Review

Recent Progress in the Isolation and Bioactivities of Carbazole Alkaloids

Natural Product Communications
Volume 19(9): 1–16

DOI: 10.1177/1934578X241285125
journals.sagepub.com/home/npx

Duc Dau-Xuan[1], Chung Nguyen-Thi[1] and Dung Vo-Cong[2]

Abstract

Objective/Background: Carbazole derivatives have a tricyclic skeleton, consisting of a central pyrrole ring fused with two benzene rings. Carbazole derivatives are an important class of nitrogen-containing heterocyclic compounds that are widely found in nature and in synthetic source. These heterocycles possess a wide range of bioactivities and some of them have been marketed as drugs for the treatment of various diseases. Although some review articles on carbazole alkaloids have appreared in the literature, they are quite outdated. The current study offers a comprehensive review on the isolation and bioactivities of carbazole alkaloids within a decade. The article might be useful for chemists who work in alkaloid chemistry as well as pharmaceutical area. **Methods: '**Carbazole alkaloids' was the most useful keyword to search for literature data. References have been collected from various resources such as Google Scholar, SciFinder, and PubMed. More than 70 electronic publications were obtained from these resources. **Results:** More than 230 carbazole alkaloids have been isolated and structurally elucidated from different sources. Carbazole alkaloids possess a wide range of bioactivities, such as antimicrobial, antiimflamatory, anticancer, neuroprotective properties activities. **Conclusion:** In this review article, we have summarized 66 studies on isolation and bioactivities of carbazole alkaloids in the literature. More than 230 carbazole alkaloid compounds have been isolated and identified. In addition, the article also gives an overview on bioactivities of carbazole alkaloids.

Keywords

carbazole, Clausena, Murraya, neuroprotective, antimicrobial, anticancer, NO production, CD analysis

Received: April 3rd, 2024; Accepted: August 23rd, 2024.

Introduction

Carbazole is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of a central pyrrole ring fused with two benzene rings. Carbazole was originally isolated from coal tar.[1] Carbazole derivatives (carbazole compounds with substituents) are an important class of nitrogen-containing heterocyclic compounds that are widely found in nature[2] and in synthetic source.[3] These heterocycles possess a wide range of bioactivities[3,4] and some of them have been marketed as drugs for the treatment of various diseases (Figure 1). For examples, ondansetron is a medication used to prevent nausea and vomiting, midostaurin is a multi-targeted protein kinase inhibitor, and cardevilol is a β-blocker. The diverse bioactivities of carbazoles such as antimicrobial, anti-inflammatory, anticancer, neuroprotective, and antidiabetic activities have been well documented in the literature.[5,6]

Although some review articles on phytochemistry of carbazole alkaloids were found in the literature, they are quite out dated and do not cover recent studies or all aspects of phytochemistry.[4–6] This article summarized studies on isolation of newly discovered naturally occurring carbazole alkaloids as well as their bioactivities which dates backs in 2012. More than 230 carbazoles have been isolated and diverse bioactivities have been discovered. The articles might be useful for scientists who work in natural products chemistry and pharmacy.

Isolation of Naturally Occuring Carbazole Alkaloids

Isolation of Simple Carbazole Alkaloids

Liu *et al* isolated three novel carbazole alkaloids, claulansines H-J (**1-3**) from the stems of *Clausena lansium*. Their structures were elucidated by analyses of extensive spectroscopic.[7] claulansines H and I are prenylated carbazole alkaloids (Figure 2). The isolation and structure determination of clausenawalline D (**4**)

[1]Department of Chemistry, College of Education, Vinh University, Vinh City, Vietnam
[2]Centre for Education Accreditation, Vinh University, Vinh City, Vietnam

Corresponding Author:
Duc Dau-Xuan, Department of Chemistry, College of Education, Vinh University, Vinh City, 4300, Vietnam.
Email: xuanduc80@gmail.com, ducdx_chem@vinhuni.edu.vn

