Phytochem Rev (2017) 16:1095–1153
DOI 10.1007/s11101-017-9521-5

Phytocarbazoles: alkaloids with great structural diversity and pronounced biological activities

Harald Greger

Received: 11 April 2017 / Accepted: 30 June 2017 / Published online: 7 July 2017

Abstract Carbazole alkaloids characterized by a heterocyclic aromatic basic skeleton are known from different organisms but do not represent a biogenetically homogenous group. The majority, comprising more than 330 derivatives, is derived from 3-methylcarbazole as common precursor and is designated as phytocarbazoles. They are nearly exclusively known from the four closely related plant genera *Bergera* (part of *Murraya* s. l.), *Clausena*, *Glycosmis*, and *Micromelum* of the family Rutaceae. Derived from anthranilic acid and malonyl-CoA the tricyclic basic skeleton is formed via a prenylated 2-quinolone intermediate. The following steps are speculated to involve the formation of 2-prenylindole and cyclization of the prenyl side chain to generate 3-methylcarbazole. Apart from different oxygenations and oxidations of the basic skeleton additional prenylations and geranylations contribute to the great structural diversity of phytocarbazoles which are grouped together according to their C_{13}-, C_{18}-, and C_{23}-basic structures. Of taxonomic significance are the different oxidations of the characteristic *C*-3 methyl group leading to 3-formyl- and 3-carboxyl derivatives particularly accumulated in *Clausena* and *Micromelum* species. Predominant prenylation at *C*-5 is typical for *Glycosmis* and *Micromelum*, whereas in *Clausena* prenylation at different positions can contribute to an infrageneric grouping. Geranylation represents a characteristic biogenetic trend of *Bergera*. A wide variety of biological activities ranges from significant antimicrobial, antiprotozoal, and insecticidal properties to anti-inflammatory, antioxidative, antiplatelet aggregative, and anti-HIV activities. Of particular interest is the cytotoxicity of phytocarbazoles against various cancer cell lines, where some derivatives turned out to act as cell cycle inhibitors and apoptosis inducers. Especially the C_{23} derivative mahanine induced different cell-signaling pathways suggesting that it represents a multi-targeted and multi-functional compound that works on an array of different cancer types and has the potential to inhibit tumor growth in vivo.

Keywords Carbazole alkaloids · Biogenetic trends · Biological activities · Rutaceae · Chemotaxonomy

Introduction

Carbazole alkaloids are characterized by a tricyclic aromatic basic skeleton consisting of a central pyrrole ring fused with two benzene rings. Carbazole itself was originally isolated from the anthracene fraction of coal tar (Graebe and Glaser 1872). As shown in Fig. 1

H. Greger (✉)
Chemodiversity Research Group, Faculty of Life Sciences, University of Vienna, Rennweg 14, 1030 Vienna, Austria
e-mail: harald.greger@univie.ac.at

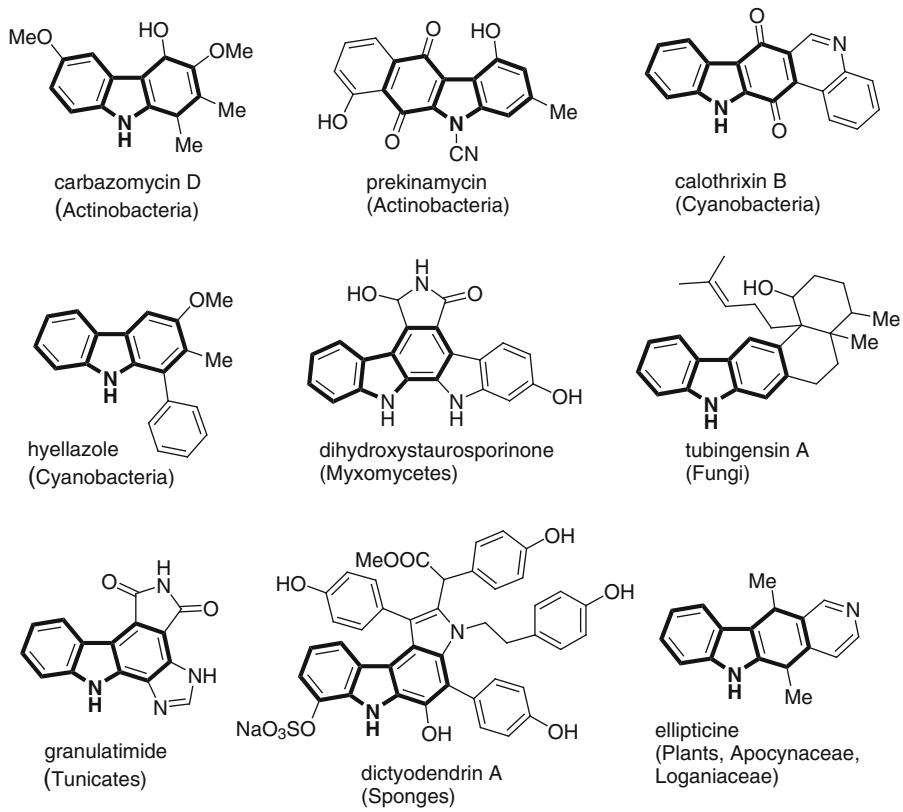


Fig. 1 Naturally occurring alkaloids containing a carbazole basic structure derived from different biosynthetic pathways

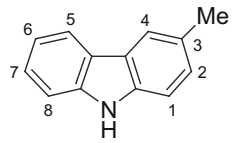
several naturally occurring alkaloids are known to contain such a heterocyclic system but do not represent a biogenetically homogenous group. They were found in bacteria, myxomycetes, fungi, sponges, tunicates, and in the related plant families Apocynaceae and Loganiaceae. However, the vast majority of carbazoles, comprising more than 330 derivatives (Tables 1, 2, 3, 4, 5, 6), was shown to be derived from 3-methylcarbazol (**1**) as common precursor. This type of carbazoles, designated as phytocarbazoles (Chakraborty 1977), was nearly exclusively isolated from the Citrus (Rutaceae) family, where they are known only from the four closely related genera *Bergera* (part of *Murraya* s. l.), *Clausena*, *Glycosmis*, and *Micromelum* of the subfamily Aurantioideae (Bhattacharyya and Chakraborty 1987; Chakraborty and Roy 1991; Knölker and Reddy 2002, 2008; Schmidt et al. 2012).

The first three derivatives girinimbine (**92**), murrayanine (**27**), and mahanimbine (**211**), were isolated from the well-known South Asian Curry-leaf Tree, *Bergera koenigii* L. (published as *Murraya koenigii* (L.) Spreng.) by Chakraborty et al. (1964, 1965, 1966), respectively (Fig. 2). They exhibited antifungal properties against some human pathogenic fungi and initiated the search for further active derivatives within that class of alkaloids (Das et al.1965). Later, various phytocarbazoles have shown to exhibit significant antimicrobial (Chakraborty et al. 1995a, b; Ramsewak et al. 1999; Pacher et al. 2001; Ma et al. 2005; Nagappan et al.2011; Maneerat et al. 2012b; Tatsimo et al. 2015) and antiprotozoal properties (Bringmann et al. 1998b; Yenjai et al. 2000; Adebajo et al. 2006; Pieroni et al. 2012). In addition, anti-inflammatory (Shen et al. 2014; Xia et al. 2015; Lv et al. 2015; Nalli et al. 2016), antiplatelet aggregation (Wu and Huang 1992; Wu et al. 1996c, 1998a), antioxidant (Ramsewak et al. 1999; Tachibana et al. 2001, 2003), and anti-HIV activities (Meragelman et al. 2000; Kongkathip et al. 2005; Wang et al. 2005) were also reported. A matter of particular interest was their cytotoxicity against various cancer cell lines

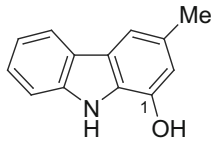
(Itoigawa et al. 2000; Ito et al. 2000, 2012; Cui et al. 2002; Roy et al. 2004, 2005; Sinha et al. 2006; Nagappan et al. 2011; Samanta et al. 2013; Das et al. 2014; Bhattacharya et al. 2014; Tatsimo et al. 2015). The bioactivities and the intricate structures of these alkaloids, sometimes leading to complex molecules,

Table 1 C_{13}-carbazoles

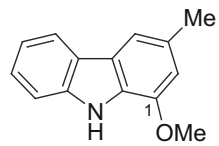
A C_{13}-type 3-methylcarbazoles



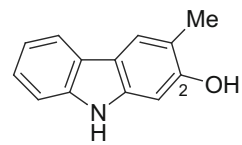
1 3-methylcarbazole
Roy et al. 1974
C. heptaphylla, B



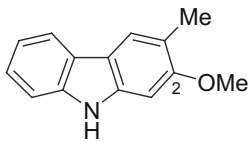
2 1-hydroxy-3-methyl-carbazole
Bhattacharyya et al. 1994
M. koenigii, B



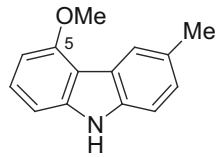
3 murrayafoline A
Furukawa et al. 1985c
M. euchrestifolia, R



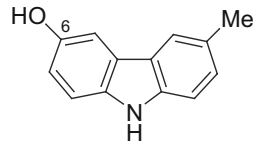
4 2-hydroxy-3-methyl-carbazole
Bhattacharyya et al. 1986
M. koenigii, R



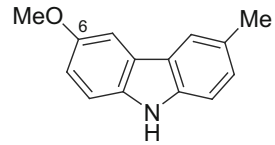
5 2-methoxy-3-methylcarbazole
Bhattacharyya & Chowdhury 1985b
M. koenigii, S



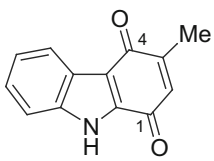
6 glycoborine
Chakravarty et al. 2001
G. arborea, R
(= glycozolicine, glycrophylamine)



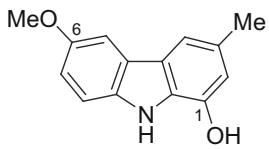
7 glycozolinine
Mukherjee et al.1983b
G. pentaphylla, S
(= glycozolinol)



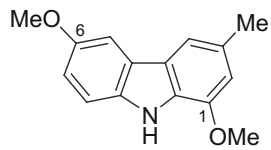
8 glycozoline
Chakraborty 1966, 1969
G. pentaphylla, R



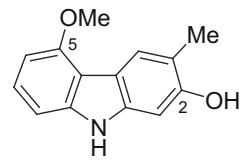
9 murrayaquinone A
Furukawa et al. 1985c
M. euchrestifolia, R



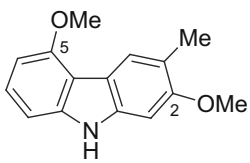
10 clausenol
Chakraborty et al. 1995b
C. anisata, B



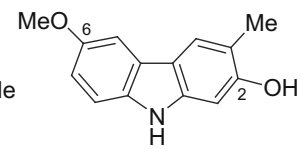
11 clausenine
Chakraborty et al. 1995b
C. anisata, B



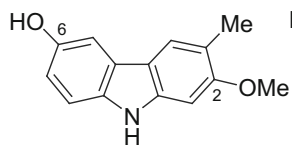
12 carbalexin A
Pacher et al. 2001
G. parviflora, L



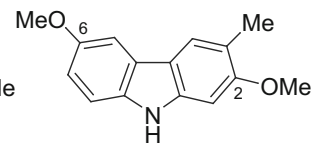
13 glybomine A
Ito et al. 2004
G. arborea, B



14 carbalexin C
Pacher et al. 2001
G. parviflora, L

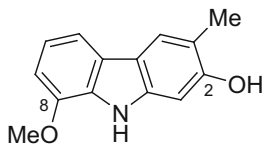


15 glycozolidol
Bhattacharyya et al. 1985
G. pentaphylla, R

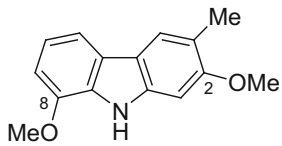


16 glycozolidine
Chakraborty & Das 1966
G. pentaphylla, R

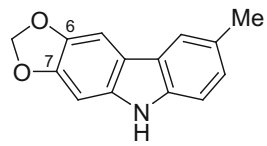
Table 1 continued



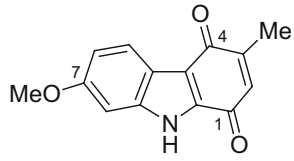
17 carbalexin B
Pacher et al. 2001
G. parviflora, L



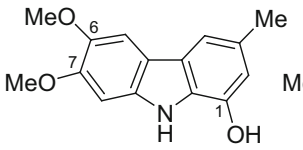
18 clausine P
Wu et al. 1999
C. excavata, R



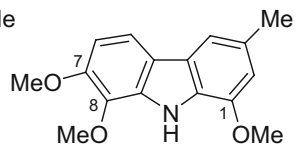
19 clausenalene
Bhattacharyya et al. 1993
C. heptaphylla, B



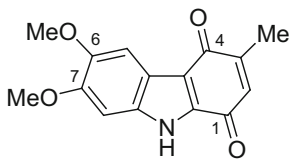
20 koenigine-quinone A
Saha and Chowdhury 1998
M. koenigii, B



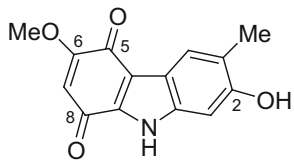
21 6,7-dimethoxy-1-hydroxy-3-methylcarbazole
Chowdhury et al. 2001
M. koenigii, L



22 murrayastine
Furukawa et al. 1986
M. euchrestifolia, B

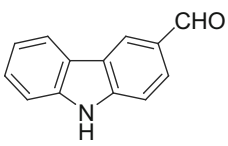


23 koenigine-quinone B
Saha and Chowdhury 1998
M. koenigii, B

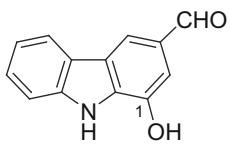


24 clausenaquinone A
Wu et al. 1994
C. excavata, B

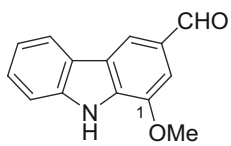
B C_{13}-type 3-formylcarbazoles



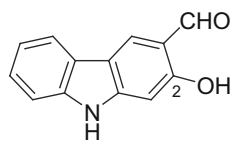
25 3-formylcarbazole
Ito et al. 1988
M. euchrestifolia, R



26 *O*-demethyl-murrayanine
Ngadjui et al. 1989
C. anisata, B+R

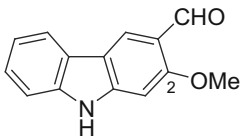


27 murrayanine
Chakraborty et al. 1965
M. koenigii, B

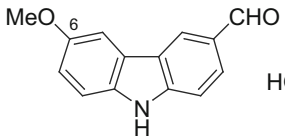


28 mukonal
Bhattacharyya & Chakraborty 1984
M. koenigii, B

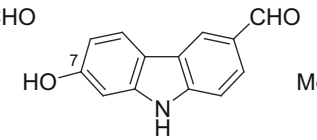
Table 1 continued



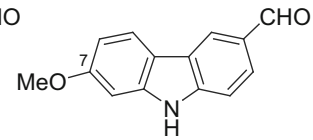
29 glycosinine
Jash et al.1992
G. pentaphylla, R
(=O-methylmukonal)



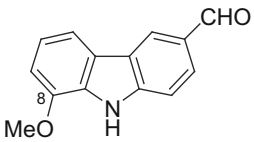
30 3-formyl-6-methoxycarbazole
Li et al. 1991
C. lansium, R



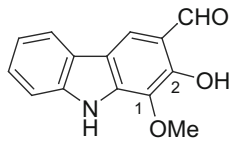
31 3-formyl-7-hydroxycarbazole
Ito et al. 1992a
M. euchrestifolia, R



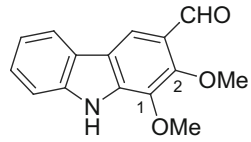
32 clauszoline K
Ito et al. 1997
C. excavata, B



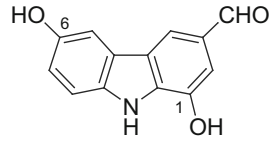
33 mukolidine
Roy et al. 1982b
M. koenigii, R



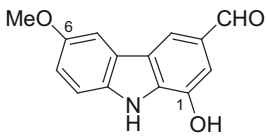
34 claulansine N
Du et al. 2015
C. lansium, B



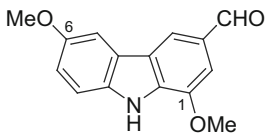
35 claulansine O
Du et al. 2015
C. lansium, B



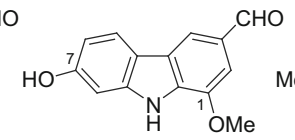
36 clausine Z
Potterat et al. 2005
C. excavata, B+L



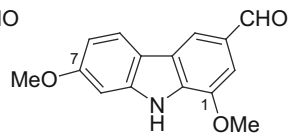
37 clausine I
Wu et al. 1996c
C. excavata, B



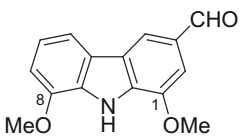
38 3-formyl-1,6-dimethoxycarbazole
Li et al. 1991
C. lansium, R



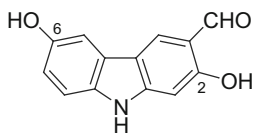
39 clausine Q
Wu et al. 1999
C. excavata, R



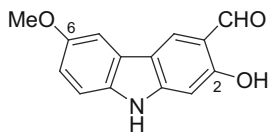
40 clauraila A
Songsiang et al. 2011
C. harmandiana, R



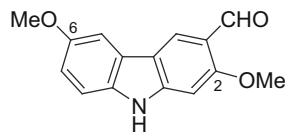
41 clausenal
Chakraborty et al. 1995a
C. heptaphylla, L



42 clauszoline N
Shi et al. 2010
C. vestita, whole plant

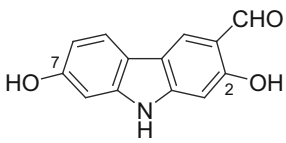


43 lansine
Prakash et al. 1980
C. lansium, L

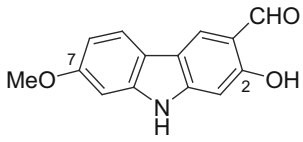


44 glycozolidal
Bhattacharyya & Chowdhury 1985a
G. pentaphylla, R

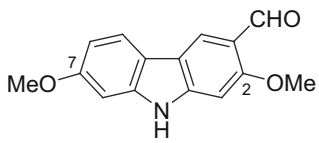
Table 1 continued



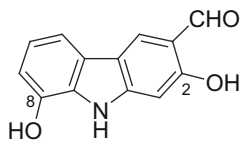
45 clausine O
Wu et al. 1999
C. excavata, R



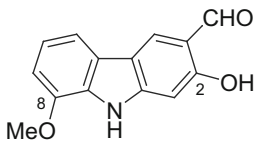
46 7-methoxymukonal
Chaichantipyuth et al. 1988
C. harmandiana, R



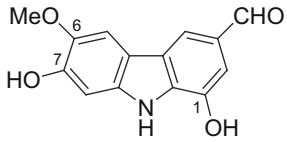
47 3-formyl-2,7-dimethoxy-carbazole
Ruangrungsi et al. 1990;
M. siamensis, R



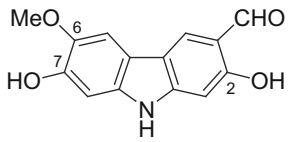
48 clauszoline M
Ito et al. 1997;
C. excavata, L



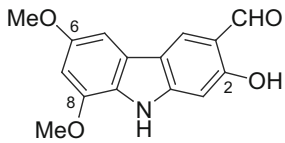
49 clausine A
Wu et al. 1996d
C. excavata, B



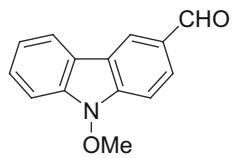
50 clausine J
Wu et al. 1996d
C. excavata, B



51 claulansine J
Liu et al. 2012
C. lansium, B

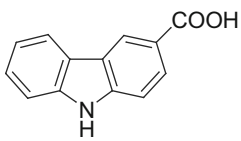


52 clausine B
Wu et al. 1996c
C. excavata, B

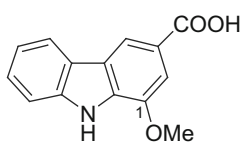


53 *N*-methoxy-3-formylcarbazole
Ito et al. 1988
M. euchrestifolia, R

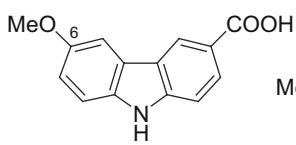
C C_{13}-type 3-carboxylcarbazoles



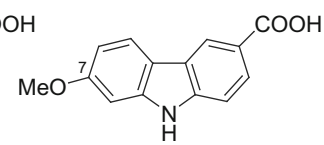
54 3-carboxyl-carbazole
Deng et al. 2014
C. lansium, FR



55 mukoeic acid
Choudhury & Chakraborty 1971
M. koenigii, B

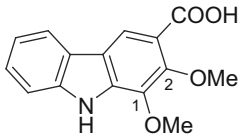


56 clausenaline E
Shen et al. 2014
C. lansium, R

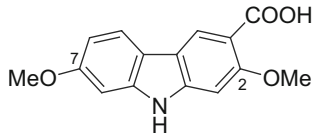


57 clausine N
Wu et al. 1999
C. excavata, R

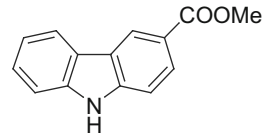
Table 1 continued



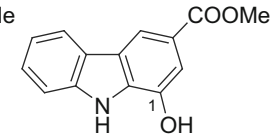
58 clausenaline F
Shen et al. 2014
C. lansium, R



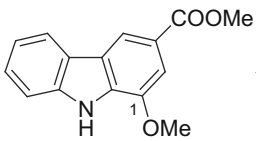
59 clausine K
Wu et al. 1996c
C. excavata, B
(=clauszoline J)



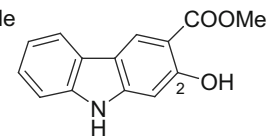
60 methyl carbazole-3-carboxylate
Li et al. 1991
C. lansium, R



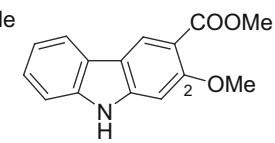
61 clausine E
Wu et al. 1996c,
C. excavata, R
(=clauszoline I)



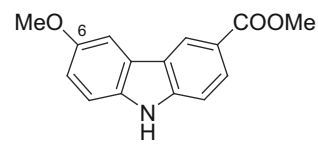
62 mukonine
Chakraborty et al. 1978
M. koenigii, R



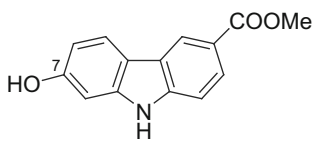
63 mukonidine
Chakraborty 1977
M. koenigii, B



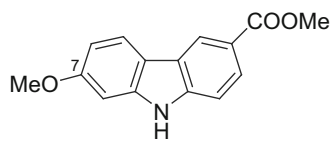
64 clausine L
Wu et al. 1993
C. excavata, L



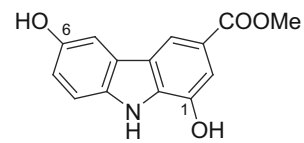
65 methyl 6-methoxy carbazole-3-carboxylate
Li et al. 1991
C. lansium, R



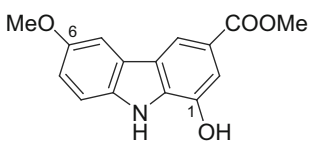
66 clausine M
Wu et al. 1999
C. excavata, R



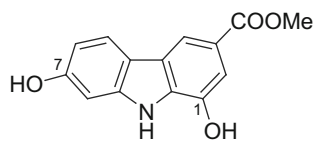
67 clausine C
Wu et al. 1996d
C. excavata, B
(= clauszoline L)



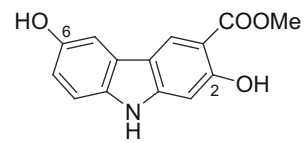
68 methyl 1,6-dihydroxy carbazole-3-carboxylate
Sripisut et al. 2010
C. excavata, B



69 clausine G
Wu et al. 1996d
C. excavata, B

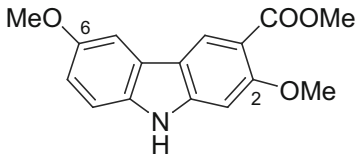


70 clausine R
Wu et al. 1999
C. excavata, R

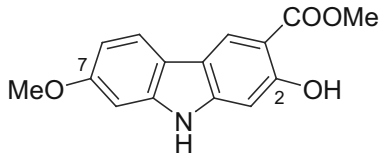


71 sansoakamine
Sripisut et al. 2010
C. excavata, B

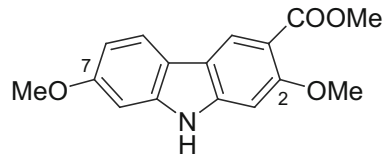
Table 1 continued



72 methyl 6-methoxy-carbazole-3-carboxylate
Li et al. 1991
C. lansium, R

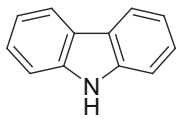


73 clausine TY
Taufiq-Yap et al. 2007
C. excavata, B

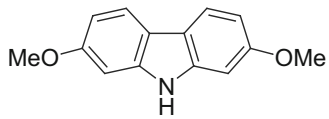


74 clausine H
Wu et al. 1996c
C. excavata, B
(=clauszoline C)

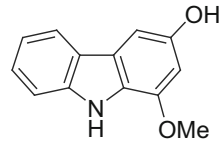
D Miscellaneous structures derived from C_{13}-carbazoles



