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Review

Stachybotrys chartarum: a fungus for our time

Bruce B. Jarvis*

Department of Chemistry & Biochemistry, University of Maryland, College Park, MD 20742, USA

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Dedicated to the memory of Professor Jeffrey B. Harborne

Abstract

Stachybotrys chartarum, a fungus found in damp buildings and sometimes ascribed a role in building-related illnesses, produces a variety of secondary metabolites including trichothecenes, triprenylated phenolics, and a new class of diterpenoids called atranones. A related fungus, *Memmoniella echinata* also produces trichothecenes and the triprenylated phenolics. Herein the production of these compounds from cultures of the above are reviewed.

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Keywords: *Stachybotrys chartarum*; *Memmoniella echinata*; Trichothecenes; Drimanes; Triprenyl phenols; Atranones; Dolabellanes

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Humans have never been particularly fond of molds. However, the appreciation of the general public for molds (fungi) increased substantially with the development and clinical use of antibiotics, first derived from a species of *Penicillium*, though most in use today come from the Actinomycete bacteria.

Molds are once again suffering “bad press,” this time in the context of health problems of those living or working in damp moldy homes and buildings. Although references to such problems can be traced back as far as the Old Testament (Leviticus, Chapter 14: 33–48), here in North America until recent events, little attention has been paid to mold problems except in the context of allergies suffered by atopic people exposed to molds.

In 1986, Croft et al. (1986) described a mold-infested home in Chicago in which the residents had suffered from various health problems. The home was heavily contaminated by the black fungus, *Stachybotrys chartarum*, also known as *S. atra* or *S. alternans*. This fungus has a long history of causing problems for animals

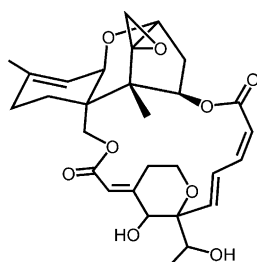
that come into contact with *S. chartarum*-contaminated straw and hay, mainly in Eastern Europe (Forgacs, 1972), but this has never been an issue in North America because of a combination of favorable farming conditions and good agriculture practices. In fact, the first case of stachybotryotoxicosis reported in North America was in this Chicago home. This report languished in the literature as something of an oddity until the mid-1990's, when a series of cases of pulmonary bleeding (idiopathic pulmonary hemosiderosis, IPH) in infants from Cleveland, Ohio was found to correlate with the presence of *S. chartarum* in their homes (Dearborn et al., 1999). The degree of this correlation and in fact, the whole area of the relationship between mold toxins (mycotoxins) and building-related illness is highly controversial (Assouline-Dayana et al., 2002; Burge, 2001; Page and Trout, 2001) and will not be dealt with in this review. Herein, I focus on the secondary metabolites produced by *S. chartarum* with reference to another closely related fungus, *Memmoniella echinata*.

By the 1930's, the Russians were well aware that *S. chartarum* was responsible for the loss of livestock (mainly horses that appear to be very sensitive to the toxins produced by *S. chartarum*) (Drobotko, 1945).

* Corresponding author. Tel.: +1-301-405-1843; fax: +1-301-314-9121.

E-mail address: bj6@umail.umd.edu (B.B. Jarvis).

Although there were several attempts at characterizing those toxins, it was not until 1973, that Eppley and Bailey (1973) reported that the high toxicity associated with *S. chartarum* was due to the production of macrocyclic trichothecenes, in particular satratoxin H (**1**). Eppley had received his MS degree in polymer chemistry under the guidance of W.J. Bailey (University of Maryland) and had taken a position at the FDA in Washington, DC. Eppley was enrolled in the PhD program and looking for a thesis problem relevant to the mission of the FDA; mycotoxin analysis was a hot topic at that time, and the identification of the toxins of *S. chartarum* was an appropriate task. Although I was a faculty member at that time in Eppley's department, I was more than three years away from taking up natural products chemistry, and it is only the sheerest of coincidence that eventually my laboratory would play a role in untangling the many products produced by this fungus—for background see Jarvis (1991). Eppley continued his interest in mycotoxins, though not with those of *S. chartarum*, and Bailey went back to polymer chemistry.