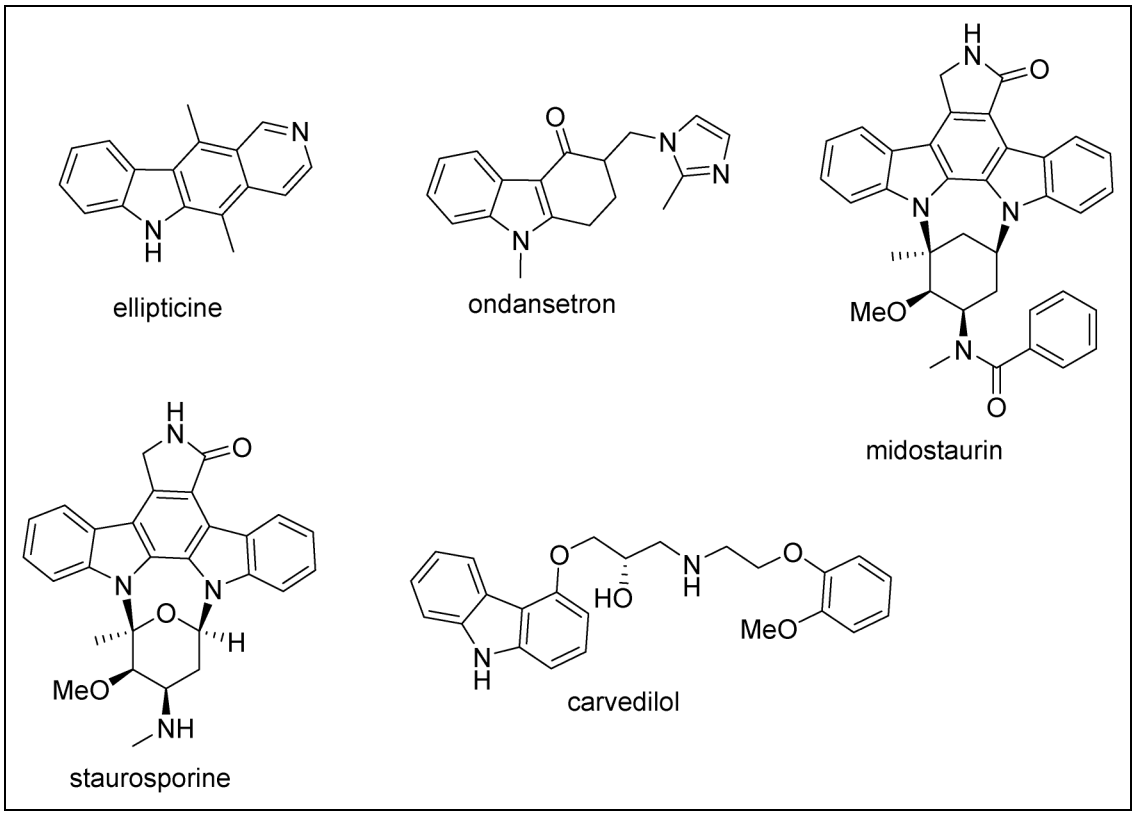

Figure 1. Some drugs with carbazole skeleton.

from the roots of *C. wallichii* was accomplished by Maneerat *et al* (Figure 2).[8] Yang *et al* obtained 4-(7-hydroxy-3-methoxy-6-methyl-9*H*-carbazol-4-yl)but-3-en-2- one (**5**) from the stems of *Glycosmis pentaphylla* (Figure 2).[9] Harmandianamine C (**6**) with two hydroxy group at the side chain was isolated by Maneerat *et al* from the twigs of *C. harmandiana* (Figure 2).[10] However, the absolute configuration of this compound was not assigned. Nakamura *et al* discovered karapinchamine A (**7**) from the leaves of *Murraya koenigii* collected in Sri Lanka (Figure 2). Its structure was elucidated by analysis of spectroscopic data.[11] Excavatine A (**8**), a new carbazole alkaloid, was yielded from the stems and leaves of *C. excavata* Burm.f. (*Rutaceae*) (Figure 2).[12] Maneerat *et al* achieved two new prenylated carbazole alkaloids, clausenawallines G (**9**) and H (**10**) from the twigs of *C. Wallichii* (Figure 2). Their structures were elucidated by mean of spectroscopic methods.[13] In 2014, Shen *et al* obtained two new carbazole alkaloids including clausenalines E (**11**) and F (**12**) from the roots of *C. lansium* (Figure 2). These compounds are rare natural carbazole carboxylic acids. Their structures were elucidated by mean of spectroscopic analysis.[14]

