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The Chemistry of Griseofulvin

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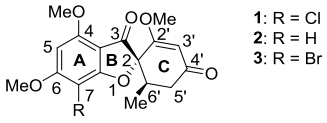
Table of Contents

1. Introduction

The natural product griseofulvin, (2*S*,6'*R*)-7-chloro-4,6-dimethoxybenzofuran-3-one-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'-one), (**1**, Figure 1) has a rich chemistry dating back to the early 1950s. Initial research was aimed at the structural elucidation of the fungal metabolite and later

emphasis was on synthesizing analogs for biological investigation of the antifungal properties, both by semisynthesis from griseofulvin and by de novo synthesis. Griseofulvin was launched on April 6, 1959 in the US by ICI under the trade name “Fulcin” and in the UK by Glaxo as “Grisovin”.[1] Griseofulvin has been in clinical use for treatment of ringworm in animals and humans since, and recently, griseofulvin has attracted renewed attention due to reports of complementary bioactivity in mammalian systems, including antiviral and anticancer effects.



1: R = Cl
2: R = H
3: R = Br

Figure 1. The structure of griseofulvin **1**, dechlorogriseofulvin **2** and 7-bromo-7-dechloro-griseofulvin **3**, with designation of the A, B and C ring including the IUPAC recommended numbering.

The chemistry of griseofulvin and analogs has not been reviewed since 1974,[2] making an updated and comprehensive overview of the literature timely. Here, we present the history of griseofulvin, its biosynthesis, an introduction to the biology of the compound class, total synthesis of **1** and analogs, as well as the chemistry used to prepare analogs of griseofulvin starting from the natural product. Specific synthetic routes are presented in schemes to illustrate the chemistry and the analogs are presented in a table format to give an accessible overview of the structures. The color-coding (blue for A ring substituents, red for C ring substituents) and substituent numbering (Figure 1) are retained in all structures throughout the review. A figure or table reference in bold indicates original research

describing synthetic preparation of a compound and in the tables, a substituent in italic signifies that it is modified compared to the parent compound.

Several patents have been published regarding the properties of griseofulvin and its derivatives including synthesis, formulation and their medicinal and agricultural applications. The emphasis of this review is not on the patent literature and they will not be discussed further – references 3,4,5,6,7,8,9,10,11,12,13,14 can be consulted for more information.

2. The Discovery and Structural Analysis of Griseofulvin and Analogs

Griseofulvin **1** was initially isolated from *Penicillium griseofulvum* in 1939 by Oxford et al.[15] In 1946 Brian et al. published studies of a compound isolated from *P. janczewskii* known as the "Curling Factor" due to its induction of curling of fungal hyphae.[16,17] It was not until 1947 that it was established that griseofulvin **1** and the "Curling Factor" were in fact the same compound.[18,19] The analogous metabolites dechlorogriseofulvin **2** (1953) and 7-bromo-7-dechloro-griseofulvin **3** (1954) were later isolated by MacMillan.[20,21]

Initially, the structural analysis was performed by means of IR, UV spectroscopy and combustion analysis of derivatives or degradation compounds. The structure of the A-B-C ring system was first correctly assigned in 1951 by Grove et al.[22] and in 1952, the stereochemistry of position 6' was determined through identification of (*R*)-(+)-methylsuccinic acid as a degradation product of the C ring.[23] The *cis* relation between the 3-oxo and 6'-methyl substituents was suggested in 1959 by MacMillan after studying the epimerization of the 2-position. He found that 2-*epi*-griseofulvin (**22**, Scheme 15) was the major product of the reaction and argued for the relative stereochemistry of **1**

based on steric repulsion between the 3-oxo and 6'-methyl moieties.[24] The absolute configuration of **1** was supported by X-ray crystallography of 5-bromogriseofulvin (**87a**, Scheme 18) in 1963 and by ^{1}H NMR studies in 1971 before final confirmation via crystallography of griseofulvin by Malmros et al. in 1977.[25,26,27] The products of epimerization of either of the two stereogenic centers in griseofulvin, position 2 and 6', have throughout the literature been referred to as *epi*-griseofulvin and these compounds are of course identical in the racemic series. Much of the pioneering work on the chemistry of griseofulvin and its analogs was done in the 1950s and early 1960s by ICI and Glaxo and published in *Journal of the Chemical Society* in 17 papers called griseofulvin part I through XVII, by ICI Research Laboratories,[20,21,23,24,28,29,30,31,32,33,34,35,36,37,38,39,40] and 9 papers called griseofulvin analogues part I through IX, by Glaxo Laboratories.[41,42,43,44,45,46,47,48,49]

Several articles do not describe synthesis of griseofulvin **1** or analogs thereof, but instead report spectroscopic studies. Page and Staniforth investigated the infrared absorption of more than 180 griseofulvin analogs.[45,48] The IR spectra were recorded in bromoform and detailed absorption values are listed for all compounds. The authors were able to distinguish analogs of griseofulvin and isogriseofulvin as well as the position 2 epimers based on the IR data. A comprehensive mass spectrometry study of griseofulvin, its analogs and their fragmentation in the spectrometer was carried out by Ballantine and Fenwick.[50] 60 MHz ^{1}H NMR was used in a study by Arison et al. covering griseofulvin and more than 25 analogs, exploring this, at the time, new technique.[51] Another NMR study by Green et al. of more than 40 analogs concluded that the assignment of the 4 and 6 methoxy groups by Arison et al. was inaccurate.[49] The assignment by Green et al. was confirmed by Rønnest et al. with 2D NMR and single crystal X-ray analysis of the position 4 and 6 norgriseofulvin analogs (**80**, Scheme 16 and **83**, Scheme 17).[52] The conformation and configuration of griseofulvin **1**, the 4'-β-

hydroxy analog (**105**, Scheme 24) and the 4'-α-methoxy analog (**135c**, Table 29) were determined by solution NMR ($CDCl_3$) by Levine and Hicks and later they investigated the ^{13}C NMR of griseofulvin **1**, 2-*epi*-griseofulvin **22** (Scheme 15), isogriseofulvin **79** (Scheme 14) and the analog **106** (Scheme 24).[26,53,54] NMR has also been used in studies of griseofulvin biosynthesis using deuterium labeling, for example in the work by Sato and Oda.[55]

3. Biological Activity of Griseofulvin and Analogs of the Natural Product

After the discovery of griseofulvin, many studies followed that reported the in vitro antifungal effects and systemic antifungal activity of **1** in plants.[56,57] However, it was the report by Gentles in 1958 that griseofulvin was active against infections with *Microsporum canis* and *Trichophyton mentagrophytes* in guinea pigs when administrated orally and the work of Williams et al. published the same year on griseofulvin treatment of ringworm in man that sparked the development of griseofulvin as an antifungal drug to treat dermatophytosis in man.[58,59] The early studies of griseofulvin as an antifungal agent have been reviewed by Bent and Moore and will therefore not be discussed further here.[60]

A large number of analogs of griseofulvin have been prepared with the aim of improving the antifungal properties of the natural product. A few, notably 3'-benzyl-2'-demethoxy-2'-ethoxygriseofulvin (**116o**, Table 15), showed increased efficacy in vitro, but none of them have been introduced to the clinic. The specific biological activity of individual analogs is beyond the scope of this review and earlier reviews can be consulted for further information.[1,61] Additionally, for all analogs reported here, references are given to biological studies where available (Tables 9-30).

The antifungal mode-of-action of griseofulvin has been the subject of considerable research efforts and some debate over the years, a discussion that is still ongoing. The action of griseofulvin has been linked to nucleic acid binding and it has also been shown that **1** interferes with mitosis through interaction with the mitotic machinery in a manner resembling colchicine.[62,63,64] Furthermore, it has been demonstrated that griseofulvin binds to tubulin,[65] inhibits tubulin polymerization and disturbs microtubule dynamics,[66] but experiments indicate that the binding to tubulin has low affinity and often occurs at concentrations higher than the fungistatic effect. Taken in combination with studies in mammalian cells this has led to speculation that the cellular target of griseofulvin at clinically relevant concentrations might not be tubulin itself but rather a microtubule-associated protein.[67]

The antimitotic and antiproliferative effect of griseofulvin in mammalian cells is weak, requiring high micromolar concentrations for a response.[68] The interest in griseofulvin was renewed when Ho et al. reported in 2001 that griseofulvin could potentiate the antitumorigenesis effect of nocodazole and induce apoptosis in cancer cell lines at concentrations down to 1 μM.[69] The report was preceded by a patent taken out on the application of griseofulvin for the treatment of cancer and viral infections and was followed by more detailed studies of the antimitotic effect of **1**,[70] confirming earlier findings of a tubulin polymerization inhibition at high doses and a lower-dose interference with microtubule dynamics.[71] The ability of griseofulvin to suppress hepatitis C virus replication in vitro was reported by Jin et al. in 2008.[72] In 2006 Oda published the cytotoxic effect of griseofulvin and three 2' modified analogs in Chinese hamster V79 cells, finding that the 2'-demethoxy-2'-propoxy analog (**115l**, Table 14) was the most potent, suggesting that the anticancer effect of **1** could be enhanced through structural modification of the natural product.[73] The following year, Rebacz et al. helped shed additional light on the mode-of-action of griseofulvin and analogs in a report linking the spirobenzofuranones to inhibition

of centrosomal clustering, a functional mechanism in cancer cells to overcome the detrimental effects of supernumerary centrosomes and avoid multipolar mitosis during cell division.[74] These findings were followed by an SAR study of 34 analogs of griseofulvin as centrosomal clustering inhibitors,[75] as well as a detailed comparison between the antifungal and anticancer effect of 54 compounds showing a disparate SAR, indicating different modes-of-action in fungal and mammalian cells.[76] For one of the most potent analogs, 2'-benzyloxy-2'-demethoxygriseofulvin (**115aa**, Table 14), a more detailed report was published including in vivo activity studies in murine xenograft models of colon cancer and multiple myeloma.[77]

Griseofulvin and its analogs continue to attract attention for the multiple biological responses the molecules can elicit. Future research aimed at a more detailed understanding of the cellular targets of this compound class and the underlying binding interactions has the promise to increase the studies and potentially the pharmaceutical applications of **1** and its derivatives further.

4. Fungal Biosynthesis of Griseofulvin

Griseofulvin was one of the first antifungal natural products found in filamentous fungi.[18] During the years, this polyketide has been found to be produced by several *Ascomycetes* including both closely and distantly related species. The majority of these are found in genus *Penicillium*, where at least sixteen species are known to be griseofulvin producers, whereas the production is seemingly rare in *Aspergillus*, as it has only been reported in *A. lanosus*.[78] Griseofulvin production appears to be very consistent in all the species that have been examined systematically so far and the wide distribution of

griseofulvin among filamentous fungi indicates that the biosynthetic capability has been developed at least 13 independent times during evolution.[78]

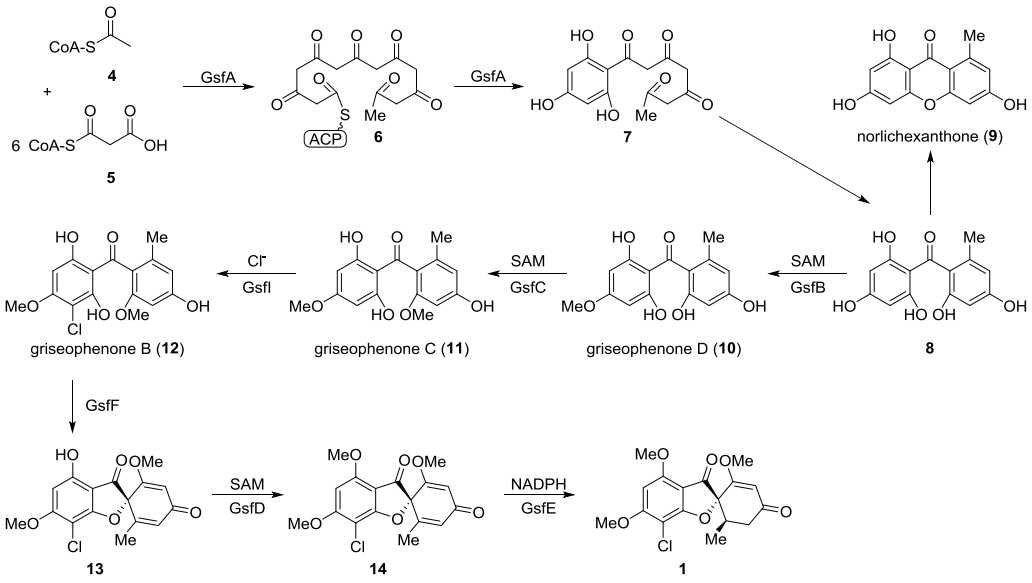
From the middle of the last century and onwards, huge efforts have been made to investigate the biosynthesis of natural products such as griseofulvin using isotope-labeled substrates. Based on the observations of incorporation of seven units of [1-^{14}C]acetic acid into griseofulvin, Birch et al. in 1958 supported the "acetic acid hypothesis", suggesting that the core ring structure of many phenolic compounds were derived by head-to-tail linkage of acetic acid units.[79] This theory was later revised as ^{13}C NMR studies clarified that only the starter unit of the growing polyketide chain is derived from acetic acid, whereas the sequential chain extension resulting in the intermediate **6** (see Scheme 1), the precursor for the two first ring formations, uses six malonate units during extension of the polyketide chain.[80] A phenoxyl radical cyclization mechanism for the formation of the core grisan ring of griseofulvin was suggested by Barton and Cohen in 1957.[81] Rhodes et al. showed that methylated benzophenones are intermediates in griseofulvin biosynthesis in 1961,[82] which was later clarified in 1976 by Harris et al.,[83] using isotope feeding experiments. The latter determined that *O*-methylation of two of the phenol groups occurs immediately after the formation of the benzophenone intermediate **8** resulting in griseophenone C (**9**), whereas the last *O*-methylation takes place later in the biosynthetic pathway.

In recent years, it has become possible and relatively inexpensive to sequence the full genomes of filamentous fungi. This has given complete new opportunities to study and understand the genomic basis and the enzymes involved in biosynthesis of polyketides such as griseofulvin. Initial efforts have

been directed towards *Aspergillus* due to its medical and commercial importance;[84] however, work has also been reported for other more exotic fungi including the investigation of griseofulvin's biosynthesis in *Penicillium aethiopicum*.[85] Analysis of the published sequenced genomes by different web-based tools, such as BLAST (Basic Local Alignment Search Tool), SMURF (Secondary Metabolite Unknown Regions Finder) and antiSMASH (antibiotics & Secondary Metabolite Analysis SHell) allows for prediction of putative polyketide synthase (PKS) genes based on sequence similarity to established genes from other species.[86,87,88,89] For example *A. nidulans* has been predicted to have thirty two genes potentially involved in polyketide production.[90] Moreover, these genes tend to be clustered together with tailoring and regulatory genes,[91] making predictions of genes related to the same pathway possible as demonstrated recently by Andersen et al.[92] The authors developed an algorithm for accurate prediction of secondary metabolite gene clusters in filamentous fungi based on analysis of transcriptome data, altogether setting the scene for linking genes to enzymatic activities for elucidation of secondary metabolic pathways, as well as heterologous expression of the proteins.[93]

In 2010, Yi Tang's group at UCLA located the genes involved in the biosynthesis of griseofulvin in *Penicillium aethiopicum* among seven non-reducing PKSs by genome scanning based on DNA pyrosequencing followed by comparative genomics to the closely related *P. chrysogenum*, which does not produce griseofulvin.[85] Key to the identification of the griseofulvin gene cluster (Gsf) was the finding of three *O*-methyl-transferase encoding genes (Gsf B/C/D) and a halogenase gene (GsfI) pointing towards correlation to signature functional groups in griseofulvin (Scheme 1). Moreover, they found a P450 oxygenase (GsfF) responsible for the stereoselective formation of the B ring leading to the signature spiro structure and that stereoselective reduction in the C ring was mediated by the

putative NADP-dependent oxidoreductase GsfK resulting in formation of the C-6' chiral center in the *R*-configuration. At the time, Chooi et al. proposed that chlorination by the halogenase GsfI was the final step in the biosynthesis of griseofulvin **1**, which was in disagreement with previous feeding experiments performed by Harris et al.[83]



Scheme 1. Proposed griseofulvin biosynthetic pathway adapted from Cacho et al. ACP is acyl carrier protein, NADPH is nicotinamide and SAM is *S*-adenosyl methionine.[94]