Satratoxin H (**1**)

By the mid-1980's, several laboratories had reported that isolates of *S. chartarum* from moldy hay that had made animals sick produced the highly toxic macrocyclic trichothecenes. Our laboratory assayed the production of *S. chartarum* toxins by isolates from Central Europe involved in livestock intoxication; of the 17 isolates studied, 14 were shown to produce the macrocyclic trichothecenes (Jarvis et al., 1986a). Although little was made of it at the time, it should be noted that we were unable to detect any macrocyclic trichothecenes in three of these isolates.

Trichothecenes are a well known class of sesquiterpenes and have been reviewed extensively (Ueno, 1983; Jarvis, 1991; Proctor, 2000). They are the most potent small molecule protein synthesis inhibitors known and are considered to be among the most important (and acutely toxic) of the mycotoxins. They are produced by a variety of the *fungi imperfecti* (Jarvis, 1991). Two unusual sources of trichothecenes are plants (Jarvis, 1992; Loukaci et al., 2000) and a poisonous mushroom (Saikawa et al., 2001), the latter producing satratoxins.

We had been studying another genus of fungus, *Myrothecium*, for sometime and had found several *M. roridum* isolates that produced satratoxins and compounds of similar structure (Jarvis and Yatawara, 1986; Jarvis et al.,

1986b). *Myrothecium* is considerably more “cooperative” when it comes to producing macrocyclic trichothecenes (Jarvis et al., 1982). This fungus grows well in submerged liquid cultures, and even more importantly, often produces individual macrocyclic trichothecenes in quantities of 100 mg or more per liter. Not so *S. chartarum*. In our hands, this fungus grows very poorly in submerged cultures, and the production of macrocyclic trichothecenes is rarely observed and then only at very low levels (El Maghraby et al., 1991), although others have reported somewhat better success (El-Kady and Moubasher, 1982). We have had to resort to growing this fungus on a solid medium, Uncle Ben's Rice, whereon this fungus produces a substantial amount of extractable organic material but only modest amounts (typically tens to a few hundred mg) of macrocyclic trichothecenes per kg of rice.

During the course of a study of isolates of *S. chartarum* obtained from various areas around the world, we discovered that the major class of secondary metabolites produced by this fungus are the spirocyclic dimeranes (**2**) (Jarvis et al., 1995). This type of compound has been reported produced by other species of *Stachybotrys*, and the Japanese have shown that members of this class are potent immunosuppressants, particularly the dialdehyde derivatives (Kaise et al., 1979) (see Fig. 1). However, these dialdehydes are relatively unstable and often undergo conversion to the stachybotrylactams and stachybotrylactones (**2**) (Ayer and Miao, 1992).

Fig. 1 shows the structures of spirocyclic dimeranes and related compounds isolated from *S. chartarum* and closely related *Stachybotrys* species, and Fig. 2 illustrates similar type congeners isolated from *Memnoniella echinata*. In this regard, *S. chartarum* has also been reported to produce an immunosuppressant of the cyclosporin family (Kazutoshi et al., 1993). Minagawa et al. (2002) (Fig. 3) have recently reported novel structural analogs (stachyflins) related to these compounds several of which exhibit potent antiviral activity. It should be noted that many of these fermentations of *M. echinata* and *Stachybotrys* are carried out by the pharmaceutical industry in search of bioactive metabolites, and that the media used may result in active derivatives that would never be produced under natural conditions. For example, the strain of *M. echinata* that produces L-671,776 (Fig. 2) also produces a decapeptide derivative of stachybotrylactam (**2**, X = N-decapeptide); the source of the decapeptide appears to be from the β -casein used in the fermentation medium (Vértesy et al., 2001).

M. echinata also produces the simple trichothecenes, trichodermol (**3**) and trichodermin (**4**) as well as griseofulvins (**5**) as major metabolites. Production of the latter is interesting in that previously, griseofulvins had been reported to be produced only by various species of *Penicillium* (Frisvad and Filtenborg, 1989); to date we have not found any isolates of *S. chartarum* that have produced griseofulvins.

