 activities. The set of compounds was divided 50 times at random into two equal subsets. The first subset was used as the training set, the second as the evaluation subset and vice versa (100 experiments). 20, 40, 60, or 80% of the information (*activity/structure data*) was randomly excluded from the training set. The average accuracy of prediction (IAP) was calculated for each type of activity. Despite the removal of up to 60% of the information, PASS continued to provide reasonable prediction accuracy [41].

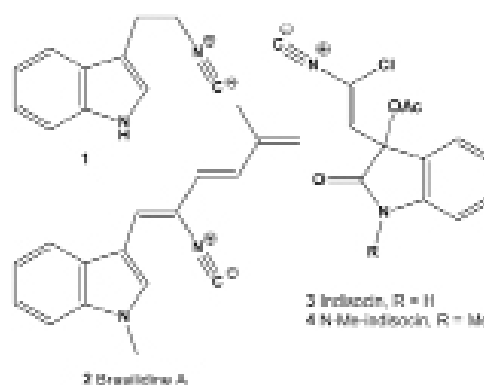
The interpretation of the prediction results and the selection of the most promising compounds are based on flexible criteria that depend on the purpose of the particular investiga-

tion. If the user chooses a higher value of Pa as a threshold for the selection of probable activities, the chance to confirm the predicted activities by the experiment is also high; however, many activities will be lost. For instance, if Pa > 80% is used as a threshold, approximately 80% of the real activities will be lost; for Pa > 70%, the portion of lost activities is 70%, etc. By default, the Pa > Pi value determined at the training is used as a threshold that provides a mean accuracy 95%. The average accuracy of the PASS predictions obtained for the heterogeneous evaluation set was nearly 90% [42-44].

Therefore, isocyano/isothiocyanato compounds can be used as a source for selecting hits in many different pharmacotherapeutic areas. In the further application of a SOSA (*Selective Optimization of Side Activities*) approach [45], desirable activities can be increased and unwanted activities can be reduced. Although the majority of the known biological activities for respective isocyano/ isothiocyanato alkaloids are associated with antineoplastic action, their number is less than 60% (51/80) among the predicted focal activities. A computer analysis of the predicted biological activity spectra showed that 58 types of biological activity are predicted with Pa > 70%, 199 with Pa > 50%, 463 with Pa > 30%, and 810 with Pa > Pi.

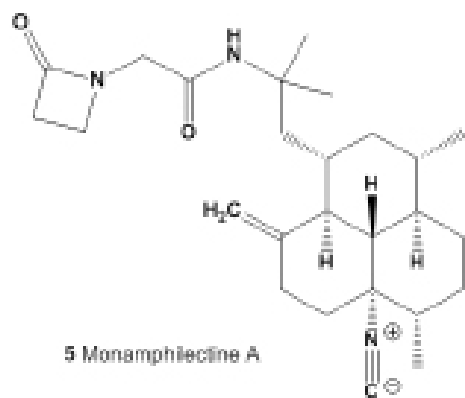
### Rare and Unusual Compounds

Compound (1), 3-(2-isocyanoethyl)-1H-indole, is produced by *Streptomyces* species [46]. An unusual indole alkaloid with cytotoxic activity, named brasilidone A (2) has been isolated from the actinomycete *Nocardia brasiliensis* IFM 0089 [47]. Two antibiotics, indisocin (3) and N-methylindisocin (4), were isolated from the soil culture filtrate of *Nocardia blackwellii* MG323-hF2, which was collected at Shinagawa-ku (Tokyo, Japan) [48]. Both compounds showed antibacterial and antifungal activities against *Bacillus anthracis*, *Bacillus cereus* ATCC 10702, *Bacillus subtilis* NRRL B-558, *B. subtilis* PCI 219, *Corynebacterium bovis* 1810, *Micrococcus luteus* FDA 16, *Micrococcus luteus* FDA 1001, *Staphylococcus aureus* 209P, *S. aureus* MS8710, *S. aureus* MS8610, *S. aureus* Smith, *Escherichia coli* K-12, *E. coli* ML 1629, *E. coli* NTHJ, *Klebsiella pneumoniae* PCI 602, *Proteus rettgeri* GN311, *P. rettgeri* GN466, *P. vulgaris* OX19, *Salmonella enteritidis*, *Salmonella typhi* T-63, *Serratia marcescens*, *Shigella dysenteriae* JS11910, *S. flexneri* 4bJS11811, *S. sonnei* JS11746, and *Mycobacterium smegmatis* ATCC 607 [49].

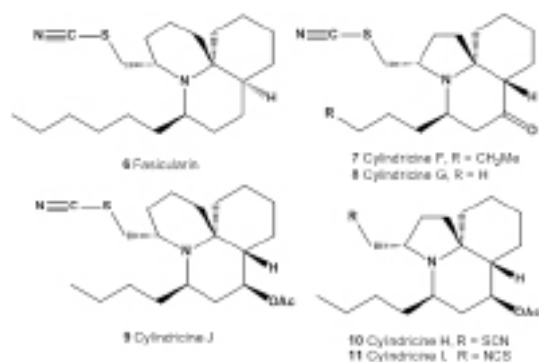


Diterpenoid  $\beta$ -lactam alkaloid, monamphilectine A (5), show-

ing potent antimalarial activity, was isolated from the Puerto Rican marine sponge *Hymeniacidon* sp. [50]. This alkaloid (5) demonstrated activity against a chloroquine-resistant protozoan parasite *Plasmodium falciparum* W2 strain at IC<sub>50</sub> values of 0.60 μM. Monamphilectine A (5) possesses also the bactericidal action against *Mycobacterium tuberculosis* H37Rv, MIC value of 15.3 μg/mL [50].