In a report described by Jiang *et al*, 6-methoxy-9*H*-carbazole-3-carboxylic acid (**13**) was isolated from the stems of *C. lansium* (Figure 2).[15] Tan *et al* afforded murrastanine A **(14)** from the bark and leaves of *Murraya koenigii* (Linn.) (Figure 2).[16] From the aerial parts of this species, Naz *et al* isolated and identified two novel carbazole alkaloids, mukoenigatin (**15**) and murrayadinal (**16**) (Figure 2).[17] Mukoenigatin is an ester of fatty acid. Unfortunately, detail about absolute configuration and optical rotation was not included. Du *et al* reported the isolation and structure determination of four new carbazole alkaloids, namely claulansines N, O, Q, and R (**17-20**), from the stems of *C. lansium* (Figure 2).[18] Du *et al* also obtained two new carbazole alkaloids, namely claulansine S (**21**) and T (**22**), from the stems of *C. lansium* (Figure 2).[19] Xia *et al* achieved five novel carbazole alkaloids named clauemarazoles A, B, and E-G (**23**, **24**, **25-27**) from the stems of *C. emarginata* (Figure 2). Compounds **23**, **24**, **26**, and **27** were resolved from the two corresponding racemic mixtures using a chiral semipreparative column and their absolute configurations were confirmed by their electronic circular dichroism (ECD) spectroscopy.[20] Tatsimo *et al* obtained one new carbazole alkaloid named clausamine H (**28**) from leaves and stem bark extracts of *C. anisata* monitored by liquid chromatography High-Resolution Mass Spectrometry (HRMS) (Figure 2).[21] A new carbazole–indole hybrid dimeric alkaloid, glycosmisine B (**29**), were isolated from the stems of *G. pentaphylla* by Chen *et al* and their structures were established by mean of spectroscopic methods (Figure 2).[22]

In 2016, Chakthong *et al* achieved a carbazole-pyranocoumarin hybrid, carbazomarin B (**30**), and two carbazole alkaloids, 6-methoxymukonidine (**31**) and 2-hydroxy-3-