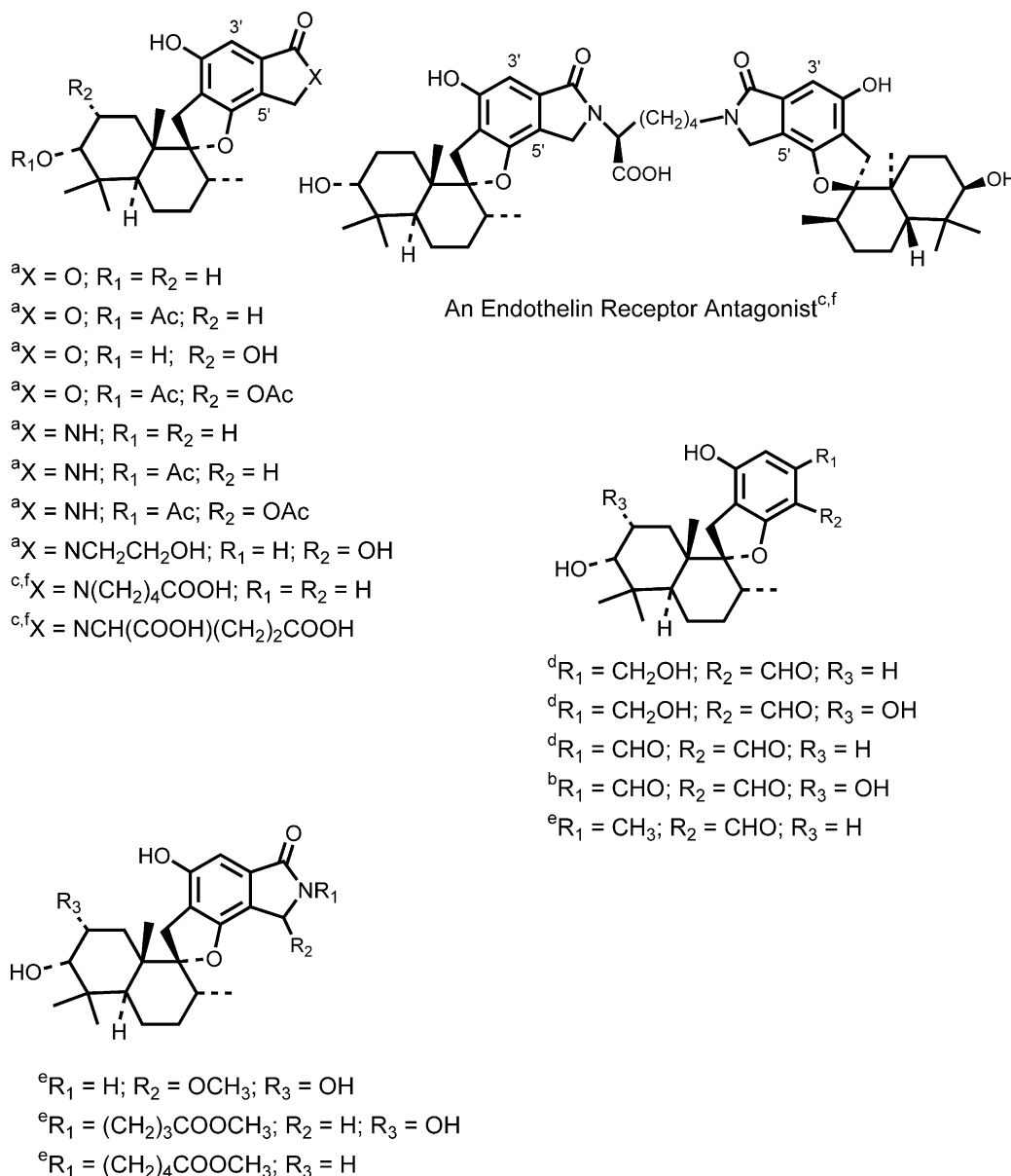


Fig. 1. Spirocyclic drimanes isolated from *S. chartarum* and closely related *Stachybotrys* sp. ^aAnticomplement-immunosuppressants (Jarvis et al., 1995). ^b(Kaise et al., 1979). ^{c,d}Endothelin receptor antagonists (Roggo et al., 1995). ^dProtease inhibitors (Kaneto et al., 1994). ^eCholesterol esterase inhibitors (Sakai et al., 1995). ^fOriginal paper (Roggo et al., 1995) showed structures with positions 3',5' transposed. This was corrected for L-671,776 (Ferrari et al., 1995) and presumably applies to these derivatives produced by a related L-671,776-producing fungus.