The tricyclic alkaloid, fascicularin (6) with cytotoxic properties against a DNA repair-deficient strain of yeast, as well as, cytotoxicity against Vero cells [30], was isolated from the ascidian *Neptheis fascicularis* collected in Pohnpei (Micronesia) [41,42].



Several structurally related tricyclic alkaloids, e.g., cylindricines F (7), G (8), J (9), H (10) and I (11) produced by the marine ascidian *Clavelina cylindrica* from Tasmania [53-55]. Cylindricine C (TKGP-100213) has showed the growth inhibition of human solid tumor cell lines [56]. Activities of compounds 1-11 are shown in Table 1.

**Table 1:** Confirmed pharmacological and probable new activities

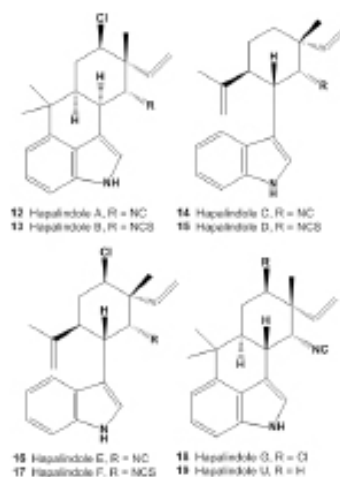
No	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa*)
1	Not studied	-	Antineurotoxic (0,773) Antineoplastic (0,718)
2	Cytotoxic	Antineoplastic (0,873)	Antacid (0,655) Gastric secretion stimulant (0,560)
3	Antifungal Antibacterial	Antifungal (0,657) Antibacterial (0,572)	Antineoplastic (0,538)

4	Antifungal Antibacterial	Antifungal (0,585) Antibacterial (0,546)	Antineoplastic (0,526)
5	Antimalarial Anti-mycobacterial	Antiprotozoal (Plasmodium) (0,938) Antiprotozoal (0,937)	Antieczematic (0,682) Antiosteoporotic (0,626) Bone diseases treatment (0,578)
6	Cytotoxic	Antineoplastic (0,734)	Cardiotonic (0,882) Antiarrhythmic (0,866) Nootropic (0,839)
7	Antineoplastic (solid tumors)	Antineoplastic (0,716)	Cardiotonic (0,824) Antiarrhythmic (0,784) Antischemic, cerebral(0,555)
8	Antineoplastic (solid tumors)	Antineoplastic (0,715)	Cardiotonic (0,834) Antiarrhythmic (0,801) Antischemic, cerebral (0,522)
9	Antineoplastic (solid tumors)	Antineoplastic (0,769)	Cardiotonic (0,856) Antiarrhythmic (0,822) Nootropic (0,634)
10	Antineoplastic (solid tumors)	Antineoplastic (0,769)	Cardiotonic (0,856) Antiarrhythmic (0,822) Nootropic (0,634)
11	Antineoplastic (solid tumors)	Antineoplastic (0,838) Apoptosis agonist (0,794)	Cardiotonic (0,882) Antiarrhythmic (0,845) Chemoprotective (0,562)

\*Activities with Pa > 0.5 are only shown.

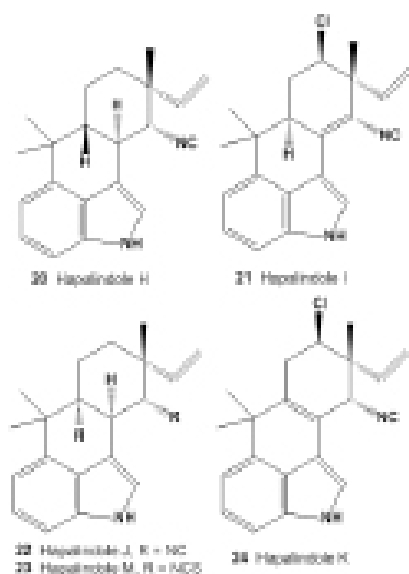
### Alkaloids of the Hapalindole Family

More than 30 years ago, Moore and co-workers isolated of alkaloids from soil cyanobacteria, that belong to the families ambiguines, fischerindoles, hapalindoles, welwitindolinones, hapalindolinones, hapaloxindoles, and fontonamides [57].