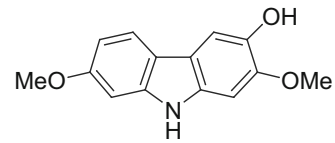
75 carbazole
Chowdhury et al. 1987
G. pentaphylla, R



76 clausine V
Wu et al. 1999
C. excavata, R

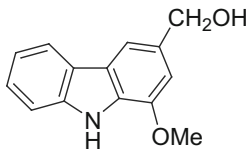


77 murrastanine A
Tan et al. 2015
M. koenigii, B

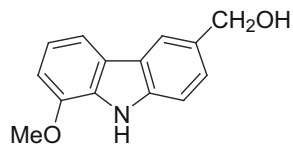


78 clausenawalline D
Maneerat et al. 2012b
C. wallichii, R

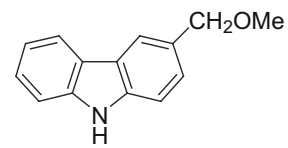
Table 1 continued



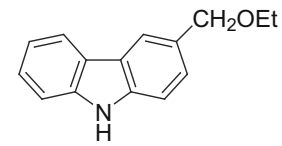
79 koenoline
Fiebig et al. 1985
M. koenigii, R



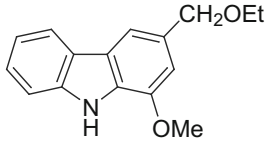
80 mukoline
Roy et al. 1982b
M. koenigii, R



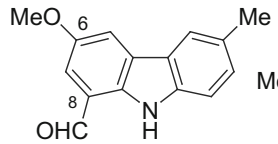
81 3-(methoxymethyl)-carbazole
Yan et al. 2001
C. dunniana, B



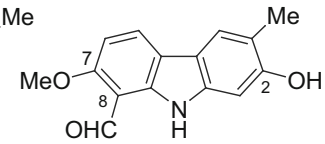
82 claulansine Q
Du et al. 2015
C. lansium, B



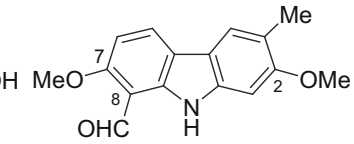
83 claulansine R
Du et al. 2015
C. lansium, B



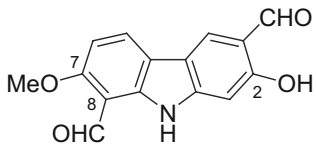
84 8-formyl-6-methoxy-3-methylcarbazole
Chowdhury et al. 2001
M. koenigii, L



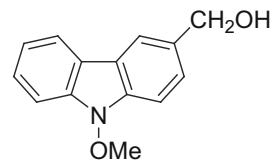
85 murrayaline B
Ito et al. 1991b
M. euchrestifolia, B



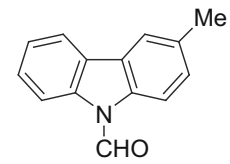
86 murrayaline A
Furukawa et al. 1986
M. euchrestifolia, B



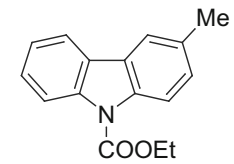
87 murrayaline C
Ito et al. 1991b
M. euchrestifolia, B



88 N-methoxy-3-hydroxy methylcarbazole
Ito et al. 1992a
M. euchrestifolia, R



89 9-formyl-3-methylcarbazole
Chakrabarty et al. 1997
M. koenigii, R



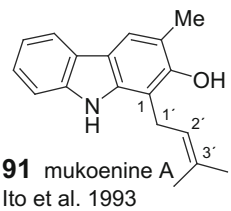
90 9-carbethox-3-methylcarbazole
Chakrabarty et al. 1997
M. koenigii, R

Compounds are listed in order of increasing oxygenation from *C*-1 to *C*-8

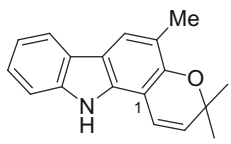
B bark, *R* root, *L* leaves, *S* seeds, *FR* fruits

Table 2 C_{18}-Carbazoles

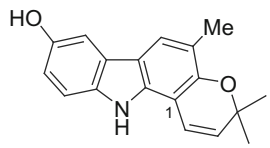
A C_{18}-type 3-methylcarbazoles



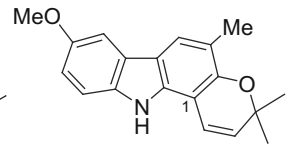
91 mukoenine A
Ito et al. 1993
M. koenigii, R
(=girinimbilol)



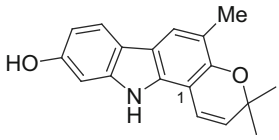
92 girinimbine
Chakraborty et al. 1964
M. koenigii, B



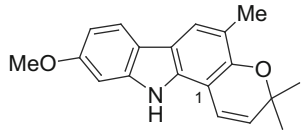
93 koenine
Narasimhan et al. 1970
M. koenigii, L



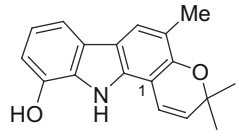
94 koenimbine
Narasimhan et al. 1968
M.koenigii, FR



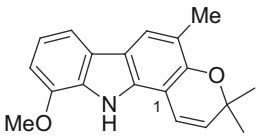
95 murrayamine A
Wu 1991
M. euchrestifolia, L
(=mukoenine C)



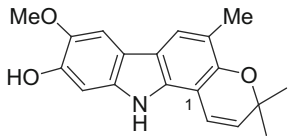
96 *O*-methylmurrayamine A
Tachibana et al. 2003
M. koenigii, S



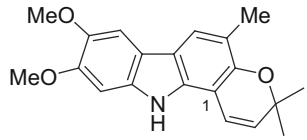
97 clauraila B
Songsiang et al. 2011
C .harmandiana, R
(=8-hydroxygirinimbine)



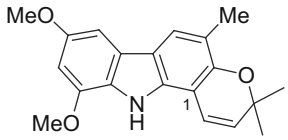
98 mupamine
Mester & Reisch 1977
C. anisata, R



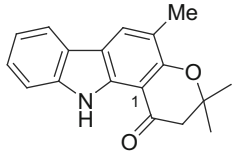
99 koenigine
Narasimhan et al. 1970
M. koenigii, L



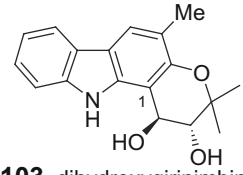
100 koenigicine
Kureel et al.1969b
M. koenigii, L
(=koenimbidine)



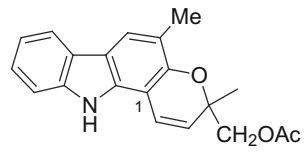
101 mukonicine
Mukherjee et al. 1983a
M. koenigii, L



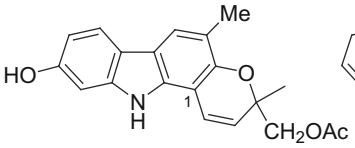
102 euchrestifoline
Wu et al. 1996e
M. euchrestifolia, L



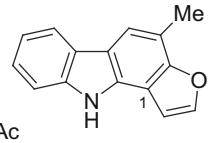
103 dihydroxygirinimbine
Furukawa et al. 1985d
M.euchrestifolia, R



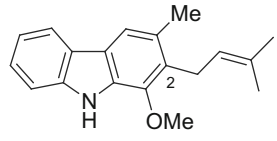
104 murrayamine K
Wu et al. 1996a
M. euchrestifolia, L



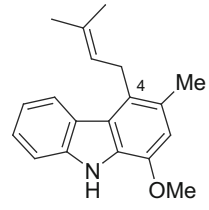
105 murrayamine I
Wu et al. 1996a
M. euchrestifolia, L



106 furostifoline
Ito & Furukawa 1990
M. euchrestifolia, R

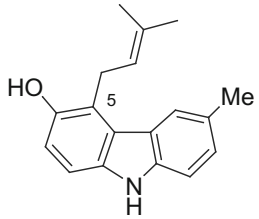


107 clausenapin
Bhattacharyya & Chowdhury 1984
C. heptaphylla, L

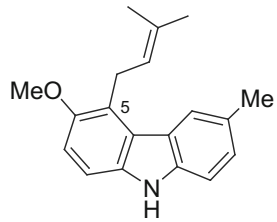


108 clausamine H
Tatsimo et al. 2015
Clausena anisata B

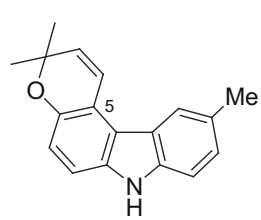
Table 2 continued



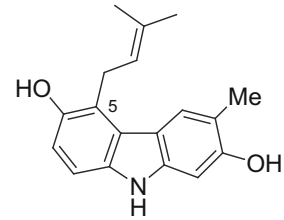
109 glycomaurrol
Kumar et al. 1989
G. mauritiana, B



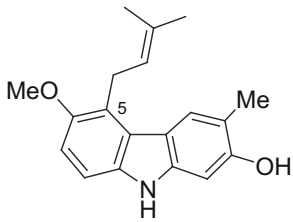
110 6-methylglycomaurrol
Bacher 1999
G. mauritiana, B



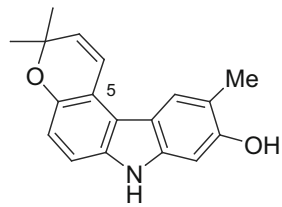
111 glycomaurin
Kumar et al. 1989
G. mauritiana, B
(=eustifoline A)



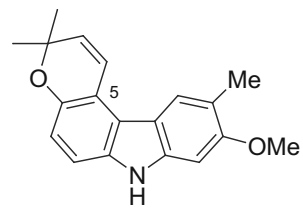
112 glybomine C
Ito et al. 2004
G. arborea, B



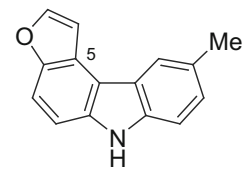
113 glybomine B
Ito et al. 2004
G. arborea, B



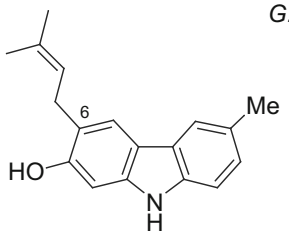
114 glycoborinine
Chakravarty et al. 1999
G. arborea, R



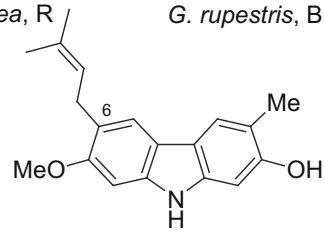
115 2-methoxyglycomaurin
(=7-methoxyglycomaurin)
Rahmani et al. 1998
G. rupestris, B



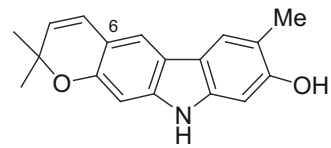
116 eustifoline D
Ito & Furukawa 1990
M. euchrestifolia, R



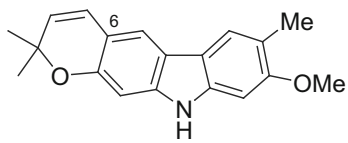
117 siamenol
Meragelman et al. 2000
M. siamensis, FR+L+TW



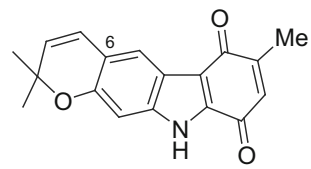
118 2-hydroxy-7-methyl-siamenol
Bacher 1999
M. siamensis, L



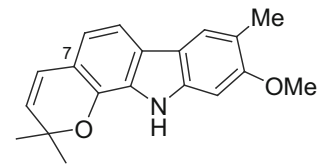
119 pyrayafoline B
Ito et al, 1991a
M. euchrestifolia, B



120 pyrayafoline C
Ito et al, 1991a
M. euchrestifolia, B

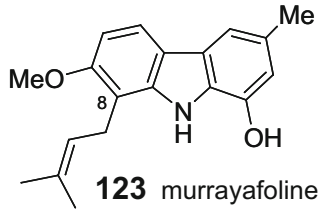


121 pyrayaquinone A
Furukawa et al. 1985a
M. euchrestifolia, R

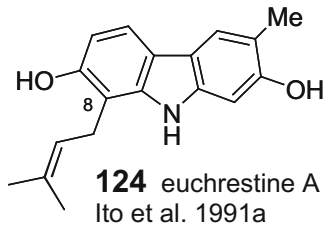


122 clauszoline H
Ito et al. 1997
C. excavata, R

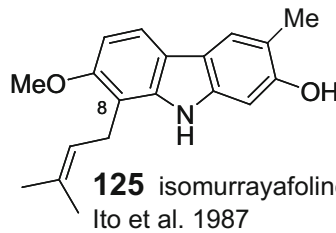
Table 2 continued



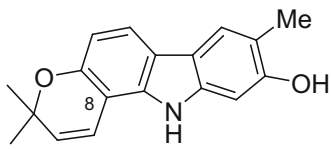
123 murrayafoline B
Furukawa et al. 1985c
M. euchrestifolia, R



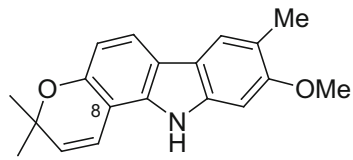
124 euchrestine A
Ito et al. 1991a
M. euchrestifolia, B



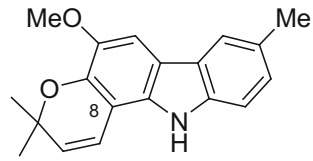
125 isomurrayafoline B
Ito et al. 1987
M. euchrestifolia, B



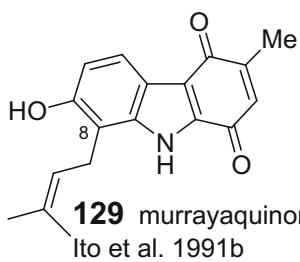
126 pyrayafoline C
Ito et al. 1991a
M. euchrestifolia, B



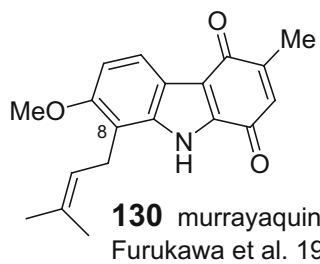
127 pyrayafoline A
Furukawa et al. 1986
M. euchrestifolia, B



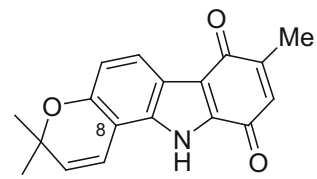
128 heptazolidine
Chakraborty et al. 1974b
C. heptaphylla, R



129 murrayaquinone E
Ito et al. 1991b
M. euchrestifolia, B



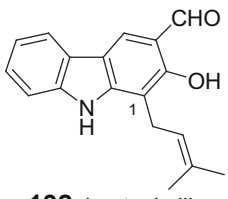
130 murrayaquinone B
Furukawa et al. 1985c
M. euchrestifolia, R



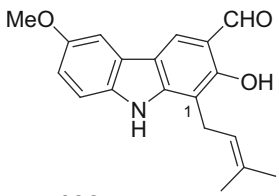
131 pyrayaquinone B
Furukawa et al. 1985a
M. euchrestifolia, R

Table 2 continued

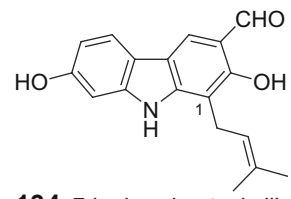
B C_{18}-type 3-formylcarbazoles



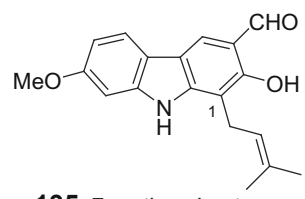
132 heptaphylline
Joshi et al. 1967
C. heptaphylla, R



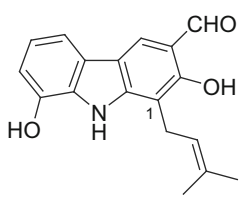
133 6-methoxy-heptaphylline
Joshi et al. 1972
C. indica, R



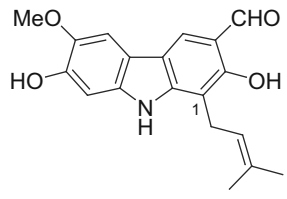
134 7-hydroxyheptaphylline
Kumar et al. 1995;
C. lansium, R
(=2,7-dihydroxy-3-formyl-1-prenylcarbazole)



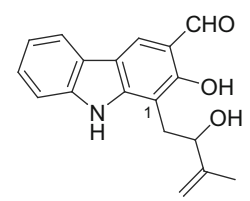
135 7-methoxyhepta-phylline
Chaichantipyuth et al. 1988;
C. harmandiana, R



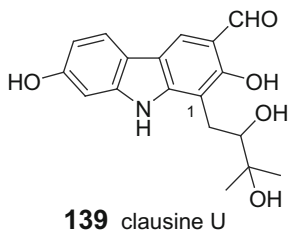
136 heptazoline
Chakraborty et al. 1970
C. heptaphylla, B



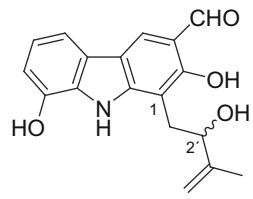
137 claulansine H
Liu et al. 2012
C. lansium, B



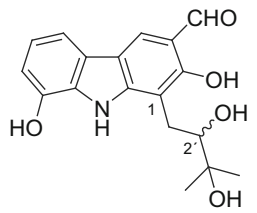
138 clausine S
Wu et al. 1999
C. excavata, R



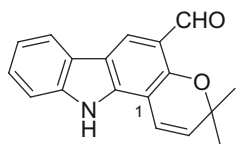
139 clausine U
Wu et al. 1999
C. excavata, B



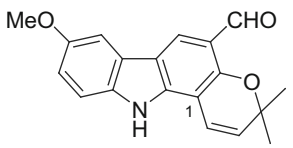
140 clauemarazoles A+B
2´R = 140A, 2´S = 140B
Xia et al. 2015
C. emarginata, B



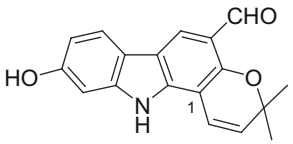
141 clauszoline D
Ito et al. 1996
C. excavata, B
= **clauemarazoles F+G**
Xia et al. 2015



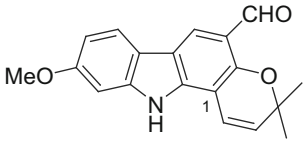
142 murrayacine
Chakraborty et al. 1971
M. koenigii, B



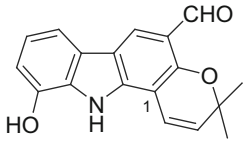
143 claulansine F
Liu et al. 2012
C. lansium, B



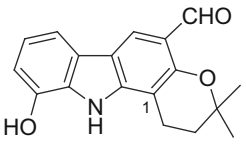
144 clauraila E
Sriphana et al. 2013
C. harmandiana, R



145 7-methoxymurrayacine
Ruangrungsi et al. 1990
M. siamensis, R

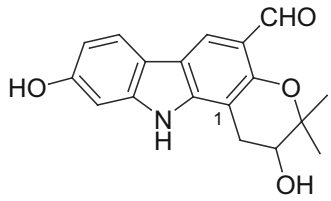


146 clauszoline G
Ito et al. 1996
C. excavata, B

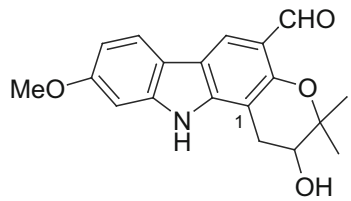


147 heptazolicine
Bhattacharyya et al. 1984
C. heptaphylla, R

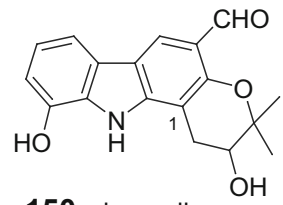
Table 2 continued



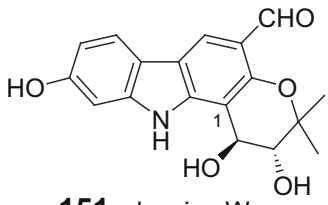
148 clausine T
Wu et al. 1997
C. excavata, R



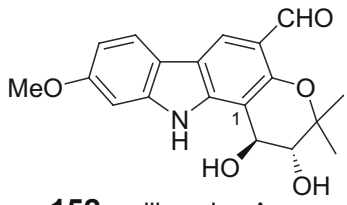
149 guillaumine B
Auranwiwat et al. 2014
C. guillauminii, R



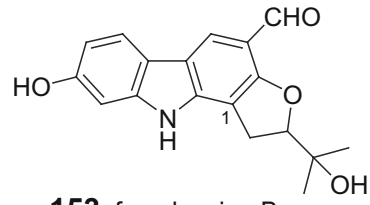
150 clauszoline E
Ito et al. 1996
C. excavata, B



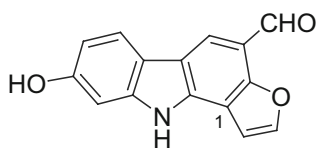
151 clausine W
Wu et al. 1997
C. excavata, R



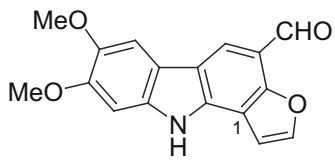
152 guillaumine A
Auranwiwat et al. 2014
C. guillauminii, R



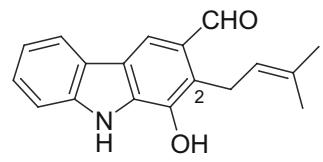
153 furoclausine B
Wu et al. 1997
C. excavata, R



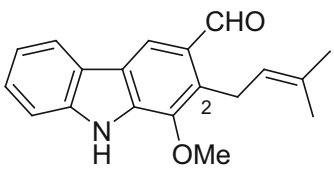
154 furoclausine A
Wu et al. 1997
C. excavata, R



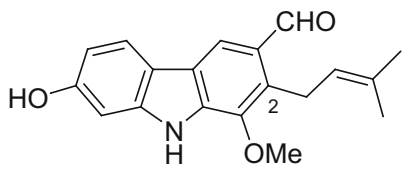
155 3-formyl-6,7-dimethoxy-furo[1,2]carbazole
Khan et al. 2016
Lonicera quinquelocularis, whole plant



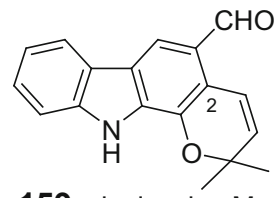
156 claulansine I
Liu et al. 2012
C. lansium, B



157 indizoline
Joshi & Gawad 1974
C. indica, R

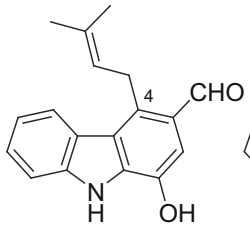


158 clauemarazole E
Xia et al. 2015
C. emarginata, B

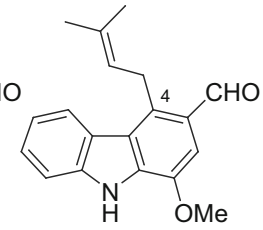


159 claulansine M
Du et al. 2015
C. lansium, B

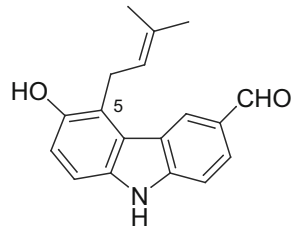
Table 2 continued



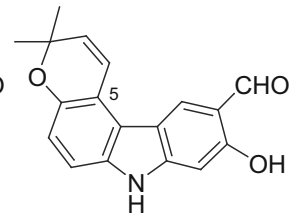
160 clausine D
Wu & Huang 1992
C. excavata, B



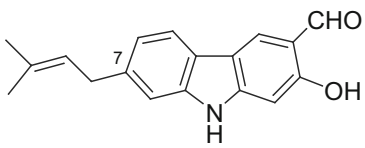
161 ekeberginine
Lontsi et al. 1985
Ekebergia senegalensis B



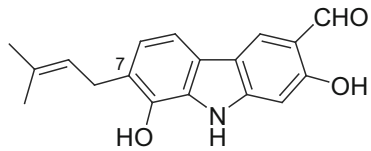
162 double named micromeline
Ma et al. 2005
Micromelum hirsutum, B



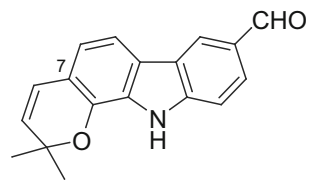
163 clauraila D
Songsiang et al. 2011
C. harmandiana, R



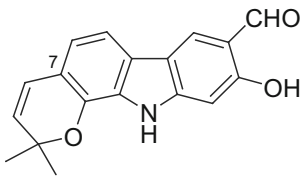
164 clausanitin
Okorie 1975
C. anisata, R



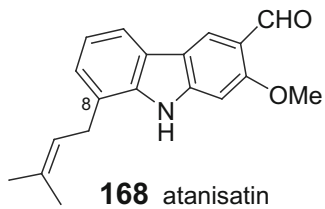
165 excavatine A
Peng et al. 2013
C. excavata, B+L



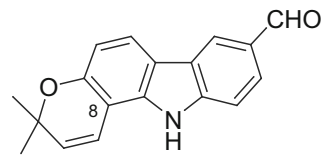
166 murrastinine C
Tan et al. 2015
M. koenigii, B+L



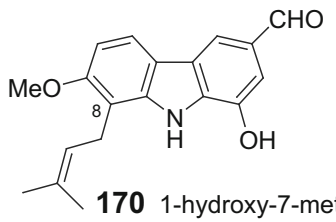
167 clauszoline B
Ito et al. 1996
C. excavata, B