Although these triprenyl phenols appear to be the signature compounds of the *S. chartarum*—*M. echinata* complex, it is the production of the highly toxic (LD₅₀ in mice ~1 mg/kg) (Jarvis, 1991) macrocyclic trichothecenes that has attracted the most attention. Amongst the many trichothecenes reported produced by *S. chartarum* are: a) simple trichothecenes trichodermol, trichodermin, and verrucarol; b) trichoverroids trichoverrols and trichoverrins; c) macrocyclic trichothecenes verrucarins B and J, roridins D, E, isoE, and L-2, satratoxins F, isoF, G, isoG, H, and isoH. When mac-

rocyclic trichothecenes are observed produced by *S. chartarum* cultures, the satratoxins G and H and roridin E are always detected (Andersen et al., 2002). However, only by about one-third of *S. chartarum* isolates actually produce macrocyclic trichothecenes; the remaining two-thirds typically produce the considerably less toxic simple trichothecenes, **3** and **4** but do not produce any of the macrocyclic derivatives (Andersen et al., 2002). We set out to find if there were other metabolic products that might distinguish these two classes of *S. chartarum* and discovered that indeed there was a most

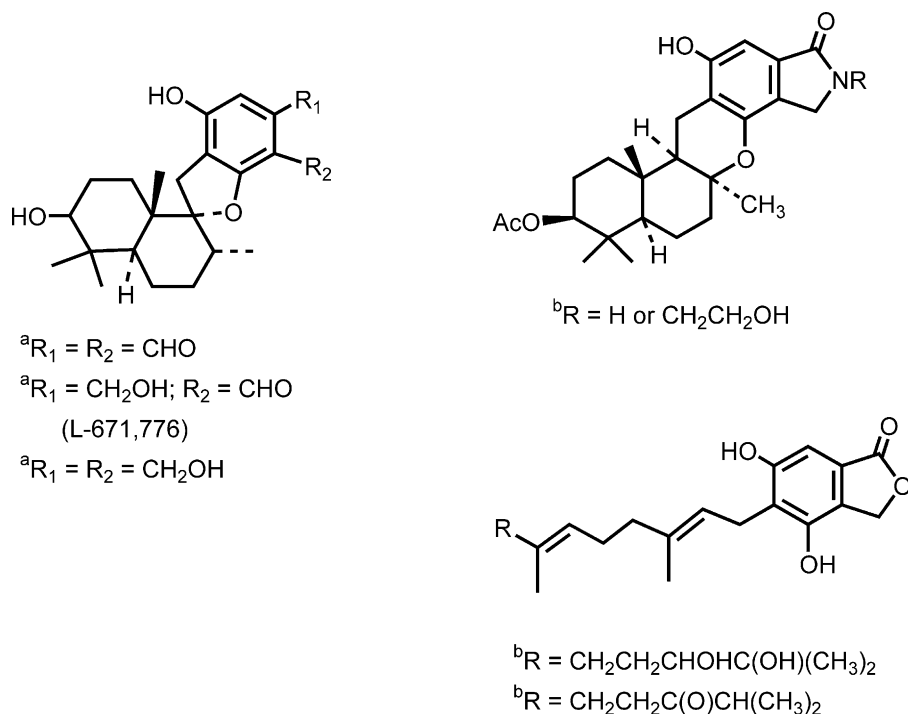


Fig. 2. Triprenyl phenols from *Memnoniella echinata*. a Inositol monophosphatase inhibitors (Stefanelli et al., 1996). b Cytotoxic (Hinkley et al., 1999a).