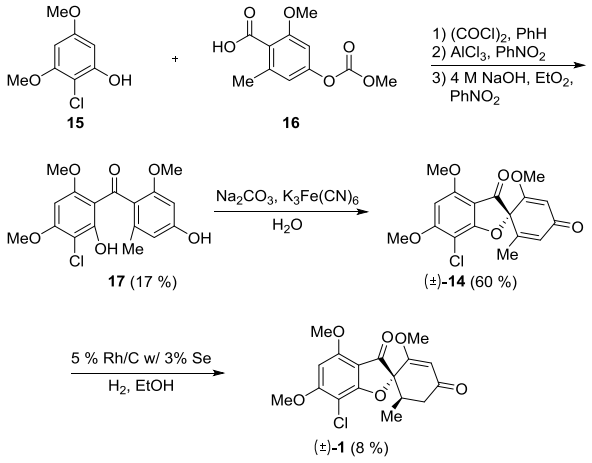
In order to fully resolve the biosynthesis of griseofulvin, Yi Tang's group followed their initial work in *P. aethiopicum* up with a comprehensive single-gene knock-out investigation leading to a complete assignment of the sequence of enzymatic events leading to biosynthesis of griseofulvin (**1**) using acetyl-CoA (**4**) as starter unit and six malonyl-CoA (**5**) as extender units (Scheme 1).[94] Again the authors concluded that the intramolecular Claisen type reaction and aldol condensation of the heptaketide backbone **6** and **7**, respectively, resulting in **8** proceeded despite neither a thioesterase nor a cyclase being part of GfsA, indicating that the PT domain promote both condensations. Deletion of

GsfB established that the initial methylation of **8** takes place at O-6 and that norlichexanthone (**9**) is formed as a shunt product, indicating that O-6 methylation resulting in griseophenone D (**10**) likely hinder dehydration and thereby suppress xanthone formation in wild type strains (Scheme 1). Similarly, deletion of the methyltransferase GsfC clarified that the second methylation takes place at 2' before formation of the grisan ring in agreement with previous feeding studies.[82] Deletion of the third methyltransferase encoding gene GsfD showed that C-7 chlorination takes place before methylation of O-4 since desmethyl-dehydrogriseofulvin (**13**) accumulated. C-7 chlorination was also demonstrated to take place prior to grisan ring formation since griseophenone B (**12**) accumulated in the GsfF knockout strain. Oxidation of the phenone ring in **12** forms the spirocyclic grisan compound **13** by a phenolic coupling catalyzed by the cytochrome P450 GsfF and the authors speculated that the mechanism could be either via a di-radical coupling or alternatively via an arene oxide intermediate.[94] Finally, GsfE catalyze the stereospecific reduction of dehydrogriseofulvin (**14**) resulting in griseofulvin (**1**).

5. Total Syntheses of Griseofulvin

Several strategies have been utilized for the total synthesis of racemic griseofulvin, while the only enantioselective synthesis of the natural product (+)-griseofulvin **1** was published in 1991. The first total synthesis was completed in 1960 by Day et al. utilizing an oxidative cyclization of the benzophenone precursor **17** (Scheme 2),[95,96] a strategy based on earlier pondering on the biosynthesis of **1**.[81,97] The two arenes 2-chloro-3,5-dimethoxyphenol **15** and 2-methoxy-4-((methoxycarbonyl)oxy)-6-methylbenzoic acid **16** were coupled by converting **16** to the acid chloride with oxalyl chloride and Friedel-Crafts acylation of **15**, which after saponification of the resulting carbonate afforded the phenol

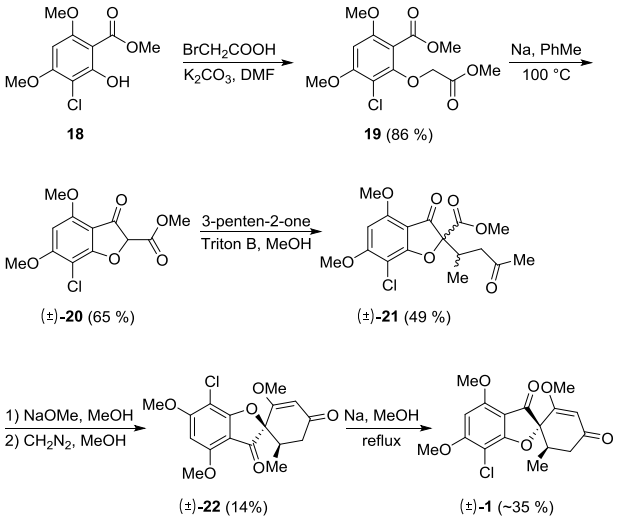
17. The formation of the spiro center was completed by a radical reaction using potassium hexacyanoferrate(III) giving (±)-dehydrogriseofulvin **14**. The final step was hydrogenation of **14** with a preformed 5 % rhodium on charcoal catalyst containing 3 % selenium yielding (±)-griseofulvin **1** in a very modest yield (**17** was isolated as the major product in 70 % yield). Day et al. also demonstrated that chiral resolution of (±)-griseofulvic acid ((±)-**78**, Scheme 14) with *N*-methylquininium hydroxide was possible.[96]



Scheme 2. Total synthesis of racemic griseofulvin by Day et al.

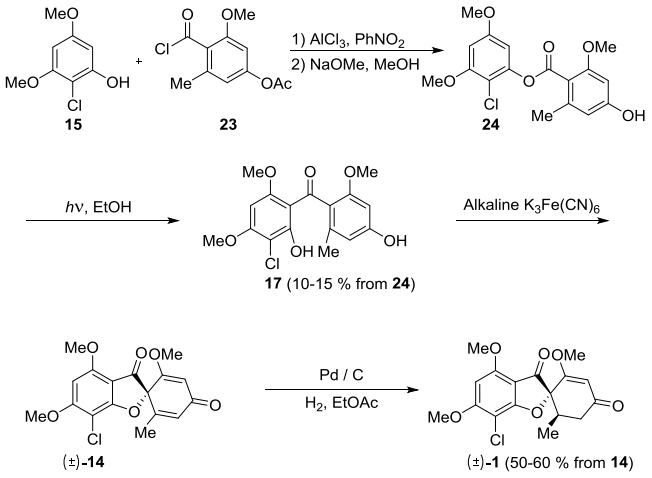
Later in 1960 Brossi et al. (from the research division of Hoffmann-La Roche) formed the C ring of griseofulvin via a Dieckmann cyclization (Scheme 3).[98,99] The synthesis of the substituted benzofuranone **20** started with **18**, which when treated with potassium carbonate and methyl 2-bromoacetate gave **19**, that was ring-closed with a Dieckmann cyclization yielding **20**. Michael addition of the benzofuranone **20** to 3-penten-2-one resulted in **21** with two diastereoisomeric products formed, where the major product was used for a second Dieckmann cyclization after which methylation

with diazomethane afforded (±)-*epi*-griseofulvin **22**. Epimerization with sodium methoxide yielded (±)-griseofulvin **1**. Brossi et al. also demonstrated that chiral resolution of (±)-griseofulvic acid ((±)-**78**, Scheme 14) with brucine was possible.[98]



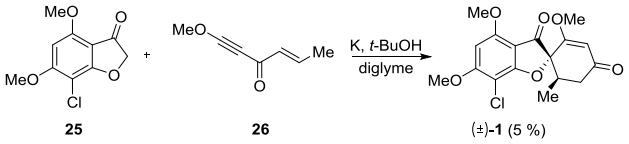
Scheme 3. Total synthesis of racemic griseofulvin by Brossi et al.

At the end of 1960 Kuo et al. (from the Merck Sharp & Dohme Research Laboratories) described a different synthetic route to the benzophenone **17** (Scheme 4).[100] When performing a Friedel-Crafts acylation with **15** and **23** they obtained **24**. Irradiation of **24** gave **17** in a modest yield, which again was cyclized with alkaline potassium hexacyanoferrate(III) giving **14**. The reduction with hydrogen and palladium on charcoal yielding (±)-griseofulvin **1** was improved giving a much higher yield compared to the conditions used by Day et al.



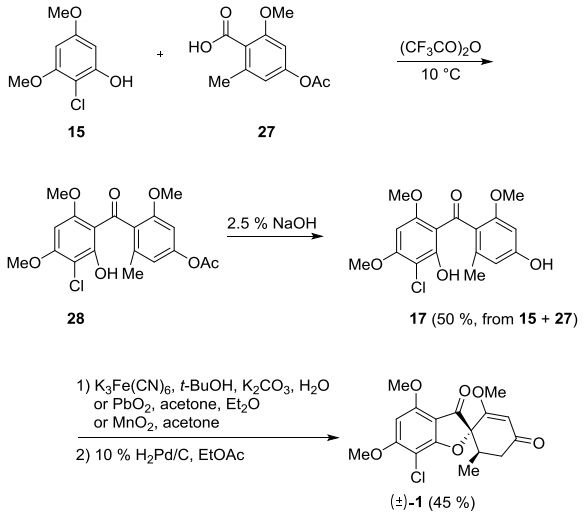
Scheme 4. Total synthesis of racemic griseofulvin by Kuo et al.

In 1962 Brossi et al. showed that chiral resolution of *epi*-griseofulvic acid (**69b**, Table 7) with enantiomerically pure 1-phenylethylamine was possible.[101] Also in 1962 Stork and Tomasz reported a one-pot synthesis using a double Michael addition to establish both stereocenters and the 2'-enol ether (Scheme 5).[102,103] The key substrate in the synthesis was the methoxyethynyl vinyl ketone **26**, which when reacted with benzofuranone **25** in the presence of potassium *tert*-butoxide gave racemic **1**.



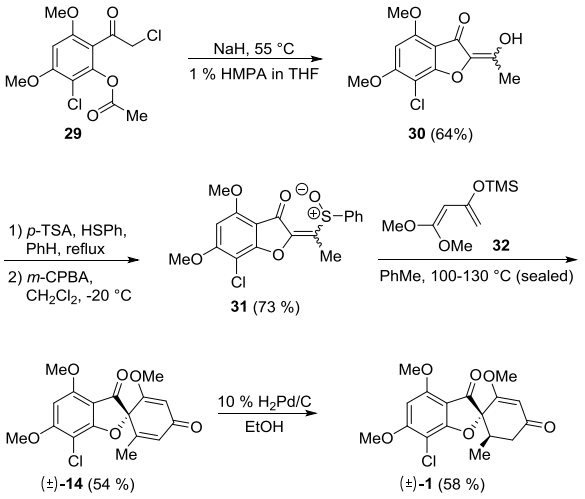
Scheme 5. Total synthesis racemic griseofulvin by Stork and Tomasz.

In 1962 Taub et al. modified the method described by Day et al. First 7-dechloro-7-fluoro-griseofulvin (**63p**, Table 1) was prepared followed by 6'-desmethyl-griseofulvin (**64g**, Table 2) and several chlorinated analogs, before publishing the optimized synthetic route to griseofulvin **1**, Scheme 6.[104,105,106,107] In the 2nd article from 1962 published in *Chemistry and Industry*, introduction of the chloro substituent was the final step.[106] The optimized total synthesis prepared the benzophenone **17** from two aromatic precursors similar to Day et al.[95,96,107] The arene **27** destined to become the C ring differed as the phenol was acetyl protected and the carboxylic acid was used instead of an acid chloride. The coupling was performed in trifluoroacetic anhydride resulting in benzophenone **28**. Reaction of the intermediate mixed trifluoroacetic anhydride of **27** (not illustrated in Scheme 6) with the phenol functionality in **15** was a major by-product, however, it could be converted into **17** by hydrolysis of the acetyl ester followed by a Fries rearrangement with titanium tetrachloride increasing the total yield of **17** from 50 % to 65 %. Ring closure of **17** to (±)-dehydrogriseofulvin **14** (not illustrated in Scheme 6) was achieved using several methods and quantitative yields were obtained using potassium hexacyanoferrate(III), lead dioxide or manganese dioxide. Hydrogenation to (±)-**1** was performed in ethyl acetate using pre-reduced 10 % palladium on charcoal as the reductant. Taub et al. also demonstrated that chiral resolution of (±)-griseofulvic acid ((±)-**78**, Scheme 14) with *N*-methylcinchonium hydroxide was possible.[107]



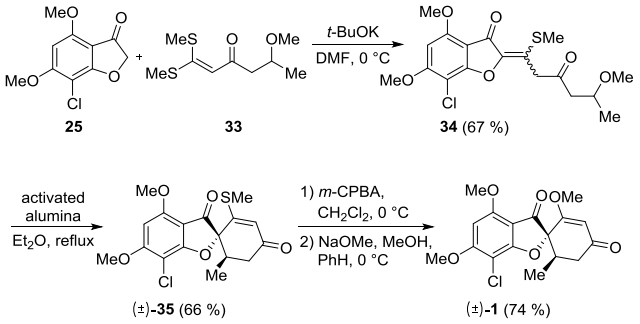
Scheme 6. Total synthesis by Taub et al.

In 1979 Danishefsky and Walker reported a total synthesis of **1** using a Diels-Alder cycloaddition strategy (Scheme 7), the synthesis was based on the total synthesis of (±)-*epi*-griseofulvin by Danishefsky and Etheredge.[108,109] The dienophile **31** was synthesized from **29** through double intramolecular nucleophilic attack giving **30**, followed by substitution with a thiophenol and oxidation with *m*-chloroperoxybenzoic acid to the sulfoxide **31**. The dienophile **31** reacted with the diene **32** in toluene at 100-135 °C yielding (±)-dehydrogriseofulvin **14**, which analogous to Taub et al. was hydrogenated with pre-reduced palladium on charcoal to (±)-griseofulvin **1**.



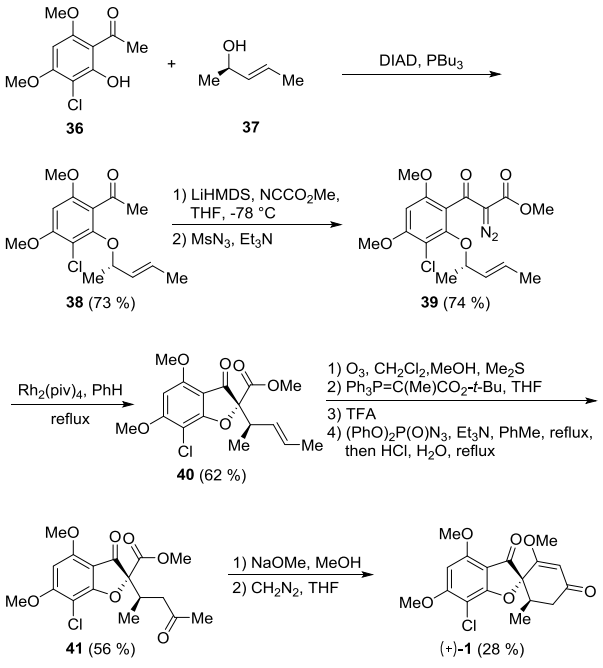
Scheme 7. Total synthesis by Danishefsky et al.

In 1990, an improvement of the method by Stork and Thomas using a double Michael addition was published by Yamato et al. Scheme 8).[110] The benzofuranone **25** was reacted with the Michael acceptor **33** giving **34** and treatment with activated alumina resulted in (±)-2'-demethoxy-2'-methylthio-griseofulvin **35**. Substitution of the thioether was achieved by oxidizing sulfur with *m*-chloroperoxybenzoic acid and reaction with sodium methoxide resulted in (±)-griseofulvin **1**.



Scheme 8. Total synthesis by Yamato et al.

In 1991 Pirrung et al. reported the first and only total synthesis of enantiomerically pure (+)-griseofulvin **1** (Scheme 9).[111] The phenol **36** was used as the nucleophile in a Mitsunobu coupling with **37** giving the triether **38**. Reacting **38** with Mander's reagent followed by a diazo transfer reaction resulted in **39**. Treatment of **39** with 5 % rhodium pivalate catalyst yielded, through a sigmatropic rearrangement, the benzofuranone **40**, which was converted by ozonolysis to an aldehyde that underwent a Wittig reaction. TFA cleaved the *tert*-butyl ester, the carboxylic acid was converted to an acyl azide, Curtius rearrangement followed by hydrolysis of the resulting enamide gave **41**. The keto ester **41** was cyclized by a Dieckmann cyclization and finally, diazomethane methylation completed the first total synthesis of (+)-griseofulvin **1**.

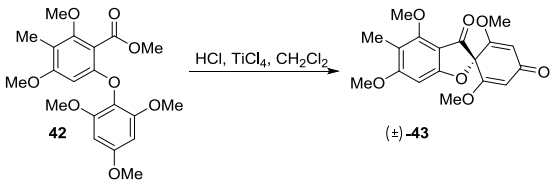


Scheme 9. Enantioselective total synthesis of griseofulvin by Pirrung et al.