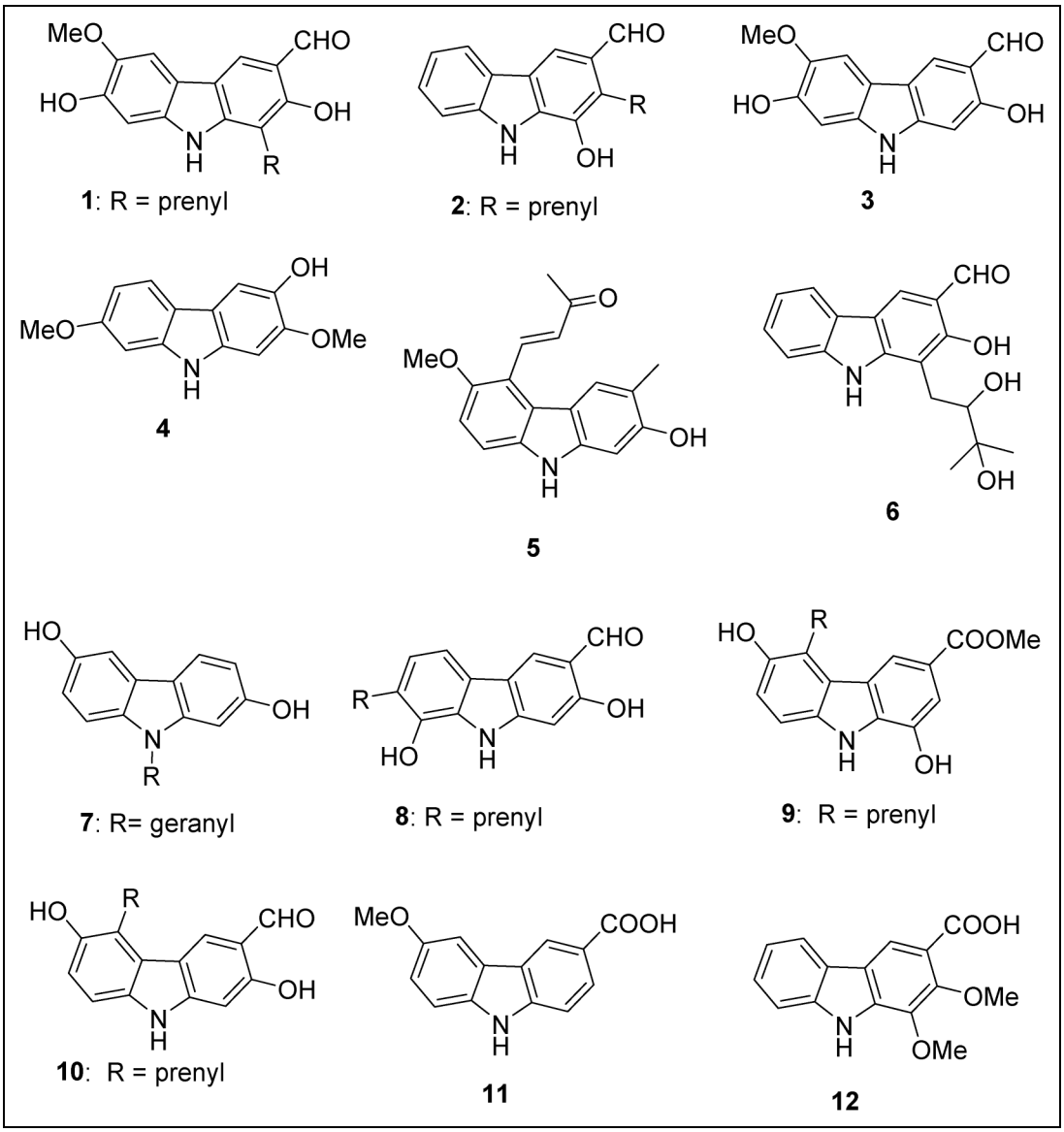

Figure 2. Simple isolated carbazole alkaloids.

methoxycarbazole **(32**) from the stems of *C. excavata*. Structure determination of these compounds was established based on spectroscopic analysis (Figure 2).[23] The absolute configuration of carbazomarin B remained unclear although its optical rotation was provided. Shen *et al* reported the isolation and structure determination of clausenaline G [33] from the leaves of *C. lansium* (Figure 2).[24] In 2018, Wei *et al* isolated 1,9-dimethoxy-3-methyl-9*H*-carbazol-2-ol (**34**) from the whole plant of *C. sanki* (Figure 2).[25] Ma *et al* achieved five new carbazole alkaloids named clausehainanines A-E (**35-39**) from the stems and leaves of *C. hainanensis* (Figure 2). Compounds **35** and **36**, **38** and **39** are two pairs of *E* and *Z* isomers. Their structures were determined based on extensive spectroscopic analysis. These compounds have diverse unusual isopentenyl derivatives as substituents at C-2.[26] In 2019, five new carbazole alkaloids, namely clausenalansines B-F (**40**-**44**), were isolated by the Liu group from the fruits of *C. Lansium* (Figure 2).[27] Compound **44** is methyl ether of compound **44**. The group also afforded a novel and rare prenylated dicarboxylic carbazole alkaloid, named as clausevestine (**45**), from the stems and leaves of *C. vestita* (Figure 2).[28] Unluckily, the configuration of this compound was not determined. Aminah *et al* reported the isolation and structure determination of carbazomarin C (**46**), a new carbazolepyranocoumarin conjugate, from the roots of *C. excavata* (Figure 2).[29] There was no information about optical rotation and configuration of this compound.

Fu *et al* isolated a previously undescribed carbazole alkaloid, clausemargine A (**47**), the stems and leaves of *C. emarginata* (Figure 2).[30] Ly *et al* afforded two novel carbazole alkaloids