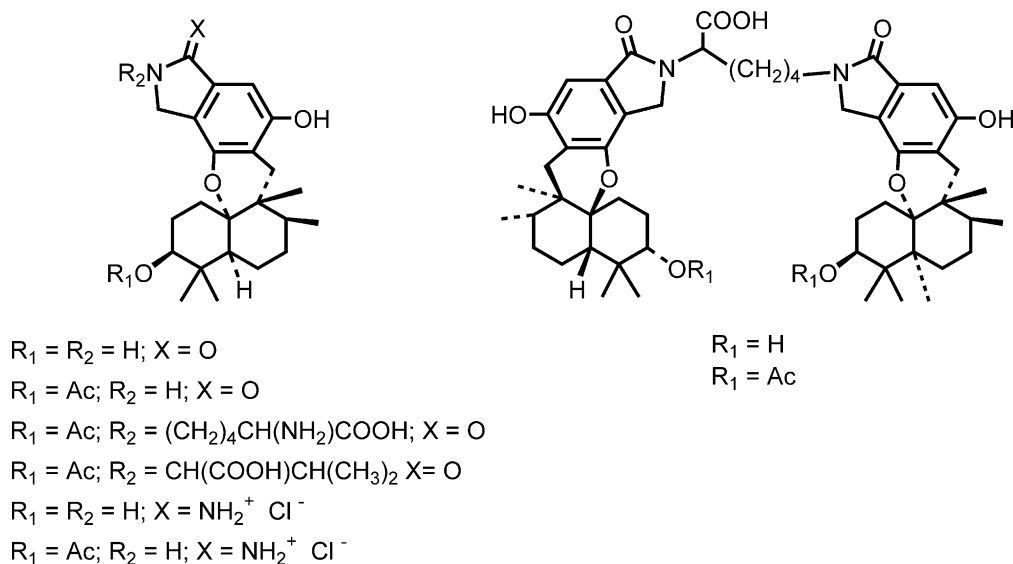


Fig. 3. Stachyflins isolated from *Stachybotrys* sp. RF-7260.

unusual distinction. *S. chartarum* split cleanly into two chemotypes: one that produced the macrocyclic trichothecenes and the other that produced a new class of diterpenoids, the atranones (Fig. 4). In the analyses of over 200 isolates of *S. chartarum*, we have never found an isolate that produces both macrocyclic trichothecenes and atranones (Andersen et al., 2002).

The atranones are structurally related to the marine diterpenoid dolabellanes (Rodríguez et al., 1998). In fact, the atranone-producing isolates of *S. chartarum* produce

two dolabellanes, **6** and **7**, that serve as markers (by LC–MS analysis) for the atranone producers (Andersen et al., 2002). To date, 11 naturally occurring atranones A–K have been characterized (Fig. 4) (Hinkley et al., 1999b, 2000, 2003). In atranones, the normal bicyclo[9.3.0] ring of the dolabellanes has been elaborated by a fused enol lactone (ring D, Fig. 4), a most unusual structural feature, especially since it lacks any further conjugative stabilization (Hinkley et al., 2000). Other structural variations include expansion of the A-ring through what

appears to be a Baeyer–Villiger oxidation (atranones A–C, F–I, and K) and an additional ring fusion as in atranones A–C (ring C, Fig. 4). All the atranones are C_{24} compounds except atranone J, which is a C_{23} congener. Atranone J also is the only atranone so far characterized that has the C-1/C-11 *cis*-fused ring junction. The origin of atranone J may be via an α -ketol rearrangement of atranone H, followed by hydrolysis of the lactone ring, decarboxylation/dehydration of the resulting inter-

mediate followed by intramolecular Michael addition of the hydroxyl group to the α,β -unsaturated ketone that regenerates the A/B-ring fusion (Hinkley et al., 2003). With one lone exception (Jenny and Borschberg, 1995), the atranones and dolabellanes **6** and **7** are the only examples of dolabellane-type diterpenes reported from fungi. Unlike the trichothecenes and spirocyclic drimanes, the atranones to date have not been found to possess significant biological activity.