6. De Novo Syntheses of Analogs

Some A ring analogs of griseofulvin can be prepared directly from the natural product (vide infra), whereas B ring and position 6' modifications are not possible by this strategy. Consequently, several A ring analogs and all B ring and position 6' analogs have been prepared by strategies developed for the total synthesis of **1**. The strategies used were oxidative cyclisation, Diels-Alder, double Michael addition, Dieckmann cyclization and the improved Michael strategy.[109,112,113,114,115,116,117,118,119,120,121,122]

In 1980, a total synthesis of a 5-methylated 6' modified dehydrogriseofulvin **43** was completed by Sargent (Scheme 10).[123] Treatment of the precursor **42** with hydrogen chloride and titanium tetrachloride in dichloromethane yielded **43** through an intramolecular *ipso*-acylation.

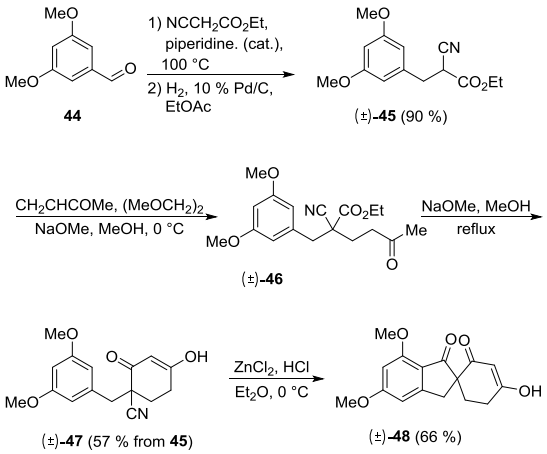


Scheme 10. Analog synthesis by Sargent.

6.1 Analogs with a Modified B Ring

Newman and Angier developed a novel strategy for the preparation of the B ring analogs, with a Hoesch condensation as the ring forming step (Scheme 11).[124] In the first step a cyano group was introduced by condensation of **44** with ethyl cyanoacetate using piperidine in a catalytic amount, which

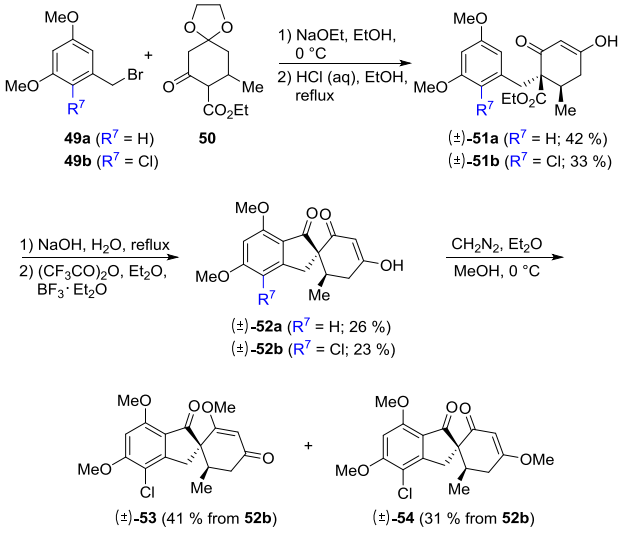
after hydrogenation with 10 % palladium on charcoal gave the nitrile **45**. The nitrile was reacted further with the Michael acceptor but-3-en-2-one using sodium methoxide yielding crude **46**. A Dieckmann condensation with methoxide in methanol resulted in **47** with the C ring formed and the following Hoesch condensation with hydrogen chloride and zinc chloride in diethyl ether gave the position 1 carbon analog of 7-dechloro-6'-desmethylgriseofulvic acid **48**.



Scheme 11. Synthesis of **48** by Newman et al.[124]

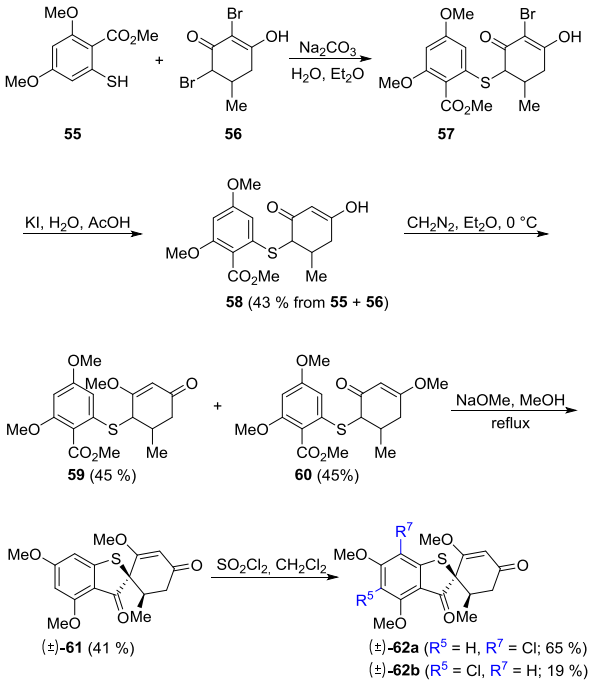
An alternative strategy had to be developed for the 6'-methyl derivative **52a** (Scheme 12) as the Hoesch condensation of its cyano precursor gave a non-spiro product.[125] The keto-ester **50** was coupled to **49a** with sodium ethoxide in ethanol followed by acetal hydrolysis to give **51a**. The ester was hydrolyzed and treatment with trifluoroacetic anhydride and boron trifluoride etherate gave the desired product **52a**.[125] This modified strategy was used to prepare the griseofulvic acid derivative **52b** and its

corresponding griseofulvin and isogriseofulvin analogs **53** and **54** by methylation with diazomethane.[126]



Scheme 12. Total synthesis of the 1-carbon analogs **52**, **53** and **54** by Newman and Angier.[125,126]

Newman and Angier also prepared 1-thio-*epi* griseofulvin analogs using the route illustrated in Scheme 13.[127] The thiophenol **55** was coupled with **56** using sodium carbonate affording **57**. The crude product was debrominated with potassium iodide in aqueous acetic acid yielding **58**, which was methylated with diazomethane in diethyl ether giving a mixture of **59** and **60**. Treatment of the **59**/**60** mixture with methanolic sodium methoxide gave **61**. Chlorination with sulfuryl chloride provided a mixture of R^5 and R^7 chlorinated *epi*-analogs **62**.

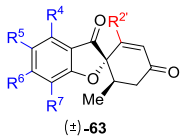


Scheme 13. Total synthesis of the 1-thio analogs **61** and **62** by Newman and Angier.[127]

In 2013, Dong et al. employed an asymmetric Michael-aldol tandem reaction to synthesize 2'-phenyl, 6'-*epi* modified analogs.[128] Different chiral 1,2-diamine catalysts were tested in the reaction and the best enantioselectivity was achieved when using 9-aminocinchonine.

6.2 Tables of Griseofulvin Analogs Prepared by de Novo Synthesis

The analogs synthesized by means of de novo synthesis are given in Tables 1-8 and Figure 2 and all compounds illustrated are racemic mixtures, if no relative stereochemistry is indicated it was not reported in the original literature. The analogs are sorted in classes based on their C ring similarity.



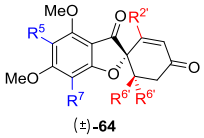
(±)-**63**

Table 1. Position 4, 5, 6, 7 and 2' modifications of griseofulvin.

Structure	R^4	R^5	R^6	R^7	$R^{2'}$	Reference
63a	*H*	H	*H*	*H*	OMe	**112**
63b	*H*	H	*H*	*H*	*OEt*	**112**
63c	*H*	H	*H*	Cl	OMe	**112**
63d	*H*	H	*H*	Cl	*OEt*	**112**
63e	*H*	H	OMe	Cl	OMe	**113**
63f	*H*	H	OMe	Cl	*SMe*	**113**
63g	*H*	H	*Cl*	*H*	*OEt*	**112**
63h	*H*	*Me*	*H*	Cl	*OEt*	**112**
63i	*H*	*OMe*	*H*	Cl	OMe	**113**
63j	*H*	*OMe*	*H*	Cl	*SMe*	**113**
63k	*H*	*Cl*	*H*	*H*	*OEt*	**112**
63l	OMe	H	*H*	Cl	OMe	**113**
63m	OMe	H	*H*	Cl	*SMe*	**113**
(±)-**2**	OMe	H	OMe	*H*	OMe	**104**,**106**,**114**,**115**
63n	OMe	H	OMe	*Me*	OMe	**115**[a]
63o	OMe	H	OMe	NO_2	OMe	**115**
63p	OMe	H	OMe	*F*	OMe	**104**,**116**
63q	OMe	H	OMe	Cl	*OEt*	**112**
(±)-**35**	OMe	H	OMe	Cl	*SMe*	**110**,**117**
63r	OMe	H	OMe	*I*	OMe	**115**
63s	OMe	*Me*	OMe	Cl	OMe	**113**
63t	OMe	*Me*	OMe	Cl	*SMe*	**113**
63u	OMe	CO_2Et	OMe	Cl	OMe	**118**
63v	OMe	NO_2	OMe	*H*	OMe	**115**
63w	OMe	*OMe*	OMe	Cl	OMe	**113**

63x	OMe	*OMe*	OMe	Cl	*SMe*	**113**
63y	OMe	*Cl*	OMe	*H*	OMe	**104**,**106**,**114**,**115**
63z	OMe	*Cl*	OMe	Cl	OMe	**106**,**113**
63aa	OMe	*Cl*	OMe	Cl	*SMe*	**113**

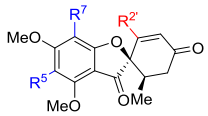
[a] Mixture of *epi*-analogs.



(±)-**64**

Table 2. Position 5, 7, 2' and 6' modifications of griseofulvin.

Structure	R^5	R^7	$R^{2'}$	$R^{6'}$ (α)	$R^{6'}$ (β)	Reference
64a	H	*H*	Me	H	*H*	**119**
64b	H	*H*	OMe	H	*H*	**115**
64c	H	*H*	OMe	H	*Et*	**120**
64d	H	*H*	OMe	*Et*	*H*	**120**
64e	H	*NO_2*	OMe	H	*H*	**115**
64f	H	*Me*	OMe	H	*H*	**115**
64g	H	Cl	OMe	H	*H*	**105**,**114**,**120**,**121**
64h	H	Cl	OMe	H	*Et*	**117**,**120**
64i	H	Cl	OMe	H	*Ph*	**117**
64j	H	Cl	OMe	*Me*	Me	**121**
64k	H	Cl	OMe	*Et*	*H*	**120**,**121**
64l	H	Cl	*SMe*	H	*Et*	**117**
64m	H	Cl	*SMe*	H	*Ph*	**117**
64n	H	Cl	*SEt*	H	*Et*	**117**
64o	H	Cl	*SEt*	H	*Ph*	**117**
64p	*NO_2*	*H*	OMe	H	*H*	**115**
64q	*Cl*	*H*	OMe	H	*H*	**115**



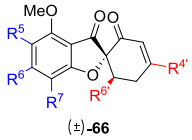
(±)-**65**

Table 3. Position 5, 7 and 2' modifications of *epi*-griseofulvin.

Structure	R^5	R^7	$R^{2'}$	Reference
65a	H	*H*	OMe	**115**
65b	H	*Me*	OMe	**115**[a]
(±)-**22**	H	Cl	OMe	**99**,**109**,**117**,**121**
65c	H	Cl	*OEt*	**112**
65d	H	Cl	*$O(CH_2)_2OMe$*	**112**
65e	H	Cl	*SMe*	**117**
65f	H	*I*	OMe	**115**
65g	*Cl*	*H*	OMe	**115**

[a] Mixture of *epi*-analogs.

6.3 Tables of Isogriseofulvin Analogs Prepared by de Novo Synthesis

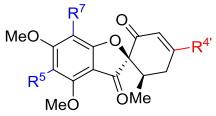


(±)-**66**

Table 4. Position 5, 6, 7, 4' and 6' modifications of isogriseofulvin.

Structure	R^5	R^6	R^7	$R^{4'}$	$R^{6'}$	Reference
66a	H	OMe	*H*	OMe	*H*	**115**
66b	H	OMe	Cl	OMe	*H*	**115**
66c	H	OMe	Cl	OMe	*Et*	**117**

66d	H	OMe	Cl	OMe	*Ph*	**117**
66e	H	OMe	Cl	*OEt*	Me	**112**
66f	H	OMe	Cl	*SEt*	*Et*	**117**
66g	H	OMe	Cl	*SEt*	*Ph*	**117**
66h	*Cl*	OMe	*H*	OMe	*H*	**115**

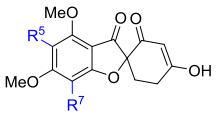


(±)-**67**

Table 5. Position 5, 7 and 4'modifications of *epi*-isogriseofulvin.

Structure	R^5	R^7	$R^{4'}$	Reference
67a	H	*H*	OMe	**115**
67b	H	*Me*	OMe	**115**
67c	H	Cl	OMe	**99**
67d	*Cl*	*H*	OMe	**115**

6.4 Tables of Griseofulvic acid Analogs Prepared by de Novo Synthesis

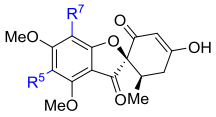


(±)-**68**

Table 6. Position 5 and 7 modifications of 6'-desmethylgriseofulvic acid.

Structure	R^5	R^7	Reference
68a	H	*H*	**115**
68b	H	*Me*	**115**

68c	H	Cl	**115**
68d	*Cl*	*H*	**115**

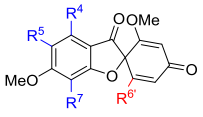


(±)-**69**

Table 7. Position 5 and 7 modifications of *epi*-griseofulvic acid.

Structure	R^5	R^7	Reference
69a	H	*H*	**115**
69b	H	Cl	**99**
69c	H	*I*	**115**
69d	H	*Me*	**115**
69e	*Cl*	*H*	**115**

6.5 Miscellaneous Analogs Prepared by de Novo Synthesis



(±)-**70**

Table 8. Position 4, 5, 7 and 6’ modifications of dehydrogriseofulvin.

Structure	R^4	R^5	R^7	$R^{6'}$	Reference
70a	*Me*	H	*H*	Me	**123**

70b	OMe	H	*H*	Me	**106**,**114**
70c	OMe	H	*F*	Me	**104**,**116**
70d	OMe	H	Cl	*H*	**105**,**114**
(±)-**14**	OMe	H	Cl	Me	**95**,**96**,**97**,**98**,**99**,**107**
70e	OMe	*Cl*	*H*	Me	**106**,**114**

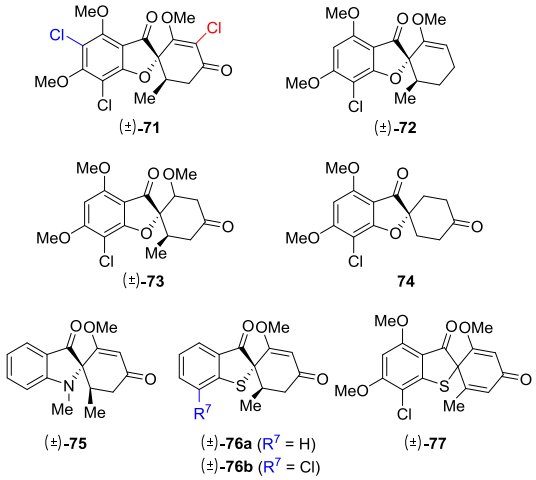
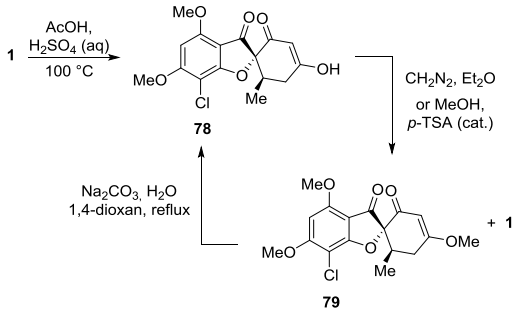


Figure 2. Structures of miscellaneous analogs prepared by de novo synthesis **71** (ref. **106**, note: inconsistent data regarding stereochemistry), **72** (ref. **120**), **73** (ref. **120**), **74** (ref. **120**), **75** (ref. **112**), **76** (ref. **112**) and **77** (ref. **122**).