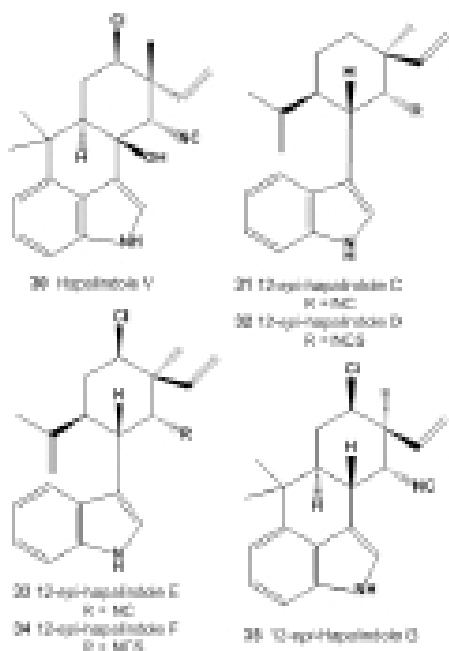


Several hapalindoles and welwitindolinones have showed insecticidal activity [58,59]. Reports have surfaced of anti-algal activity from the hapalindoles, anti-mycotic activity from

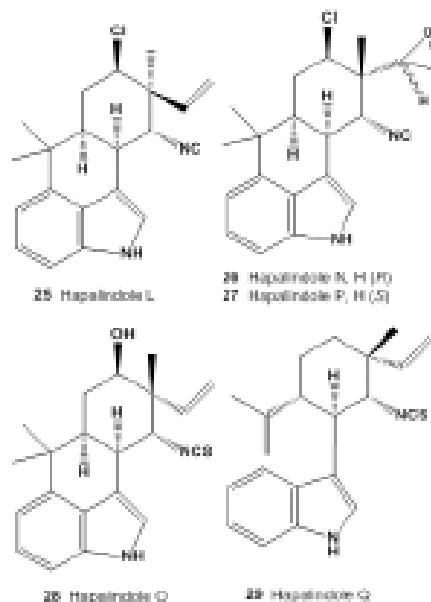
the hapalindoles, welwitindolinones, and ambiguines and antibacterial activity from the hapalindoles and ambiguines [7,8,57,60-65]. Furthermore, hapalindolinone A inhibits arginine vasopressin binding [66]. The welwitindolinones have showed an anticancer activity against multiple drug-resistant ovarian cancer cell lines [59,67,68].



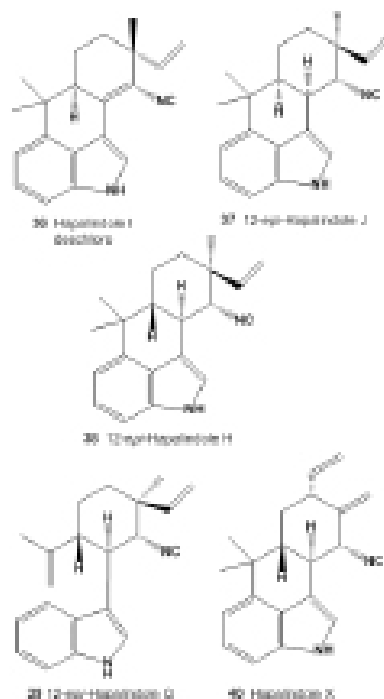
The antibacterial agents hapalindoles A (12), B (13), C (14), D (15), E (16), F (17), G (18), H (20) and I (21) were prepared by culturing the cyanobacterium *Hapalosiphon fontinalis* ATCC 39694 (Stigonemataceae) [69].



All obtained indole alkaloids showed antibacterial activity against *Staphylococcus aureus* X1.1, *S. aureus* V41, *S. aureus* X400, *S. aureus* S13E, *S. epidermidis* EPI1, *S. epidermidis* 222, *S. pyogenes* C203, *S. pneumoniae* Park 1, *S. faecium* ATCC 9790, *Streptococcus* sp. group D 2041, *Haemophilus influenzae* C.L., *H. influenzae* 76, *E. coli* N10, *E. coli* EC14, *E. coli* TEM, *Klebsiella pneumoniae* X26, *K. pneumoniae* X68, *K. pneumoniae* KAE, *Salmonella* sp. X514, *Shigella sonnei* N9, *Proteus morganii* PR15, and *Acinetobacter calcoaceticus* AC12.



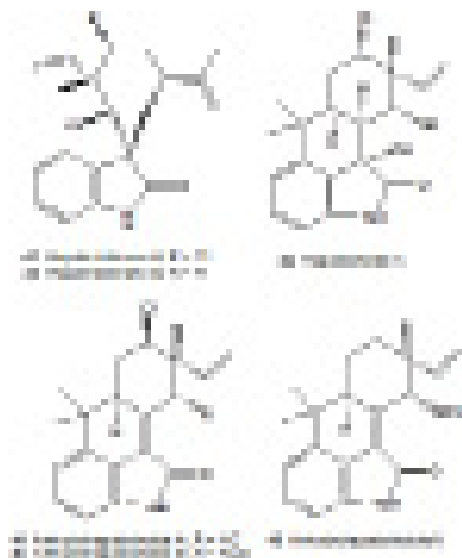
The antifungal agents hapalindoles A (12), C (14), E (16), G (18) and H (20) obtained from culturing the cyanobacterium *Hapalosiphon fontinalis* ATCC 39694 (Stigonemataceae) showed *in vivo* activity against *Candida albicans* and *Trichophyton mentagrophytes* [69].