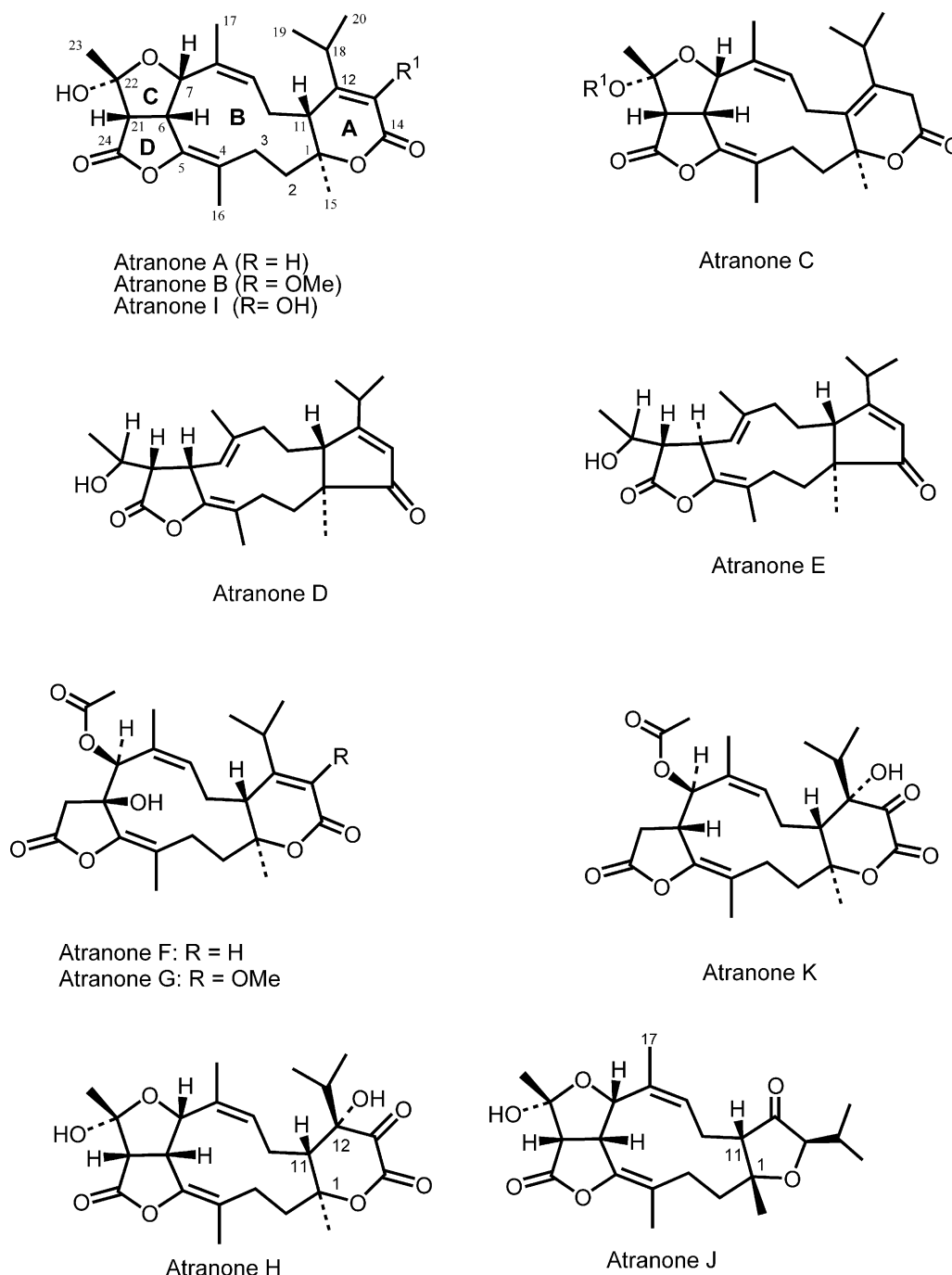
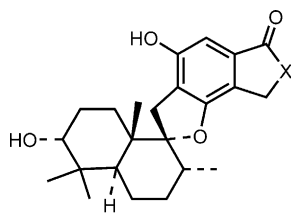
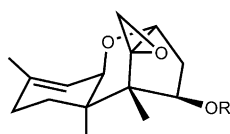


Fig. 4. Atranones isolated from *S. chartarum*.

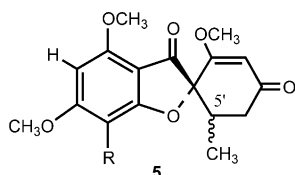


2

Stachybotrylactone: X = O
Stachybotrylactam: X = NH

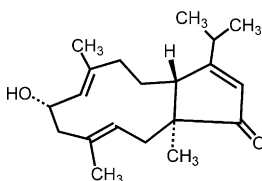


3: R = H
4: R = Ac

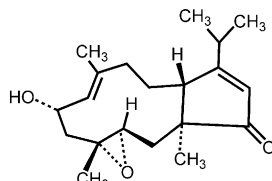


5

Griseofulvin: R = Cl; C-5'R
Dechlorogriseofulvin: R = H; C-5'R
Epidechlorogriseofulvin: R = H; C-5'S



6



7

It is most unusual, perhaps unprecedented, for a single fungal species to exhibit two distinct chemotypes wherein each chemotype is strictly relegated to producing one or the other class of metabolite, but none that can produce both. Actually in the case of *S. chartarum*, this division is not quite as clean as it first appears since most of the atranone-producers in fact do produce simple trichothecenes [trichodermol (**3**) and trichodermin (**4**)]. And of course, it is always risky making conclusions based on a negative result; some isolates may make both atranones and macrocyclic trichothecenes, but our analytical techniques may not be sufficiently sensitive to detect this (Hinkley and Jarvis, 2000).