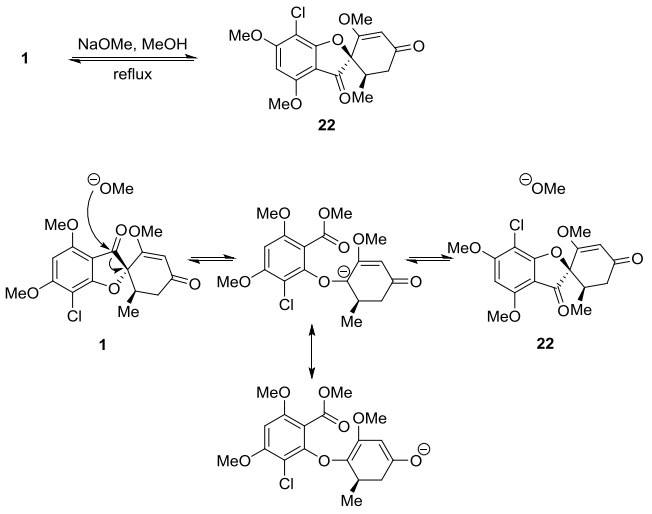
7. Synthetic Griseofulvin Analogs

Numerous analogs of (+)-griseofulvin **1** have been synthesized, common for all is their syntheses from enantiomerically pure **1**, which generally resulted in single antipodes.



Scheme 14. Conversion between griseofulvin **1**, griseofulvic acid **78** (drawn as the predominant tautomer in solution) and isogriseofulvin **79**.

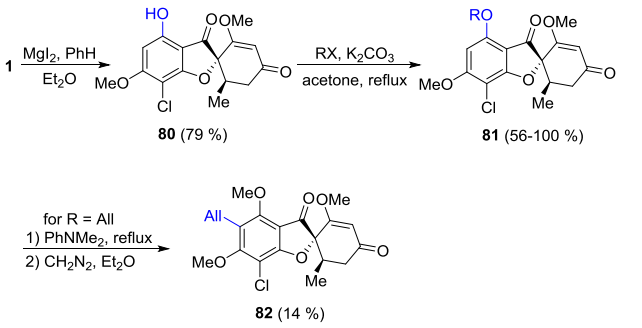
Analogs of griseofulvin are sorted into four major classes primarily depending on the substitution on the C ring. The three first consist of griseofulvin **1**, griseofulvic acid **78** and isogriseofulvin **79** analogs, after which comes a section describing the remaining analogs. In Scheme 14 the three compounds and the interconversion between them are given. Griseofulvin **1** can be hydrolyzed with dilute aqueous sulfuric acid yielding **78**, which can be converted into griseofulvin **1** and isogriseofulvin **79** with diazomethane in diethyl ether or more selectively into isogriseofulvin **79** with acid-catalyzed methanolysis based on the findings by Duncanson et al.[37,41] Brossi et al. found that (±)-**79** can be hydrolyzed to (±)-**78** by 0.1 M sodium carbonate in 1,4-dioxane.[99] If more alkaline conditions are used epimerization of the spiro center in griseofulvin **1** (Scheme 15) occurs, e.g. by refluxing **1** in methanolic sodium methoxide as described by Mulholland et al.[24] Two epimerization mechanisms were initially suggested by MacMillan et al. and the one illustrated in Scheme 15 was later supported by Brossi et al.[24,99]



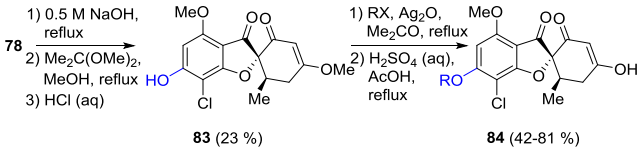
Scheme 15. Epimerization of **1** into **22** and the suggested mechanism for the reaction.

Some of the earlier A ring modifications were made by MacMillan et al. in the late 1950s to determine the absolute structure, stability and reaction of griseofulvin **1** and some of its derivatives upon treatment with various reagents and under different conditions.[24,36]

In 1962, Arkley et al. showed that griseofulvin **1** could be selectively demethylated in the 4 position with magnesium iodide giving **80** followed by O-4 alkylation with various alkylating reagents using either potassium carbonate or silver oxide resulting in **81** (Scheme 16).[41] The 5-allyl modified griseofulvin **82** was synthesized from the 4-*O*-allyl derivative of **81** by a Claisen rearrangement (Scheme 16) and Arkley et al. also showed that position 6 modified griseofulvin compounds could be synthesized from griseofulvic acid **78** by position 6 demethylation followed by position 4' methylation resulting in the 6-desmethyl isogriseofulvin analog **83**, which was subsequently alkylated and converted to griseofulvin analogs of the general structure**84** by hydrolysis. The griseofulvic acid derivatives could be converted into the griseofulvin analogs (Scheme 17, conversion not illustrated).[41]



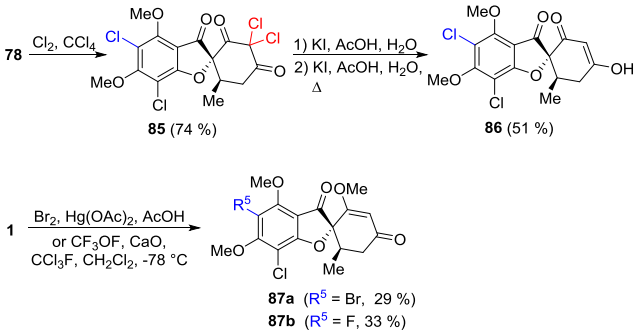
Scheme 16. Position 4 demethylation and a typical position 4 alkylation, followed by Claisen rearrangement of the 4-allyloxy analog.



Scheme 17. Position 6 demethylation of griseofulvic acid **78** followed by silver oxide mediated alkylation of the phenol.[41]

Later in 1962, Walker et al. determined that position 5 chlorination could be made via griseofulvic acid with chlorine in carbon tetrachloride resulting in the 3',3',5-trichloride **85**. The trichloride was selectively 3'-dehalogenated using potassium iodide resulting in the griseofulvic acid analog **86** followed by alkylation of O-2'/O-4' with either diazo alkyls or alkyl halides giving mixtures of halogenated griseofulvin and isogriseofulvin analogs (Scheme 18, alkylation not illustrated).[43] Position 3' was the initial halogenation site on griseofulvic acid **78** with either chlorine in carbon tetrachloride

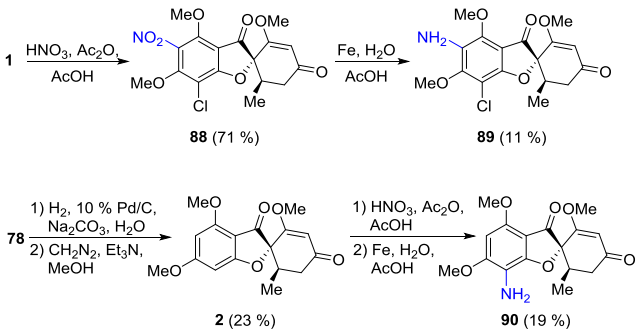
or bromine and iodine respectively in DMF.[43] Bromination of the 5 position could be done directly on griseofulvin **1** with bromine and mercury(II) acetate yielding **87a** (Scheme 18).[43] In 1972 Barton et al. discovered direct fluorination of griseofulvin **1** with trifluoromethyl hypofluorite, which yielded 5-fluorogriseofulvin **87b** as the major product and 3'-fluoro (10 %) and 3',5-difluorogriseofulvin (10 %) as minor products (Scheme 18), while Rønnest et al. in 2009 showed that direct 3'-iodination of griseofulvin could be performed with *N*-iodosuccinimide and triethylsilyl trifluoromethanesulfonate in dichloromethane resulting in 3'-iodogriseofulvin (**116m**, Table 15).[75,129]



Scheme 18. Typical halogenation with chlorine in carbon tetrachloride and de-chlorination of griseofulvic acid **78** or position 5 bromination/fluorination of griseofulvin **1** with bromine or the fluorination reagent trifluoromethyl hypofluorite, respectively.[43,129]

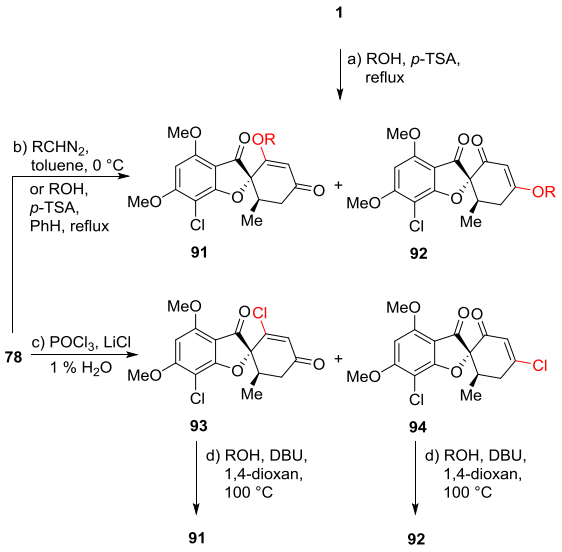
In 1963 Arkley et al. demonstrated that nitration of griseofulvin **1** in the 5 position affording **88** was possible as well as nitration in position 7 giving **90** when starting from 7-dechloro griseofulvin **2**.[46] Arkley et al. also demonstrated that the nitro functionality could be reduced with iron in acetic acid yielding the 5-amino analog **89** (Scheme 19).[46] MacMillan had originally discovered that de-chlorination of position 7 occurred during reduction of griseofulvin **1** with hydrogen in the presence of

palladium on charcoal, with concomitant reduction of the C ring alkene.[31] Arkley et al. discovered that griseofulvic acid **78** should be used as the precursor for 7-dechlorogriseofulvin **2** (Scheme 19).[46]



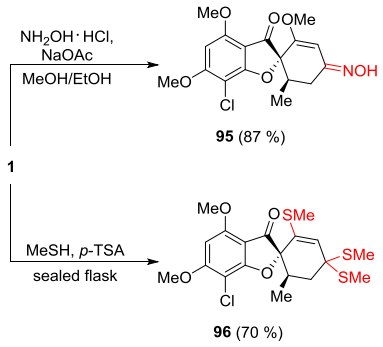
Scheme 19. Nitration reactions and the position 7 de-chlorination from griseofulvic acid (**78**).[46]

Duncanson et al. showed in 1958 that mixtures of 2'-griseofulvin analogs **91** and 4'-isogriseofulvin analogs **92** could be prepared by alkylation of griseofulvic acid **78** with either diazo alkyls or acid-catalyzed alcoholysis of griseofulvin **1** with varying yields.[37] In 1962 Gregory et al. employed base mediated 3'-alkylation of griseofulvic acid followed by conversion into mixtures of the griseofulvin and isogriseofulvin analogs similar to the route for 3' halogenated analogs.[42] Later in 1962 a more selective 2' substitution method using a 2'-chloro precursor **93** was developed (Scheme 20).[44] Griseofulvic acid **78** was treated with moist phosphoryl chloride and lithium chloride giving a mixture of **93** and **94** and after separation, the respective chloro-compounds were treated with different nitrogen-, oxygen- and sulfur-based nucleophiles resulting in analogs of griseofulvin **91** and isogriseofulvin **92**, respectively.[44,47,75,76]



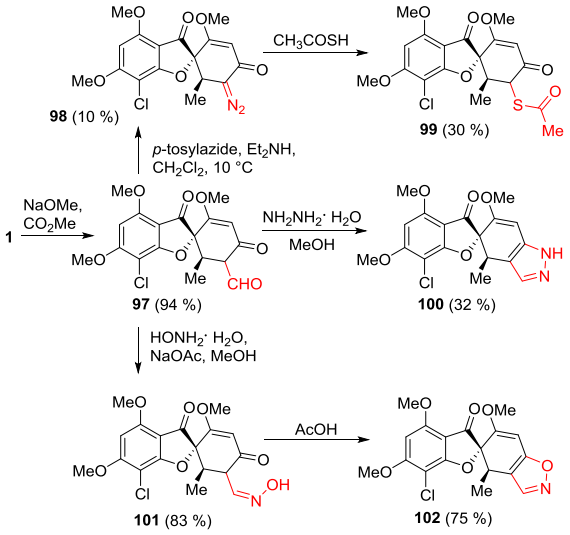
Scheme 20. Typical examples of conditions for synthesizing 2'- and 4'-analogs of griseofulvin **91** and isogriseofulvin **92** (R ≠ Me) prepared by: a) alcoholysis of griseofulvin **1** or griseofulvic acid **78**; b) alkylation of griseofulvic acid **78** with diazoalkyls or c) chlorination of griseofulvic acid's C ring at the 2' or 4' positions (**93** and **94**, 99 % conversion) and d) nucleophilic conjugate addition and chloride elimination illustrated with ROH. [37,44,47,75,76]

Nitrogen-containing 4'-griseofulvin analogs, illustrated with the 4'-oxime analog **95**, were prepared by treating the 4'-oxo precursor with the relevant azane using suitable conditions, [75,76,130,131] while the sulfur analogs, illustrated with the dimethyl dithioacetal analog **96**, were prepared from **1**, the corresponding thiol and *p*-TSA (Scheme 21).[132]



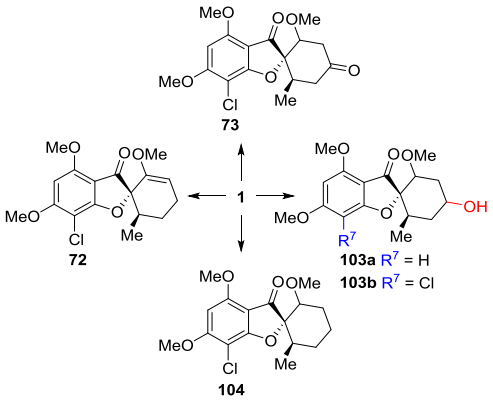
Scheme 21. 4'-Analogs prepared from griseofulvin **1**.

In 1970, Newman and Fields treated griseofulvin with methyl formate and sodium methoxide and accomplished 5'-formylation in high yield (**97**).[133] Together with Angier they later showed that the 5'-formyl derivative could be converted to the 5'-diazo analog **98** using *p*-tosyl azide and diethyl amine in dichloromethane and the 5'-diazo analog could be reacted further illustrated with thioacetic acid in Scheme 22.[134] The two 5' modified griseofulvin analogs **97** and **98** have been the precursors for many of the 5'-derivatives described in the literature.[133,134,135] Stereoselective 5' hydroxylation by fermentation with *Streptomyces Cinereocrocatus* was done on gram scale by Andres et al.[136] By treating 5'-formylgriseofulvin **97** with hydrazine Newman et al. synthesized the new tetracyclic analog **100** and when reacting **97** with hydroxyl amine followed by acetic acid, an isoxazole analog **102** was prepared (Scheme 22).[135]

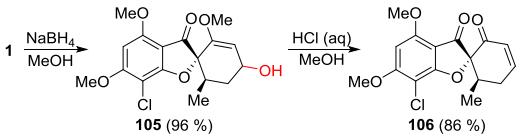


Scheme 22. Synthesis of the 5'-formyl analog **97** and conversion of the 5'-formyl analog into the 5'-diazo analog **98**, its derivatization and synthesis of two tetracyclic compounds from **97**.[133,134,135]

In 1952, Mulholland prepared additional analogs by hydrogenation of griseofulvin (and isogriseofulvin) with either palladium or platinum on charcoal.[31] In Scheme 23, some of the products (**72**, **73**, **103** and **104**) from griseofulvin reduction with palladium on charcoal and hydrogen gas are illustrated. Mulholland later used reductions and oxidations to prepare a variety of different analogs.[32] In 1960 Kyburz et al. used sodium borohydride to reduce the 4'-oxo functionality of griseofulvin yielding the hydroxy analog **105** and 2'-oxo functionality in isogriseofulvin, the reduced hydroxy compounds were used as precursors for further analogs illustrated by compound **106** (Scheme 24).[137]

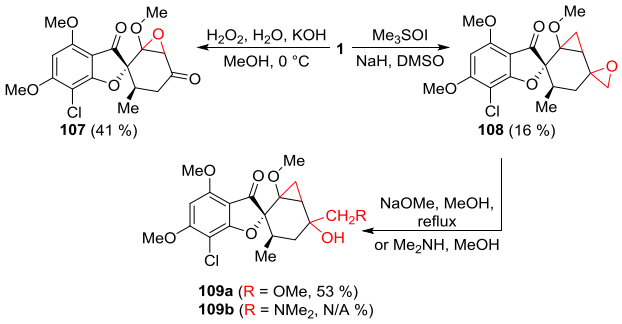


Scheme 23. Typical products from hydrogen reductions of griseofulvin **1** in ethyl acetate with 10 % palladium on charcoal.[31]



Scheme 24. Sodium borohydride reduction of griseofulvin's 4'-oxo functionality and hydrolysis-elimination to form the analog **106**.[137]

In 1970, Newman showed that treatment of griseofulvin **1** with alkaline hydrogen peroxide afforded 2'-3'-epoxidation (the use of benzoyl peroxide resulted in lower yields) giving the oxirane analog **107** and in 1971 published that treatment of **1** with sodium dimethylsulfoxide methylide resulted in the analog **108** where 2'-3'-cyclopropanation and 4'-methylene transfer / epoxidation of griseofulvin **1** had occurred (Scheme 25).[138,139] Newman proceeded to synthesize two new cyclopropyl analogs **109** when treating **108** with methanolic sodium methoxide or dimethylamine in methanol.