168 atanisatin
Okorie 1975
C. anisata, B



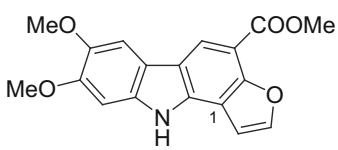
169 murrastinine C
Tan et al. 2015
M. koenigii, B



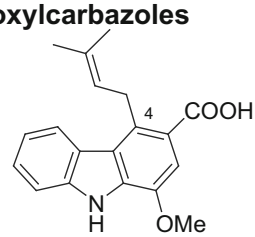
170 1-hydroxy-7-methoxy-8-prenyl-3-formylcarbazole
Nalli et al. 2016
M. koenigii, B+L

Table 2 continued

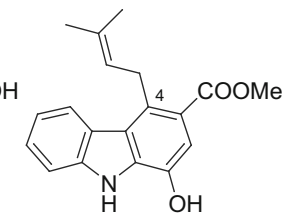
C C_{18}-type 3-carboxylcarbazoles



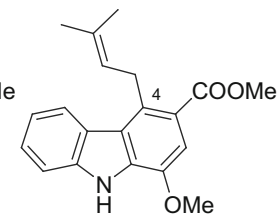
171 methyl-6,7-dimethoxy-furo [1,2]carbazole-3-carboxylate
Khan et al. 2016
Lonicera quinquelocularis, whole plant



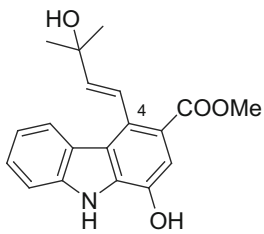
172 1-methoxy-3-carboxyl-4-prenylcarbazole
Herdits-Riemer 2002
C. harmandiana, B



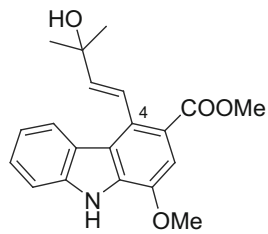
173 clausine F
Wu & Huang 1992
C. excavata, B



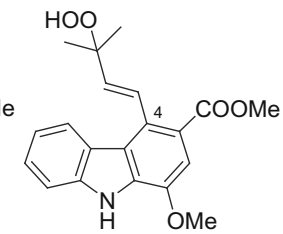
174 clausamine D
Ito et al. 2000
C. anisata, TW



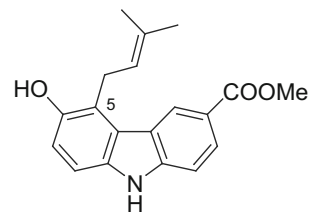
175 clausamine F
Ito et al. 2000
C. anisata, TW



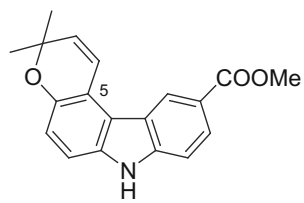
176 clausamine E
Ito et al. 2000
C. anisata, TW



177 clausamine G
Ito et al. 2000
C. anisata, TW



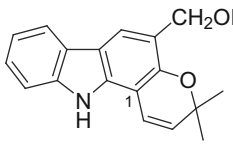
178 "microfalcatine"
Grassi 1998
Micromelum cf. *falcatum*, B



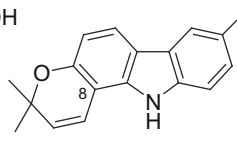
179 clauraila C
Songsiang et al. 2011
C. harmandiana, R

Table 2 continued

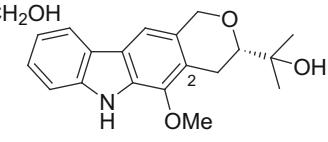
D Miscellaneous structures derived from C_{18}-carbazoles



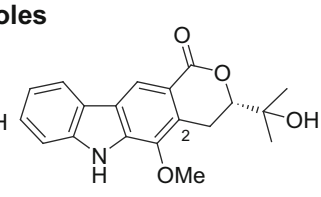
180 murrastinine B
Tan et al. 2015
M. koenigii, B



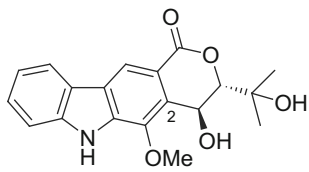
181 murrayacol
Bacher 1999
M. siamensis, L



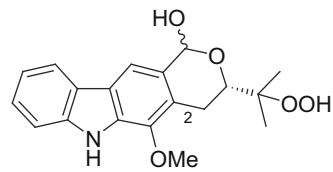
182 claulamine E
Shen et al. 2014
C. lansium, R



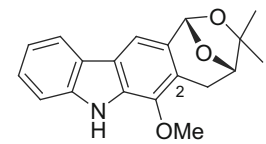
183 mafaicheenamine A
Maneerat & Laphookhieo 2010
C. lansium, TW



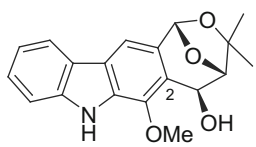
184 claulansine C
Liu et al. 2012
C. lansium, B



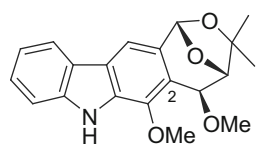
185 mafaicheenamine B
Maneerat & Laphookhieo 2010
C. lansium, TW



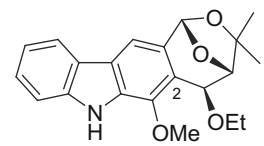
186 claulansine A
Liu et al. 2012
C. lansium, B



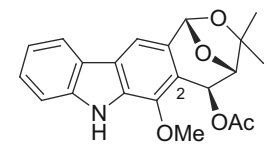
187 claulansine B
Liu et al. 2012
C. lansium, B
(= claulamine B)



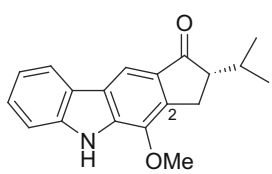
188 1´-O-methylclaulamine B
Shen et al. 2014
C. lansium, R



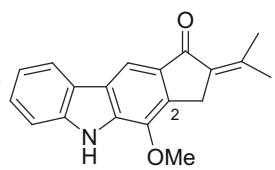
189 claulansine P
Du et al. 2015
C. lansium, B



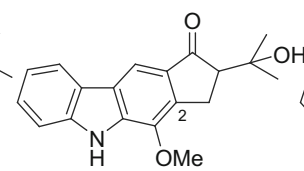
190 1´-acetylclaulamine B
Shen et al. 2014
C. lansium, R



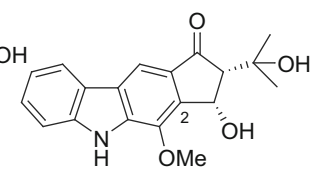
191 clausenaline B
Shen et al. 2014
C. lansium, R



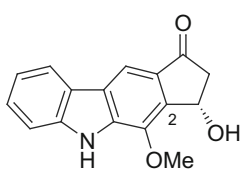
192 mafaicheenamine D
Maneerat et al. 2012a
C. lansium, R
(=claulansine G)



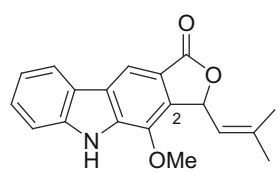
193 mafaicheenamine C
Maneerat & Laphookhieo 2010
C. lansium, TW



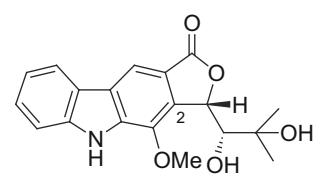
194 clausenaline C
Shen et al. 2014
C. lansium, R



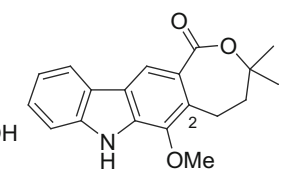
195 claulansine E
Liu et al. 2012
C. lansium, B



196 mafaicheenamine E
Maneerat et al. 2012a
C. lansium, R

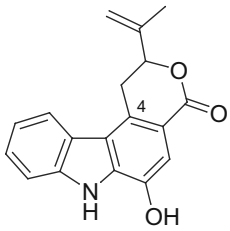


197 claulansine D
Liu et al. 2012
C. lansium, B

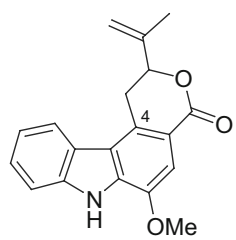


198 clauemarazole C
Xia et al. 2015
C. emarginata, B

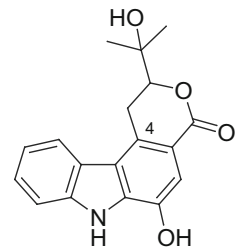
Table 2 continued



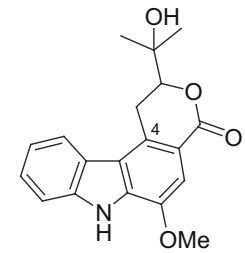
199 clausamine A
Ito et al. 1998
C. anisata, TW



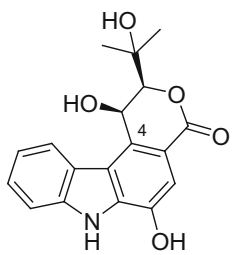
200 clausamine B
Ito et al. 1998
C. anisata, TW



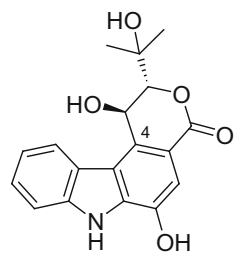
201 clausevatine D
Wu et al. 1998b
C. excavata, R



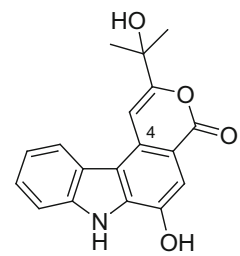
202 clausamine C
Ito et al. 1998
C. anisata, TW



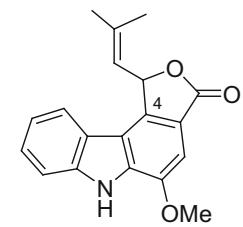
203 clausevatine E
Wu et al. 1998b
C. excavata, R



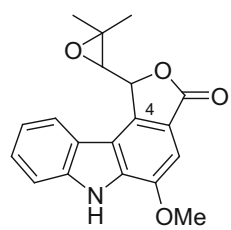
204 clausevatine F
Wu et al. 1998b
C. excavata, R



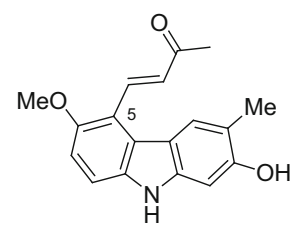
205 clausevatine G
Wu et al. 1998b
C. excavata, R



206 furanoclausamine B
Ito et al. 2009
C.anisata, B



207 furano-clausamine A
Ito et al. 2009
C.anisata, B



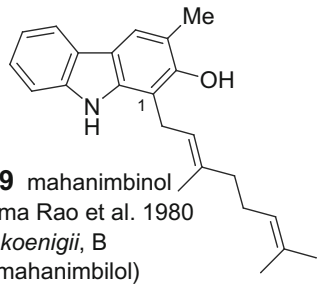
208 4′-(2-hydroxy-6-methoxy-3-methylcarbazol-5-yl) but-3′-en-2′-one
Yang et al. 2012
G. pentaphylla, B

Compounds are listed in order of prenylation from *C*-1 to *C*-8 and increasing oxygenation

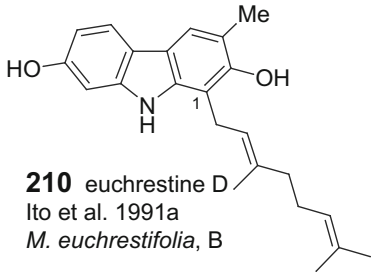
B bark, *R* root, *L* leaves, *S* seeds, *FR* fruits, *TW* twigs

Table 3 C_{23}-Carbazoles

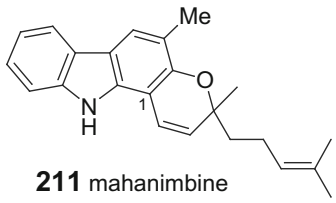
A C_{23}-type 3-methylcarbazoles



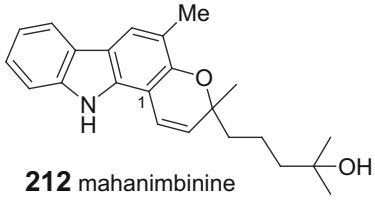
209 mahanimbinol
Rama Rao et al. 1980
M. koenigii, B
(= mahanimbilol)



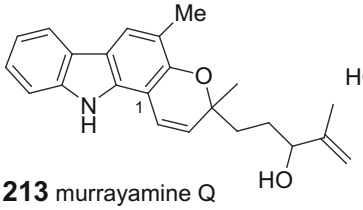
210 euchrestine D
Ito et al. 1991a
M. euchrestifolia, B



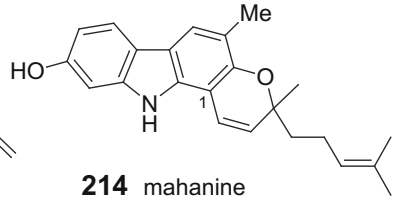
211 mahanimbine
Narasimhan et al. 1968
M. koenigii, B



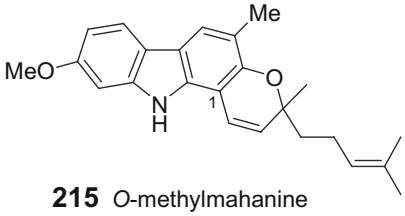
212 mahanimbinine
Kureel et al. 1970a
M. koenigii, B



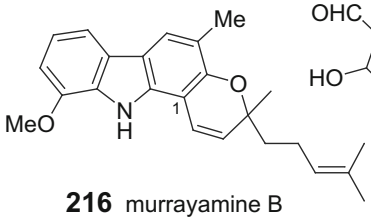
213 murrayamine Q
renamed
(= murrayamine C)
Ito et al. 1992b
M. euchrestifolia, FR



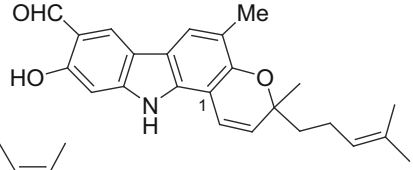
214 mahanine
Narasimhan et al. 1970
M. koenigii, L



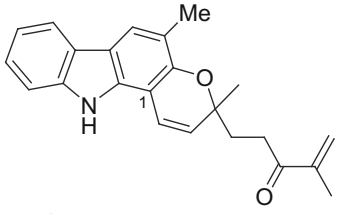
215 *O*-methylmahanine
Tachibana et al. 2003
M. koenigii, L



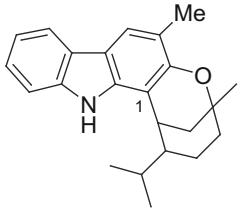
216 murrayamine B
Wu 1991
M. euchrestifolia, L



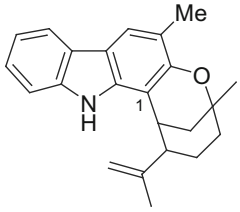
217 murrayakonine C
Nalli et al. 2016
M. koenigii, L



218 murrastinine A
Tan et al. 2015
M. koenigii, B

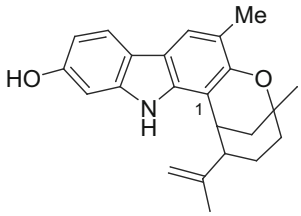


219 exozoline
Ganguly & Sarkar 1978
M. exotica, L

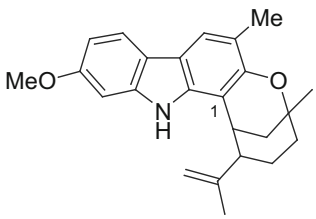


220 cyclomahanimbine
Kureel et al. 1969a
M. koenigii, L
(=murrayazolidine, curryanin)

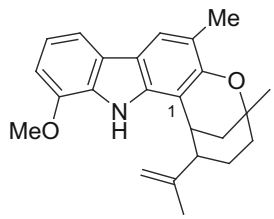
Table 3 continued



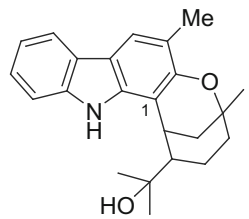
221 murrayamine D
Wu et al. 1995a
M. euchrestifolia, L



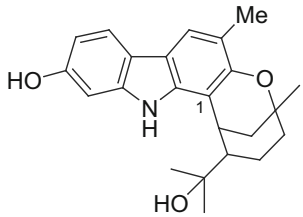
222 murrayatanine A
Tan et al. 2015
M. koenigii, L



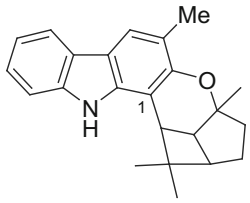
223 murrayamine H
Wu et al. 1996e
M. euchrestifolia, L



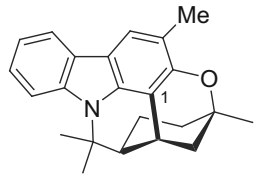
224 murrayazolinine
Chakraborty et al. 1973
M. koenigii, B



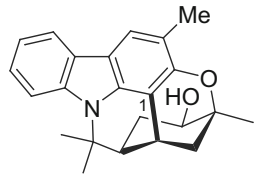
225 7-hydroxy-murrayazolinine
Sim & Teh 2011
M. koenigii, L



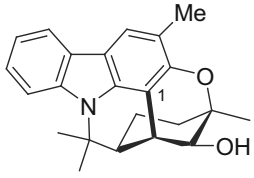
226 bicyclomahanimbine
Kureel et al.1969a
corrected structure:
Whiting et al. 1970
M. koenigii, L



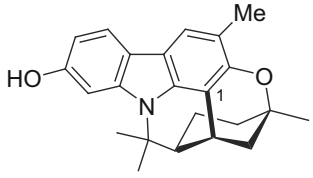
227 murrayazoline
Bordner et al. 1972
M. koenigii, B
(=mahanimbidine, curryangin)



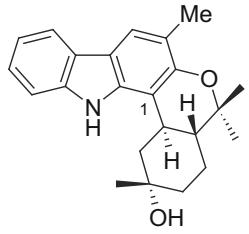
228 murrayazolinol
Bhattacharyya et al.1989
M. koenigii, R



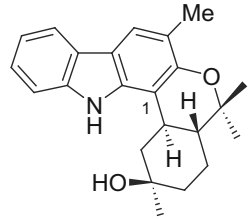
229 murrayakoeninol
Chakraborty et al. 2009
M. koenigii, L



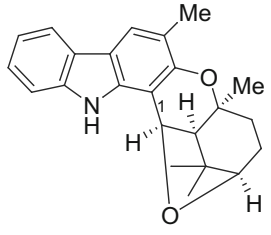
230 murrayamine E
Wu et al. 1995a
M .euchrestifolia, L



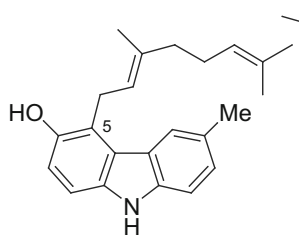
231 murrayamine O
Wu et al. 1995b
M. euchrestifolia, R



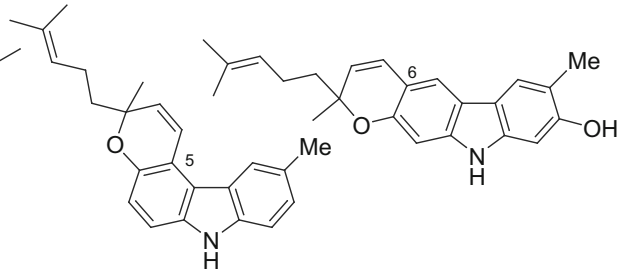
232 murrayamine P
Wu et al. 1995b
M. euchrestifolia, R



233 murrayakonine D
Nalli et al. 2016
M. koenigii, L



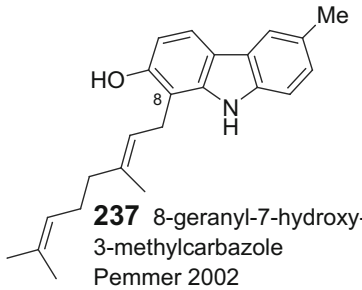
234 eustifoline C
Ito & Furukawa 1990
M. euchrestifolia, R



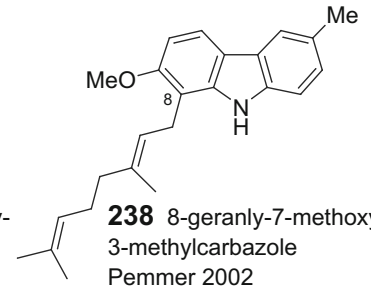
235 eustifoline B
Ito & Furukawa 1990
M. euchrestifolia, R

236 pyrayafoline E
Ito et al. 1991b
M. euchrestifolia, B

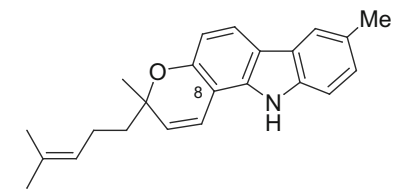
Table 3 continued



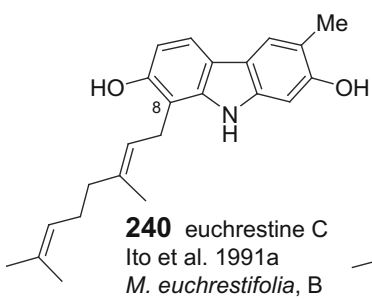
237 8-geranyl-7-hydroxy-3-methylcarbazole
Pemmer 2002
M. siamensis, L



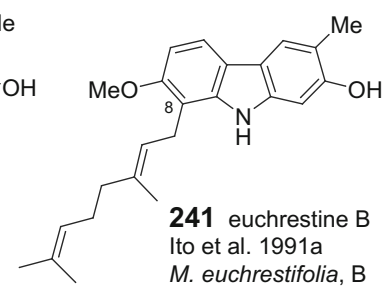
238 8-geranly-7-methoxy-3-methylcarbazole
Pemmer 2002
M. siamensis, FR



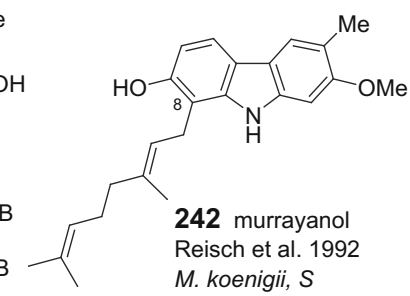
239a (-) isomahanimbine
Joshi et al. 1970
239b (+) mahanimbicine
Kureel et al. 1970b
M. koenigii, L



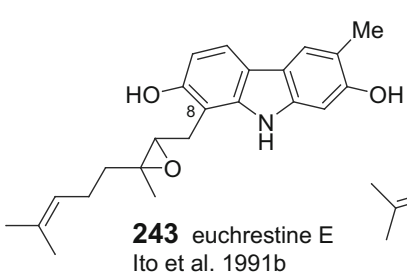
240 euchrestine C
Ito et al. 1991a
M. euchrestifolia, B



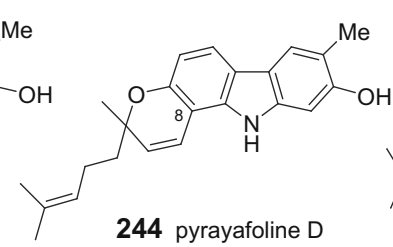
241 euchrestine B
Ito et al. 1991a
M. euchrestifolia, B



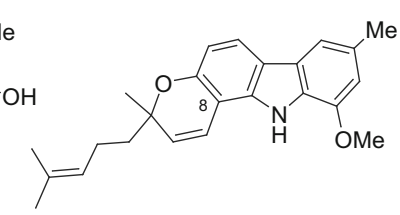
242 murrayanol
Reisch et al. 1992
M. koenigii, S



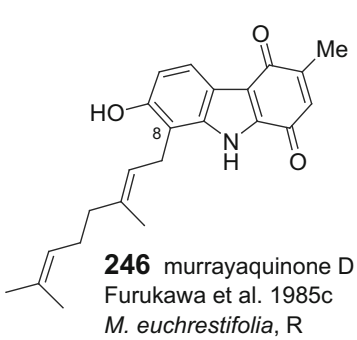
243 euchrestine E
Ito et al. 1991b
M. euchrestifolia, B



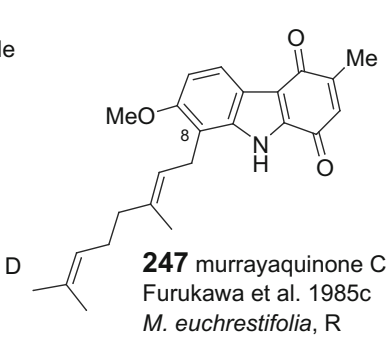
244 pyrayafoline D
Ito et al. 1991a
M. euchrestifolia, B
(=isomahanine)



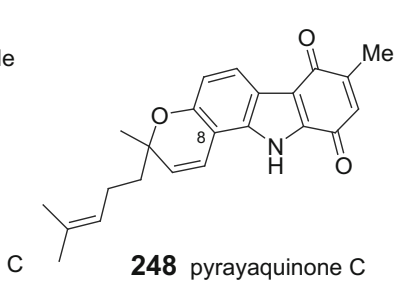
245 murrayamine C
Wu 1991
M. euchrestifolia, L