Cultured *Westiellopsis* sp. SAG 20.93 and *Fischerella muscivola* UTEX LB1829 cyanobacteria led to the isolation of several alkaloids, namely deschlorohapalindole I (36), hapalindole X (40) and other indole alkaloids: hapalindoles (12), C (14), G (18), H (20), I (21), J (22), U (19), anhydrohapaloxindole A (44), and fischerindole L (68) [70].

All examined compounds exhibited weak to moderate cytotoxicity against HT-29, MCF-7, NCI-H460, SF268, and IMR90 cells. The hapalindole X (40) and A (12) and hapalonamide H (20) have showed activity against both *M. tuberculosis* and *C. albicans*, MIC values at 0.6 to 2.5  $\mu$ M, respectively

[71]. As antibacterial and antifungal agents, indole alkaloids, known as hapalindoles J (22), K (24), L (25), M (23), N (26), O (28), P (27), Q (29), U (19) and V (30), were prepared by cyanobacterium *Hapalosiphon fontinalis* ATCC 39694 [72]. Isolated alkaloids demonstrated antibacterial and antifungal activities against *Staphylococcus aureus* X1.1, *Bacillus subtilis* X12, *Micrococcus luteus* X186, *Streptococcus pneumoniae* X647, *Proteus vulgaris* X45, *Salmonella gallinarum* X142, *E. coli* X161, *E. coli*X580, *Saccharomyces pastorianus* X52, *Neurospora crassa* X846, and *Candida albicans* X657 [72].



Freshwater cyanobacterium *Fischerella* ATCC 43239 have produced of 12-*epi*-hapalindole C isonitrile (31), 12-*epi*-hapalindole E isonitrile (33), 12-*epi*-hapalindole J isonitrile (37), and hapalindole L (25). Compounds 25, 31 and 33 have showed insecticidal activities [58].

The alkaloids 12-*epi*-hapalindole E isonitrile (33), isolated from the cyanobacterium *Fischerella* sp., and the indolophenanthridinecalothrixin A from *Calothrix* sp., were characterized in terms of their ability to kill several organisms and cell types and their biochemical modes of action. Both compounds inhibited RNA synthesis, and consequently protein synthesis, in *Bacillus subtilis*.

Calothrixin A also inhibited DNA replication, the hapalindole having little effect on this process. Measurements of *in vitro* RNA synthesis confirmed the *in vivo* results and suggested that both compounds inhibit RNA polymerase directly; the degree of inhibition was independent of the DNA concentration but strongly dependent on the polymerase concentration [64]. Activities of compounds belonging to the hapalindole family are shown in Table 2.

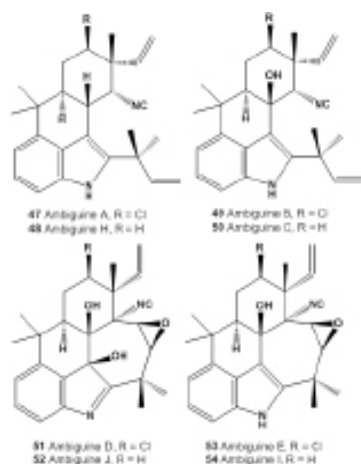
**Table 2:** Confirmed pharmacological and SAR activities.

No	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa*)
12	Antibacterial Antifungal Antituberculous Cytotoxic	Antibacterial (0,487) Antifungal (0,535) Antimycobacterial (0,503) Antineoplastic(0,749)	Anti-Plasmodium (0,589) Urolithiasis treatment (0,587) Antiprotozoal (0,532)
13	Antibacterial	Antibacterial (0,383)	Antineoplastic (0,693) Antifungal (0,531)