Scheme 25. Synthesis of the oxirane and cyclopropyl analogs by Newman.[138,139]

7.1 Tables of Griseofulvin Analogs

In the cases where the relative stereochemistry is not indicated for compounds in tables 9-30 and Figure 3, it was not reported in the original literature. The analogs are mainly sorted in classes depending on their C ring similarity.

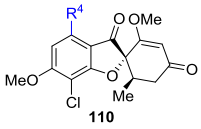
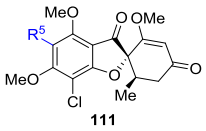


Table 9. Position 4 modifications of griseofulvin.

Structure	R^4	Reference
110a	*Me*	**47**,49,50
110b	*1-Pyrrolidinyl*	**47**,49,50
80	*OH*	**41**,52,75,76
110c	*OEt*	**41**,45,49,75,76

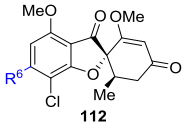
110d	*OPr*	**41**,45
110e	*OBu*	**41**,45,61
110f	*Opentyl*	**76**
110g	*Ocitronellyl*	**140**,141
110h	*$O(CH_2)_2NMe_2$*	**41**
110i	*$O(CH_2)_2NEt_2$*	**41**
110j	*$O(CH_2)_2$-1-pyrrolidinyl*	**41**
110k	*$O(CH_2)_2$-1-piperidinyl*	**41**
110l	*$O(CH_2)_2N^+(Me)_2(Et)\ Br^-$*	**41**
110m	*OAll*	**41**,45,61,142,143
110n	*OBn*	**41**,45,61,75,76,142,143
110o	*OCH_2-(4-methoxyC_6H_4)*	**140**,141
110p	*OCH_2-(3-diethylcarbamoylC_6H_4)*	**140**,141
110q	*OCH_2-1-naphtyl*	**76**
110r	*$OCH_2CONH(CH_2)_2NEt_2$*	**41**
110s	*$OCH_2CONH(CH_2)_3NEt_2$*	**41**
110t	*$OCH_2CONHBn$*	**41**
110u	*$OCH_2CONHPh$*	**41**
110v	*OCH_2CONH-(4-chloroC_6H_4)*	**41**
110w	*OCH_2CO_2H*	**41**
110x	*OCH_2CO_2Me*	**41**
110y	*OCH_2CO_2Bn*	**41**
110z	*O*-i-*Pr*	**41**,45,49
110aa	*$OCH(Me)CH_2NMe_2$*	**41**
110ab	*OAc*	41,49
110ab	*OSO_2Me*	50



111

Table 10. Position 5 modifications of griseofulvin.

Structure	R^5	Reference
111a	*Pr*	**41**,45,49
82	*All*	**41**,45
89	*NH_2*	**46**,75,76,**130**
111b	*NHBn*	**75**
88	*NO_2*	**46**,75,76,130,144
87b	*F*	**129**
111c	*Cl*	**43**,45,49,50,51
87a	*Br*	**43**,45,144

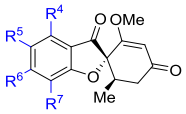


112

Table 11. Position 6 modifications of griseofulvin.

Structure	R^6	Reference
112a	*1-Pyrrolidinyl*	**47**,49
112b	*OH*	**41**,50,**52**,76,145
112c	*OEt*	**41**,45,49,61,**76**,142,143
112d	*OPr*	**41**,45,61,142,143
112e	*OBu*	**41**,45
112f	*Ohexadecyl*	**41**,45
112g	*OBn*	**41**,45

112h	*OCH_2CO_2Me*	**41**
112i	*O*-i-*Pr*	**41**,45,49,61
112j	*OAll*	**41**,45,61,142,143
112k	*OAc*	**41**,49

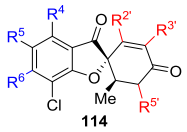


113

Table 12. Position 4, 5, 6 and 7 modifications of griseofulvin.

Structure	R^4	R^5	R^6	R^7	Reference
113a	*OH*	*OH*	OMe	Cl	**146**
113b	*OH*	*NO_2*	*OH*	Cl	**46**
2	OMe	H	MeO	*H*	35,45,**46**,49,50,51[a],147,148, 149
113c	OMe	H	OMe	*F*	51,**116**
90	OMe	H	OMe	*NH_2*	**46**,50
113d	OMe	H	OMe	*NO_2*	**46**
113e	OMe	H	OMe	*$N_2^+ BF_4^-$*	**46**
113f	OMe	*NH_2*	OMe	*H*	**46**,50
113g	OMe	*NHBz*	OMe	*H*	**46**
113h	OMe	*NO_2*	OMe	*H*	**46**
113i	OMe	*OH*	*OH*	Cl	**146**
63y	OMe	*Cl*	OMe	*H*	51
113j	OMe	*Cl*	OMe	Cl	**114**
113k	*OEt*	H	*OEt*	Cl	**24**,45
113l	*SMe*	H	*SMe*	Cl	**47**,49

[a] Racemic mixture

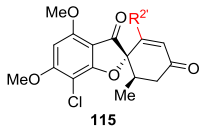


114

Table 13 Position 4, 5, 6, 2', 3' and 5' modifications of griseofulvin.

Structure	R^4	R^5	R^6	$R^{2'}$	$R^{3'}$	$R^{5'}$	Reference
114a	*1-Pyrrolidinyl*	H	OMe	*1-Pyrrolidinyl*	H	H	**47**
114b	*OH*	*Br*	OMe	OMe	*Br*	H	**43**
114c	OMe	H	*1-Pyrrolidinyl*	*1-Pyrrolidinyl*	H	H	**47**
114d	OMe	H	OMe	*H*	H	*Br*	**159**
114e	OMe	H	OMe	*H*	*Br*	H	**159**
114f	OMe	H	OMe	CH_2Br	H	*Br*	**150**[a]
114g	OMe	H	*OEt*	*OEt*	H	H	**36**,45,49,147,149
114h	OMe	H	*OBu*	*OBu*	H	H	**41**,45
114i	OMe	*F*	OMe	OMe	*F*	H	**129**
114j	OMe	*Cl*	OMe	OMe	H	*Cl*	**114**
114k	OMe	*Cl*	OMe	OMe	*Cl*	H	**43**,45,49,51,**114**
114l	OMe	*Br*	OMe	OMe	*Br*	H	**43**
114m	*OEt*	H	*OEt*	*OEt*	H	H	**24**,45,49

[a] $R^{5'\alpha}$ configuration



115

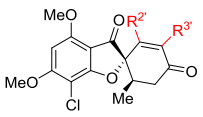
Table 14. Position 2' modifications of griseofulvin.

Structure	$R^{2'}$	Reference

115a	*H*	**32**,45,48,49,50,73,147,148,151,159
115b	*Me*	**150**
115c	*CH_2Br*	**150**
115d	*NH_2*	**28**,**47**,48,147,148,149,152
115e	*NHMe*	**47**,48,49,152
115f	*NHEt*	**47**,48
115g	*$NH(CH_2)_3NMe_2$, HCl*	**44**
115h	*$NH(CH_2)_3NEt_2$, HCl*	**44**
115i	*$NH(CH_2)_2NEt_2$*	**44**,48
115j	*1-Pyrrolidinyl*	**47**,48,49,50
115k	*OEt*	24,**42**,**44**,45,49,51,61,**75**,76,142,143,147,148
115l	*OPr*	**37**,45,61,73,**75**,76,142,143,147,149
115m	*OBu*	**37**,45,61,**75**,142,143,147,149
115n	*Opentyl*	**37**,**75**
115o	*Ohexyl*	**37**,45,61,**75**
115p	*Oheptyl*	**37**
115q	*Ooctyl*	**37**
115r	*Odecyl*	**37**
115s	*Opentadecyl*	**37**
115t	*$O(CH_2)_2Ph$*	**75**,76
115u	*$O(CH_2)_2Br$*	**153**
115v	*$O(CH_2)_2{}^{125}I$*	**153**
115w	*O*-i-*Bu*	**37**
115x	*OCH_2*-cyclo-*Pr*	**75**,76
115y	*OAll*	**42**,45,61,142,143
115z	*OCH_2-1-adamantyl*	**75**,76
115aa	*OBn*	**42**,45,61,**75**,76,142,143
115ab	*OCH_2-(4-methylC_6H_4)*	**75**,76
115ac	*OCH_2-4-biphenyl*	**75**,76
115ad	*OCH_2-(4-trifluoromethylC_6H_4)*	**76**
115ae	*OCH_2-(4-hydroxymethylC_6H_4)*	**76**
115af	*OCH_2-(4-methoxyC_6H_4)*	**76**

115ag	*OCH_2-(3-methoxyC_6H_4)*	**76**
115ah	*OCH_2-(2-methoxyC_6H_4)*	**76**
115ai	*OCH_2-(4-fluoroC_6H_4)*	**76**
115aj	*OCH_2-1-naphtyl*	**76**
115ak	*OCH_2-4-pyridyl*	**76**
115al	*OCH_2-3-pyridyl*	**76**
115am	*OCH_2-2-pyridyl*	**76**
115an	*O*-i-*Pr*	**41**,45,**75**,76
115ao	*O*-cyclo-*pentyl*	**75**,76
115ap	*Tetra*-O-*acetyl-α-D-glucosyloxy*	**37**[a],147
115aq	*OPh*	45,61,**75**,76,142,143
115ar	*SMe*	**44**,45,48,49,50,61,**132**
115as	*SEt*	**44**,45,61,**117**,**132**
115at	*SPr*	**44**,45,61,**132**
115au	*SBu*	**44**,45,61,**132**
115av	*S(CH_2)$_2$NEt_2*	**44**
115aw	*S(CH_2)$_2$*-N-*phthalimidyl*	**44**
115ax	*S(CH_2)$_2$OH*	**44**
115ay	*SAll*	**44**,45,61
115az	*SBn*	**44**,45,61,75,76
115ba	*S*-i-*Pr*	**132**
115bb	*SPh*	**44**,61
115bc	*S-2-imidazolyl*	**44**
93	*Cl*	**44**,45,48,49,50,75

[a] Not fully characterized – could be the 4'-substituted isogriseofulvin

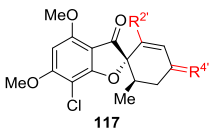


116

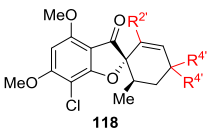
Table 15. Position 2' and 3' modifications of griseofulvin.

Structure	$R^{2'}$	$R^{3'}$	Reference
116a	OMe	*NHAc*	**46**
116b	OMe	*NHBz*	**46**
116c	OMe	*NC(OMe)Ph*	**46**
116d	OMe	*NO_2*	**46**
116e	OMe	*Me*	**42**,45,49,50,61,142,143,152
116f	OMe	*Pr*	**42**,45,61,142,143,152
116g	OMe	*$(CH_2)_2C(O)Me$*	**42**
116h	OMe	*All*	**42**,45,61,142,143
116i	OMe	*Bn*	**42**,45,61,142,143,152
116j	OMe	*F*	**129**
116k	OMe	*Cl*	**43**,45,49,51,61,142,143,152
116l	OMe	*Br*	**43**,45,61,142,143
116m	OMe	*I*	**43**,45,61,**75**,76,142,143
116n	*OEt*	*Et*	**42**,45,61,142,143
116o	*OEt*	*Bn*	**42**,45,61,142,143
116p	*OEt*	*Cl*	**43**,45,61,142,143
116q	*OEt*	*Br*	**43**,45,61,142,143
116r	*OEt*	*I*	**43**,45,61,142,143
116s	*OPr*	*Pr*	**42**,45,61,142,143
116t	*OPr*	*Bn*	**42**,45,61,142,143
116u	*OPr*	*Cl*	**43**,45,61
116v	*OPr*	*Br*	**43**,45,61,142,143
116w	*OPr*	*I*	**43**,45,61,**75**,76,142,143
116x	*OBu*	*Bn*	**42**,45,61,142,143
116y	*OBu*	*Cl*	**43**,45,61
116z	*OBu*	*Br*	**43**,45,61
116aa	*OBu*	*I*	**43**,45,61
116ab	*$O(CH_2)_3Br$*	*Bn*	**42**
116ac	*OBn*	*Cl*	**43**,61
116ad	*OBn*	*Br*	**43**
116ae	*OBn*	*I*	**43**,75,76

116af	*OPh*	*Cl*	**44**
116ag	*SMe*	*Pr*	**44**,45
116ah	*SMe*	*Bn*	**44**,45,61
116ai	*SMe*	*Cl*	**44**,45,61
116aj	*SMe*	*Br*	**44**,45
116ak	*SEt*	*Bn*	**44**,45,61
116al	*SEt*	*Cl*	**44**,45,61
116am	*SPr*	*Pr*	**44**,45,61
116an	*SPr*	*Bn*	**44**,45,61
116ao	*SPr*	*Cl*	**44**,45,61
116ap	*SPr*	*Br*	61
116aq	*SBu*	*Pr*	**44**,45
116ar	*SBu*	*Bn*	**44**,45
116as	*SBu*	*Cl*	**44**,45
116at	*SAll*	*Pr*	**44**,45
116au	*SAll*	*Bn*	**44**,45,61
116av	*SAll*	*Cl*	**44**,45,61
116aw	*SBn*	*Pr*	**44**,45
116ax	*SBn*	*Bn*	**44**,45
116ay	*SBn*	*Cl*	**44**,45
116az	*Cl*	*Pr*	**44**,45
116ba	*Cl*	*Bn*	**44**,45
116bb	*Cl*	*Cl*	**44**,45
116bc	*Cl*	*Br*	45



117

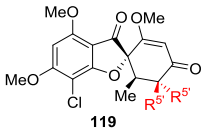


118

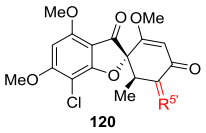
Table 16. Position 2’ and 4’ modifications of griseofulvin.

Structure	$R^{2'}$	$R^{4'}$	$R^{4'}$	Reference
117a	OMe	*=NNMe$_2$*		**75**[a]
117b	OMe	*=NNHS(O)NH$_2$*		**131**
95	OMe	*=NOH*		75,76,**130**,154,**155**
117c	OMe	*=NOCH$_2$CO$_2$H*		154
117d	*OBn*	*=NOH*		**75**,76
117e	*OCH$_2$-1-naphtyl*	*=NOH*		**76**
117f	*SMe*	*=NOH*		**132**
96	*SMe*	*SMe*	*SMe*	**132**
118a	*SEt*	*SEt*	*SEt*	**132**
118b	*SPr*	*SPr*	*SPr*	**132**
118c	*SBu*	*SBu*	*SBu*	**132**

[a] The (*E*)-isomer



119



120

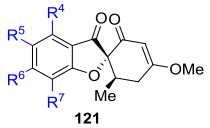
Table 17. Position 5' modifications of griseofulvin.

Structure	$R^{5'}$ (α)	$R^{5'}$ (β)	Reference
119a	H	*CH$_2$OH*	**156**
119b	*Me* / H		**135**
119c	*CH$_2$-1-piperidinyl* / H		**135**
119d	*CH=NN(Me)$_2$* / H		**135**
101	*CH=NOH* / H		**135**
119e	*CN* / H		**135**
119f	*CH$_2$OH*	H	**156**,157
97[a]	*CHO* / H		**133**,134,135,156,157
119g	*CHO*	*Br*	**133**

119h	*C(O)CO$_2$Me* / H		**133**,135
119i	*C(O)CO$_2$Et* / H		**133**,135
119j	*CH$_2$SPh* / H		**135**
119k	*CH$_2$SAc* / H		**135**
120a	*=CH$_2$*		**135**
120b	*=CH-1-pyrrolidinyl*		**135**
120c	*=NNHPh*		**135**
98	*=N$_2$*		**134**
119l	*OH*	H	**136**,158
119m	*OMe*	H	**136**
119n	*OAc*	H	**134**[b],**136**
119o	*F*	H	**133**,135[b]
119p	*SMe* / H		**135**
99	*SAc* / H		**134**
119q	*SO$_2$Me* / H		**138**
119r	*4-Tosyloxy* / H		**133**
119s	*Cl*	H	**133**,135[b]
119t	*Br*	H	**133**,134[b],135[b],138[b]
119u	*Br*	*CHO*	**133**
119v	*I*	H	**133**,135[b]

[a] Illustrated as the carbonyl tautomer. [b] Mixture of 5' isomers / stereochemistry not defined.