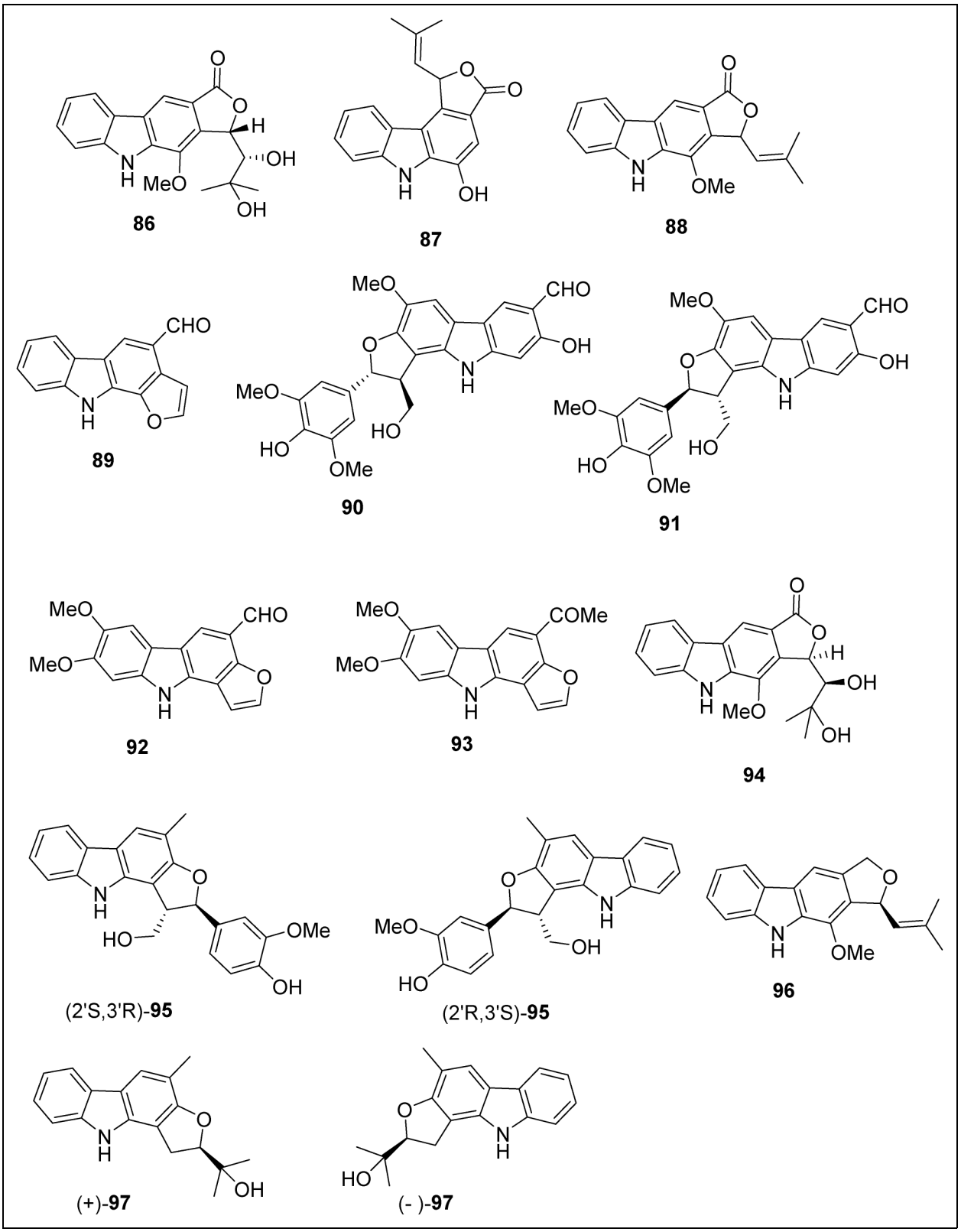

Figure 3. Simple isolated furanocarbazole alkaloids.