246 murrayaquinone D
Furukawa et al. 1985c
M. euchrestifolia, R

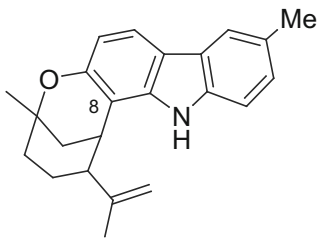


247 murrayaquinone C
Furukawa et al. 1985c
M. euchrestifolia, R

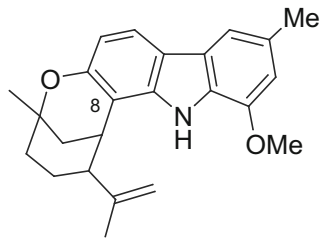


248 pyrayaquinone C
Ito et al. 1988
M. euchrestifolia, R

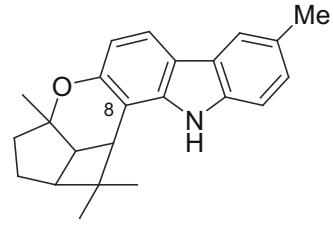
Table 3 continued



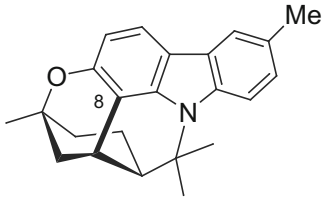
249 murrayamine G
Wu et al. 1996e
M. euchrestifolia, L



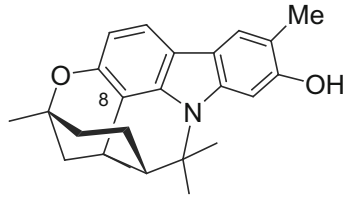
250 murrayamine F
Wu et al. 1996e
M. euchrestifolia, L



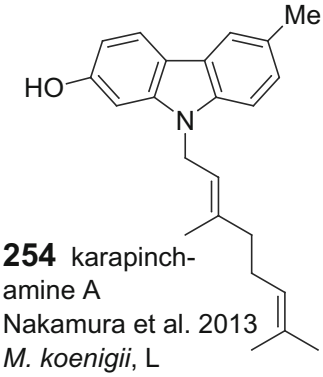
251 bicyclomahanimbicine
Kureel et al. 1970b
M. koenigii, L



252 isomurrayazoline
Bhattacharyya et al. 1982
M. koenigii, B



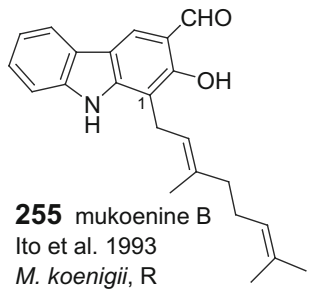
253 karapinchamine B
Nakamura et al. 2013
M. koenigii, B



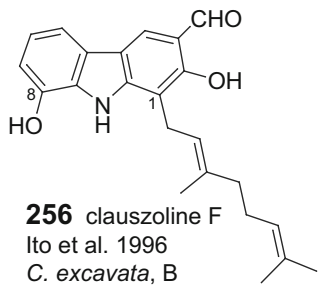
254 karapinch-amine A
Nakamura et al. 2013
M. koenigii, L

Table 3 continued

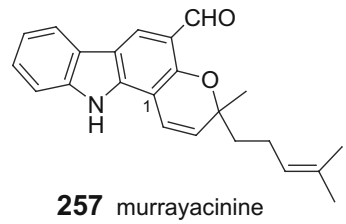
B C_{23}-type 3-formylcarbazoles



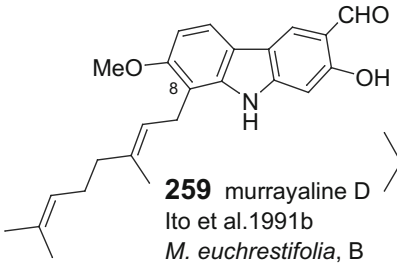
255 mukoenine B
Ito et al. 1993
M. koenigii, R
(=clausenatine A)



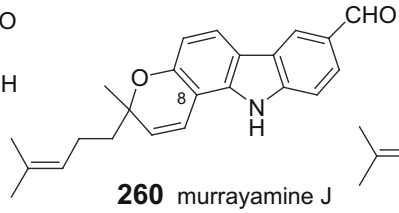
256 clauszoline F
Ito et al. 1996
C. excavata, B



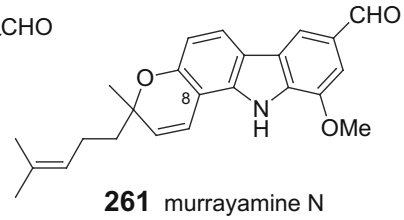
257 murrayacinine
Chakraborty et al. 1974a
M. koenigii, B



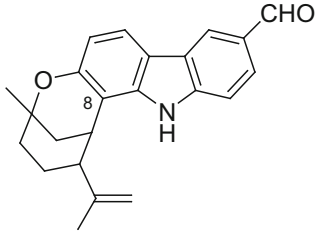
259 murrayaline D
Ito et al.1991b
M. euchrestifolia, B



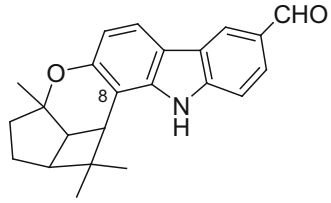
260 murrayamine J
Wu et al. 1996a
M. euchrestifolia, L



261 murrayamine N
Wu et al. 1996a
M. euchrestifolia, L



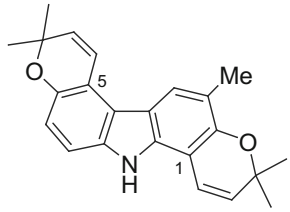
262 murrayakonine B
Nalli et al. 2016
M. koenigii, B



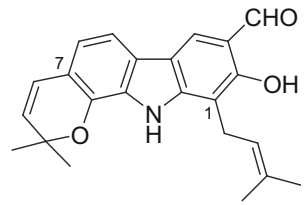
263murrayamine M
Wu et al. 1996a
M. euchrestifolia, L

Table 3 continued

C Twofold prenylated C_{23}-carbazoles



264 clausenawalline C
Maneerat et al. 2012b
C. wallichii, R



265 clauszoline A
Ito et al. 1996
C. excavata, B

Compounds are listed in order of geranylation and increasing oxygenation from C1 to C8

B bark, *R* root, *L* leaves, *FR* fruits, *TW* twigs, *S* seeds

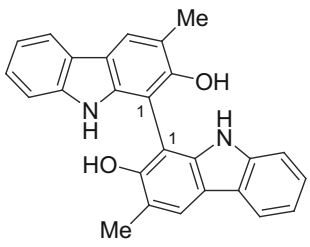
have already attracted considerable synthetic interest. They served as a stimulus for the development of new strategies for the construction of the skeleton as well as for successful total syntheses of a number of derivatives (e.g. Bringmann et al. 1998a; Knölker and Reddy 2002; Lebold and Kerr 2007; Schmidt et al. 2012; Qiu et al. 2013; Hesse et al. 2014; Börger et al. 2014; Dai et al. 2015; Markad and Argade 2016).

Apart from synthetic-chemical and pharmaceutical considerations the formation of phytocarbazoles awaked also biological interest. This biogenetic trend represents an important chemotaxonomic criterion apparently restricted to the Rutaceae family, where it separates the tribe Clauseneae from the Citreae within the subfamily Aurantioideae (Kong et al. 1986, 1988a, b; Samuel et al. 2001; Bayer et al. 2009; But et al. 2009; Shivakumar et al. 2016). With regard to the limited distribution the frequently cited report on the isolation of the phytocarbazole ekeberginin (**160**) from *Ekebergia senegalensis* A. Juss. of the Meliaceae family (Lontsi et al.1985) appears dubious. It might be explained by a confusion with *Clausena anisata* (Willd.) Hook.f. ex Benth., a well-known and widely distributed medicinal plant, superficially showing morphological similarities in leaves and inflorescence. Another exception is the recently published occurrence of the furocarbazoles **155** and **171** in *Lonicera quinquelocularis* Hard. of the Caprifoliaceae (Khan et al. 2016). However, regarding the chemical make-up of that family and the biogenetic trends already known from the genus *Lonicera*, the formation of phytocarbazoles is surprising and should be reconfirmed with properly identified plant material.

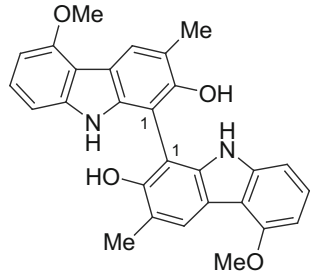
Although the chemistry of different types of carbazoles was comprehensively reviewed by Knölker and Reddy (2002, 2008), Schmidt et al. (2012), and some of their pharmacological values were summarized therein, a biologically orientated interpretation of the structural diversity and distribution of phytocarbazoles as well as their various activities is missing. In the course of our broad-based phytochemical comparison in Rutaceae, particularly within the subfamily Aurantioideae, distinct accumulation trends towards different types of phytocarbazoles, coumarins, quinolones, acridones, quinazolines, flavonoids, or amides were found in different genera and species as well as in different plant parts (Greger et al. 1996; Riemer et al. 1997; Vajrodaya et al. 1998; Grassi 1998; Lukaseder 2000; Lukaseder et al. 2009; Pacher et al. 2001; Herdits-Riemer 2002; Pemmer 2002). In accordance with previous reports (Wu 1991; Wu et al. 1991, 1996a, e; Ito et al. 1997) geographical and seasonal variation of carbazole profiles were also detected in different collections and even individuals of the same species.

Table 4 Dimeric carbazoles

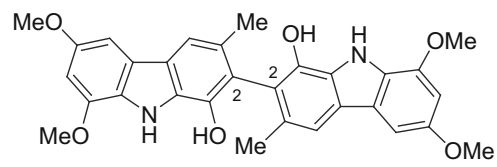
A Symmetrical dimers



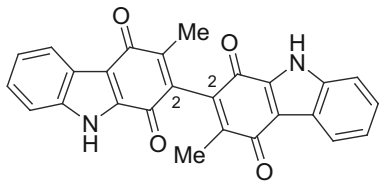
266 bis-2-hydroxy-3-methylcarbazole
Ito et al. 1993
M. koenigii, R



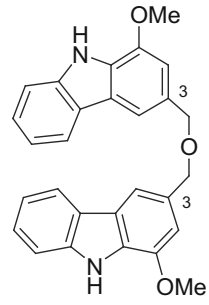
267 biscarbalexine A
Yang et al. 2012
G. pentaphylla, B



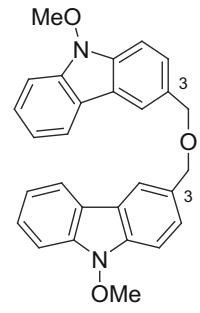
268 clausenamine A
Wu et al. 1996b
C. excavata, B



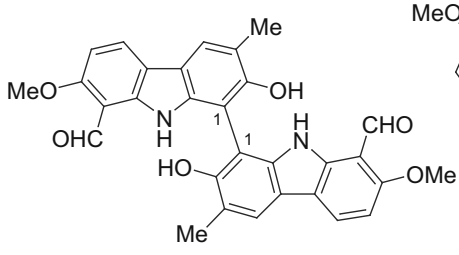
269 bismurrayaquinone A
Ito et al. 1993
M. koenigii, R



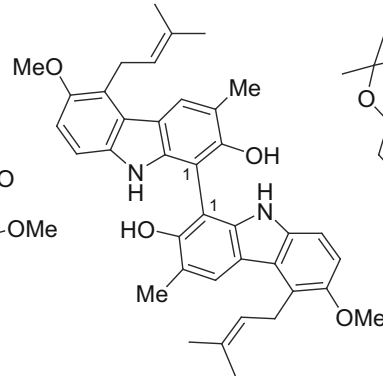
270 oxydimurrayafoline
Ito et al. 1987
M. euchrestifolia, B



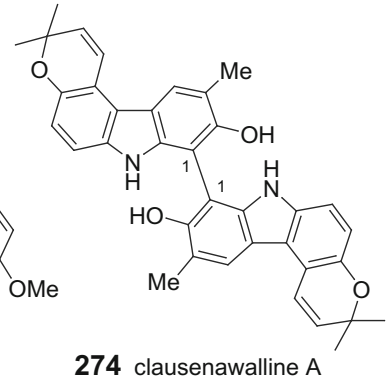
271 3,3′-[oxybis(methylene)] bis(9-methoxy-9*H*-carbazole)
Rahman & Gray, 2005
M. koenigii, B



272 murradine J
Lv et al. 2015
M. tetramera, L+B

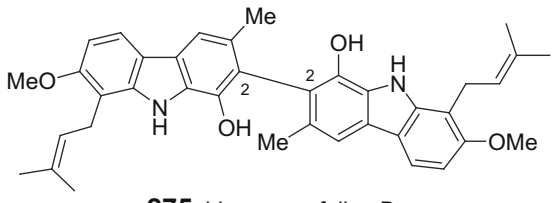


273 bisglybomine B
Yang et al. 2012
G. pentaphylla, B

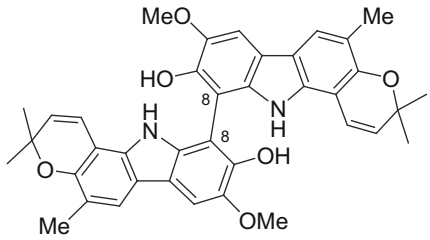


274 clausenawalline A
Maneerat et al. 2011
C. wallichii, R

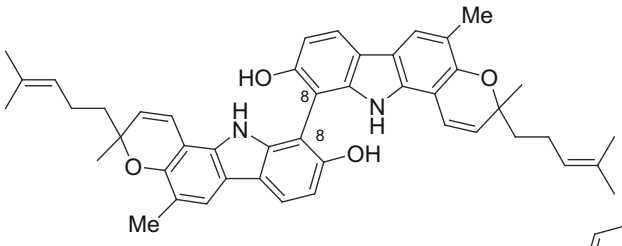
Table 4 continued



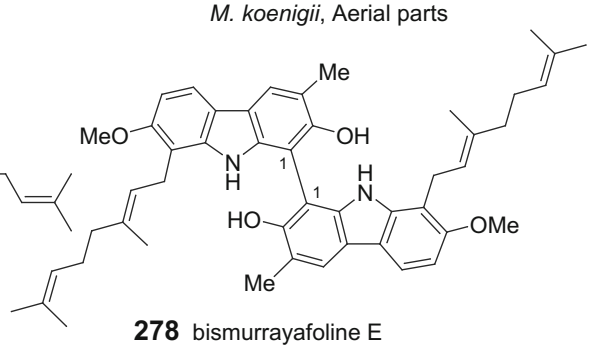
275 bismurrayafoline B
Furukawa et al. 1983
M. euchrestifolia, R



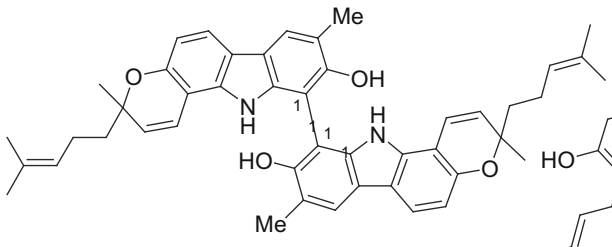
276 8,8-biskoenigine
Wang et al. 2003
M. koenigii, Aerial parts



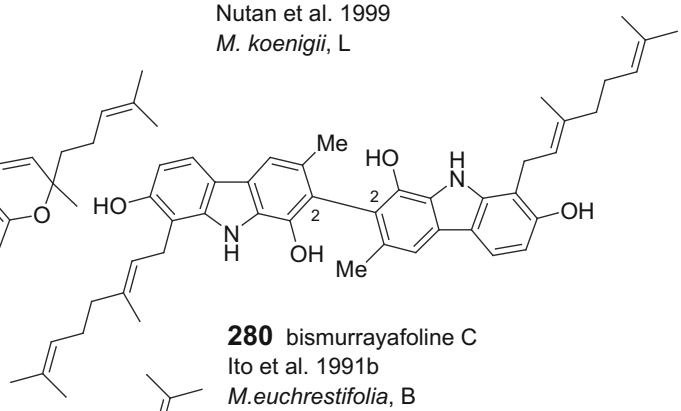
277 bispyrayafoline
Tachibana et al. 2003
M. koenigii, L



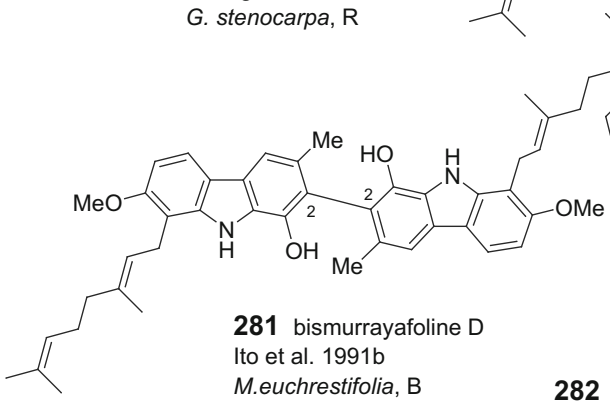
278 bismurrayafoline E
Nutan et al. 1999
M. koenigii, L



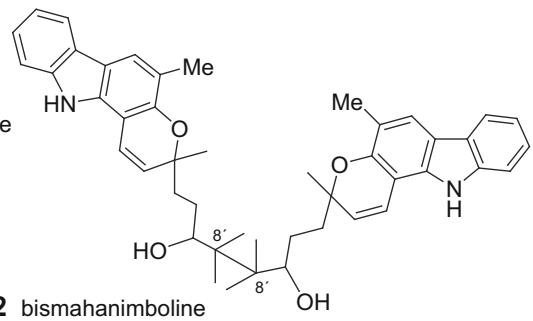
279 bisisomahanine
Cuong et al. 2004
G. stenocarpa, R



280 bismurrayafoline C
Ito et al. 1991b
M.euchrestifolia, B



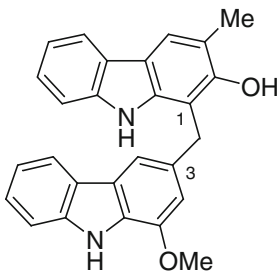
281 bismurrayafoline D
Ito et al. 1991b
M.euchrestifolia, B



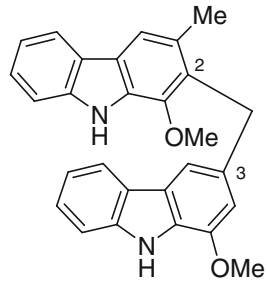
282 bismahanimboline
Tan et al. 2015
M.koenigii, B

Table 4 continued

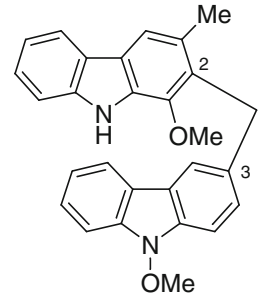
B Asymmetrical dimers



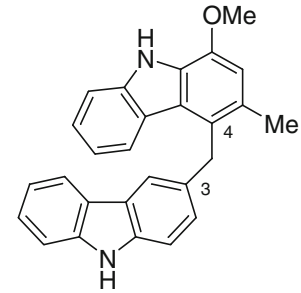
283 murradine A
Lv et al. 2015
M. tetramera, L+B



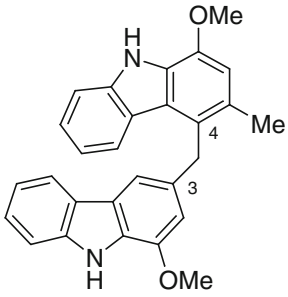
284 murradine B
Lv et al. 2015
M. tetramera, L+B



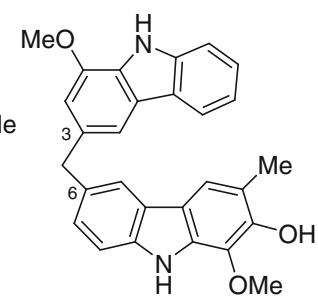
285 murrafoline F
Ito et al. 1988
M. euchrestifolia, R



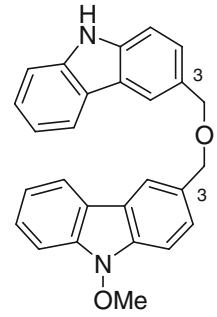
286 murradine C
Lv et al. 2015
M. tetramera, L+B



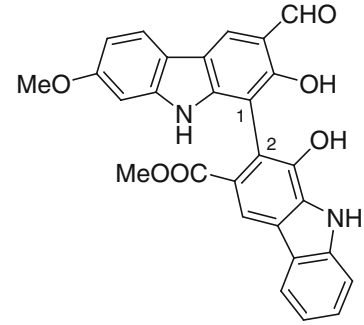
287 chrestifoline A
Ito et al. 1990
M. euchrestifolia, R



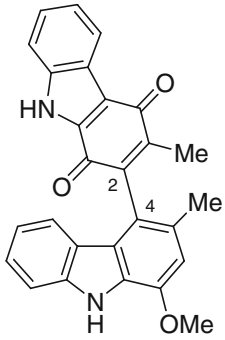
288 murradine D
Lv et al. 2015
M. tetramera, L+B



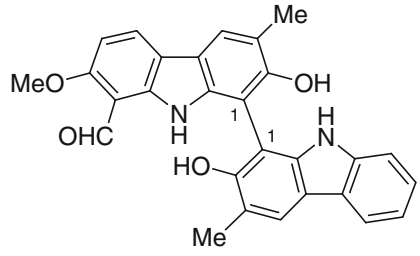
289 murradine K
Lv et al. 2015
M. tetramera, L+B



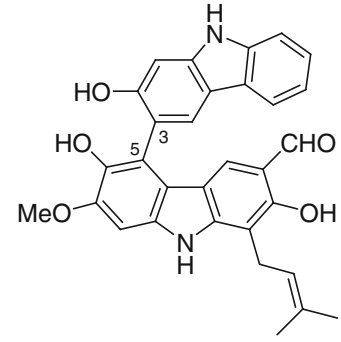
290 clausenawalline F
Maneerat et al. 2012b
C. wallichii, R



291 bikoeniquinone
Ito et al. 1993
M. koenigii, R



292 murradine I
Lv et al. 2015
M.tetramera, L+B



293 clausenawalline B
Maneerat et al. 2011
C. wallichii, R

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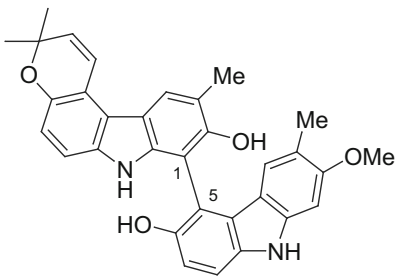
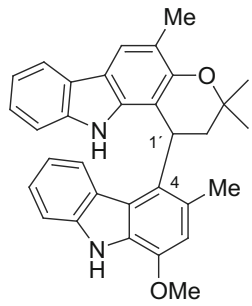
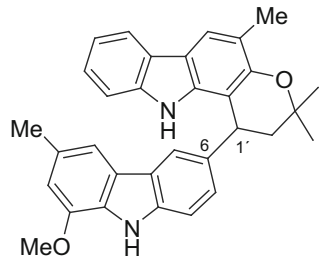


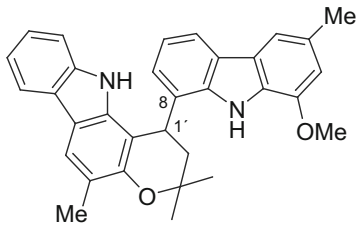
294 clausenawalline E
Maneerat et al. 2012b
C. wallichii, R



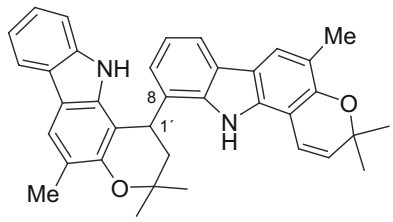
295 murrafoline G
Furukawa et al. 1993
M. euchrestifolia, R



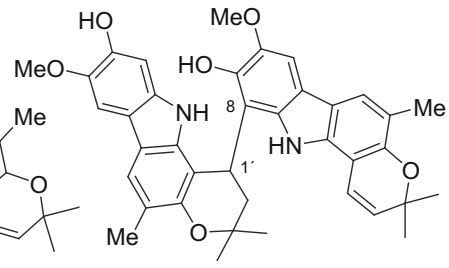
296 murrafoline D
Furukawa et al. 1993
M. euchrestifolia, R



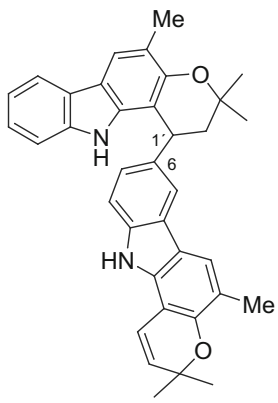
297 murrafoline B
Furukawa et al.1985b
M. euchrestifolia, R



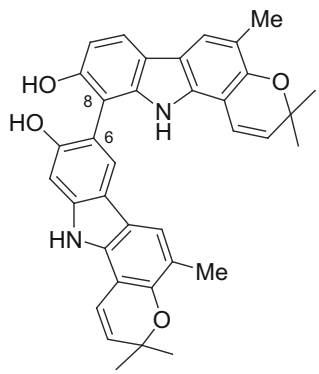
298 murrafoline C
Furukawa et al.1985b
M. euchrestifolia, R



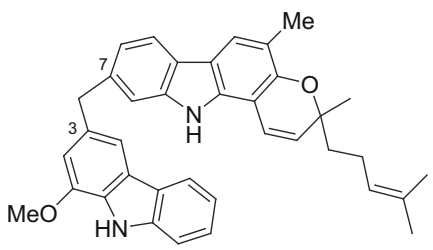
299 murrafoline I
Ito et al. 2006
M. koenigii, L