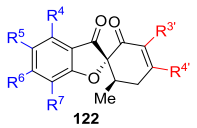
7.2 Tables of Isogriseofulvin Analogs



121

Table 18. Position 4, 5, 6 and 7 modifications of isogriseofulvin.

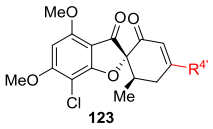
Structure	R^4	R^5	R^6	R^7	Reference
121a	*Me*	H	*OH*	Cl	**47**,49,50
121b	*Me*	H	OMe	*H*	50
121c	*Me*	H	OMe	Cl	**47**,49
121d	*1-Pyrrolidinyl*	H	OMe	Cl	**47**,50
121e	*OH*	H	OMe	Cl	**41**,76
83	OMe	H	*OH*	Cl	**41**,50
121f	OMe	H	OMe	*H*	45,**46**
121g	OMe	H	OMe	NH_2	**46**,50
121h	OMe	H	OMe	NO_2	**46**
121i	OMe	H	*OEt*	Cl	**41**,45
121j	OMe	H	*OPr*	Cl	**41**,45
121k	OMe	H	*OBu*	Cl	**41**,45
121l	OMe	H	*OAll*	Cl	**41**,45
121m	OMe	H	*OBn*	Cl	**41**,45
121n	OMe	H	*O*-i-*Pr*	Cl	**41**,45
121o	OMe	H	*OAc*	Cl	49
121p	OMe	*F*	OMe	Cl	**129**
121q	OMe	*NHBz*	OMe	*H*	**46**
121r	OMe	NO_2	OMe	*H*	**46**
121s	OMe	*Cl*	OMe	Cl	**43**,45,49
121t	*OEt*	H	*OEt*	Cl	**24**,45
121u	*SMe*	H	OMe	Cl	50
121v	*SMe*	H	*SMe*	Cl	**47**,49



122

Table 19. Position 4, 5, 6, 7, 3’ and 4’ modifications of isogriseofulvin.

Structure	R^4	R^5	R^6	R^7	$R^{3'}$	$R^{4'}$	Reference
122a	OMe	H	*OH*	*F*	H	*O*-i-*Pr*	**104**
122b	OMe	H	*OH*	Cl	H	*O*-i-*Pr*	**51**,**104**
122c	OMe	H	OMe	*F*	H	*O*-i-*Pr*	**51**,**104**
122d	OMe	H	*OEt*	Cl	H	*OEt*	**36**,45,61
122e	OMe	H	*OBu*	Cl	H	*OBu*	45
122f	OMe	*Cl*	OMe	Cl	*Cl*	OMe	**43**,45,49
122g	OMe	*Cl*	OMe	Cl	*Cl*	*O*-i-*Pr*	51
122h	OMe	*Br*	OMe	Cl	*Br*	OMe	45
122i	*OEt*	H	*OEt*	Cl	H	*OEt*	**24**,45,49



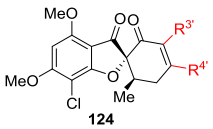
123

Table 20. Position 4' modifications of isogriseofulvin.

Structure	$R^{4'}$	Reference
106	*H*	**32**,45,48,49,50,53,**137**,152
123a	*NH_2*	**44**,**47**,48
123b	*NHMe*	**47**,48,49
123c	*NHBu*	**47**,48
123d	*$NH(CH_2)_2NEt_2$*	**44**,48
123e	*$NH(CH_2)_2$-4-morpholinyl, HCl*	**47**
123f	*NEt_2*	**47**,48
123g	*$NMe(CH_2)_2NEt_2$*	**47**,48
123h	*1-Pyrrolidinyl*	**44**,**47**,48,49,50
123i	*1-Piperidinyl, HCl*	**44**,**47**,48[a]
123j	*4-Morpholinyl*	**47**,48
123k	*OEt*	45,49,61,**76**,51,147
123l	*OPr*	**37**,45,**76**,147
123m	*OBu*	**37**,45,61,147

123n	*Opentyl*	**37**
123o	*Ohexyl*	**37**,45,147
123p	*Oheptyl*	**37**
123q	*Ooctyl*	**37**
123r	*Odecyl*	**37**
123s	*O(CH$_2$)$_2$Br*	**153**
123t	*O*-i-*Bu*	**37**
123u	*OCH$_2$*-cyclo-*Pr*	**76**
123v	*OAll*	**42**,45,61
123w	*OBn*	**42**,45,**76**
123x	*OCH$_2$-(3-methoxyC$_6$H$_4$)*	**76**
123y	*O*-i-*Pr*	**37**,**41**,45,51,76,**104**,**116**
123z	*O*-s-*Bu*	**37**
123aa	*O*-cyclo-*pentyl*	**76**
123ab	*OCy*	**37**
123ac	*OPh*	**44**,45,61
123ad	*SH*	**44**,50
123ae	*SMe*	**44**,45,48,50,**132**
123af	*SEt*	**44**,45,**132**
123ag	*SPr*	**132**
123ah	*SBu*	**132**
123ai	*S(CH$_2$)$_2$NMe$_2$*	**44**
123aj	*S(CH$_2$)$_2$OH*	**44**
123ak	*S(CH$_2$)$_2$OAc*	**44**
123al	*SBn*	**44**,45
123am	*S*-i-*Pr*	**132**
123an	*SPh*	**44**,45
94	*Cl*	**44**,45,48,49,50,**76**

[a] Not the hydrochloride



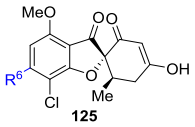
124

Table 21. Position 3’ and 4’ modifications of isogriseofulvin.

Structure	$R^{3'}$	$R^{4'}$	Reference
124a	*Me*	OMe	**42**,45,49,50,152
124b	*Et*	*OEt*	**42**,45
124c	*Pr*	*NH_2*	**44**
124d	*Pr*	OMe	**42**,45
124e	*Pr*	*OPr*	**42**,45
124f	*Bu*	*OBu*	**37**
124g	*$(CH_2)_2C(O)Me$*	OMe	**42**
124h	*All*	OMe	**42**,45
124i	*Bn*	*NH_2*	**44**
124j	*Bn*	OMe	**42**,45,61,152
124k	*Bn*	*OEt*	**42**,45
124l	*Bn*	*OPr*	**42**,45
124m	*Bn*	*OBu*	**42**,45
124n	*Bn*	*$O(CH_2)_3Br$*	**42**
124o	*Bn*	*OAll*	**42**
124p	*Bn*	*Cl*	**44**,45
124q	*NHBz*	OMe	**46**
124r	*Cl*	*NH_2*	**44**
124s	*Cl*	OMe	**43**,44,45,49,51
124t	*Cl*	*OEt*	**43**,45
124u	*Cl*	*OPr*	**43**,45
124v	*Cl*	*OBu*	**43**,45
124w	*Cl*	*OAll*	**43**
124x	*Cl*	*OBn*	**43**

124y	*Cl*	*Cl*	**44**,45
124z	*Br*	*NH_2*	**44**
124aa	*Br*	OMe	**43**,44,45,49
124ab	*Br*	*OEt*	**43**,45
124ac	*Br*	*OPr*	**43**,45
124ad	*Br*	*OBu*	**43**,45
124ae	*Br*	*OAll*	**43**
124af	*Br*	*OBn*	**43**
124ag	*Br*	*Cl*	**44**,45
124ah	*I*	OMe	**43**,45
124ai	*I*	*OEt*	**43**,45
124aj	*I*	*OPr*	**43**,45
124ak	*I*	*OBu*	**43**,45
124al	*I*	*OAll*	**43**
124am	*I*	*OBn*	**43**

7.3 Tables of Griseofulvin Acid Analogs

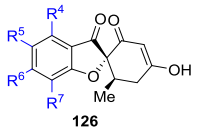


125

Table 22. Position 6 modifications of griseofulvic acid.

Structure	R^6	Reference
125a	*1-Pyrrolidinyl*	**47**,48
125b	*OH*	**28**,36,**41**,48,50,76
125c	*OEt*	**24**,48

125d	*OPr*	**41**,48
125e	*OBu*	**41**,48
125f	*Ohexadecyl*	**41**,48
125g	*O(CH$_2$)$_2$NEt$_2$, HCl*	**41**
125h	*OAll*	**41**,48
125i	*OBn*	**41**,48
125j	*OCH$_2$CO$_2$H*	**41**
125k	*O*-i-*Pr*	**41**,48



126

Table 23. Position 4, 5, 6 and 7 modifications of griseofulvic acid.

Structure	R^4	R^5	R^6	R^7	Reference
126a	*Me*	H	OMe	Cl	**47**,50
126b	*1-Pyrrolidinyl*	H	OMe	Cl	**47**
126c	*OH*	H	OMe	*H*	48
126d	*OH*	H	OMe	Cl	**41**,48,50
126e	*OH*	*NO$_2$*	*OH*	Cl	**46**
126f	OMe	H	OMe	*H*	**46**,48,50
126g	OMe	H	OMe	*F*	**116**
126h	OMe	*NH$_2$*	OMe	*H*	**46**
126i	OMe	*NHBz*	OMe	*H*	**46**,48
126j	OMe	*NO$_2$*	OMe	Cl	**46**,48,144
126k	OMe	*F*	OMe	Cl	**129**
86	OMe	*Cl*	OMe	Cl	**43**,48,51,**114**
126l	OMe	*Br*	OMe	Cl	**43**,48,144

126m	*OEt*	H	*OEt*	Cl	**24**,48
126n	*SMe*	H	*SMe*	Cl	**47**,48,50

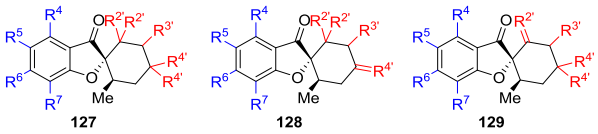
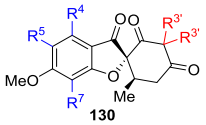


Table 24. Position 4, 5, 6, 7, 2', 3' and 4' modifications of griseofulvic acid acetal analogs.

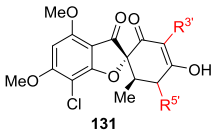
Structure	R^4	R^5	R^6	R^7	$R^{2'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$ $R^{4'}$	Reference
127a	*Me*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**
127b	*NH$_2$*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**,48
127c	*NHBn*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**,48
127d	*NHAc*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**,48
127e	*1-Pyrrolidinyl*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**,48
127f	*OH*	H	OMe	*H*	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**46**,48
127g	*OH*	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**41**,48
128a	OMe	H	*OH*	Cl	*-(OCH$_2$CH$_2$O)-*		H	=O	**41**
127h	OMe	H	*OH*	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**41**,48
127i	OMe	H	OMe	*H*	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**46**,48
129a	OMe	H	OMe	Cl	=O		H	*-(OCH$_2$CH$_2$O)-*	**41**
128b	OMe	H	OMe	Cl	*OMe* / *OMe*		*OH*	=O	**138**
128c	OMe	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	=O	**41**
127j	OMe	H	OMe	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**41**,47,48,49
128d	OMe	*Br*	OMe	Cl	*OMe* / *OAc*		*Br*	=O	**43**
127k	*SMe*	H	*SMe*	Cl	*-(OCH$_2$CH$_2$O)-*		H	*-(OCH$_2$CH$_2$O)-*	**47**,48,49



130

Table 25. Position 5, 7 and 3’ modifications of griseofulvic acid.

Structure	R^4	R^5	R^7	$R^{3'}$	$R^{3'}$	Reference
130a	*OH*	H	Cl	*Bn* / H		**42**
130b	OMe	H	*H*	*NHBz* / H		**46**,48
130c	OMe	H	Cl	*Me*	*Me*	**42**,48,49,50,75,76
130d	OMe	H	Cl	*All*	*All*	42
130e	OMe	H	Cl	*Bn*	*Bn*	**42**,48
130f	OMe	*Cl*	Cl	*Cl* / H		**43**,48,**114**
85	OMe	*Cl*	Cl	*Cl*	*Cl*	**43**,48
130g	OMe	*Br*	Cl	*Br* / H		**43**,48
130h	OMe	*Br*	Cl	*Br*	*Br*	**43**,48

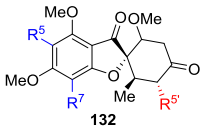


131

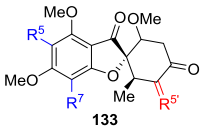
Table 26. Position 3’ and 5’ modifications of griseofulvic acid.

Structure	$R^{5'}$	$R^{5'}$	Reference
131a	H	*F*	**133**
131b	*Me*	H	**42**,48
131c	*Et*	H	**42**,48
131d	*Pr*	H	42,48
131e	*$(CH_2)_2C(O)Me$*	H	**42**,48
131f	*All*	H	**42**
131g	*Bn*	H	**42**,48,75
131h	*NH_2*	H	**46**
131i	*NHAc*	H	**46**,48
131j	*NHBz*	H	**46**,48
131k	*NO_2*	H	**46**,48
131l	*OH*	H	**138**
131m	*Na*	H	49
131n	*Cl*	H	**43**,48,50
131o	*Br*	H	**43**,44,48
131p	*I*	H	**43**,48,144

7.4 Tables of Miscellaneous Analogs of Griseofulvin



132

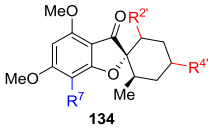


133

Table 27. Position 5, 7 and 5' modifications of **132** and **133**.

Structure	R^5	R^7	$R^{5'}$	Reference
132a	H	*H*	H	**35**,51[a]
132b	H	Cl	H	**31**,32,45,50,51,148,151,**159**
132c	H	Cl	*CH_2OH*	**157**
132d	*Cl*	*H*	H	51
133a	H	Cl	*=CHOH*	**157**

[a] Racemic mixture

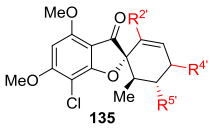


134

Table 28. Position 7, 2' and 4' modifications of **134**.

Structure	R^7	$R^{2'}$	$R^{4'}$	Reference
134a	*H*	OMe	*H*	**35**
103a	*H*	OMe	*OH*	**31**,32
134b	Cl	*H*	*H*	**137**,148
134c	Cl	*H*	*OH*	**32**
134d	Cl	*OH*	*H*	**32**,147,149
134e	Cl	*OH*	*OH*	147,149
134f	Cl	*OH*	*OMe*	**31**,148
104	Cl	OMe	*H*	**31**,32
103b	Cl	OMe	*OH*	**31**,32,50,75[a],76[a]
134g	Cl	OMe	*OAc*	**31**

[a] $R^{2'\beta}$ & $R^{4'\beta}$ configuration.

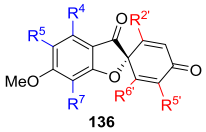


135

Table 29. Position 2', 4' and 5' modifications of **135**.

Structure	$R^{2'}$	$R^{4'}$	$R^{5'}$	Reference
135a	OMe	*H*	H	**31**,32,137
105	OMe	*OH*	H	53[a],75[a],**130**,**137**,152,154
135b	OMe	*OH*	*CH_2OH*	**156**[a]
135c	OMe	*OMe*	H	**53**[b],**137**
135d	OMe	*OAc*	H	53,**137**
135e	OMe	*OC(O)Et*	H	**137**
135f	OMe	*$OC(O)(CH_2)_2CO_2H$*	H	154
135g	OMe	*$OC(O)CH_2OPh$*	H	**137**
135h	OMe	*OC(O)-t-Bu*	H	**137**
135i	OMe	*OC(O)Ph*	H	**137**
135j	OMe	*OC(O)-(4-hydroxyC_6H_4)*	H	**137**
135k	*SMe*	*OH*	H	**132**

[a] $R^{4'\beta}$ configuration. [b] $R^{4'\alpha}$ configuration



136

Table 30. Position 5, 7, 2', 5' and 6' modifications of dehydrogriseofulvin.