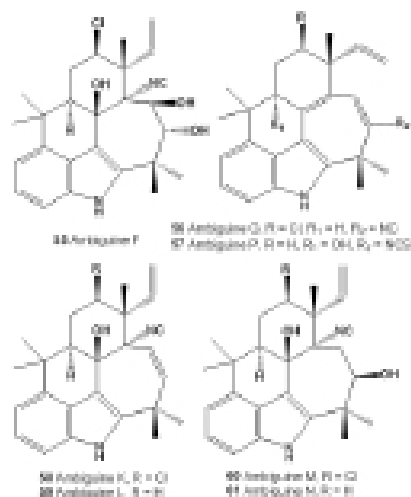
14	Antibacterial Antifungal Cytotoxic	Antibacterial (0,312) Antifungal (0,436) Antineoplastic(0,696)	Antieczemetic (0,693) Urolithiasis treat-t (0,630) Psychostimulant (0,546)
15	Antibacterial	Antibacterial (0,194)	Apoptosis agonist (0,631) Antieczemetic (0,641) Antineoplastic (0,613)
16	Antibacterial Antifungal	Antibacterial (0,385) Antifungal (0,485)	Urolithiasis treatment (0,757) Antineoplastic (0,735) Antieczemetic (0,568)
17	Antibacterial	Antibacterial (0,268)	Urolithiasis treat-t (0,723) Antineoplastic (0,679) Apoptosis agonist (0,552)
18	Antibacterial Antifungal Cytotoxic	Antibacterial (0,487) Antifungal (0,535) Antineoplastic(0,749)	Antiprotozoal (0,729) Antiprotozoal (0,699) Antieczemetic (0,530)
19	Antibacterial Antifungal Cytotoxic	Antibacterial (0,357) Antifungal (0,394) Antineoplastic (0,709)	Anti-Plasmodium (0,729) Antiprotozoal (0,699) Antieczemetic (0,530)
20	Antibacterial Antifungal Antituberculous	Antibacterial (0,357) Antifungal (0,394) Antineoplastic (0,709)	Anti-Plasmodium (0,729) Antiprotozoal (0,699) Antieczemetic (0,530)
21	Antibacterial Cytotoxic	Antibacterial (0,487) Antineoplastic(0,749)	Anti-Plasmodium (0,589) Urolithiasis treat-t (0,587) Antifungal (0,535)
22	Antibacterial Antifungal Cytotoxic	Antibacterial (0,357) Antifungal (0,394) Antineoplastic(0,709)	Anti-Plasmodium (0,729) Antiprotozoal (0,699) Antieczemetic (0,530)
23	Antibacterial Antifungal	Antibacterial (0,240) Antifungal (0,390)	Antineoplastic (0,628) Apoptosis agonist (0,508)
24	Antibacterial Antifungal	Antibacterial (0,447) Antifungal (0,275)	Antineoplastic (0,852) Antiinflammatory (0,710)
25	Antibacterial Antifungal	Antibacterial (0,487) Antifungal (0,535)	Antineoplastic (0,749) Anti-Plasmodium (0,589)
26	Antibacterial Antifungal	Antibacterial (0,285) Antifungal (0,326)	Antineoplastic (0,670) Urolithiasis treatment (0,582)
27	Antibacterial Antifungal	Antibacterial (0,285) Antifungal (0,326)	Antineoplastic (0,670) Urolithiasis treat-t (0,582)
28	Antibacterial Antifungal	Antibacterial (0,392) Antifungal (0,542)	Antineoplastic (0,705) Apoptosis agonist (0,571)
29	Antibacterial Antifungal	Antibacterial (0,194) Antifungal (0,431)	Apoptosis agonist (0,631) Antieczemetic (0,641)
30	Antibacterial Antifungal	Antibacterial (0,548) Antifungal (0,594)	Antineoplastic (0,810) Urolithiasis treat-t (0,601)
31	Insecticide	-	Anti-Plasmodium (0,759) Antineoplastic (0,696)
32	Not studied	-	Apoptosis agonist (0,631) Antieczemetic (0,641)
33	Insecticide RNA inhibitor	-	Urolithiasis treat-t (0,757) Antineoplastic (0,735) Antiprotozoal (0,610)

34	Not studied	-	Antineoplastic (0,679) Apoptosis agonist (0,552)
35	Not studied	-	Antineoplastic (0,749) Anti-Plasmodium (0,589)
36	Not studied	-	Antineoplastic (0,743) Antiallergic (0,740)
37	Insecticide	-	Antineoplastic (0,709) Antiprotozoal (0,699)
38	Not studied	-	Antineoplastic (0,709) Antiprotozoal (0,699)
39	Not studied	-	Antiprotozoal (0,745) Antineoplastic (0,696)
40	Anti-mycobacterial	Antimycobacterial (0,309)	Antieczematic (0,771) Antipsoriatic (0,747)Antineoplastic (0,712)
41	Vasopressin antagonist	-	Anti-Plasmodium(0,823) Antiprotozoal (0,813)
42	Vasopressin antagonist	Kidney function stimulant (0,279)	Anti-Plasmodium(0,823) Antiprotozoal (0,813)
43	Not studied	-	Antineoplastic (0,803) Antibacterial (0,630)
44	Not studied	-	Antineoplastic (0,807) Urolithiasis treat-t (0,573)
45	Not studied	-	Antineoplastic (0,763) Apoptosis agonist (0,529)
46	Not studied	-	Antineoplastic (0,730) Apoptosis agonist (0,620)

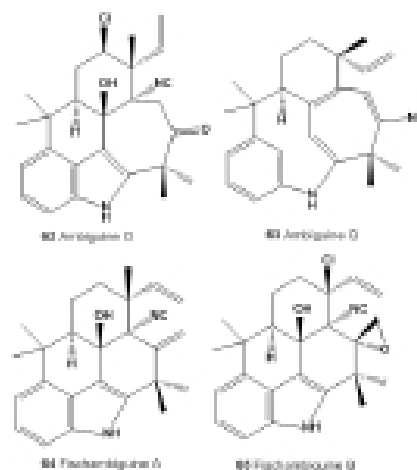
\*Activities with Pa > 0.5 are only shown.



Ambiguine A (47), B (49), C (50), D (51), E (53), I (54) and F (55) demonstrated antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes*, and *Aspergillus fumigatus*[72]. Ambiguine A (47), C (50), D (51), E (53) and I (54) have showed anticancer activity against L1210 (murine leukemia cell line), P03 (murine pancreatic tumor cell line), C38 (murine colon tumor cell line), Maml7 (murine mammary tumor cell line), CX -1, H8 (both human colon tumor cell line) and LML (low-malignant L cells) [72]. In the terrestrial cyanobacterium *Hapalosiphon delicatulus* UH IC-13-1) has been found an ambiguityine G nitrile [30].