300 murrafoline H
Furukawa et al. 1993
M. euchrestifolia, R

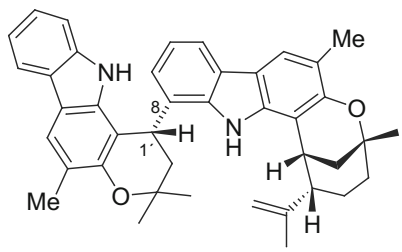


301 bis-7-hydroxygirinimbine B
Wu et al. 1991
M. euchrestifolia, L

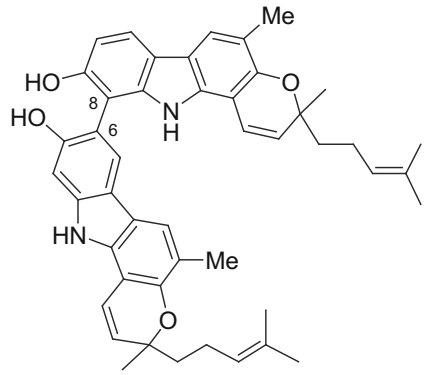


302 murrayakonine A
Nalli et al. 2016
M. koenigii, B

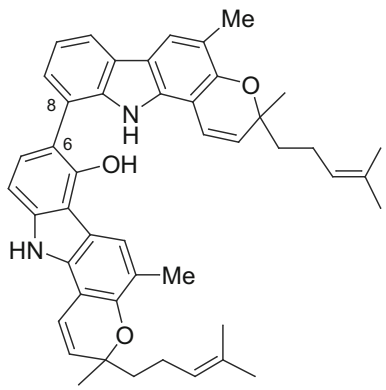
Table 4 continued



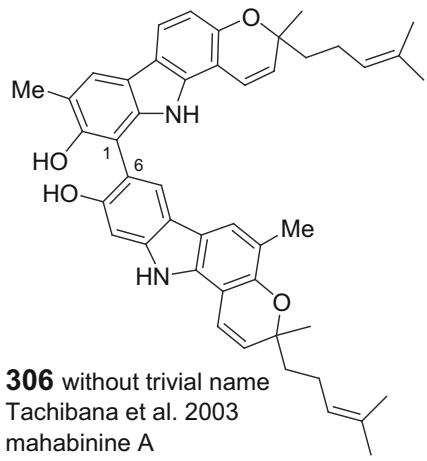
303 murrafoline A
McPhail et al. 1983
M. euchrestifolia, R
(= (±) murrafoline)



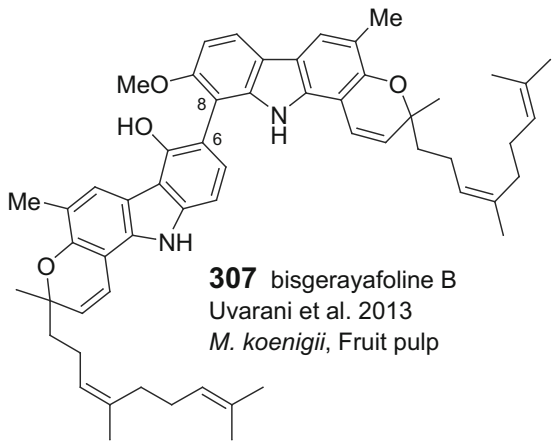
304 bismahanine
Ito et al. 1993
M. koenigii, B



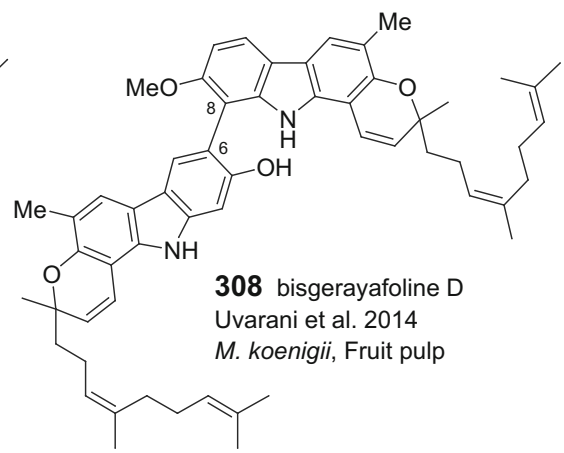
305 bismahanimbinol
Uvarani et al. 2014
M. koenigii, Fruit pulp



306 without trivial name
Tachibana et al. 2003
mahabinine A
Ito et al. 2006
M. koenigii, L

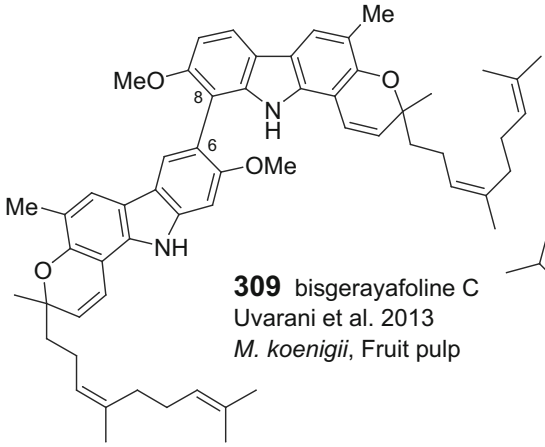


307 bisgerayafoline B
Uvarani et al. 2013
M. koenigii, Fruit pulp

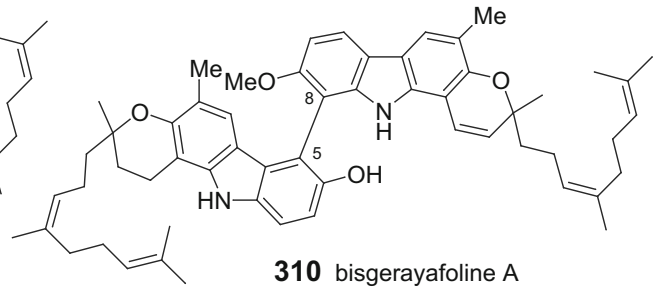


308 bisgerayafoline D
Uvarani et al. 2014
M. koenigii, Fruit pulp

Table 4 continued

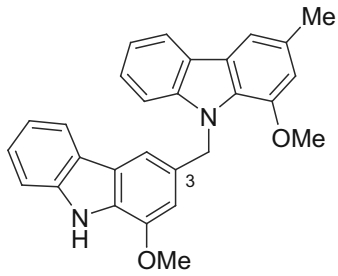


309 bisgerayafoline C
Uvarani et al. 2013
M. koenigii, Fruit pulp

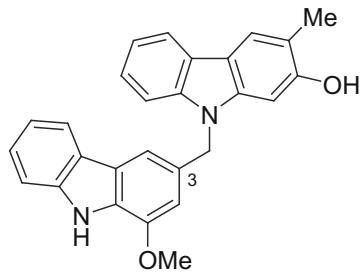


310 bisgerayafoline A
Uvarani et al. 2013
M. koenigii, Fruit pulp

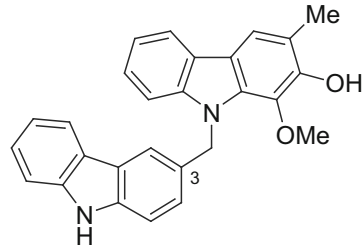
C *N*-Linked dimers



311 bismurrayafoline A
Furukawa et al. 1983
M. euchrestifolia, R

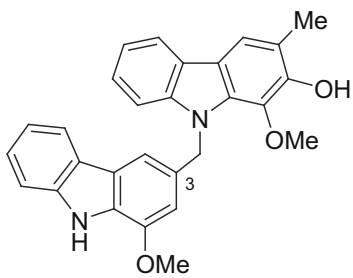


312 murradine G
Lv et al. 2015
M. tetramera, L+B

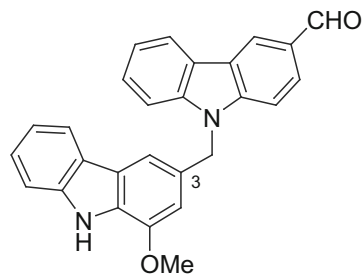


313 murradine F
Lv et al. 2015
M. tetramera, L+B

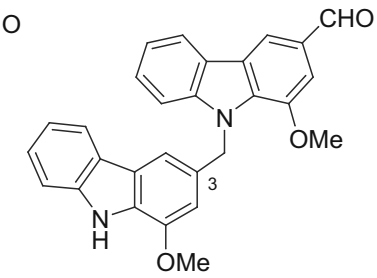
Table 4 continued



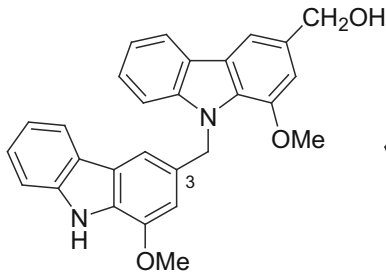
314 murradine E
Lv et al. 2015
M. tetramera, L+B



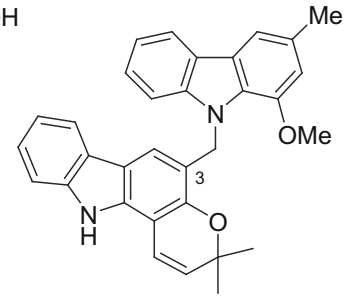
315 murradine H
Lv et al. 2015
M. tetramera, L+B



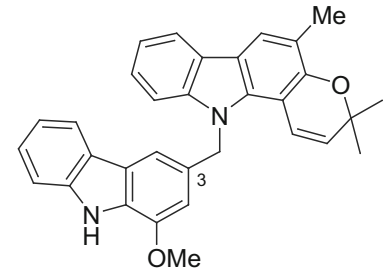
316 chrestifoline D
Ito et al.1992a
M. euchrestifolia, R



317 bismurrayafolinol
Ito et al. 1987
M. euchrestifolia, B

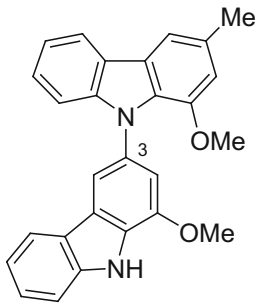


318 murrafoline E
Ito et al. 1988
M. euchrestifolia, R

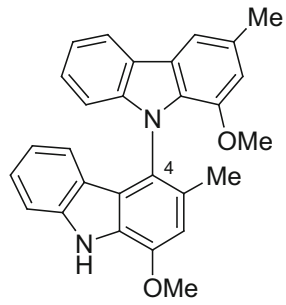


319 chrestifoline B
Ito et al. 1990
M. euchrestifolia, R

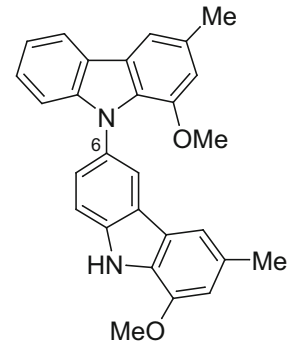
Table 4 continued



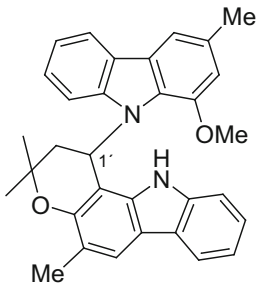
320 murrastifoline B
Ito et al. 1990
M. euchrestifolia, R



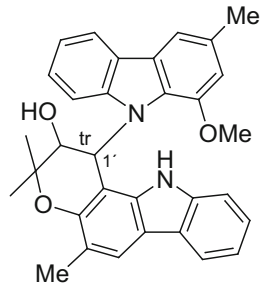
321 murrastifoline F
Ito et al. 1993
M. koenigii, R



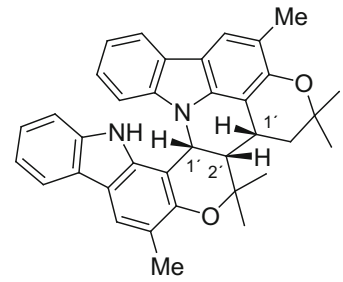
322 murrastifoline A
Ito et al. 1990
M. euchrestifolia, R



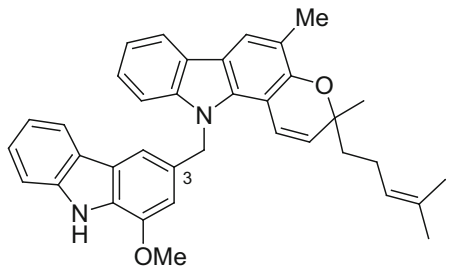
323 murrastifoline E
Ito & Furukawa 1990
M. euchrestifolia, R



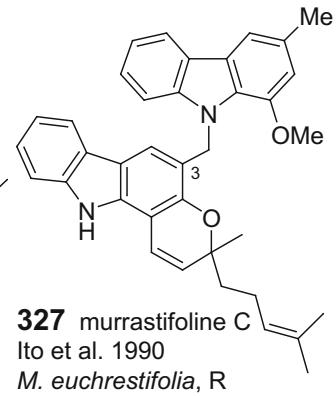
324 murrastifoline D
Ito & Furukawa 1990
M. euchrestifolia, R



325 murranimbine
Ito & Furukawa 1991
M. euchrestifolia, R



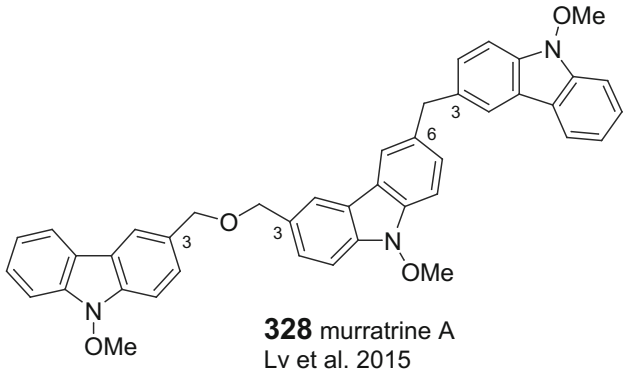
326 chrestifoline C
Ito et al. 1990
M. euchrestifolia, R



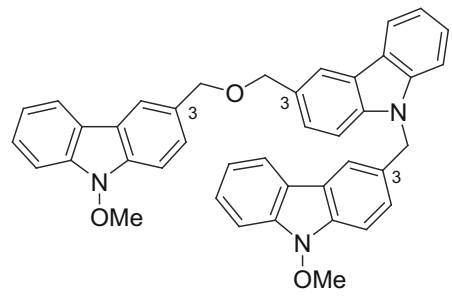
327 murrastifoline C
Ito et al. 1990
M. euchrestifolia, R

B bark, *R* root, *L* leaves, *S* seeds

Table 5 Trimeric carbazoles

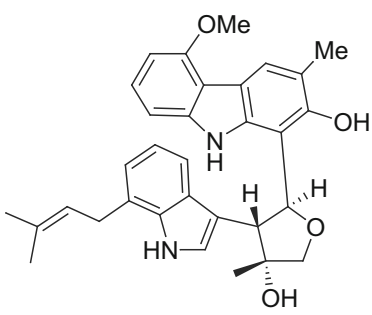


328 murratrine A
Lv et al. 2015
M. tetramera, L+B

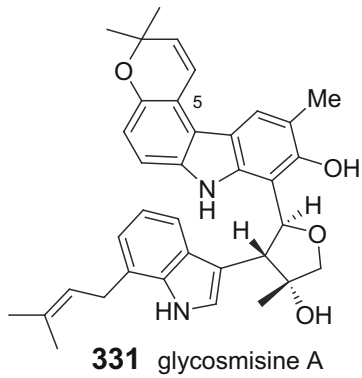


329 murratrine B
Lv et al. 2015
M. tetramera, L+B

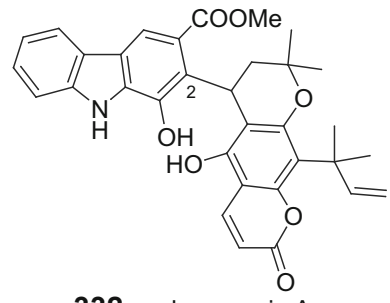
Table 6 Phytocarbazoles linked with different biogenetic moieties



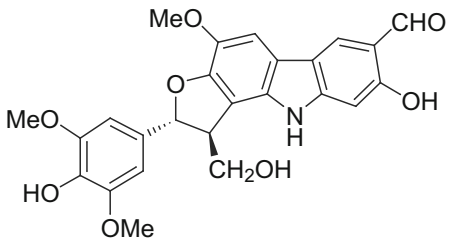
330 glycosmisine B
Chen et al. 2015
G. pentaphylla, B



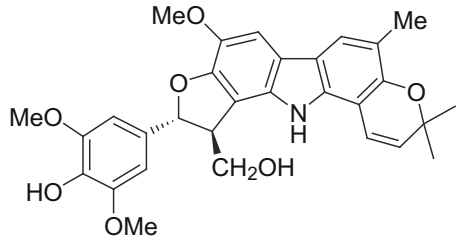
331 glycosmisine A
Chen et al. 2015
G. pentaphylla, B



332 carbazomarin A
Wu et al. 1996b
C. excavata, R



333 claulansine K
Deng et al. 2014
C. lansium, Fruit pulp



334 double named as ´murrayanine´
Wang et al. 2003
M. koenigii, Aerial parts

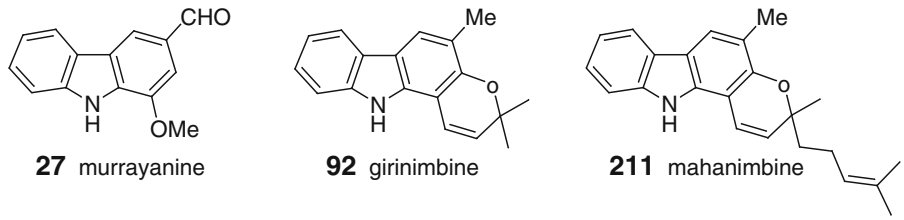


Fig. 2 Structures of the first three phytocarbazoles isolated from *Bergera* (=*Murraya*) *koenigii*

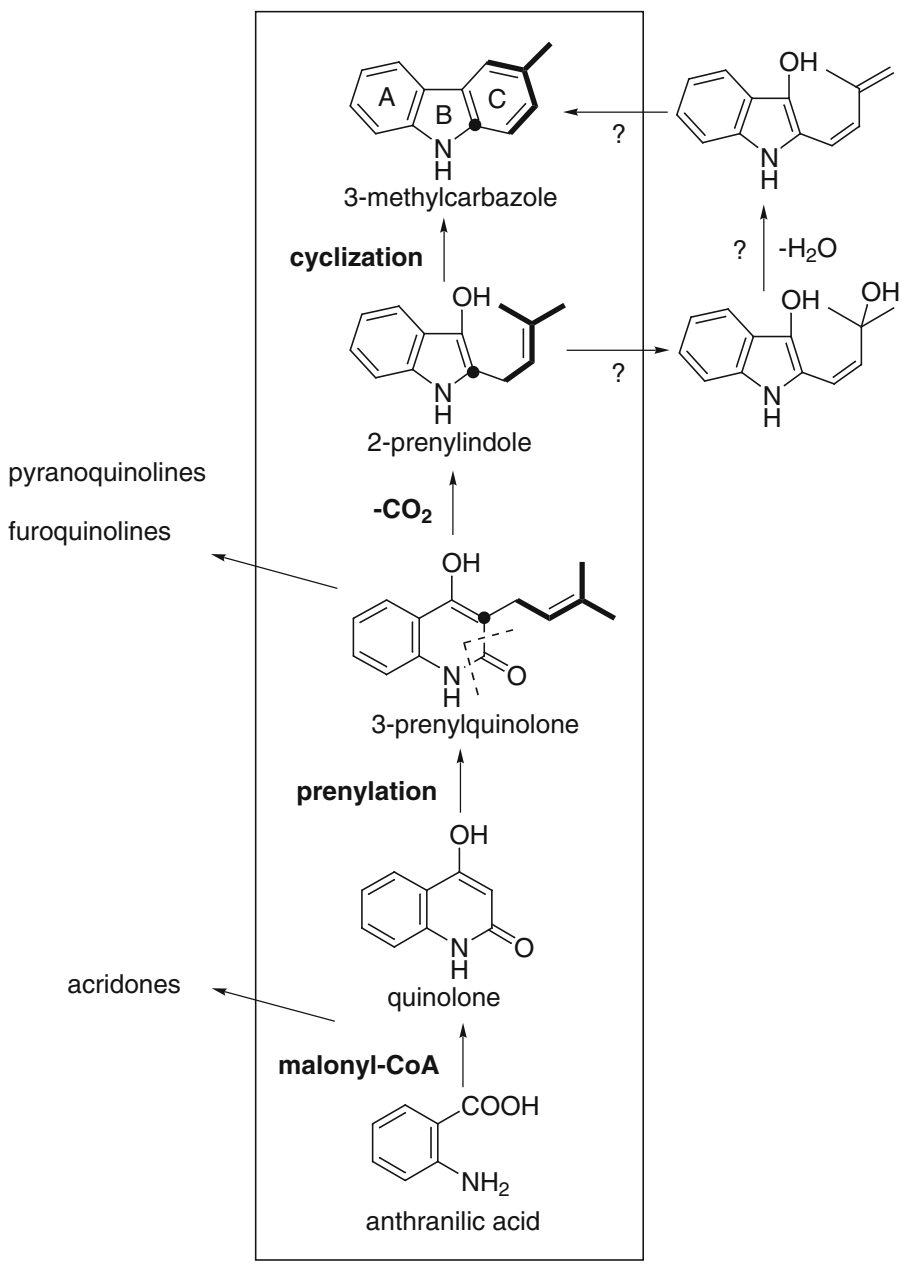


Fig. 3 Proposed biosynthetic pathway of 3-methylcarbazole

Of special biological interest was the discovery of the stress induced formation of carbazole phytoalexins suggesting an important ecological role of that type of alkaloids (Pacher et al. 2001).

In order to get an overview about the great variability of phytocarbazoles and to provide a quick visual reference guide for the different structures, all naturally occurring derivatives are grouped together in Tables 1, 2 and 3 according to their C_{13}-, C_{18}-, and C_{23}-basic skeleton. In addition, di- and trimeric derivatives are shown in Tables 4 and 5, respectively, whereas phytocarbazoles linked with other biogenetic moieties are presented in Table 6.

Structural relationships

To date not all steps in the biosynthesis of phytocarbazoles are confirmed experimentally, but the pathway depicted in Fig. 3 is now widely accepted. According to that anthranilic acid and malonyl-CoA form a 2-quinolone intermediate, which is prenylated at the nucleophilic *C*-3 position. The next steps are speculated to involve decarboxylation and the formation of 2-prenylindole (Lee et al. 1996; Schmidt et al. 2012). Since prenylation of indole at position *C*-2 is only rarely reported it should be pointed out that 2-dehydroprenylindole, previously only known as a synthetic product (Lee et al. 1996), was isolated from the roots of *Glycosmis macrophylla* (Blume) Miquel (=*G. sapindoides* Lindley) (Lukaseder 2000) and *G. parviflora* (Sims) Little (Bacher 1999; Pacher 2005). The following formation of the aromatic ring C is interpreted as cyclization product with the dehydroprenyl side chain (Fig. 3). A similar formation of a methylated aromatic ring involving a prenyl group with a conjugated diene system was already assumed for the quinolone derived phenaglydon isolated from *G. cyanocarpa* (Blume) Spreng. (Wurz et al. 1993). With regard to the still unconfirmed biosynthetic steps of phytocarbazole formation the alternative accumulation of pyranoquinolones in infected leaves of *G. parviflora* supports a common biosynthetic origin (Pacher et al. 2001).

2-Hydroxylation of 3-methylcarbazole (**1**) was suggested to play a key role in the biogenesis of many phytocarbazoles (Kureel et al. 1970b). Biomimetic studies have shown that hydroxylations are preferably attached at *C*-2 and *C*-1 position (Roy et al. 1982a). This is also suggested by the stress-induced formation of carbalexins A–C (**12**, **17**, **14**) together with 2-hydroxy-3-methylcarbazole (**4**) in *G. parviflora* (Pacher et al. 2001). As shown in the structural overview (Tables 1, 2, 3, 4, 5, 6), hydroxylations and methoxylations are found at almost each position of the two aromatic rings A and C with a noteworthy exception: they are generally missing at *C*-4, where in murrayaquinones A–E (**9**, **130**, **247**, **246**, **129**), koenigine-quinones A, B (**20**, **23**), pyrayaquinones A–C (**121**, **131**, **248**), bismurrayaquinone A (**269**), and bikoeni-quinone (**291**) only an oxygen atom is attached as part of a 1–4 quinoid system. In five derivatives (**53**, **88**, **271**, **285**, **289**) methoxylation is also shown to be linked to nitrogen.

Of taxonomic significance are the different oxidations of the characteristic *C*-3 methyl group leading either to the many 3-formylcarbazoles of the C_{13}, C_{18}, and C_{23} series (Tables 1B, 2B, 3B), or to corresponding 3-carboxylcarbazoles (Tables 1C, 2C, 3C) (Fig. 7). By contrast, only a few derivatives are reported with a 3-hydroxymethyl group (**79**, **80**, **88**, **180**, **181**, **317**) or the corresponding methyl- (**81**) and ethylether (**82**, **83**). The co-occurrence of the 3-hydroxymethyl carbazole mukoline (**80**) and its 3-formyl congener mukolidine (**33**) in the roots of *B. koenigii* suggested a biogenetic connection (Roy et al. 1982b). Taking into account the partial conversion of koenoline (**79**) to the corresponding formyl derivative murrayanine (**27**) on standing at room temperature, the rare reports on 3-hydroxymethyl derivatives might be explained by their labile nature (Fiebig et al. 1985). The loss of the characteristic carbon atom at position 3, interpreted as product of oxidative decarboxylation (Chowdhury et al. 1987), results in the two 3-hydroxycarbazoles murrastanine A (**77**) and clausenawalline D (**78**), as well as in carbazole itself (**75**) and clausine V (**76**). The linkages between *C*-3 and *C*-5 in the dimeric clausenawalline B (**293**) and between *C*-3 and *N* in murrastifoline B (**320**) may also be explained by a foregoing 3-decarboxylation of the corresponding monomeric units. The incorporation of an additional carbon atom into position *C*-8 of the basic skeleton leads to the rare C_{14}-derivatives **84**–**87** and the dimers **272** and **292** with an 8-formyl group. If this additional carbon in murrayakonine C (**217**) is represented either by the methyl or by the formyl group, remains unclear. A specific enzymatic activity was discussed for the formation of the unique *N*-formyl- (**89**) and *N*-

carbethoxy-3-methylcarbazole (**90**) (Kedderis et al. 1986; Chakrabarty et al. 1997).