Structure	R^4	R^5	R^7	$R^{2'}$	$R^{5'}$	$R^{6'}$	Reference
136a	*Me*	H	*H*	OMe	H	Me	50
70b	OMe	H	*H*	OMe	H	Me	51
136b	OMe	H	Cl	*H*	H	Me	151,**159**

136c	OMe	H	Cl	*Me*	H	Me	**150**
14	OMe	H	Cl	OMe	H	Me	50,51,**96**,**107**,**133**,151,159
136d	OMe	H	Cl	OMe	*OH*	Me	**160**
136e	OMe	H	Cl	OMe	*OAc*	Me	**160**
136f	OMe	H	Cl	*OPr*	H	Me	151,159
70c	OMe	H	*F*	OMe	H	Me	51
136g	OMe	*Cl*	*H*	OMe	H	Me	51

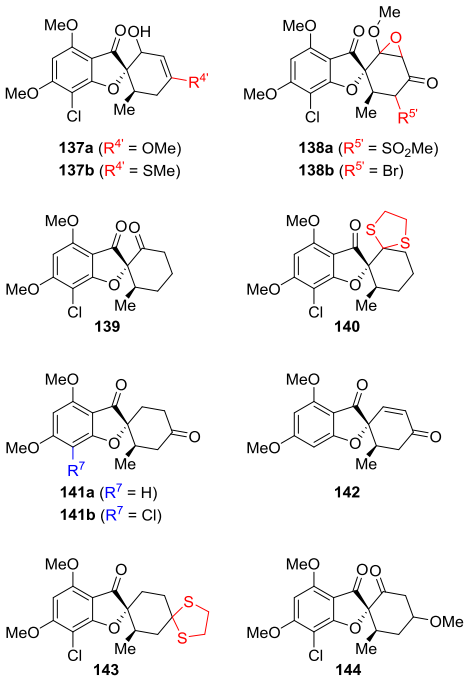


Figure 3. Additional analogs of griseofulvin (a reference in bold indicates synthetic procedure): **137a** (ref. **137**), **137b** (ref. **132**), **138** (ref. **138**), **139** (ref. **32**,36,45,50,**137**), **140** (ref. **137**), **141a** (ref. **35**), **141b** (ref. **32**,45,50,**137**,148,**159**), **142** (ref. **35**), **143** (ref. **137**) and **144** (ref. **31**,45,50).

8. Summary and Outlook

Since the discovery of griseofulvin in 1937, the natural product has been the subject of intensive research efforts including the preparation and biological evaluation of diverse analog structures. The recent discovery of especially the anticancer bioactivity of griseofulvin and some of its analogs holds promise that these spirobenzofuranones will continue to have relevance in the years to come, even as more modern antifungal agents are reducing the clinical use of griseofulvin in the treatment of fungal infections.

We anticipate that additional analogs of griseofulvin will surface in the years to come. The advances in the knowledge of its biosynthesis and the exciting possibilities within fungal molecular biology suggests that traditional synthetic chemical methods will be supplemented by chemoenzymatic synthesis and analogs stemming from manipulation of fungal polyketide gene clusters. We hope that this review will serve as a good starting point for following this development and we look forward to the future of griseofulvin chemistry.

Biographies

Asger B. Petersen

Asger B. Petersen obtained his Ph.D. in 2007 from the University of Copenhagen under the supervision of Prof. Peter E. Nielsen and Prof. John Nielsen working with peptide nucleic acid (PNA). He was a Visiting Fellow at the University of Warwick from 2007 to 2008 before returning to Copenhagen in the Nano-Science Center doing research on molecular electronics. In 2010, he joined a collaboration between Procter and Gamble, Colloidal Resource and Lund University investigating the formulation and behavior of aqueous phase-separating polymer-surfactant systems and in 2013, he joined Prof.

Mads H. Clausen at the Technical University of Denmark as a researcher. His interests in chemistry spans from practical synthetic organic chemistry to theoretical physical chemistry.

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Mads H. Rønnest

Mads H. Rønnest obtained his M.Sc. (2007) and Ph.D. (2011) from the Technical University of Denmark under the supervision of Prof. Mads H. Clausen. Both thesis subjects revolved around synthesis of griseofulvin analogs. In the Ph.D., he also worked with natural products chemistry, searching for anti-cancer active secondary metabolites from fungi. He continued his career at the Danish company Niels Clauson-Kaas as project manager, doing process development and production of API's for preclinical or early phase clinical trials.

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Thomas O. Larsen

Thomas O. Larsen obtained his Ph.D. from the Technical University of Denmark (DTU) in 1994 under the supervision of Prof. Jens C. Frisvad. He was a postdoctoral fellow at the University of Copenhagen from 1996-1998 in the group of Prof. Carsten Christophersen, where he worked on natural product discovery from filamentous fungi. In 1999, he became an Assistant Prof. at Department of Systems Biology and was promoted to Associate Professor in 2003 and also became part of the management

group of the Danish Engineering Center for Microbial Biotechnology. His current research interests are focused on discovery of bioactive fungal, algal and bacterial natural products, including linking of fungal secondary metabolite genes to their products for pathway characterization and engineering.

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Mads H. Clausen

Mads H. Clausen obtained his Ph.D. from the Technical University of Denmark in 2002 under the supervision of Prof. Robert Madsen. He was a postdoctoral fellow at Harvard University from 2002–2004 in the group of Prof. Andrew G. Myers, where he worked on total synthesis of enediyne antibiotics. In 2004, he started his independent career at the Department of Chemistry, Technical University of Denmark, where he has been Professor of Chemical Biology since 2014. His research interests center on chemical biology and bioorganic chemistry and include medicinal chemistry, oligosaccharide and lipid synthesis and developing methods for library synthesis.

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Captions

Figure 1. The structure of griseofulvin **1**, dechlorogriseofulvin **2** and 7-bromo-7-dechloro-griseofulvin **3**, with designation of the A, B and C ring including the IUPAC recommended numbering.

Figure 2. Structures of miscellaneous analogs prepared by de novo synthesis **71** (ref. **106**, note: inconsistent data regarding stereochemistry), **72** (ref. **120**), **73** (ref. **120**), **74** (ref. **120**), **75** (ref. **112**), **76** (ref. **112**) and **77** (ref. **122**).

Figure 3. Additional analogs of griseofulvin (a reference in bold indicates synthetic procedure): **137a** (ref. **137**), **137b** (ref. **132**), **138** (ref. **138**), **139** (ref. **32**,36,45,50,**137**), **140** (ref. **137**), **141a** (ref. **35**), **141b** (ref. **32**,45,50,**137**,148,**159**), **142** (ref. **35**), **143** (ref. **137**) and **144** (ref. **31**,45,50).

Table 1. Position 4, 5, 6, 7 and 2’ modifications of griseofulvin.

Table 2. Position 5, 7, 2’ and 6’ modifications of griseofulvin.

Table 3. Position 5, 7 and 2’ modifications of *epi*-griseofulvin.

Table 4. Position 5, 6, 7, 4’ and 6’ modifications of isogriseofulvin.

Table 5. Position 5, 7 and 4’modifications of *epi*-isogriseofulvin.

Table 6. Position 5 and 7 modifications of 6’-desmethylgriseofulvic acid.

Table 7. Position 5 and 7 modifications of *epi*-griseofulvic acid.

Table 8. Position 4, 5, 7 and 6’ modifications of dehydrogriseofulvin.

Table 9. Position 4 modifications of griseofulvin.

Table 10. Position 5 modifications of griseofulvin.

Table 11. Position 6 modifications of griseofulvin.

Table 12. Position 4, 5, 6 and 7 modifications of griseofulvin.

Table 13. Position 4, 5, 6, 2’, 3’ and 5’ modifications of griseofulvin.

Table 14. Position 2’ modifications of griseofulvin.

Table 15. Position 2’ and 3’ modifications of griseofulvin.

Table 16. Position 2’ and 4’ modifications of griseofulvin.

Table 17. Position 5’ modifications of griseofulvin.

Table 18. Position 4, 5, 6 and 7 modifications of isogriseofulvin.

Table 19. Position 4, 5, 6, 7, 3’ and 4’ modifications of isogriseofulvin.

Table 20. Position 4’ modifications of isogriseofulvin.

Table 21. Position 3’ and 4’ modifications of isogriseofulvin.

Table 22. Position 6 modifications of griseofulvic acid.

Table 23. Position 4, 5, 6 and 7 modifications of griseofulvic acid.

Table 24. Position 4, 5, 6, 7, 2', 3' and 4' modifications of griseofulvic acid acetal analogs.

Table 25. Position 5, 7 and 3' modifications of griseofulvic acid.

Table 26. Position 3' and 5' modifications of griseofulvic acid.

Table 27. Position 5, 7 and 5' modifications of **132** and **133**.

Table 28. Position 7, 2' and 4' modifications of **134**.

Table 29. Position 2', 4' and 5' modifications of **135**.

Table 30. Position 5, 7, 2', 5' and 6' modifications of dehydrogriseofulvin.

Scheme 1. Proposed griseofulvin biosynthetic pathway adapted from Cacho et al. ACP is acyl carrier protein, NADPH is nicotinamide and SAM is *S*-adenosyl methionine.[94]

Scheme 2. Total synthesis of racemic griseofulvin by Day et al.

Scheme 3. Total synthesis of racemic griseofulvin by Brossi et al.

Scheme 4. Total synthesis of racemic griseofulvin by Kuo et al.

Scheme 5. Total synthesis racemic griseofulvin by Stork and Tomasz.

Scheme 6. Total synthesis by Taub et al.

Scheme 7. Total synthesis by Danishefsky et al.

Scheme 8. Total synthesis by Yamato et al.

Scheme 9. Enantioselective total synthesis of griseofulvin by Pirrung et al.

Scheme 10. Analog synthesis by Sargent.

Scheme 11. Synthesis of **48** by Newman et al.[124]

Scheme 12. Total synthesis of the 1-carbon analogs **52**, **53** and **54** by Newman and Angier.[125,126]

Scheme 13. Total synthesis of the 1-thio analogs **61** and **62** by Newman and Angier.[127]

Scheme 14. Conversion between griseofulvin **1**, griseofulvic acid **78** (drawn as the predominant tautomer in solution) and isogriseofulvin **79**.

Scheme 15. Epimerization of **1** into **22** and the suggested mechanism for the reaction.

Scheme 16. Position 4 demethylation and a typical position 4 alkylation, followed by Claisen rearrangement of the 4-allyloxy analog.

Scheme 17. Position 6 demethylation of griseofulvic acid **78** followed by silver oxide mediated alkylation of the phenol.[41]

Scheme 18. Typical halogenation with chlorine in carbon tetrachloride and de-chlorination of griseofulvic acid **78** or position 5 bromination/fluorination of griseofulvin **1** with bromine or the fluorination reagent trifluoromethyl hypofluorite, respectively.[43,129]

Scheme 19. Nitration reactions and the position 7 de-chlorination from griseofulvic acid (**78**).[46]

Scheme 20. Typical examples of conditions for synthesizing 2'- and 4'-analogs of griseofulvin **91** and isogriseofulvin **92** (R ≠ Me) prepared by: a) alcoholysis of griseofulvin **1** or griseofulvic acid **78**; b).

Scheme 21. 4'-Analogs prepared from griseofulvin **1**.

Scheme 22. Synthesis of the 5'-formyl analog **97** and conversion of the 5'-formyl analog into the 5'-diazo analog **98**, its derivatization and synthesis of two tetracyclic compounds from **97**.[133,134,135]

Scheme 23. Typical products from hydrogen reductions of griseofulvin **1** in ethyl acetate with 10 % palladium on charcoal.[31]

Scheme 24. Sodium borohydride reduction of griseofulvin's 4'-oxo functionality and hydrolysis-elimination to form the analog **106**.[137]

Scheme 25. Synthesis of the oxiran and cyclopropyl analogs by Newman.[138,139]

References

(1) Davenport-Hines, R. P. T.; Slinn, J. *Glaxo: a History to 1962*; Cambridge University Press: Cambridge, 1992; p 219.

(2) Mustafa, A. *Chemistry of Heterocyclic Compounds, Vol. 29*; John Wiley and Sons: New York, 1974; pp 370-430.

(3) Rhodes, A.; Ball, S.; Boothroyd, B. (Glaxo Laboratories Ltd.) United Kingdom Patent GB863342, **1961**.

(4) Taub, D. (Merck & Co., Inc.) American Patent US3055933, **1962**.

(5) Korger, G.; Nesemann, G.; König, J. (Farbwerke Hoechst A.-G.) German Patent DE1145180, **1963**.

(6) Martin, A. R. (Imperial Chemical Industries Ltd.) American Patent US3084102, **1963**.

(7) Brossi, A.; Riehen, M. G.; Kyburz, E. (F. Hoffmann-La Roche & Co., A.-G.) American Patent US3114753, **1963**.

(8) Clark, V. M.; Walker, T.; Webb, G. B. (Glaxo Group Ltd.) United Kingdom Patent GB981521, **1965**.

(9) Kuo, C.-H.; Taub, D.; Wendler, N. L. (Merck & Co., Inc.) American Patent US3192234, **1965**.

(10) Andres, W. W.; Kunstmann, M. P. (American Cyanamid Co.) American Patent US3557151, **1971**.

(11) Newman, H.; Fields, T. L. (American Cyanamid Co.) American Patent US3734931, **1973**.

(12) Yamato, M. (MECT Corp.) Japanese Patent JP03255081, **1991**.

(13) Clausen, M. H.; Krämer, A.; Larsen, T. O.; Rebacz, B. (DKFZ Deutsches Krebsforschungszentrum, Germany; Technical University of Denmark) European Patent EP2008652, **2008**.

(14) Marion, F.; Lieby-Muller, F.; Grisoni, S.; Rahier, N.; Perez, M.; Sartori, I. (Pierre Fabre Medicament, France) International Patent WO2014020105, **2013**.

(15) Oxford, A. E.; Raistrick, H.; Simonart, P. *Biochem. J*. **1939**, *33*, 240.

(16) Brian, P. W.; Curtis, P. J.; Hemming, H. G. *Trans. Br. Mycol. Soc.* **1946**, *29*, 173.

(17) McGowan, J. C. *Trans. Br. Mycol. Soc.* **1946**, *29*, 188.

(18) Grove, J. F.; McGowan, J. C. *Nature* **1947**, *160*, 574.

(19) Brian, P. W.; Curtis, P. J.; Hemming, H. G. *Trans. Br. Mycol. Soc.* **1949**, *32*, 30.

(20) MacMillan, J. *J. Chem. Soc.* **1953**, 1697.

(21) MacMillan, J. *J. Chem. Soc.* **1954**, 2585.

(22) Grove, J. F.; Ismay, D.; Macmillan, J.; Mulholland, T. P. C.; Rogers, M. A. T. *Chem. Ind.* **1951**, 219.

(23) Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Zealley, J. *J. Chem. Soc.* **1952**, 3967.

(24) MacMillan, J. *J. Chem. Soc.* **1959**, 1823.

(25) Brown, W. A. C.; Sim, G. A. *J. Chem. Soc.* **1963**, 1050.

(26) Levine, S. G.; Hicks, R. E. *Tetrahedron Lett*. **1971**, *12*, 311.

(27) Malmros, G.; Wägner, A.; Maron L. *Cryst. Struct. Comm.* **1977**, *6*, 463.

(28) Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Rogers, M. A. T. *J. Chem. Soc.* **1952**, 3949.

(29) Grove, J. F.; Ismay, D.; MacMillan, J.; Mulholland, T. P. C.; Rogers, M. A. T. *J. Chem. Soc.* **1952**, 3958.

(30) Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Rogers, M. A. T. *J. Chem. Soc.* **1952**, 3977.

(31) Mulholland, T. P. C. *J. Chem. Soc.* **1952**, 3987.

(32) Mulholland, T. P. C. *J. Chem. Soc.* **1952**, 3994.

(33) MacMillan, J.; Mulholland, T. P. C.; Dawkins, A. W.; Ward, G. *J. Chem. Soc.* **1954**, 429.

(34) Grove, J. F.; Jeffs, P. W.; Rustidge, D. W. *J. Chem. Soc.* **1956**, 1956.

(35) MacMillan, J.; Suter, P. J. *J. Chem. Soc.* **1957**, 3124.

(36) Duncanson, L. A.; Grove, J. F.; MacMillan, J.; Mulholland, T. P. C. *J. Chem. Soc.* **1957**, 3555.

(37) Duncanson, L. A.; Grove, J. F.; Jeffs P. W. *J. Chem. Soc.* **1958**, 2929.

(38) Dawkins, A. W.; Mulholland, T. P. C. *J. Chem. Soc.* **1959**, 1830.

(39) Dawkins, A. W.; Mulholland, T. P. C. *J. Chem. Soc.* **1959**, 2203.

(40) Dawkins, A. W.; Mulholland, T. P. C. *J. Chem. Soc.* **1959**, 2211.

(41) Arkley, V.; Attenburrow, J.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1962**, 1260.

(42) Gregory, G. I.; Holton, P. J.; Robinson, H.; Walker, T. *J. Chem. Soc.* **1962**, 1269.