It occurred to us that the two chemotypes could be actually two species of *Stachybotrys*. There are clearly variations in the morphology of *S. chartarum* that have been described (Jong and Davis, 1976; Koster et al., 2003), and we felt that perhaps these variations would parallel the chemistry we observed. As matters often turn out, the true picture is even more complicated. Indeed, there appears to be two species of *Stachybotrys* that had been lumped together under the species, *S. chartarum*, but this split does not correspond to our two chemotypes (Andersen et al., 2003). Two recent publications presaged this finding in reporting that ca. 20% of isolates that had been labeled *S. chartarum* have distinct morphological (Andersen et al., 2002) and poly-

morphic protein coding loci (Cruse et al., 2002) differences from the main body of *S. chartarum*. We have now shown that these two findings are congruent and have therefore suggested that what had been called a single species of *S. chartarum* be split into *S. chartarum* and *S. chlorohalonata* (Andersen et al., 2003). Although all isolates of *S. chlorohalonata* examined to date are atranone producers, the members of the “new” *S. chartarum* are split: ca. 60% are atranone producers and ca. 40% are macrocyclic trichothecene producers (Andersen et al., 2002, 2003).

Although the divisions by chemotypes and by species for *S. chartarum* are not in agreement, this still leaves open the question of the genomic and biosynthetic relationship between the atranones and the trichothecenes. Why is it that those *Stachybotrys* fungi that produce the atranones, produce the simple but not the macrocyclic trichothecenes, and those that produce the macrocyclic trichothecenes never produce the atranones? One possibility is that the (presumed) cluster of genes that encodes for the atranones has disrupted the biosynthesis of the macrocyclic trichothecenes (Trapp et al., 1998) at the stage where trichodermol (**3**) would normally be further elaborated into the macrocyclic derivatives. The solution to this puzzle will likely come from a study of the molecular biology of the biosynthesis of the trichothecenes and atranones in these *Stachybotrys* species.

As noted earlier, *M. echinata* and *S. chartarum* have long been recognized as being closely related (Jong and Davis, 1976). Both produce similar spirocyclic drimanes and related triphenyl phenols as well as the trichothecenes, although *M. echinata* appears to produce only simple trichothecenes, **3** and **4** (Jarvis et al., 1996, 1998). We have never observed atranones produced by *M. echinata*, and as noted earlier, *M. echinata* produces griseofulvins, metabolites never observed produced by *Stachybotrys*. The principal morphological distinction between *M. echinata* and *Stachybotrys* is that the latter encases its spores (clumped together) in a polysaccharide coating; whereas, the spores (phialoconidia) of *M. echinata* almost always appear in “dry” chains. However, exceptions to this occur, and there is an increasing consensus to relegate *M. echinata* to the species *Stachybotrys* (Haugland et al., 2001; Peltola et al., 2002).

Stachybotrys presents a challenging problem to the chemist and toxicologist to characterize, both in terms of the natural products produced and their effects on the health of those exposed to this mold. In addition to the plethora of small molecule metabolites (MW < 800) produced by this mold, *S. chartarum* produces proteins with hemolysin (Vesper et al., 2001) and proteinase (Kordula et al., 2002) activities, both of which have been suggested as possible contributing agents in the IPH syndrome in infants. The assessment of the effects of exposure to this myriad of chemicals produced by *S.*

chartarum to people living and working in buildings contaminated by this mold will take quite some time.

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Bruce B. Jarvis was born in Van Wert, Ohio (1942), graduated from Ohio Wesleyan University (BS, 1963) and the University of Colorado (PhD, 1966). Following a year of post-doctoral study at Northwestern University, he joined the faculty of the Department of Chemistry and Biochemistry, University of Maryland, College Park in 1967, where he is currently Professor of Chemistry and former Chair of the Department (1993–1998). His research program has ranged from basic studies in physical organic chemistry to natural products chemistry. Currently his research is focused on the chemistry and toxicology of molds associated with damp buildings that can have serious health effects on those living and/or working in these buildings. B.B.J. was designated as a Distinguished Scholar-Teacher by the University in 1992, and was Visiting Professor at the Technical University of Denmark in 1999–2000.