Apart from different oxygenations and oxidations of the 3-methylcarbazole basic skeleton shown in Table 1 prenylations and geranylations play a major role in structural diversification (Tables 2, 3), most likely catalyzed by specific prenyltransferases (Winkelblech et al. 2015). The prenyl moieties are found at each position of the two aromatic rings A and C, but are preferably linked to positions *C*-1 and *C*-8 (Tables 2, 3, 4). Exceptions are a twofold insertion of a prenyl group each in the rings A and C, leading to the C_{23} carbazoles clausenawalline C (**264**) and clauszoline A (**265**), and the *N*-geranylation in karapinchamine A (**254**). Moreover, from the fruit pulp of *B. koenigii* the four dimeric bisgerayafolines A–D (**307**–**310**) were isolated, which deviate by the insertion of *C*-15 farnesyl groups (Uvarani et al. 2013, 2014). Unlike the co-occurring coumarins, where prenyl groups are frequently linked in a "reverse" way via their *C*-3′ (e.g. dentatine, nordentatine, clausarin), in phytocarbazoles they are solely connected in a "regular" way with *C*-1′. As in the co-occurring coumarins, quinolones, acridones, and flavonoids, prenyl groups give rise to the formation of pyrano and, to a lesser extent, furano carbazoles. The six- and five-membered carbazolelactones (Ito et al. 1998; Wu et al. 1998b), grouped together in Table 2D, can be interpreted as result of esterification between the 3-carboxyl group and the hydroxyl groups at 2′- or 1′-position, respectively, of the prenyl group. Consequently, lactonization with the hydroxyl group at *C*-3′ can be assumed for the formation of the seven-membered ring of clauemarazole C (**198**) and the related derivatives **186**–**190** with an additional ether bridge. Transformations of the geranyl side chain in the C_{23} series contribute to a great variety of complex derivatives generating various ring systems (Fig. 4; Table 3A, B).

The formation of dimeric phytocarbazoles in plants was already expected by biomimetic studies (Roy et al. 1982a). The first derivatives bismurrayafolines A, B (**311**, **275**) (Furukawa et al. 1983), and murrafoline A (**303**) (McPhail et al. 1983) were isolated from the roots of "*Murraya*" *euchrestifolia* Hayata.[1] In the meantime 61 bis-carbazoles have been isolated most likely representing products of oxidative dimerisation (Wu et al. 1991). They are grouped together in Table 4 according to the various combinations of monomeric units: in the symmetrical dimers two identical monomers are linked to each other via the corresponding positions at *C*-1, *C*-2, *C*-3, *C*-8, and *C*-8′ (Table 4A), whereas in the asymmetrical dimers different monomers are attached to almost each position (Table 4B). The *N*-linked dimers are presented separately in Table 4C. They are additionally characterized by frequent combinations with the *C*-3 methyl group of the second monomer. Two structurally unique trimeric phytocarbazoles, murratrines A (**328**) and B (**329**), were recently isolated from the leaves and stems of the Chinese "*Murraya*" (sect. Bergera) *tetramera* C. C. Huang together with 15 dimers (Lv et al. 2015) (Table 5).

The phytocarbazoles shown in Table 6 contain building blocks originating from different biosynthetic pathways. Carbazomarin A (**332**) from the roots of *Clausena excavata* Burm. f. is characterized by an incorporation of a pyranocoumarin moiety (Wu et al. 1996b). The double named "murrayanin" (**334**) from the aerial parts of *B. koenigii*, collected in Yunnan province (P. R. China), contains a phenylpropanyl unit linked to koenigine (**99**) (Wang et al. 2003). This building block was also found to be linked to claulansine J (**51**), forming claulansine K (**333**), which was isolated from the fruit peels of *C. lansium* (Lour.) Skeels, known as "Wampee" in China (Deng et al. 2014). In a subsequent investigation **333** was isolated as a mixture of two enantiomers in equal amounts (Du et al. 2015). The glycosmisines A (**331**) and B (**330**) from the stem bark of *Glycosmis pentaphylla* (Retz.) DC. deviate by an incorporation of a prenylindol moiety (Chen et al. 2015) (see "Appendix").

Biological activities

Antimicrobial properties

The nitrogen-containing aromatic heterocyclic system of carbazoles possessing desirable electronic and charge-transport properties represents the structural basis for many biological activities (Zhang et al. 2010). Preliminary bioassays with phytocarbazoles for antimicrobial properties were carried out initially by Chakraborty and co-workers using the standard agar-

[1] as a member of the section Bergera *M. euchrestifolia* should be placed in the genus *Bergera* (Samuel et al. 2001).

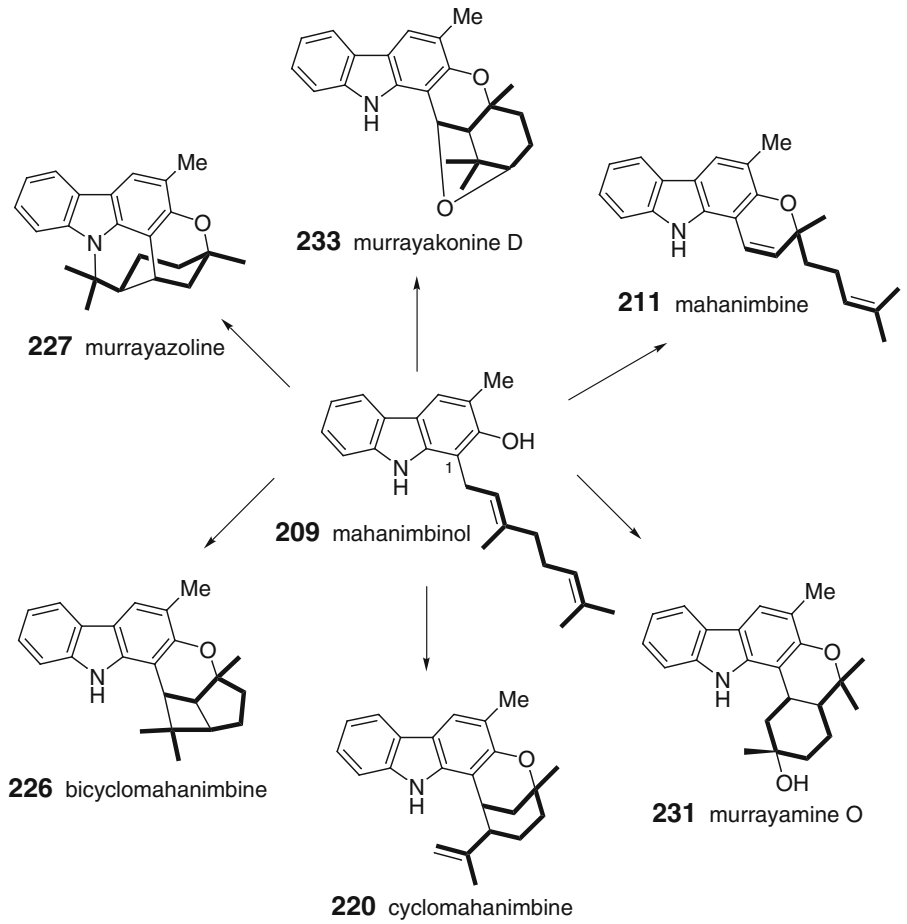


Fig. 4 Transformations of the geranyl moiety by various cyclizations

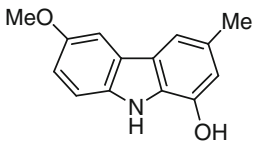
cup assay method with nutrient agar for bacterial strains and Sabouraud's medium for fungal strains. Although the activities were only moderate in comparison to standard antibiotics used in practice, considerable activities against the human pathogenic fungi *Microsporum gypseum*, *Trichophyton rubrum*, *Candida albicans* and the Gram-positive bacterium *Nocardia asteroides* were shown for murrayanine (**27**), girinimbine (**92**), and mahanimbine (**211**) (Das et al. 1965) (Fig. 2). Comparing the minimum inhibition zones of some related derivatives glycozolinine (**7**) exhibited the highest activity, especially against *M. gypseum* and *T. rubrum* (Chakraborty et al. 1975). The 2-methoxylated glycozolidol (**15**) from the roots of *G. pentaphylla* showed more activity against Gram-positive bacteria than against Gram-negative ones (Bhattacharyya et al. 1985). In a disc diffusion assay against different bacteria activities were observed for the C_{23} derivatives murrayanol (**242**) and pyrayafoline D (=isomahanine) (**244**) from leaves of *B. koenigii* (Nutan et al.1998). Minimum inhibitory concentration (MIC) values against both types of bacteria and fungi were determined for clausenalene (**19**) from the stem bark of *C. heptaphylla* (Bhattacharyya et al. 1993) and for clausenal (**41**) from the leaves (Chakraborty et al. 1995a). The latter revealed pronounced activities against both Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*), and fungi (*T. rubrum*, *C. albicans*) with MIC-values ranging from 3 to 25 µg/ml. Similar values against these organisms were obtained for clausenol (**10**) from the stem bark of *C. anisata* (Chakraborty et al. 1995b), and 6,7-dimethoxy-1-hydroxy-3-methylcarbazole (**21**) from the leaves of *B. koenigii* (Chowdhury et al. 2001) (Table 7).

Comparative bioassays with stem bark carbazoles from *B. koenigii* revealed the strongest activity for girinimbine (**92**) against the Gram-positive *S. aureus* (MIC = 3.17 μg/ml), whereas the newly described dimeric carbazole **271** was the most potent compound against the Gram-negative *E. coli* (MIC = 25 μg/ml) and *Proteus vulgaris* (MIC = 6.25 μg/ml) as well as against the fungi *Apergillus niger* and *C. albicans* (MIC = 25 μg/ml) (Rahman and Gray 2005) (Table 7).

A bioassay guided fractionation of the leaf extract of *B. koenigii* resulted in the three active C_{23}-derivatives mahanimbine (**211**), mahanine (**214**), and murrayanol (**242**) when tested against *Candida kruseii*, *C. parapsilasis*, *E. coli*, *S. aureus* and *Streptococcus pyogenes*. The most active compound was **214** with MIC_{100}-values of 100 μg/ml against *C. kruseii*, *C. parapsilasis*, and *E. coli*, but 25 μg/ml against *S. aureus* and *S. pyogenes*, whereas **211** was least active with an MIC_{100} of 50 μg/ml against *S. aureus* and *S. pyogenes*, and no activity against the other organisms tested. These differences were speculated to be attributed to the free phenolic OH-group and the inhibition of topoisomerase I and II activities (Ramsewak et al. 1999). Similar results of leaf carbazoles from *B. koenigii* were later reported by Nagappan et al. (2011). The activities of compounds **214**, **211**, and its isomer (+) mahanimbicine (**239b**) were tested against antibiotic resistant bacterial strains involving the evaluation of the diameter of inhibition zone, minimum inhibition concentration (MIC), and minimum bactericidal concentration. In spite of the similar structures selective activities were shown for the three derivatives with the highest MIC value at 12.5 μg/ml for **214**, and the lowest at 175 μg/ml for **211** against *Streptococcus pneumoniae*.

The C_{13}-derivatives 7-methoxymukonal (**46**) and methyl carbazole-3-carboxylate (**60**), isolated from rhizomes and roots, respectively, of *Clausena excavata* exhibited significant antifungal activities against *C. albicans* with IC_{50}-values at 2.8 μg/ml for **46** and 9.5 μg/ml for **60**. In addition, the latter showed moderate activities (MIC = 50 μg/ml) against *Mycobacterium tuberculosis* (Sunthitikawinsakul et al. 2003). Higher anti-tuberculosis activities were reported for lansine (**43**), 3-formyl-6-methoxycarbazole (**30**), micromeline (**162**), and 3-formylcarbazole (**25**) from the stem bark of *Micromelum hirsutum* Oliv. Their MIC_{90} values against the *M. tuberculosis* strain H37Rv were 14.3, 15.6, 31.5, and 42.3 μg/ml, respectively (Ma et al. 2005). Based on these results a comparison of the activities of a series of naturally occurring and synthetic carbazoles informed about structure–activity relationships and the in vitro cytotoxicities against Vero cells (Choi et al. 2006, 2008). Due to the anti-periodontopathogenic activity against the Gram negative *Porphyromonas gingivalis*, the compounds **43**, **30**, and glycozolidal (**44**) deserve some interest for use in the treatment of periodontal diseases (Rodanant et al. 2015). 7-Hydroxyheptaphylline (**134**) and the dimeric clausenawallines B (**293**), and E (**294**), isolated from the roots of *C. wallichii* Oliv. showed pronounced antibacterial activity against the *S. aureus* strain TISTR 1466 with an MIC value at 8 μg/ml. Compound **134** was even more active against the methicillin-resistent *strain* SK1 with an MIC at 4 μg/ml, whereas **293** was weaker with 16 μg/ml. By contrast, all three derivatives were less active against the Gram-negative *E. coli* TISTR 780 and *Salmonella typhimurium* TISTR 292 with MIC values at 128 μg/ml for **293** and **294**, and 64 μg/ml for **134** (Maneerat et al. 2012b). Six phytocarbazoles from the roots of *Clausena harmandiana* (Pierre) Guillaumin were tested for their activity against the oomycete *Pythium insidiosum*, the causative agent of the granulomatous disease pythiosis. In a disc diffusion assay clausine L (**64**) and especially clausine K (**59**) exhibited higher inhibition of the mycelial growth compared to the commercial antifungal agents terbinafine and itraconazole (Sriphana et al. 2013). Pronounced antibacterial activities against *Shigella flexneri* 2a and *S. aureus* ATCC 25923 (MIC = 64 μg/ml) as well as against different strains of *Vibrio cholerae* (MIC = 32–128 μg/ml) were reported for murrayamine A (**95**) isolated from *C. anisata* (Tatsimo et al. 2015). A reinvestigation of the antimicrobial activities of carbazoles from *B. koenigii* exhibited prominent IC_{50} values at 3.4 and 10.9 μmol for girinimbine (**92**) and 1-hydroxy-7-methoxy-8-prenyl-3-formylcarbazole (**170**), respectively, against *Bacillus cereus* IIIM 25, and moderate activities at 11.7, 17.0, and 20.9 μmol for murrayamine J (**260**), koenimbine (**94**), and koenigicine (**100**), respectively, against *S. aureus* ATCC 29213 (Nalli et al. 2016).

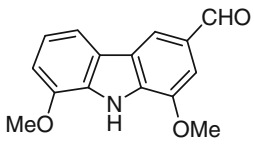
Table 7 Structures with pronounced antimicrobial properties



10 clausenol

	MIC [µg/ml]
Escherichia coli	**7**
Salmonella typhi	**12**
Pseudomonas aeruginosa	**14**
Bacillus subtilis	**14**
Staphylococcus aureus	**1.3**
Candida albicans	**5**
Trichophyton rubrum	**2**

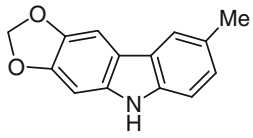
(Chakraborty et al. 1995b)



41 clausenal

Escherichia coli	**6**
Salmonella typhi	**25**
Pseudomonas aeruginosa	**20**
Bacillus subtilis	**18**
Staphylococcus aureus	**3**
Candida albicans	**8**
Trichophyton rubrum	**3**

(Chakraborty et al. 1995a)

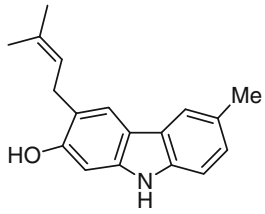


19 clausenalene

Escherichia coli	**25**
Proteus vulgaris	**20**
Bacillus subtilis	**15**
Staphylococcus aureus	**33**
Micrococcus luteus	**18**

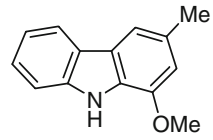
(Bhattacharyya et al. 1993)

Activities against phytopathogenic fungi



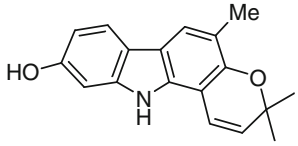
117 siamenol

EC_{50} 0.7 µg/ml, EC_{90} 45 µg/ml



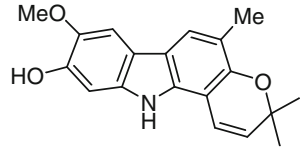
3 murrayafoline A

EC_{50} 2 µg/ml, EC_{90} 32 µg/ml



95 murrayamine A

EC_{50} 3 µg/ml, *EC_{90} 54 µg/ml*



99 koenigine

EC_{50} 22 µg/ml, EC_{90} 262 µg/ml

Effective concentration (EC)-values were determined in a germ-tube inhibition test against *Curvularia eragrostidis* (Pemmer 2002)

Activities against phytopathogenic fungi

In contrast to the activities reported for murrayanine (**27**), girinimbine (**92**), and mahanimbine (**211**) against human pathogenic fungi their antibiotic action against some plant pathogenic fungi was not promising (Das et al. 1965). These findings were also confirmed in the author's laboratory by biotests against the facultative phytopathogenic fungi *Cladosporium herbarum* (Pers.) Link and *Curvularia eragrostidis* Boedijn. In bioautography on TLC plates sprayed with a conidial suspension of *C. herbarum* no activities were observed for girinimbine (**92**) and mahanimbine (**211**), but clear inhibition spots were shown for siamenol (**117**) from the leaves and fruits of "*Murraya*" (=*Bergera*) *siamensis* Craib and for murrayafoline A (**3**) from the underground parts. More detailed information about the different activities were obtained with germtube inhibition tests against *C. eragrostidis* showing EC_{50} values at 0.7 µg/ml for **117**, and 2 µg/ml for **3** (Pemmer, 2002) (Table 7). The fungicidal activity of **3** was compared with that of three further 1-oxygenated derivatives, the demethylated 1-hydroxy-3-methylcarbazole (**2**), and the synthetic 1-*O*-prenylated and 1-*O*-glycoyslated 3-methylcarbazoles. Growth inhibition areas against the phytopathogenic fungus *Cladosporium cucumerinum* Ell. et Arth. at dose of 12.5 µg exhibited the highest activity for **3** (213 mm^2) followed by **2** (205 mm^2) and the 1-*O*-prenylated derivative (95 mm^2). No inhibition zone was observed for the 1-*O*-glycosylated derivative (Cuong et al. 2008).

As shown in the literature and in broad-based phytochemical analyses in the author's laboratory phytocarbazoles of the genus *Glycosmis* are mainly accumulated in the stem bark and to a lesser extent in the roots, but are rarely found in the leaves (Kamaruzzman and Chakraborty 1989; Greger et al. 1992). However, wounding, UV-irradiation, and especially infection with the fungus *Botrytis cinerea* resulted in an accumulation of phytocarbazoles in the leaves of *G. parviflora* and *G. pentaphylla*. Since the isolated carbalexins A, B, C (**12**, **17**, **14**) and 2-hydroxy-3-methylcarbazole (**4**) displayed pronounced antifungal activity in bioautographic tests on TLC plates against *C. herbarum*, they were regarded as a new class of phytoalexins (Pacher et al. 2001). In view of these results the previously published glycozolidol (**15**) (Greger et al. 1992) was also suggested to be formed after induction. This hypothesis could later be confirmed by reinvestigation of small samples of the corresponding (10 years-old!) hebarium material exhibiting an accumulation of **15** only in infested leaves, whereas intact leaves of the same individual did not show any carbazole. Comparing the structures of **12**, **14**, and **17** with **4** it was tempting to suggest that their antifungal properties were due to the free hydroxy group at *C*-2. However, the very weak activity of the co-occurring glycoborinine (**114**) containing such a hydroxy group but an additionally condensed pyran ring in aromatic ring A demonstrated that other substitutions also play an important role in bioactivity (Fig. 5) (Pacher et al. 2001).

Antiprotozoal activities

A series of natural and synthetic carbazoles were tested for activity against *Plasmodium falciparum*. 1-Hydroxy-3-methylcarbazole (**2**), isolated from *M. euchrestifolia*, exhibited promising antiplasmodial activity in vitro with an IC_{50} value at 7.62 µg/ml, whereas the 1-O-methylated derivative murrayafoline A (**3**) were virtually inactive. Interestingly, the synthetic 1,4-diacetoxy-3-methylcarbazole gave the highest activity in this series with an IC_{50} at 1.79 µg/ml. The results suggested that either the free phenolic hydroxy group of **3** is not required for the high activity or that the ester functionalities are cleaved by *P. falciparum* (Bringmann et al. 1998b). Similar antiplasmodial activities were reported for different carbazoles from *Clausena* species: IC_{50} values at 3.2–6.4 and 5.5–10.7 µg/ml were determined for heptaphylline (**131**) and clausine H (**74**), respectively (Yenjai et al. 2000), and at 2.46 µg/ml for the dimeric clausenawalline A (**273**) (Maneerat et al. 2011). Significant activities against the *P. falciparum* strain K1 were determined for mukonal (**28**), clauszoline K (**32**) and glycoborinine (**114**) with IC_{50} values at 4.03, 3.46, and 3.41 µg/ml, respectively (Auranwiwat et al. 2014), and a MIC value at 6.74 µg/ml for glycosinine (**29**) (Sripisut and Laphookhieo 2010). The leaf extract of *B. koenigii* exhibited activity against *Trichomonas gallinae*. A comparison between eight isolated and four structurally modified carbazoles provided information about structure–activity relationships. The C_{18}-derivatives girinimbine (**92**) and mukoenine A (=girinimbilol) (**91**) were the most active with IC_{50}

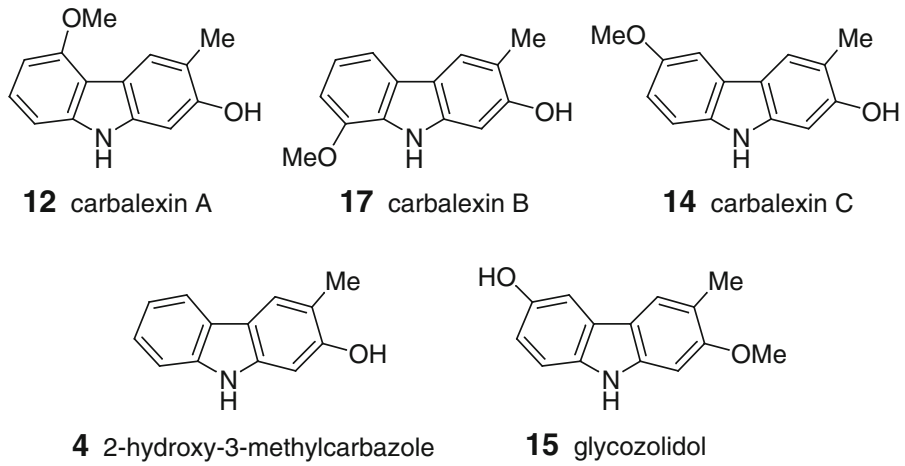


Fig. 5 Stress induced carbazole phytoalexins from Glycosmis species (Pacher et al. 2001)

values at 1.08 and 1.20 μg/ml, respectively. Concerning the different basic skeletons of the derivatives the order of activity was $C_{18} > C_{23} > C_{13}$. Insertion of a 7-OH group into mahanimbine (**211**) reduced the activity by about 29 and 27% at 24 and 48 h, respectively. Interestingly, acetylation of the OH-group in **91** and mahanimbinol (**209**) improved their activities from 1.20 and 4.00 to 0.60 and 1.08 μg/ml, respectively (Adebajo et al. 2006). The anti-trichomonal activity of 3-formylcarbazole (**25**), isolated from the stem bark of *C. lansium*, was determined with LC_{50} and LC_{90} values at 3.6 and 243.9 μg/ml, respectively, after 24 h, and at 9.7 and 41.4 μg/ml after 48 h (Adebajo et al. 2009). Lansine (**43**) was investigated for its activity against *Leishmania donovani*, the causative agent of visceral leishmaniasis. The synthesis of a series of analogues, and the rational modifications made at positions *C*-2, *C*-3, *C*-6, and *N* allowed to elucidate plausible structure–activity relationships with respect to their antileishmanial activity. Six derivatives demonstrated improved potency against *L. donovani* promastigotes in comparison to **43**, and four also significantly enhanced activity against axenic amastigotes (Pieroni et al. 2012).

Insecticidal activities

Mosquitocidal assays against larvae of *Aedes aegyptii* exhibited high activity for the three carbazoles mahanimbine (**211**), mahanine (**214**), and murrayanol (**242**). The two compounds **214** and **242**, possessing a free phenolic OH group, had an LD_{100} (24 h) at 12.5 μg/ml, while **211** showed 100% mortality at 100 μg/ml. Compound **211** showed 20% mortality at 6.25 μg/ml, while **214** and **242** showed 49 and 69% mortality, respectively, at 1 μg/ml (Ramsewak et al. 1999).