(43) Walker, T.; Warburton, W. K.; Webb, G. B. *J. Chem. Soc.* **1962**, 1277.

(44) Stephenson, L.; Walker, T.; Warburton, W. K.; Webb, G. B. *J. Chem. Soc.* **1962**, 1282.

(45) Page, J. E.; Staniforth, S. E. *J. Chem. Soc.* **1962**, 1292.

(46) Arkley, V.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1963**, 1603.

(47) Goodall, S. R.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1963**, 1610.

(48) Page, J. E.; Staniforth, S. E. *J. Chem. Soc.* **1963**, 1814.

(49) Green, G. F. H.; Page, J. E.; Staniforth, S. E. *J. Chem. Soc.* **1964**, 144.

(50) Ballantine, J. A.; Fenwick, R. G. *Org. Mass. Spectrom.* **1969**, *2*, 1145.

(51) Arison, B. H.; Wendler, N. L.; Taub, D.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Trenner, N. R. *J. Am. Chem. Soc*. **1963**, *85*, 627.

(52) Rønnest, M. H.; Harris, P.; Gotfredsen, C. H.; Larsen, T. O.; Clausen, M. H. *Tetrahedron Lett*. **2010**, *51*, 5881.

(53) Levine, S. G.; Hicks, R. E. *Tetrahedron Lett*. **1968**, *9*, 5409.

(54) Levine, S. G.; Hicks, R. E. *J. Org. Chem*. **1975**, *40*, 2540.

(55) Sato, Y.; Oda, T. *J. Chem. Soc., Chem. Comm.* **1978**, 135.

(56) Brian, P. W. *Ann. Bot.* **1949**, *13*, 59.

(57) Brian, P. W.; Wright, J. M., Stubbs, J.; Way, A. M. *Nature* **1951**, *167*, 347.

(58) Gentles, J. C. *Nature* **1958**, *182*, 476.

(59) Williams, D. I.; Marten, R. H.; Sarkany, I. *Lancet* **1958**, *272*, 1212.

(60) Bent, K. J.; Moore, R. H. *Symp. Soc. Gen. Microbiol.* **1966**, *16*, 82.

(61) Crosse, R.; McWilliam, R.; Rhodes, A. *J. Gen. Microbiol.***1964**, *34*, 51.

(62) Osment, L. S. *Ala. J. Med. Sci.* **1969**, *6*, 392.

(63) Gull, K.; Trinci, A. P. J. *Nature* **1973**, *244*, 292.

(64) Grisham, L. M.; Wilson, L.; Bensch, K. G. *Nature* **1973**, *244*, 294.

(65) Chaudhuri, A. R.; Ludueña, R. F. *Drug Dev. Res.* **2001**, *53*, 44.

(66) Keates, R. A. B. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 746.

(67) Rathinasamy, K.; Jindal, B.; Asthana, J.; Singh, P.; Balaji, P. V.; Panda, D. *BMC Cancer* **2010**, *10*, 213.

(68) Weber, K.; Wehland, J.; Herzog, W. *J. Mol. Biol.* **1976**, *102*, 817.

(69) Ho, Y.-S.; Duh, J.-S.; Jeng, J.-H.; Wang, Y.-J.; Liang, Y.-C.; Lin, C.-H.; Tseng, C.-J.; Yu, C.-F.; Chen, R.-J.; Lin, J.-K. *Int. J. Cancer* **2001**, *91*, 393.

(70) Camden, J. B. (Procter & Gamble Company) International Patent WO9705870, **1997**.

(71) Panda, D.; Rathinasamy, K.; Santra, M. K.; Wilson, L. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 9878.

(72) Jin, H.; Yamashita, A.; Maekawa, S.; Yang, P.; He, L. M.; Takayanagi, S.; Wakita, T.; Sakamoto, N.; Enomoto, N.; Ito, M. *Hepatol. Res.* **2008**, *38*, 909.

(73) Oda, T. *J. Antibiot*. **2006**, *59*, 114.

(74) Rebacz, B.; Larsen, T. O.; Clausen, M. H.; Rønnest, M. H.; Löffler, H.; Ho, A. D.; Krämer, A. *Cancer Res.* **2007**, *67*, 6342.

(75) Rønnest, M. H.; Rebacz, B.; Markworth, L.; Terp, A. H.; Larsen, T. O.; Krämer, A.; Clausen, M. H. *J. Med. Chem.* **2009**, *52*, 3342.

(76) Rønnest, M. H.; Raab, M. S.; Anderhub, S.; Boesen, S.; Krämer, A.; Larsen, T. O.; Clausen, M. H. *J. Med. Chem.* **2012**, *55*, 652.

(77) Raab, M. S.; Breitkreutz, I.; Anderhub, S.; Rønnest, M. H.; Leber, B.; Larsen, T. O.; Weiz, L.; Konotop, G.; Hayden, P. J.; Podar, K.; Fruehauf, J.; Nissen, F.; Mier, W.; Haberkorn, U.; Ho, A. D.; Goldschmidt, H.; Anderson, K. C.; Clausen, M. H.; Krämer, A. *Cancer Res.* **2012**, *72*, 5374.

(78) Larsen, T. O.; Smedsgaard, J.; Nielsen, K. F.; Hansen, M. E.; Frisvad, J. C. *Nat. Prod. Rep.* **2005**, *22*, 672.

(79) Birch, A. J.; Massy-Westropp, R. A.; Rickards, R. W.; Smith, H. *J. Chem. Soc.* **1958**, 360.

(80) Simpson, T. J.; Holker, J. S. E. *Phytochemistry* **1977**, *16*, 229.

(81) Barton, D. H. R.; Cohen, T. *Festschrift Prof. Dr. Arthur Stoll, Birkhäuser, Basel*, **1957**, 117.

(82) Rhodes, A.; Boothroyd, B.; McGonagle, M. P.; Somerfield, G. A. *Biochem. J.* **1961**, *81*, 28.

(83) Harris, C. M.; Roberson, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1976**, *98*, 5380.

(84) Sanchez, J. F.; Somoza, A. D.; Keller, N. P.; Wang, C. C. C. *Nat. Prod. Rep.* **2012**, *29*, 351.

(85) Chooi, Y.-H.; Cacho, R.; Tang, Y. *Chem. Biol.* **2010**, *17*, 483.

(86) Altschul, S. F.; Gish, W.; Miller, W.; Myers, E. W.; Lipman, D. J. *Mol. Biol.* **1990**, *215*, 403.

(87) Khaldi, N.; Seifuddin, F. T.; Turner, G.; Haft, D.; Nierman, W. C.; Wolfe, K. H.; Fedorova, N. D. *Fungal Genet. Biol.* **2010**, *47*, 736.

(88) Medema, M. H.; Blin, K.; Cimermancic, P.; de Jager, V.; Zakrzewski, P.; Fischbach, M. A.; Weber, T.; Takano, E.; Breitling, R. *Nucleic Acids Res.* **2011**, *39*, 339.

(89) Blin, K.; Medema, M. H.; Kazempour, D.; Fischbach, M. A.; Breitling, R.; Takano, E.; Weber, T. *Nucleic Acids Res.* **2013**, *41*, 204.

(90) Nielsen, M. L.; Nielsen, J. B.; Rank, C.; Klejnstrup, M. L.; Holm, D. K.; Brogaard, K. H.; Hansen, B. G.; Frisvad, J. C.; Larsen, T. O.; Mortensen, U. M. *FEMS Microbiol. Lett.* **2011**, *321*, 157.

(91) Hoffmeister, D.; Keller, N. P. *Nat. Prod. Rep.* **2007**, *24*, 393.

(92) Andersen, M. R.; Nielsen, J. B.; Klitgaard, A.; Petersen, L. M.; Zachariasen, M.; Hansen, T. J.; Blicher, L. H.; Gotfredsen, C. H.; Larsen, T. O.; Nielsen, K. F.; Mortensen, U. H. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, E99.

(93) Nielsen, M. T.; Nielsen, J. B.; Anyaogu, D. C.; Holm, D. K.; Nielsen, K. F.; Larsen, T. O.; Mortensen, U. H. *PLoS ONE* **2013**, *8*, e72871.

(94) Cacho, R. A.; Chooi, Y.-H.; Zhou, H.; Tang, Y. *ACS Chem. Biol.* **2013**, *8*, 2322.

(95) Day, A. C.; Nabney, J.; Scott, A. I. *Proc. Chem. Soc*. **1960**, 284.

(96) Day, A. C.; Nabney, J.; Scott, A. I. *J. Chem. Soc.* **1961**, 4067.

(97) Scott, A. I. *Proc. Chem. Soc.* **1958**, 195.

(98) Brossi, A.; Baumann, M.; Gerecke, M.; Kyburz, E. *Helv. Chim. Acta* **1960**, *43*, 1444.

(99) Brossi, A.; Baumann, M.; Gerecke, M.; Kyburz, E. *Helv. Chim. Acta* **1960**, *43*, 2071.

(100) Kuo, C. H.; Hoffsommer, R. D.; Slates, H. L.; Taub, D.; Wendler, N. L. *Chem. Ind.* **1961**, 1627.

(101) Brossi, A.; Baumann, M.; Burkhardt, F. *Helv. Chim. Acta* **1962**, *45*, 1292.

(102) Stork, G.; Tomasz, M. *J. Am. Chem. Soc.* **1962**, *84*, 310.

(103) Stork, G.; Tomasz, M. *J. Am. Chem. Soc*. **1964**, *86*, 471.

(104) Taub, D.; Kuo, C. H.; Wendler, N. L. *Chem. Ind*. **1962**, 557.

(105) Taub, D.; Wendler, N. L. *Angew. Chem*. **1962**, *74*, 586.

(106) Taub, D.; Kuo, C. H.; Wendler, N. L. *Chem. Ind.* **1962**, 1617.

(107) Taub, D.; Kuo, C. H.; Slates, H. L.; Wendler, N. L. *Tetrahedron* **1963**, *19*, 1.

(108) Danishefsky, S.; Walker, F. J. *J. Am. Chem. Soc*. **1979**, *101*, 7018.

(109) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1978**, *43*, 4604.

(110) Yamato, M.; Takeuchi, Y.; Tomozane, H. *Synthesis* **1990**, *7*, 569.

(111) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc*. **1991**, *113*, 8561.

(112) Mulholland, T. P. C.; Honeywood, R. I. W.; Preston, H. D.; Rosevear, D. T. *J. Chem. Soc*. **1965**, 4939.

(113) Takeuchi, Y.; Watanabe, I.; Misumi, K.; Irie, M.; Hirose, Y.; Hirata, K.; Yamato, M.; Harayama, T. *Chem. Pharm. Bull*. **1997**, *45*, 2011.

(114) Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem*. **1963**, *28*, 3344.

(115) Gerecke, M.; Kyburz, E.; Planta, C. v.; Brossi, A. *Helv. Chim. Acta* **1962**, *45*, 2241.

(116) Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem*. **1963**, *28*, 2752.

(117) Takeuchi, Y.; Tomozane, H.; Misumi, K.; Yata, K.; Kawata, T.; Niino, Y.; Yamato, M.; Harayama, T. *Chem. Pharm. Bull.* **1997**, *45*, 327.

(118) Yamato, M.; Yoshida, H.; Ikezawa, K.; Kohashi, Y. *Chem. Pharm. Bull*. **1986**, *34*, 71.

(119) Curtis, R. F.; Hassall, C. H.; Jones, D. W. *J. Chem. Soc*. **1965**, 6960.

(120) Ko, B.-S.; Oritani, T.; Yamashita, K. *Agric. Biol. Chem*. **1990**, *54*, 2199.

(121) Tomozane, H.; Takeuchi, Y.; Choshi, T.; Kishida, S.; Yamato, M. *Chem. Pharm. Bull*. **1990**, *38*, 925.

(122) Newman, H.; Angier, R. B. *J. Org. Chem.* **1969**, *34*, 1463.

(123) Sargent, M. V. *J. Chem. Soc., Chem. Comm*. **1980**, 285.

(124) Newman, H.; Angier, R. B. *J. Org. Chem*. **1966**, *31*, 1451.

(125) Newman, H.; Angier, R. B. *J. Org. Chem*. **1966**, *31*, 1456.

(126) Newman, H.; Angier, R. B. *J. Org. Chem*. **1966**, *31*, 1462.

(127) Newman, H.; Angier, R. B. *J. Org. Chem*. **1969**, *34*, 3484.

(128) Dong, N.; Li, Xin; Wang, F.; Cheng, J.-P. *Org. Lett.* **2013**, *15*, 4896.

(129) Barton, D. H. R.; Hesse, R. H.; Ogunkoya, L.; Westcott, N. D.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, *22*, 2889.

(130) Delgado, L.; De Croos, P. Z.; Lu, M. C. H.; Currie, B. L. *Gaoxiong Yixue Kexue Zazhi* **1992**, *8*, 632.

(131) Pan, Z.-Z.; Zhu, Y.-J.; Yu, X.-J.; Lin, Q.-F.; Xiao, R.-F.; Tang, J.-Y.; Chen, Q.-X.; Liu, B. *J. Agri. Food Chem.* **2012**, *60*, 10784.

(132) Koe, B. K.; Celmer, W. D. *J. Med. Chem*. **1964**, *7*, 705.

(133) Newman, H.; Fields, T. L. *J. Org. Chem*. **1970**, *35*, 3156.

(134) Fields, T. L.; Newman, H.; Angier, R. B. *J. Med. Chem.* **1970**, *13*, 1242.

(135) Fields, T. L.; Newman, H.; Angier, R. B. *J. Med. Chem.* **1971**, *14*, 767.

(136) Andres, W. W.; McGahren, W. J.; Kunstmann, M. P. *Tetrahedron Lett.* **1969**, *10*, 3777.

(137) Kyburz, E.; Geleick, H.; Frey, J. R.; Brossi, A. *Helv. Chim. Acta* **1960**, *43*, 2083.

(138) Newman, H. *J. Org. Chem.* **1970**, *35*, 3990.

(139) Newman, H. *J. Org. Chem.* **1971**, *36*, 2375.

(140) Dev, V.; Quintana, R. P.; Lasslo, A. *J. Med. Chem.* **1966**, *9*, 242.

(141) Crounse, R. G. *J. Pharm. Sci.* **1969**, *58*, 1022.

(142) Hansch, C.; Lien, E. J. *J. Med. Chem.* **1971**, *14*, 653.

(143) Juvale, D. C.; Kadam, S. S.; Kulkarni, V. M. *Indian. J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **2006**, *45A*, 194.

(144) Unterman, H. W.; Duca, A. *Rev. Roum. Chim.* **1971**, *16*, 843.

(145) Belofsky, G. N.; Gloer, K. B.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1998**, *61*, 1115.

(146) Auterhoff, H.; Kliem, M. *Arch. Pharm. (Weinheim, Germany)* **1976**, *309*, 326.

(147) Crowdy, S. H.; Grove, J. F.; McCloskey, P. *Biochem. J.* **1959**, *72*, 241.

(148) Schneck, D. W.; Racz, W. J.; Hirsch, G. H.; Bubbar, G. L.; Marks, G. S. *Biochem. Pharmacol.* **1968**, *17*, 1385.

(149) Crowdy, S. H.; Green, A. P.; Grove, J. F.; Mcloskey, P.; Morrison, A. *Biochem J.* **1959**, *72*, 230.

(150) Oda, T.; Hashimoto, H., Sato, Y. *Chem. Pharm. Bull.* **1990**, *38*, 525.

(151) Sato, Y.; Tezuka, T.; Oda, T.; Hosoi, J. *J. Pharmacobio-Dyn.* **1984**, *7*, 156.

(152) Unterman, H. W.; Duca, A. *Isr. J. Chem.* **1974**, *12*, 985.

(153) Lecointe, P.; Wright, M.; Dedieu, A. *J. Antibiot*. **1977**, *30*, 965.

(154) Fischer, L. J.; Riegelman, S. *J. Pharm. Sci.* **1967**, *56*, 469.

(155) El-Adl, S.; Lashine, S.; Shanawani, A. *Spectrosc. Lett.* **1994**, *27*, 281.

(156) Oda, T.; Sueyoshi, Y.; Hirota, K.; Sato, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3878.

(157) Oda, T.; Sato, R.; Sato, Y. *Chem. Pharm. Bull.* **1989**, *37*, 502.

(158) Sato, Y.; Oda, T. *J. Chem. Soc., Chem. Commun.* **1977**, 415.

(159) Oda, T.; Sato, Y. *Chem. Pharm. Bull.* **1983**, *31*, 934.

(160) Newman, H. *J. Heterocycl. Chem*. **1970**, *7*, 957.