Cultured cyanobacterium *Fischerella* sp. yielded alkaloids which contained isonitrile moiety. Ambiguine A isonitrile (47), ambiguityine H isonitrile (48), ambiguityine B isonitrile (49), ambiguityine D isonitrile (51), ambiguityine E isonitrile (53), ambiguityine J isonitrile (52), ambiguityine I isonitrile (54), and 12-*epi*-hapalindole H (38) have been isolated from *Fischerella ambigua*. Ambiguine H isonitrile (48) and ambiguityine I isonitrile (54) possessed antibacterial and anti-mycotic activities [62].



Several indole alkaloids were isolated from the cultured cyanobacteria *Hapalosiphon laingii*. Those include 12-*epi*-hapalindole C isonitrile (31), 12-*epi*-hapalindole E isonitrile (33), 12-*epi*-hapalindole G isonitrile (35), 12-*epi*-hapalindole H isonitrile (38), 12-*epi*-hapalindole Q isonitrile (39), in addition to the known metabolites hapalindolinones A (41) and B (42) [61].

The compounds (41) and (42) are antagonists of vasopressin. Vasopressin antagonists were useful in the treatment and prevention of renal and cardiovascular disorders [66]. Anhydrohapaloxindoles A (44) B (45) and M (46) and hapalonamides G (18), H (20), and V (30) have been isolated as minor indole alkaloids from a cultured strain of the terrestrial cyanobacteria *Hapalosiphon fontinalis*[7,73]. Antibacterial ambiguityine K (58), L (59), M (60), N (61) and O (62) isonitriles and previously described indole alkaloids ambiguityine A (47), B (49), C (50), E (53), F (55), and I (54) isonitriles and hapalindole G (18) and H (20) were isolated from the cyanobacterium *F. ambigua* UTEX

1903 via bioassay-guided fractionation.

Two ambiguline K (58) and M (60) isonitriles have showed the most potent activity against *Mycobacterium tuberculosis*, with MIC values of 6.6 and 7.5 µM, respectively. Although ambiguline Aisonitrile (47) has showed activity against *B. anthracis*, MIC of 1.0 µM.

Ambiguline K isonitrile (58) was active against *Mycobacterium tuberculosis*, MIC 6.6 µM. Ambiguline A isonitrile (47) has showed activity against *Bacillus anthracis*, MIC of 1.0 µM, similar to ambiguline K (58), L (59) M (60), N (61), and O (62) isonitriles [74]. Most ambiguline isonitrile and hapalindole alkaloids possessed strong antifungal activities and only moderately toxic in a Vero cell assay (IC50 26.0 to 120 µM). Hapalindole-related alkaloids, namely ambiguline G (56), ambiguline P (57), ambiguline Q (63) nitriles, and fischambigulines A (64) and B (65) have been found in extracts of the cultured cyanobacterium *Fischerella ambigua* UTEX 1903. Fischambiguline B has been displayed strong inhibitory activity against *Mycobacterium tuberculosis*, MIC value of 2 µM [74]. Activities of compounds belonging to the ambiguline family are shown in Table 3.

**Table 3:** Confirmed pharmacological and SAR activities.

No	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa*)
47	Antifungal Antineoplastic	Antifungal (0,415) Antineoplastic (0,803)	Anti-Plasmodium (0,532) Antibacterial (0,516)
48	Antibacterial Anti-mycobacterial	Antibacterial (0,394) Antimycobacterial (0,165)	Antineoplastic (0,781) Antiprotozoal (0,645) Antieczematic (0,575)
49	Antifungal	Antifungal (0,527)	Antineoplastic (0,851) Antimitotic (0,563)
50	Antifungal Antineoplastic	Antifungal (0,384) Antineoplastic (0,838)	Antimitotic (0,629) Anti-Plasmodium (0,545) Antieczematic (0,573)
51	Antifungal Antineoplastic	Antifungal (0,779) Antineoplastic (0,847)	Antimycobacterial (0,881) Antibacterial (0,704) Urolithiasis treatment (0,615)
52	Not studied	-	Antineoplastic (0,849) Anti-Plasmodium (0,765) Antiprotozoal (0,731) Antifungal (0,692)
53	Antifungal Antineoplastic	Antifungal (0,786) Antineoplastic (0,826)	Antimycobacterial (0,917) Antibacterial (0,705)
54	Antifungal Antineoplastic Antibacterial	Antifungal (0,701) Antineoplastic (0,826) Antibacterial (0,615)	Antiprotozoal (Plasmodium) (0,679) Antiprotozoal (0,617)

55	Antifungal	Antifungal (0,803)	Antimycobacterial (0,931) Antineoplastic (0,845) Antibacterial (0,737)
56	Not studied	-	Antineoplastic (0,805) Antimycobacterial (0,592)
57	Not studied	-	Antineoplastic (0,726) Antipsoriatic (0,563) Antischistosomal (0,526)
58	Antibacterial Anti-mycobacterial	Antibacterial (0,765) Antimycobacterial (0,960)	Antifungal (0,823) Antineoplastic (0,811)
59	Antibacterial	Antibacterial (0,686)	Antimycobacterial (0,929) Antineoplastic (0,809) Antifungal (0,770)
60	Antibacterial	Antibacterial (0,710)	Antimycobacterial (0,908) Antineoplastic (0,844) Antifungal (0,787)
61	Antibacterial	Antibacterial (0,622)	Antineoplastic (0,845) Anti-Plasmodium (0,825) Antiprotozoal (0,813)
62	Antibacterial	Antibacterial (0,660)	Antimycobacterial (0,833) Antineoplastic (0,805) Antifungal (0,752)
63	Not studied	-	Antineoplastic (0,867) Antipsoriatic (0,563) Dermatologic (0,542)
64	Not studied	-	Antineoplastic (0,874) Antimycobacterial (0,816) Antieczematic (0,763) Antifungal (0,714)
65	Not studied	-	Antineoplastic (0,821) Antifungal (0,743) Antiprotozoal (0,625)