Cytotoxic activities

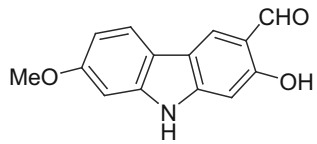
In the search for new naturally occurring cytotoxic antitumor compounds many carbazole alkaloids turned out to act as cell cycle inhibitors or apoptosis inducers (Shaikh et al. 2015). Initially, bioassays have focused on phytocarbazoles isolated from *B. koenigii* and the closely related *M. euchrestifolia* which were tested against cultured nasopharyngeal carcinoma (KB) cells. Significant cytotoxicity was observed for koenoline (**79**) and murrayanine (**27**) from the roots of *B. koenigii* with ED_{50} values at 4.0 and 26 μg/ml, respectively (Fiebig et al. 1985), and for murrayamine A (**95**) and (+) mahanine (**214**) from the leaves of *M. euchrestifolia* at 3.0 and 3.3 μg/ml, respectively (Wu 1991). Among the six pyranocarbazoles **94**, **214**, **215**, **277**, **305**, and **308** from the fruit pulp of *B. koenigii* an increased cytotoxicty of mahanine (**214**) was reported against human cervical cancer (HeLa), stomach adenocarcinoma (AGS), and colorectal adenocarcinoma (HCT-116) cells, showing only weak activity against normal mouse embryonic fibroblasts (NIH3T3). In this connection the interactive behavior of the six carbazoles with calf thymus DNA was also evaluated. It was found that pyranocarbazoles containing either

prenyl or geranyl moieties possessed more DNA binding properties than the parent compound suggesting that the cyclic planar part can intercalate with DNA while the prenyl or geranyl residue interacts externally with the minor groove of DNA. The higher binding constants of **214** also indicated stronger interaction between **214** and DNA (Uvarani et al. 2014). In a broad-based screening of 20 carbazoles against a panel of about 60 tumor cell lines murrayaquinone A (**9**) from the roots of *M. euchrestifolia* had a broad cytotoxic profile against KB, melanoma (SK-MEL-5), colon carcinoma (Colo-205), and ileocecal adenocarcinoma (HCT-8) cells with ED_{50} values at 5.18, 2.58, 3.85, and 5.50 μg/ml, respectively (Itoigawa et al. 2000). Another cytotoxic carbazole quinone, clausenaquinone A (**24**), previously isolated from the stem bark of *C. excavata*, also exhibited significant activity against HCT-8, malignant melanoma (RPMI7951), and rhabdomyosarcoma (TE671) cell lines with IC_{50} values at 0.92, 0.22, and 3.82 μg/ml, respectively (Wu et al. 1994). These results suggest that carbazole quinone derivatives have potential as cytotoxic agents with cell line selectivity (Table 8).

As shown in Table 8 different phytocarbazoles were tested against a panel of cancer cell lines. Apart from the active carbazole quinones **9** and **24**, the majority of active derivatives are characterized by a 3-formyl and 2-hydroxy substitution. Increased cytotoxicity was observed by *C*-1-prenylation in 7-methoxyheptaphylline (**135**) against four different cell lines compared to methoxymukonal (**46**) (Chaichantipyuth et al. 1988), and by *C*-4-prenylation in clausine D (**160**) compared to *O*-demethylmurrayanine (**26**) (Jiang et al. 2014). On the other hand, unprenylated **46** exhibited a high IC_{50} value at 1.74 μg/ml against KB cells compared to the weak activities of the related *C*-1-prenylated heptazoline (**136**) (Thongthoom et al. 2010) and heptaphylline (**132**) (Sripisut et al. 2012) at 23.54 and 26.31 μg/ml, respectively (Table 8). Dramatic differences in activity against small cell lung cancer (NCI-H187) and KB cells were shown between the three *C*-1-prenylated heptaphylline derivatives **132**, **134**, and **135**, differing only in *C*-7-substitution: heptaphylline (**132**) and its 7-methoxy derivative **135** exhibited strong cytotoxicity against NCI-H187 cells with IC_{50} values at 1.32 and 1.68 μmol, respectively, and at 1.61 and 2.75 μmol against KB cells. By contrast, the 7-hydroxylated **134** showed about 8- to 17-fold weaker activity at 14.59 and 27.9 μmol (Songsiang et al. 2011). Significant cytotoxic effects against breast cancer (MCF-7) cells were determined for lansine (**43**) and glycozolidal (**44**) from the roots of *C. lansium* both with an IC_{50} value at 0.78 μg/ml, which is higher active than the standard drug doxorubicin with 1.25 μg/ml. Also strongly active were the co-occurring mafaicheenamines A (**183**), E (**196**), and murrayanine (**27**) with IC_{50} values at 2.96, 3.1, and 3.76 μg/ml, respectively (Maneerat and Laphookhieo 2010; Maneerat et al. 2012a). A selective cytotoxic activity of clausine TY (**73**) from the bark of *C. excavata* was reported against T-lymphoblastic leukemia (CEM-SS) ($IC_{50} = 8.2$ μg/ml) (Taufiq-Yap et al. 2007), and a moderate activity of clausamine E (**176**) against promyelocytic leukemia (HL-60) cells (Ito et al. 2009). Using cell-based small molecule screening an anti-proliferative effect of murrayafoline A (**3**) on colon cancer cells was detected. It was shown that it suppressed Wnt/β-catenin signaling by promoting the degradation of β-catenin (Choi et al. 2010). The two recently described carbazoles murrastinine C (**166**) and murrayatanine A (**222**), isolated from the leaves and stems of *B. koenigii* collected in Malaysia, exhibited potent cytotoxic activity via the colorimetric (MTT) assay against HL-60 and HeLa cells, with CD_{50} values less than 20 μg/ml (Tan et al. 2015). Significant activity of murrayamine A (**95**) against HeLa cells was recently reported with an LC_{50} value at 3.26 μg/ml showing no toxicity to Vero cells (Tatsimo et al. 2015).

In continuation of their screening for antitumor-promoting agents in the family Rutaceae Ito et al. (2000) reported on potent inhibitory effects of phytocarbazoles from *C. anisata*. The activity was determined by assaying the capability to inhibit the expression of early antigen of Epstein-Barr virus (EA-EBV) in Raji cells which was induced by the tumor promoter phorbol 12-myristate 13-acetate (PMA). In the structure activity relationship analysis of nine active carbazoles prenylation at *C*-4 was shown to play an important role for inhibitory activity and especially ekeberginine (**161**) might be valuable as antitumor promoter in chemical carcinogenesis. Using the same test system, four carbazoles from the stem bark of *G. pentaphylla* (syn.: *G. arborea* (Roxb.) DC) showed weak dose-dependent inhibitory effects: glybomines B (**113**) and C (**112**) with an open prenyl group at *C*-5 were more effective at all concentrations

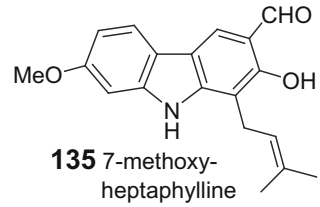
Table 8 Structures with significant cytotoxic activity against different tumor cell lines



46 7-methoxymukonal
(= 2-hydroxy-3-formyl-7-methoxycarbazole)

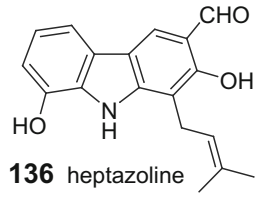
IC_{50} [μg/ml]:
1.74 KB
2.21 MCF-7
15.68 NCI-H187
15.68 Vero cells
(Thongthoom et al. 2010)

ED_{50} [μg/ml]:
5.70 9KB
4.48 KBMRI
2.74 A-549
4.00 HT-29
(Chaichantipyut et al.1988)



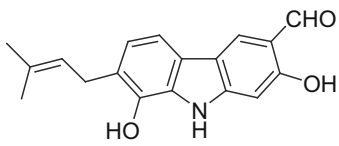
135 7-methoxy-heptaphylline

ED_{50} [μg/ml]:
3.01 9KB
2.87 KBMRI
2.16 A-549
1.36 HT-29
(Chaichantipyut et al. 1988)



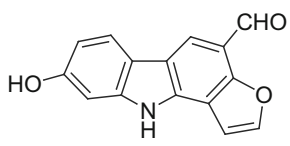
136 heptazoline

IC_{50} [μg/ml]:
23.54 KB
4.83 MCF-7
1.63 NCI-H187
15.50 Vero cells
(Thongthoom et al. 2010)



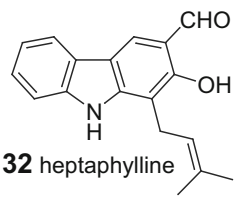
165 excavatine A

IC_{50} [μg/ml]:
5.25 A-549
1.91 HeLa
(Peng et al. 2013)



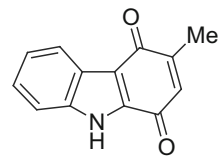
154 furoclausine A

IC_{50} [μg/ml]:
1.35 KB
7.44 NCI-H187
5.60 Vero cells
(Auranwiwat et al. 2014)



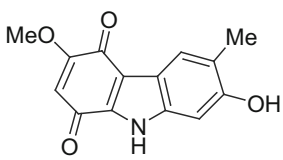
132 heptaphylline

IC_{50} [μg/ml]:
26.31 KB
47.75 MCF-7
5.65 NCI-H187
(Sripisut et al. 2012)



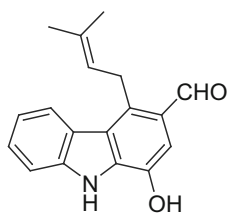
9 murrayaquinone A

ED_{50} [μg/ml]:
5.18 KB
2.58 SK-MEL-5
3.85 Colo-205
5.50 HCT-8
(Itoigawa et al. 2000)



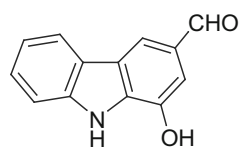
24 clausenaquinone A

IC_{50} [μg/ml]:
0.92 HCT-8
0.22 RPMI-7951
3.82 TE671
(Wu et al. 1994)



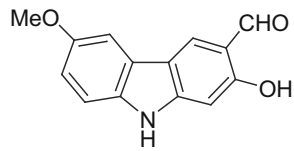
160 clausine D

IC_{50} [μg/ml]:
3.72 H1299
2.63 MCF-7
3.38 SMMC-7721
(Jiang et al. 2014)



26 *O*-demethylmurrayanine

IC_{50} [μg/ml]:
22.10 H1299
4.42 MCF-7
7.59 SMMC-7721
(Jiang et al. 2014)



43 lansine

IC_{50} [μg/ml]:
6.84 KB
0.78 MCF-7
7.74 NCI-H187
(Maneerat & Laphookhieo 2010)

A-549 = lung adenocarcinoma; Colo-205 = colon carcinoma; H1299 = non-small lung carcinoma; HCT-8 = ileocecal adenocarcinoma; HeLa = cervical cancer; HT-29 = colon adenocarcinoma; KB, 9KB, KBMRI = nasopharyngeal carcinoma; MCF-7 = breast cancer; NCI-H187 = small-cell lung cancer; RPMI-7951, SK-MEL-5 = melanoma; SMMC-7721 liver cancer; TE-671 = rhabdomyosarcoma; Vero cells = normal kidney cells from African green monkey

than glycoborinine (**114**) and glycozolidine (**16**) (Ito et al. 2004). Kok et al. (2012) reported on the strong effect of girinimbine (**92**) on EA-EPV activation and the viability of Raji cells.

Cell cycle inhibition and apoptosis induction

In the course of a screening for new cell cycle inhibitors and apoptosis inducers Cui et al. (2002) examined more than thousand Chinese medicinal plants and found that *C. dunniana* H. Levl. exhibited strong activity in inducing apoptosis and inhibiting cell cycle at the G2/M phase on mouse tsFT210 cells. Bioassay-guided fractionation of the stem extract led to the isolation of the four 3-methylcarbazoles murrayafoline A (**3**), girinimbine (**92**), mahanimibine (**211**), and bicyclomahanimbine (**226**). Their activities were assayed by flow cytometry accompanied with morphological observation of the cells and their nuclei by light and fluorescent microscopy. Induction of apoptosis was observed in all four alkaloids with MIC values at 1.56, 25, 20, and 30 μg/ml for **3**, **92**, **211**, and **226**, respectively, while pronounced cell cycle inhibition in M-phase was determined for **3** with an MIC value 0.78 μg/ml (Cui et al. 2002). The antiproliferative and apoptosis inducing mechanisms of girinimbine (**92**) were later determined in-depth with colorectal carcinoma (HCT-15) (Wang et al. 2008) and human liver cancer (HepG2) cells (Syam et al. 2011). Among thirteen carbazoles from the bark of *M. euchrestifolia* murrayafoline A (**3**) and murrayazolinine (**224**) exhibited significant growth suppression in human promyelocytic leukemia (HL)-60 cells due to apoptosis mediated by the activation of the caspase-9/caspase-3 pathway (Ito et al. 2012). From *C. vestita* D. D. Tao eleven carbazoles were evaluated for their growth inhibitory activities against human liver cancer (HepG2). The various IC_{50} values revealed that the activities were significantly affected by structural modifications of the compounds showing the highest values for clauszoline K (**32**) at 4.23 μmol, 2-hydroxy-3-methylcarbazole (**4**) at 14.4 μmol, and clausine E (=clauszoline I) (**61**) at 15.8 μmol. Since clausine E (**61**) showed almost no cytotoxic effect against the normal liver cell line LO2 compared to **32** and **4**, its potential anti-tumor activity and underlying mechanism as a novel anti-cancer drug was further investigated against HeLa, glioblastoma (T98G), nasopharyngeal carcinoma (CNE2), and hormon-independent breast cancer (MDA-MB-231). As a result clausine E (**61**) showed significant anti-tumor activity against all four cancer cell lines through its ability to induce cell cycle arrest in the S and G2/M phases (Lin et al. 2012). By contrast, a dramatic loss of activity against five human cancer cell lines was observed by 1-*O*-methylation in mukonine (**62**) (Liger et al. 2007). A reinvestigation of the anti-tumor activity of glycoborinine (**114**) (Ito et al. 2004), aimed at finding out the cell-signaling pathway related to its activity against human liver cancer (HepG2). It was shown that **114** could induce HepG2 apoptosis through the mitochondrial-dependent pathway, which might provide a promising approach to cure liver cancer (Yang et al. 2014). The cytotoxic effects of the recently described glycosmisines A (**331**) and B (**330**), and the dimeric biscarbalexine A (**267**) from the stem bark of *G. pentaphylla* were determined against HepG-2, lung adenocarcinoma (A549), and hepato cellular carcinoma (HuH-7) using the colorimetric (MTT) assay: glycosmisine A (**331**) inhibited cell proliferation in a dose-dependent manner with IC_{50} values at 50.30, 43.68, and 30.60 μmol in HepG-2, A549, and HuH-7 cells, respectively, and glycosmisine B (**330**) at 62.89, 57.10, and 62.87 μmol. Similar IC_{50} values at 60.06, 56.06, and 73.16 μmol were determined for biscarbalexine A (**267**) after 48 h of incubation. The three carbazoles also induced apoptosis in the same cell lines as evidenced by changes in the morphological features and their dose-dependent accumulation of a sub-G1 population (Chen et al. 2015).

Mahanine as inducer of different cell-signaling pathways

Mahanine (**214**) was identified as potent apoptosis-inducing agent in human promyelocytic leukemia (HL-60) cells. At a concentration of 10 μmol it caused a complete inhibition of cell proliferation and the induction of apoptosis in a time dependent manner. The cell death was characterized with changes in nuclear morphology, DNA fragmentation, activation of caspase like activities, and release of cytochrome c into cytosol (Roy et al. 2004). In a following study the authors investigated in-depth the various mechanisms induced by **214** on the activation of the apoptotic pathway in human leukemia U937 cells. They concluded that the cytotoxic effect of **214** can be compared with that of many anti-cancer drugs which

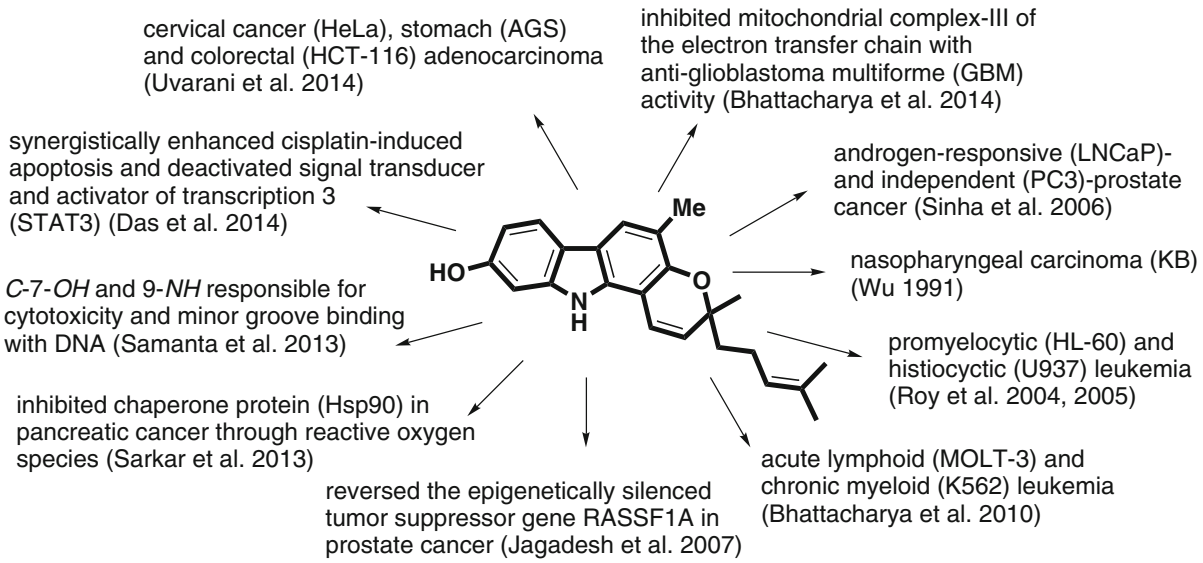


Fig. 6 Various anti-proliferative and apoptosis-inducing activities of mahanine (**214**)

induce apoptosis in tumor cells by permeabilizing mitochondrial membranes (Roy et al. 2005). In addition to **214** the isomeric pyrayafoline D (**244**) and the dimeric murrafoline I (**299**), isolated from the leaves of *B. koenigii*, were also shown to induce apoptosis in HL-60 cells. It was found that these compounds also induced the loss of mitochondrial membrane potential and the subsequent activation of caspase-9/caspase-3 (Ito et al. 2006). Of special interest was the anti-proliferative and apoptosis-inducing activity of **214** on prostate cancer. Sinha et al. (2006) showed that it was active both on androgen-responsive (LNCaP) and androgen-independent (PC3) cells and did not affect normal hepatocytes, cardiomyocytes, and skeletal muscle cells. Moreover, the concentration used were clearly below that used to induce apoptosis in the leukemic cell lines U937 and HL-60 mentioned above. In a following study the same authors showed that **214** can reverse the epigenetically silenced tumor suppressor gene RASSF1A (Ras association domain family member 1) in human prostate cancer cells (Jagadeesh et al. 2007). The involvement of various apoptotic pathways in the mahanine-induced cell death was investigated in the acute lymphoid (MOLT-3) and chronic myeloid (K562) leukemic cells using both in vitro and in vivo models. The results suggested that **214** is a multi-targeted or multi-functional compound that works on an array of different cancer types and has the potential to inhibit tumor growth in vivo (Bhattacharya et al. 2010) (Fig. 6). The authors also investigated the oxidative stress-mediated dysfunction of the chaperone protein Hsp90 by **214** as a possible strategic therapeutic in pancreatic cancer (Sarkar et al. 2013). To recognize structure–activity correlation the functional groups of **214** were chemically modified and the anti-proliferative activity of these derivatives was determined in 19 different cancer cell lines from 7 different types of cancer. Mahanine (**214**) showed enhanced apoptosis compared to its dehydroxylated derivative mahanimbine (**211**) indicating significant contribution of the *C*-7-*OH*-group. *O*-Methylated mahanine (**215**)- and *N*-methylated mahanimbine-treated cells exhibited apoptosis only at higher concentrations, suggesting additional contribution of the –*NH* group (Fig. 6).

Using biophysical techniques it was demonstrated that **214** interacts through strong association with the phosphate backbone of DNA, but is unable to induce any conformational change in DNA, hence suggesting the possibility of being a minor groove binder (Samanta et al. 2013; Uvarani et al. 2014). It was also reported that **214** synergistically increase cisplatin-mediated apoptosis in cervical cancer cells (HeLa, SiHa), thereby reducing the concentration of the toxic cisplatin by ~5–8 folds. Moreover, **214** potentially

deactivated the signal transducer and activator of transcription 3 (STAT3) by suppressing its phosphorylation (Das et al. 2014). Based on extensive studies it was suggested that **214** is a novel mitochondrial complex-III inhibitor of the electron transfer chain with potent anti-glioblastoma multiforme activity both in in vitro and in vivo model triggering cell death by inducing cell cycle arrest through reactive oxygen species. Since it showed high therapeutic potential in several other cancer models **214** is regarded as a potential agent for future chemotherapy (Bhattacharya et al. 2014). Later, Bhattacharya et al. (2016) showed that **214** is involved in the cellular cross-talk between the tumor suppressor protein PTEN (phosphatase and tensin homolog) and the two protein complexes mTORC1 and mTORC2 (mammal target of rapamycin complex 1 and 2), having a central role in cell growth and proliferation. In a more recent paper **214** and pyrayafoline D (=isomahanine) (**244**) were shown to be cytotoxic to oral squamous cell carcinoma (CLS)-354 cells, triggering apoptosis via caspase-dependent and -independent mechanisms and inhibition of autophagic flux (Utaipan et al. 2017).

Anti-inflammatory activities

From twentyfive phytocarbazoles isolated from the roots of *C. lansium* five were assayed for their in vitro anti-inflammatory effects on superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB (formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B). The results showed that *O*-demethylmurrayanine (**26**), methyl carbazole-3-carboxylate (**60**), murrayanine (**27**), and glycozolidal (=*O*-methyllansine) (**44**) exhibited strong inhibition of superoxide anion generation with IC_{50} values ranging from 3.5 to 4.6 μmol, while compounds **26**, **27**, and clausine D (**160**) inhibited elastase release with IC_{50} values at 6.9, 3.9, and 2.0 μmol, respectively (Shen et al. 2014). From twentyfour carbazoles from the stems of *C. emarginata* four displayed anti-inflammatory activity as measured by nitric oxide (*NO*) production in lipopolysaccharide (LPS)-induced microglia BV2 cells. Clausine K (**59**) exhibited the highest IC_{50} value at 4.61 μmol followed by clausine O (**45**) with 6.37, murrayanine (**27**) with 9.94, and clauemarazole E (**158**) with 10.91 μmol (Xia et al. 2015). A similar IC_{50} value at 6.13 μmol was reported for claulansine R (**83**) isolated from the stems of *C. lansium* (Du et al. 2015). Consistent with the traditional use of *M. tetramera* for the treatment of inflammation-related diseases five dimeric carbazoles with anti-inflammatory activities were isolated from leaves and stems. The inhibitory effects of murradines B (**284**), H (**315**), chrestifoline A (**287**), bismurrayafolinol (**317**), and 3,3′-[oxybis(methylene)]bis(9-methoxy-9*H*-carbazole (**271**) on LPS-induced *NO* production in BV2 microglia cells displayed IC_{50} values ranging from 11.2 to 19.3 μmol (Lv et al. 2015). In a more recent study the anti-inflammatory activities of carbazoles from leaves and stems of *B. koenigii* were evaluated against the LPS-induced inflammatory mediators tumor necrosis factor (TNF)-α and interleukin (IL)-6. In the in vitro experiments murrayakonine A (**302**), *O*-methylmurrayamine A (**96**), and murrayanine (**27**) were proven the most potent derivatives with IC_{50} values at 10, 9.4, and 7 μmol, respectively, against TNF-α, and with 8.4 μmol for **96** and **27** against IL-6 (Nalli et al. 2016). In a further investigation of twigs of *C. lansium* only 3-formyl-6-methoxycarbazole (**30**) was significantly active in inhibiting LPS-induced monocyte secretion of TNF-α. It showed comparable efficacy to the control dexamethasone (Rodanant et al. 2015).

Antiplatelet aggregation activities and vasorelaxing effects

Wu and Huang (1992) reported for the first time on the antiplatelet activity of phytocarbazoles from the stem bark of *C. excavata*. The aggregation of rabbit platelets induced by arachidonic acid (AA) showed 53 and 37% inhibition by the two 4-prenylated derivatives clausine D (**160**) and clausine F (**173**), respectively, at 1 μg/ml. Clausenaquinone A (**24**) showed 100% inhibition at 10 μg/ml, induced by AA (100 μmol) (Wu et al. 1994). In a further extensive investigation the same authors isolated seventeen carbazoles from the stembark. Most of them showed significant antiplatelet aggregative activity and vasorelaxing effect. Especially clausine E (**61**) exhibited 58.3 and 89.3% inhibition of rat aorta phasic and tonic contraction induced by norepinephrine (3 μmol), together with 87.0% inhibition of tonic contraction induced by K^+ (80 mmol) + Ca^{2+} (1.9 mmol) (Wu et al. 1996c). Girinimbine (**92**), isolated from *M. euchrestifolia*, inhibited AA-, collagen-, U46619 (a synthetic analog of prostaglandin PGH_2)-, and PAF

(platelet-activating factor)-induced aggregation of rabbit platelets and ATP release in a concentration-dependent manner with IC_{50} values at 9.1, 16.7, 60, and 71.9 μmol, respectively. Compound **92** also inhibited cyclooxygenase activity as reflected by the attenuation of prostaglandin E_2 (PGE_2) formation (Ko et al. 1994). From the acetone extract of the leaves and roots of *M. euchrestifolia* bioassay-guided fractionation showed that twelve carbazoles have antiplatelet aggregative activity. Interestingly, murrayafoline A (**3**), murrayamine M (**263**), and (+) mahanine (**214**) promoted platelet aggregation or lysis at high dose, but they also exhibited antiplatelet aggregation activity at low concentration. These results might explain the use in Chinese medicine in that the dose and content variation in a prescription produced different, promotive or inhibitive, effects on therapy (Wu et al. 1998a).