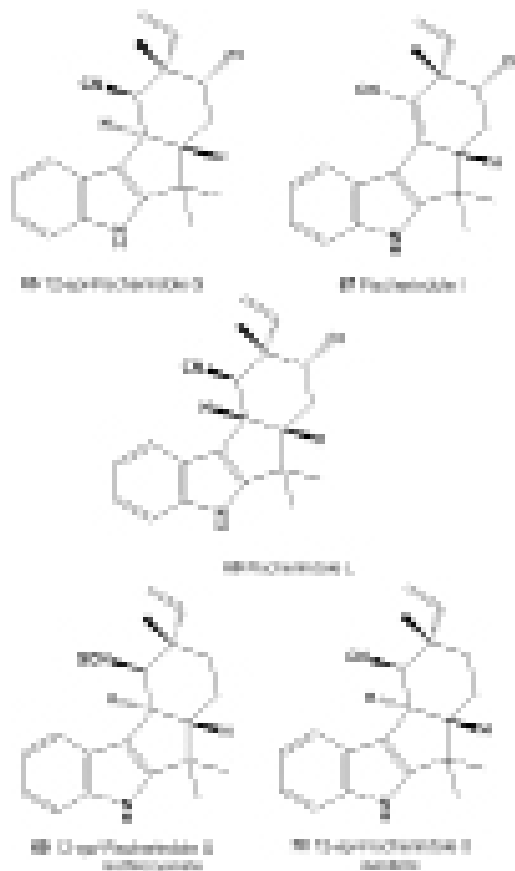
\*Activities with Pa > 0.5 are only shown.

### Alkaloids of the Fischerindole Family

Two alkaloids, fischerindole L (67) isonitrile and hapalindole L (25) have been found in extract of the terrestrial cyanobacterium *Fischerella muscicola* [50]. The culturing of cyanobacterium *Fischerella* sp. SAG 46.79 led to the isolation of fischerindole L (67), 12-epi-fischerindole G (66), 12-epi-fischerindole U isonitrile (70), and 12-epi-fischerindole U isothiocyanate

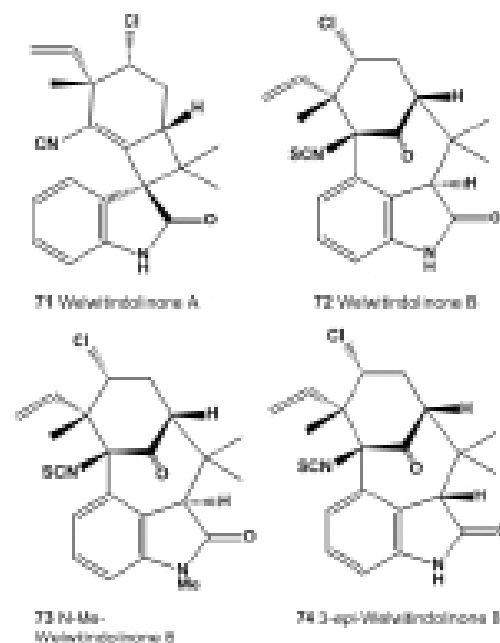
(69) [71]. Stratmann and co-workers found that cyanobacterium *Hapalosiphon welwitschii* UH IC-52-3 possessed antifungal properties and inhibited P-glycoprotein-mediated multidrug resistance in a vinblastine-resistant sub-line SK-VLB of a human ovarian adeno-carcinoma line (SK-OV-3) and that extracts of *Westiella intricata* (UH strain HT-29-1) has shown insecticidal activity against blowfly larvae [59].

Unique family of monoterpene indole alkaloids named welwitindolinones for the first time have been isolated from true branching heterocystous filamentous in the freshwater cyanobacterium *Hapalosiphon welwitschii* (family Hapalosiphonaceae) with a broad range of biological activities [59]. In particular, N-methyl-welwitindolinones B (73) and C (76) are dual-function antitumor agents that exhibit antimitotic activity with multidrug resistance reversal properties [33,59,67,68].

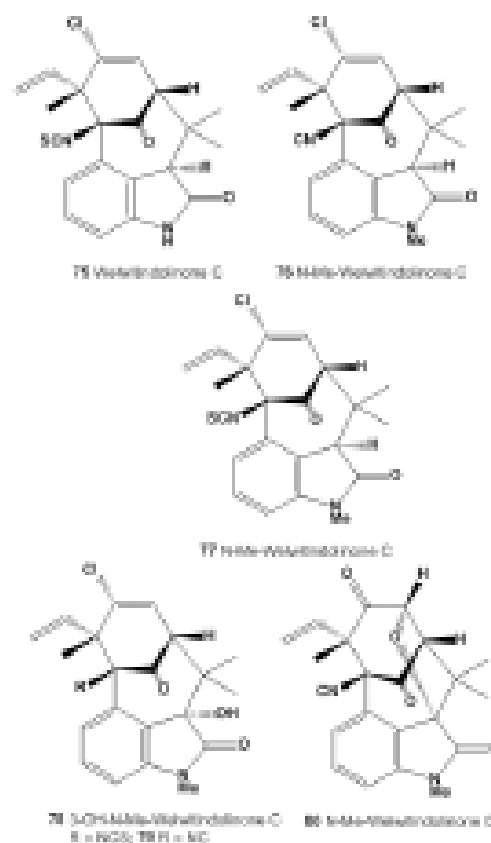


Moore and co-workers isolated oxidized welwitindolinones (78-80) from the epilithic algae *Fischerella muscicola* HG-39-5 and *Fischerella* sp. HX-7-4. Moore's investigation of the isolated compounds revealed that N-methyl-welwitindolinone C isothiocyanate (78) was responsible for the MDR-reversing activity associated with the cyanobacterial extracts [73]. A detailed investigation of the welwitindolinone (71-74) congeners found that N-methyl-welwitindolinone C isothiocyanate (76) and its demethylated analogue, welwitindolinone C isothiocyanate (75), possessed the most relevant biological activity of the entire family. Smith and co-workers have shown that N-methyl-welwitindolinone C isothiocyanate (76) potentiates vinblastine and actinomycin accumulations in the MCF-7/ADR cell lines with chemosensitization doses as low as 1  $\mu$ M [67].

It was also found that alkaloid (75) possessed significant cytotoxicity towards MCF-7 cell lines with an  $IC_{50}$  value of approximately 0.12  $\mu$ M [67]. Additional assays found that compound (75) inhibited the cell proliferation of SK-OV-3 and A-10 cells with  $IC_{50}$  values of 72 nM and 900 nM, respectively.



Compound, N-methyl welwitindolinone C isothiocyanate has showed anticancer activity, and several compounds, such as ambiguines K and M, fischambiguine B and hapalindoles X and A have shown an anti-tuberculosis activity [34,67,68,71,74]. Activities of compounds belonging to the fischerindole family are shown in Table 4.





**Table 4:** Confirmed pharmacological and SAR activities.

No	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa*)
66	Not studied	-	Antineoplastic (0,743) Urolithiasis treatment (0,611) Antifungal (0,597) Anti-Plasmodium (0,534)
67	Not studied	-	Antineoplastic (0,792) Urolithiasis treatment (0,598) Antifungal (0,501)
68	Not studied	-	Antineoplastic (0,743) Urolithiasis treatment (0,611) Antifungal (0,597) Anti-Plasmodium (0,534)
69	Not studied	-	Antineoplastic (0,600) Antifungal (0,485) Immunomodulator (HIV) 0,501
70	Not studied	-	Anti-Plasmodium (0,707) Antiprotozoal (0,675) Antineoplastic (0,698) Antieczematic (0,548) Immunomodulator (HIV) (0,611)
71	Not studied	-	Antineoplastic (0,739) Urolithiasis treatment (0,687)
72	Not studied	-	Antineoplastic (0,583)
73	Antineoplastic Antimitotic	Antineoplastic (0,454)	Antineoplastic (0,559)
74	Not studied	-	Antineoplastic (0,583)
75	Cytotoxic	Antineoplastic (0,546)	Anti-Plasmodium (0,714) Antiprotozoal (0,714)
76	Antineoplastic Antimitotic	Antineoplastic (0,480)	Anti-Plasmodium (0,779) Antiprotozoal (0,775) Prostate disorders treatment (0,552) Allergic conjunctivitis treatment (0,539)
77	Not studied	-	Antiprotozoal (0,676) Prostate disorders treatment (0,529) Allergic conjunctivitis treatment (0,511)
78	MDR-reversing-activity	Not predicted by the current PASS version	Antineoplastic (0,663) Anti-Plasmodium (0,602) Antiprotozoal (0,596)
79	Not studied	-	Anti-Plasmodium (0,733) Antiprotozoal (0,705) Antineoplastic (0,699) Prostate disorders treatment (0,506)
80	Not studied	-	Antiprotozoal (0,763) Anti-Plasmodium (0,677) Antiinflammatory (0,668) Antineoplastic (0,579)

\*Activities with Pa > 0.5 are only shown.

## CONCLUSION

Isocyano/isothiocyanato metabolites are rare group of N-containing natural compounds. They are mainly discovered in microorganisms and plants, and have also been detected in some marine species. Little information is known about biological activities of these metabolites. Nevertheless, re-

ported activities for isolated compounds have shown strong antineoplastic, antifungal, antibacterial, anti-mycobacterial, antiprotozoal and others activities. The widest spectra of pharmacological activities are exhibited by isolated alkaloids and/or their synthesized derivatives. Therefore, synthetic methodologies have been investigated in recent years, as this is a growing field of interest for chemists, biologists and pharmacologists.

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## CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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