Antioxidative properties

Antioxidant bioassays on phytocarbazoles were first conducted by Ramsewak et al. (1999) by analysis of model liposome oxidation using fluorescence spectroscopy. From the three leaf carbazoles mahanimbine (**211**), mahanine (**214**), and murrayanol (**242**) of *B. koenigii* the two latter showed only weak antioxidant activity. This was interpreted to be partially due to the precipitation of these compounds in the buffer solution used in the assay. However, compound **211** displayed 49% inhibition of lipid peroxidation after 21 min at 33.1 μg/ml. Tachibana et al. (2001) evaluated the antioxidant properties of the five leaf carbazoles euchrestine B (**241**), bismurrayafoline E (**278**), mahanine (**214**), mahanimbicine (**239**), and mahanimbine (**211**) on the basis of the oil stability index (OSI) (Nakatani et al. 2001) and their radical scavenging ability against 2,2-diphenyl-1-picrylhydrazyl (DPPH). The OSI values of compounds **241** and **214** were higher than those of α-tocopherol or butylated hydroxytoluene (BHT) and were assumed to contribute to the high value of the CH_2Cl_2 crude extract of *B. koenigii*. The DPPH radical scavenging activity increased with the number of hydroxyl groups in the order ascorbic acid (AA) > **278** > **241**, **214** and α-tocopherol > BHT > **239**, **211** (Tachibana et al. 2001). In a following study the same authors compared the activities of twelve carbazoles for antioxidative properties measuring OSI values and DPPH radical scavenging activity. Among nine monomeric carbazoles the three derivatives euchrestine B (**241**), mahanine (**214**), and pyrayafoline D (**244**), characterized by free phenolic OH groups, showed significantly higher activity. Free phenolic OH groups are also present in the four dimeric derivatives bismahanine (**304**), bispyrayafoline (**277**), mahabinine A (=8,10′-[3,3′,11,11′-tetrahydro-9,9′-dihydroxy-3,3′,5,8′-tetramethyl-3,3′-bis(4-methyl-3-pentenyl)]bipyrano[3,2-*a*]carbazole) (**306**), and bismurrayafoline E (**278**), but the activity of compound **278** was clearly weaker. This discrepancy might be explained by the fact that the OH-group of **278** is hindered by the ortho-substituent, whereas the OH-groups of **304**, **277**, and **306** are located at the outer part of the molecule. In comparison to the monomeric derivatives the dimeric carbazoles showed a tendency to raise DPPH radical scavenging activity (Tachibana et al. 2003). Kok et al. (2012) reported on the antioxidant activity of girinimbine (**92**) isolated from *B. koenigii*. It was shown to be comparable with that of α-tocopherol when measured with the ferric thiocyanate (FTC) method and was able to inhibit superoxide generation in the phorbol 12-myristate 13-acetate (PMA)-induced promyelocytic HL-60 cells. However, in cotrast to α-tocopherol **92** failed to scavenge the DPPH-free radical.

Anti-HIV activities

The lipophilic extract of the aerial parts of "*Murraya*" (=*Bergera*) *siamensis* showed anti-HIV activity in the XTT-tetrazolium assay. Bioassay-guided fractionation led to the three phytocarbazoles siamenol (**117**), mahanimbine (**211**), and mahanimbinol (=mahanimbilol) (**209**). The newly described *C*-6-prenylated siamenol (**117**) exhibited the highest activity (EC_{50} = 2.6 μg/ml), reaching 50–60% maximum protection in the XTT-tetrazolium assay. Compound **209** was less active with an EC_{50} value at 8.6 μg/ml, whilst **211** was shown to be inactive (Meragelman et al. 2000). The crude extract from the underground parts of *C. excavata* was found to inhibit HIV-1 activity by the syncytium assay. Beside a limonoid and a pyranocoumarin the three carbazoles glycosinine (=*O*-methylmukonal) (**29**), 3-formyl-2,7-dimethoxycarbazole (**47**), and clausine K (=clauszoline J) (**59**) were shown to contribute to the activity. The results showed that compound **29** strongly exhibited anti-HIV-1 activity with an EC_{50} value at 12 μmol and an IC_{50} value at 680 μmol for inhibition of tetrazolium

conversion to formazan. Compounds **47** and **59** exhibited activities with EC_{50} values at 29 and 34 μmol, and IC_{50} values at 232 and 54 μmol, respectively (Kongkathip et al. 2005). The two *C*-5-prenylated carbazoles glybomine B (**113**) and glycoborinine (**114**) from the twigs and leaves of *G. montana* were tested for in vitro inhibitory effects against HIV replication in C8166 lymphocytes. They demonstrated only weak to moderate anti-HIV activity with IC_{50} values at 9.73 and 4.47 μg/ml, respectively (Wang et al. 2005).

Anti-hyperlipidemic and anti-hyperglycemic activities

In the search for new pancreatic lipase inhibitors from plants 63 extracts from 21 different plants were screened for their inhibitory activity in vitro. All leaf extracts (CH_2Cl_2, EtOAc, MeOH) from *B. koenigii* exhibited antilipase activity greater than 80% which was shown to be correlated with the presence of carbazoles. Bioactivity guided fractionation led to the isolation of the four carbazoles mahanimbine (**211**), koenimbine (**94**), koenigicine (**100**), and clauszoline K (**32**) with IC_{50} values of 17.9, 168.6, 428.6, and <500 μmol, respectively (Birari et al. 2009). The most active mahanimbine (**211**) when given orally (30 mg/kg/day) significantly lowered the body weight gain as well as plasma total cholesterol and triglyceride levels in rats (Birari et al. 2010). The leaf extract of *B. koenigii* was also shown to decrease hyperglycemia and insulin resistance in dexamethasone-treated mice (Pandey et al. 2014). Based on preliminary evaluations of carbazoles on glucose uptake and GLUT4 (glucose transporter type 4) translocation in L6-GLUT4myc myotubes the activity of the four derivatives koenimbine (**94**), *O*-methylmurrayamine A (**96**), koenigicine (=koenidine) (**100**), and mahanimbine (**211**) were investigated in streptozotocin-induced diabetic mice. Koenigicine (**100**) was identified as a metabolically stable antidiabetic compound, when evaluated in a rodent type 2 model and showed a considerable reduction in the postprandial blood glucose profile with an improvement in insulin sensitivity (Patel et al. 2016). Mahanimbine (**211**) was shown to prevent high-fat diet-induced hyperlipidemia and fat accumulation in adipose tissue and liver along with the restricted progression of systemic inflammation and oxidative stress. Since adiposity and inflammation are major factors responsible for insulin resistance, benefits of compound **211** can be extended in improvement of insulin sensitivity (Jagtap et al. 2016).

Melanogenesis inhibition

The EtOAc fraction of the methanolic leaf extract of Sri Lankan *B. koenigii* was shown to significantly inhibit melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells with an IC_{50} value at 11.6 μg/ml. Fourteen carbazoles were isolated from this fraction and tested for their inhibitory properties. Among eight active derivatives koenimbine (**94**) showed the highest activity with an IC_{50} value of 1.2 μmol. A high inhibition ($IC_{50} = 1.4$ μmol) was also determined for mahanimbine (**211**), but a considerable cytotoxic effect was observed at 10 μmol. Mahanimbicine (**239**) and murrayamine E (**230**) inhibited melanogenesis with IC_{50} values at 2.2 and 2.9 μmol (Nakamura et al. 2013).

Hepatoprotective effects

From the stems of *C. emarginata* twentyfour carbazoles were isolated and assayed for their hepatoprotective effects. The six derivatives claulansine I (**156**), clausine F (**173**), clauszoline E (**150**), methyl 6-methoxycarbzole-3-carboxylate (**65**), methyl carbazole-3-carboxylate (**60**), and *O*-demethylmurrayanine (**26**) displayed activities against DL-galactosamine-induced toxicity in hepatocytic precursor (WB-F344) cells (Xia et al. 2015). Moderate hepatoprotective activity against *N*-acetyl-*p*-aminophenol (APAP)-induced toxicity in human liver cancer (HepG2) cells was determined for the five derivatives claulansines N (**34**), P (**189**), Q (**82**), glycozoline (**8**), and methyl carbazole-3-carboxylate (**60**) from the stems of *C. lansium* (Du et al. 2015).

Miscellaneous properties

Mahanimbine (**211**), mahanine (**214**), and mahanimbicine (**239**) were investigated for their efficacy in healing subcutaneous wounds. Compound **239** showed the highest rate of collagen deposition with well-organized collagen bands, formation of fibroblasts, hair follicle buds and with reduced inflammatory cells

compared to wounds treated with the compounds **214** and **211** (Nagappan et al. 2012). In an antimutagenic assay (+) mahanine (**214**) inhibited approximately 99% of the mutation induced by heterocyclic amines such as Trp-P-1 (tryptophan pyrolysis product 1) with an IC_{50} value of 5.2 µmol (Nakahara et al. 2002). Murrayafoline A (**3**) was shown to inhibit the proliferation of vascular smooth muscle cells and hence, may be a good candidate for the management of and protection from atherosclerosis and vascular restenosis (Han et al. 2015). Clausine Z (**36**) isolated from the leaves and stems of *C. excavata* exhibited potent inhibition of CDK5 (cyclin-dependent kinase 5), an essential kinase in sensory pathways, in a filter plate assay with an IC_{50} value at 0.11 µmol and showed protective effects on cerebellar granule neurons in vitro (Potterat et al. 2005). Claulansine F (**143**) from the stems of *C. lansium* was shown to promote neuritogenesis in PC12 cells via the extra cellular signal-regulated kinase (ERK) pathway (Ma et al. 2013). In a more recent study this working group demonstrated that compound **143** also initiated neuronal differentiation with a significant increase of TuJ-1 (neuron-specific β-III tubulin antibody) positive cells and TuJ-1 protein levels. They also found that **143** promoted the maturity and sustainability of neurons by increasing MAP2 (microtubule-associated protein)-positive cells and MAP2 protein levels (Huang et al. 2016). Hyperphosphorylation of tau protein is thought to play an important role in the etiology of Alzheimer's disease. A possible new therapeutic strategy was discussed by reducing the phosphorylation by activation of phospho-tau phosphatase (PP2A) by carbazoles, e.g. 6,7-dimethoxy-1-hydroxycarbazole (**21**), from *B. koenigii* (Manimekalai et al. 2015).

Chemotaxonomy

The ability to produce and accumulate phytocarbazoles appears to be restricted to the four genera *Murraya*, *Clausena*, *Glycosmis*, and *Micromelum* of the family Rutaceae, grouped together in the tribe Clauseneae of the subfamily Aurantioideae. Within the genus *Murraya* there is a clear morphological and chemical dichotomy leading to the recognition of the two sections Murraya and Bergera (Kong et al. 1986; Wu et al. 1996e). Species of the section Murraya (e.g. *M. paniculata* (L.) Jack, *M. exotica* L., *M. gleniei* Thw. ex Oliver, etc.) are characterized by 8-prenylated coumarins, polyoxygenated flavonoids, and 3-prenylindols, whereas those of the section Bergera (e.g. *M. koenigii* (L.) Spreng., *M. euchrestifolia* Hayata, *M. siamensis* Craib., etc.) clearly deviate by the formation of many different phytocarbazoles at present unknown in section Murraya (Kong et al. 1988a; Reisch et al. 1994; Pemmer 2002). According to phylogenetic analyses of the subfamily Aurantioideae based on non-coding plastide DNA sequences the classical subdivision into tribes Clauseneae and Citreae is only justified if the genus *Murraya* (exclusive the species segregated as Bergera) is transferred to the tribe Citreae (Samuel et al. 2001; But et al. 2009). The reinstatement of *Bergera* as a separate genus is also supported by pollen morphology (Mou and Zhang 2009) and analysis of chloroplast genomes (Shivakumar et al. 2016). In view of the chemical characters the genus *Micromelum* takes a somewhat intermediate position containing carbazoles as well as 8-prenylated coumarins and polyoxygenated flavonoids (Bowen and Perera 1982; Kong et al. 1988b; Grassi 1998). Regarding the available plastid DNA data of the tribe Clauseneae, *Micromelu*m forms a weakly supported clade with *Glycosmis*, whereas *Bergera* shows close relationships to *Clausena* (Samuel et al. 2001; But et al. 2009).

Broad-based phytochemical comparisons within the tribe Clauseneae exhibited a predominant formation of carbazoles in the genera *Clausena* (Herdits-Riemer 2002) and *Bergera* (Pemmer 2002), while in *Glycosmis* (Vajrodaya 1998) and *Micromelum* (Grassi 1998) they represented only minor constituents. Generally, carbazoles are mainly found in stem bark and roots but occur also as major compounds in the leaves of *Bergera* species (listed as *Murraya* in Tables 1, 2, 3, 4, 5, 6 according to literature). The ability to produce carbazoles appears to have reached its peak in *B. koenigii* which has already yielded around 80 different derivatives (Nalli et al. 2016). Structurally simple C_{13}-carbazoles preferentially occur in the roots while the more complex C_{18}- and C_{23}-derivatives accumulate in the stem bark. However, in *Bergera* large amounts of C_{23}-derivatives (e.g. mahanimbine (**211**) and mahanine (**214**)) were also isolated from the leaves and fruits. A remarkable seasonal variation of carbazole profiles was observed in the leaves of *B.* ("*Murraya*") *euchrestifolia* by different cyclizations of the geranyl chain of the C_{23}-derivatives cyclomahanimbine (=murrayazolidine) (**220**), murrayazoline (**227**), murrayamine F (**250**)), and the formation of the dimers

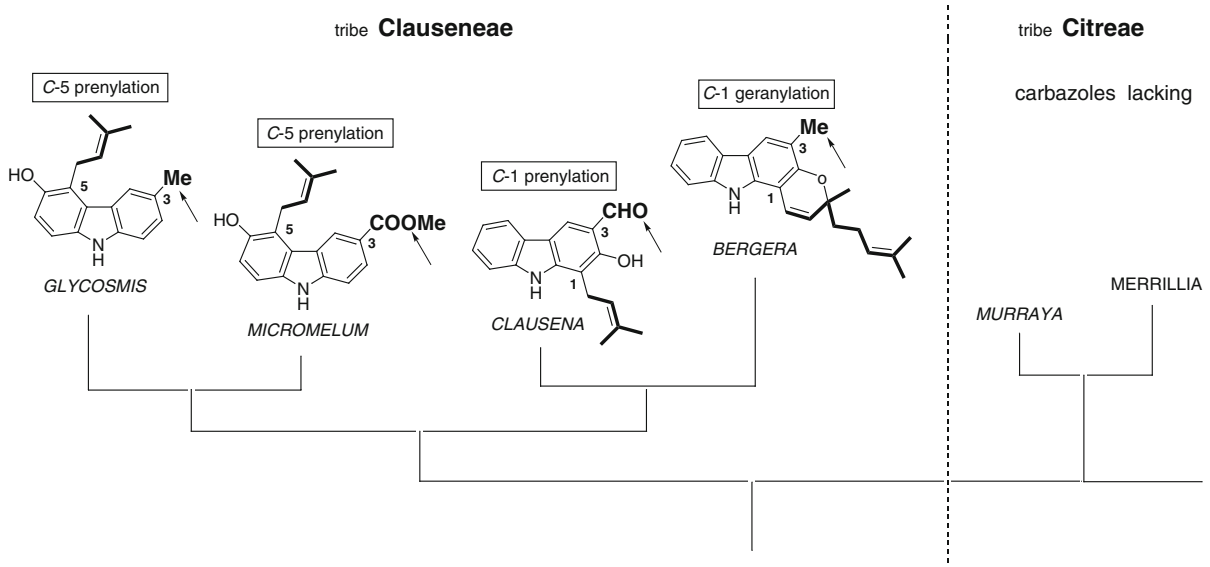


Fig. 7 Major biosynthetic trends in the formation of phytocarbazoles and their chemotaxonomic significance

bis-7-hydroxygirinimbines B (**301**) and A.[2] While the C_{18}-pyranocarbazole girinimbine (**92**) was detected in all seasons, the C_{23}-derivatives **220**, **227**, and **250** were found only in spring (May), and the dimer **301** only in winter (February). Variations were also found in autumn (November) by the oxidation of the 3-methyl group leading to the murrayamines J (**260**), N (**261**), M (**263**) and the oxidation of one methyl group of the dimethylpyran rings leading to the murrayamines K (**104**) and I (**105**) (Wu et al. 1996e). In spite of these seasonal variations and the differences observed between geographical provenances (Pemmer 2002; Herdits-Riemer 2002), some general trends become apparent from the present overview which are obviously of chemotaxonomic significance.

The carbazoles of the genus *Glycosmis* are characterized by the common trend towards 5-prenylation, such as in glycomaurrol (**109**), glycomaurin (**111**), glybomine C (**112**), glycoborinine (**114**), and glycosmisine A (**331**), as well as by the mostly unoxidised C-3 methyl group (Kumar et al. 1989; Rahmani et al. 1998; Vajrodaya 1998; Lukaseder 2000; Pacher et al. 2001; Ito et al. 2004; Wang et al. 2005; Yang et al. 2012; Chen et al. 2015). With respect to these common trends the accumulation of the 3-formylcarbazole murrayanine (**27**) and the dimeric bisisomahanine (**279**) together with murrayafoline A (**3**) in *G. stenocarpa* (Cuong et al. 2004) appears "unusual" for *Glycosmis*, but suggests relations to *Bergera* or *Clausena*. The trend towards 5-prenylation is also typical for the genus *Micromelum*, where, however, the carbazoles deviate by frequent oxidations of the *C*-3 methyl group leading to formyl derivatives such as 3-formyl-6-methoxycarbazole (**30**), lansine (**43**), the double named micromeline (**162**) (cf. Lamberton et al. 1967), as well as to the 3-carboxyl derivatives methyl carbazole-3-carboxylate (**60**), the newly named "microfalcatine" (**178**), and clauraila C (**179**) (Kong et al. 1988b; Grassi 1998; Bacher 1999; Ma et al. 2005) (Fig. 7).

To determine chemotaxonomic relevant characters in the genus *Clausena* and to detect species-specific chemical profiles a broad-based UV-HPLC comparison was carried out with different collections from Thailand. In this connection the HPLC profiles of 19 samples of the widepread *C. excavata* showed that carbazoles are accumulated mainly in the stem bark and roots but were only occasionally detected in small amounts in the leaves (Herdits-Riemer 2002). In contrast to *Glycosmis* the carbazoles showed a predominant trend towads oxidation of the *C*-3 methyl group leading to the formation of many 3-formyl and 3-carboxyl derivatives. Mostly small amounts of structurally simple derivatives such as 3-formylcarbazole (**25**), glycosinine (**29**), *O*-demethylmurrayanine (**26**), 7-methoxymukonal (=2-hydroxy-3-formyl-

[2] The structure of the C-8–C-8 symetrically linked isomer bis-7-hydroxygirinimbine A is not shown in Table 4.

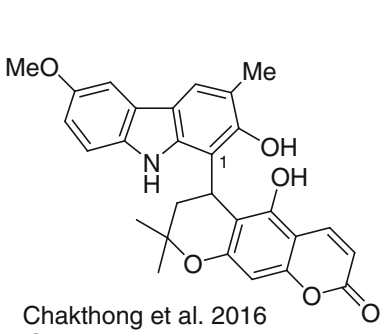
7-methoxycarbazole) (**46**), 3-formyl-2,7-dimethoxycarbazole (**47**) as well as methyl carbazole-3-carboxylate (**60**), clausines E (**61**), and L (**64**) were shown to be widespread in the stem bark and roots. Only the 3-carboxylcarbazole clausine K (=clauszoline J) (**59**) was frequently accumulated in bigger amounts. A characteristic trend of the stem bark of all collections was the accumulation of the 1-prenylated heptazoline (**136**) and the structurally related 1-geranylated clauszoline F (**257**) as major constituents. In addtion, clauszoline B (**167**), a pyranocarbazole closely related to **136**, was found in bigger amounts in collections from N-Thailand (Herdits-Riemer 2002). Higher quantities of plant material led to extraction of further closely related unprenylated derivatives (Wu et al. 1996c, d). In view of this common biogenetic trend the preferred formation of the 4-prenylated carbazoles clausines D (**160**) and F (**173**) in the stem bark (Wu and Huang 1992) and the related lactones clausevatines D (**201**), E (**203**), F (**204**), G (**205**), and clausamine A (**199**) in the roots (Wu et al. 1998b) appears "irregular" for that species.

Due to its wide use as medicinal plant *C. anisata* was already subject of many phytochemical analyses, especially in Africa. Apart from the "unusual" 7- and 8-prenylated carbazoles clausanitin (**164**) and atanisatin (**168**) (Okorie 1975), not found in subsequent investigations, the profiles were characterized by a predominant trend towards 4-prenylation such as in ekeberginine (**161**) (Ngadjui et al. 1989; Songue et al. 2012), clausamines A (**199**), B (**200**), C (**202**), D (**174**), E (**176**), F (**175**), G (**177**), clausine F (**173**) (Ito et al. 1998, 2000), furanoclausamines A (**207**), B (**206**) (Ito et al. 2009), and murrayamine H (**108**) (Tatsimo et al. 2015).

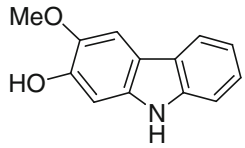
C. lansium, known as "wampee" in China or "mafaicheen" in Thailand, is a popular fruit tree in Southeast Asia. Since it is also used in traditional Chinese medicine a number of phytochemical investigations have already been carried out. As in other *Clausena* species the root extract was shown to contain mainly simple C_{13}-formyl derivatives such as 3-formylcarbazole (**25**), O-demethylmurrayanine (**26**), murrayanine (**27**), 3-formyl-6-methoxycarbazole (**30**), 3-formyl-1,6-dimethoxycarbazole (**38**), lansine (**43**), glycozolidal (**44**). A more specific trend is the formation of 2-prenylated derivatives related to indizoline (**157**), found in the roots, twigs, and stems. They are additionally characterized by oxidations and cyclizations of the prenyl unit leading to the mafaicheenamines A (**183**), B (**185**), C (**193**), D (**192**), E (**196**) (Maneerat and Laphookhieo 2010; Maneerat et al. 2012a), claulansines A (**186**), B (**187**), C (**184**), D (**197**), E (**195**), I (**156**), M (**159**), P (**189**), clausenalines B (**191**), C (**194**), claulamine E (**182**), 1′-O-methylclaulamine B (**188**), and 1′-acetylclaulamine B (**190**) (Li et al. 1991; Liu et al. 2012; Shen et al. 2012, 2014; Du et al. 2015). Regarding this characteristic biogenetic capacity it is tempting to assume a close relationship to *C. emarginata* C. C. Huang, showing a very similar carbazole profile predominated by the 2-prenylated derivatives clauemarazoles E (**158**), C (**198**), the mafaicheenamines C (**193**), D (**192**), E (**196**), claulamine E, and clauslansine I (**156**) (Xia et al. 2015). Generally, phytocarbazoles of *Clausena* species accumulate mainly in the stem bark, where prenylation at position *C*-1 frequently leads to the formation of derivatives of heptaphylline (**132**) and girinimbine (**92**) as major constituents (Fig. 7). However, additional prenylations at *C*-4 in *C. anisata* or *C*-2 in *C. lansium* apparently reflect species-specific biogenetic trends. Further comparisons of different geographical provenances of the morphologically similar *C. harmandiana* (Pierre) Guillaumine, *C. heptaphylla* (Roxb.) Wight & Arn., and *C. indica* (Dalz.) Oliv. will have to show whether these chemical trends can contribute to a better species delimitation.

Of great taxonomic significance is the formation of geranylated derivatives. With the exception of mukoenine B (=clausenatine A) (**255**) and clauszoline F (**256**), isolated from *C. excavata*, the C_{23}-carbazoles shown in Table 3 are only known from species of the genus *Bergera* (part of *Murraya* s. l.). Most of them are additionally characterized by an unoxidized *C*-3 methyl group (Fig. 7). Regarding these biogenetic trends the carbazoles reported for *C. dunniana* Lév, containing mahanimbine (**211**) and bicyclomahanimbine (**226**) (Cui et al. 2002), don't fit to the chemical profiles of *Clausena*, but show great similarities with those of the genus *Bergera*. The formation of the unique trimeric carbazoles murratrines A (**328**) and B (**329**) in *M. tetramera* C. C. Huang together with a series of dimeric derivatives deserves special taxonomic interest (Lv et al. 2015). Due to its preferred accumulation of carbazoles it should be removed from the genus *Murraya*. Although no C_{23}-carbazoles have as yet been isolated structural similarities of the monomeric subunits as well as morphological characters suggest close relationship with *B.* ("Murraya") *euchrestifolia*.

Appendix



Chakthong et al. 2016
C. excavata



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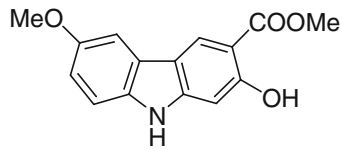

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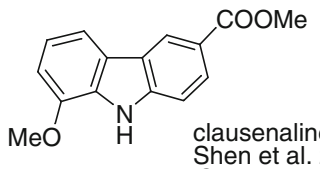

clausenaline G
Shen et al. 2017
C. lansium

Four additional phytocarbazoles recently isolated from *C. excavata* and *C. lansium* not shown in Tables 1-7

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