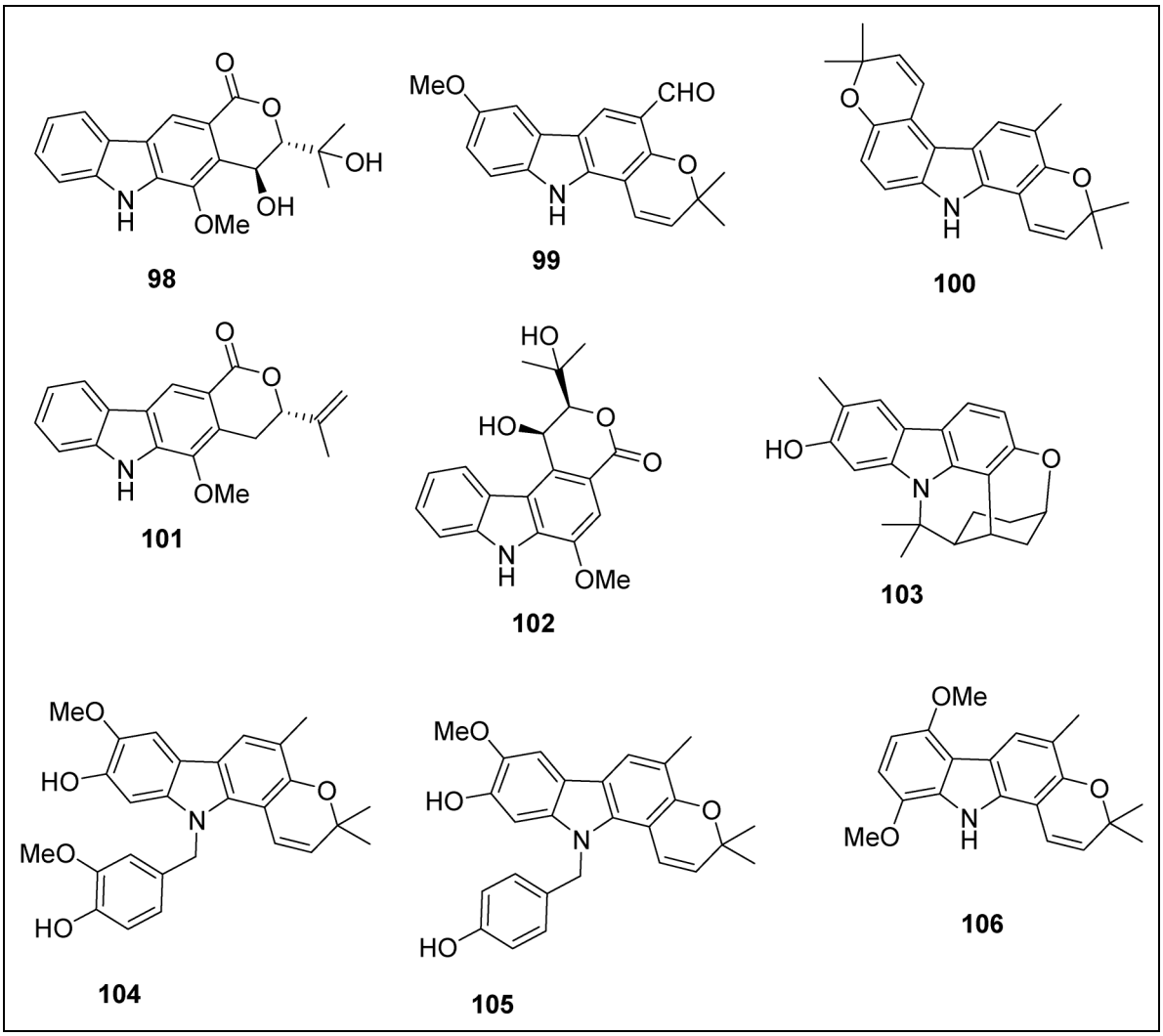

Figure 4. Isolated pyranocarbazole alkaloids.

1-ethoxy-2-hydroxy-3-methylcarbazole (**48**) and 1,7-dimethoxy-8-formyl- 2-hydroxy-3-methylcarbazole (**49**) from the leaves and stems of *M. tetramera* C. C. Huang (Figure 2).[31] Cao *et al* isolated integerrines A (**50**) and G (**51**) from the dried leaves and stems of *Micromelum integerrimum* (Figure 2).[32] Integerrine A is a racemic heterodimer of carbazole and indole. The racemic compound was then further resolved using chiral-phase high-performance liquid chromatography (HPLC) and configurations of enantiomerically pure compounds, (-)-**50** and (+)-**50**, were established by comparison of experimental and calculated ECD data. The absolute configuration of (-)-**50** was defined as *aR* and (+)-**50** was defined as *aS*. Two novel carbazole alkaloids, zanthoaustrones A (**52**) and B (**53**) were isolated and identified by Fu *et al* from the roots of *Zanthoxylum austrosinense* Huang (*Rutaceae*) (Figure 2). Their structures were determined by mean of extensive and comprehensive spectroscopic methods.[33] Yang *et al* achieved two new carbazole alkaloids, named clauolenzoles A [54] and B [55], from the ethanolic extract of the aerial parts of *C. anisum-olens* (Figure 2).[34] Zhang *et al* demonstrated the isolation of two new carbazole alkaloids with amide side chain, namely antiostatin A5 (**56**) and antiostatin A6 (**57**), from a new soil-derived Streptomyces sp (Figure 2). Antiostatin A6 possesses a new cyclohexene side chain.[35] Claulansine W (**58**) was afforded from the stems of *C. lansium* (Figure 2).[36] In 2020, Liu *et al* demonstrated the isolation and structure elucidation of one novel carbazole alkaloids clausenanisine C (**59**), and three new naturally occurring carbazole alkaloids, clausenanisines D-F (**60-62**) from the fresh ripe fruits of *C. anisum-olens* (Figure 2).[37]

Sun *et al* isolated claulansine X (**63**) from the stems of *C. lansium* (Figure 2).[38] A previously undescribed carbazole alkaloid, clausenalenine A (**64**), was obtained from the stems and leaves of *C. lenis* (Figure 2).[39] Claulansine X and clausenalenine A are prenylated carbazole alkaloids. Four new chlorinated carbazole alkaloids, chlocarbazomycins A-D (**65**-**68**), were isolated by Cheng *et al* from sponge associated bacterium *S. diacarni* LHW51701 (Figure 2). Their structures were determined by analysis of spectroscopic data and the structures of **64** and **67**

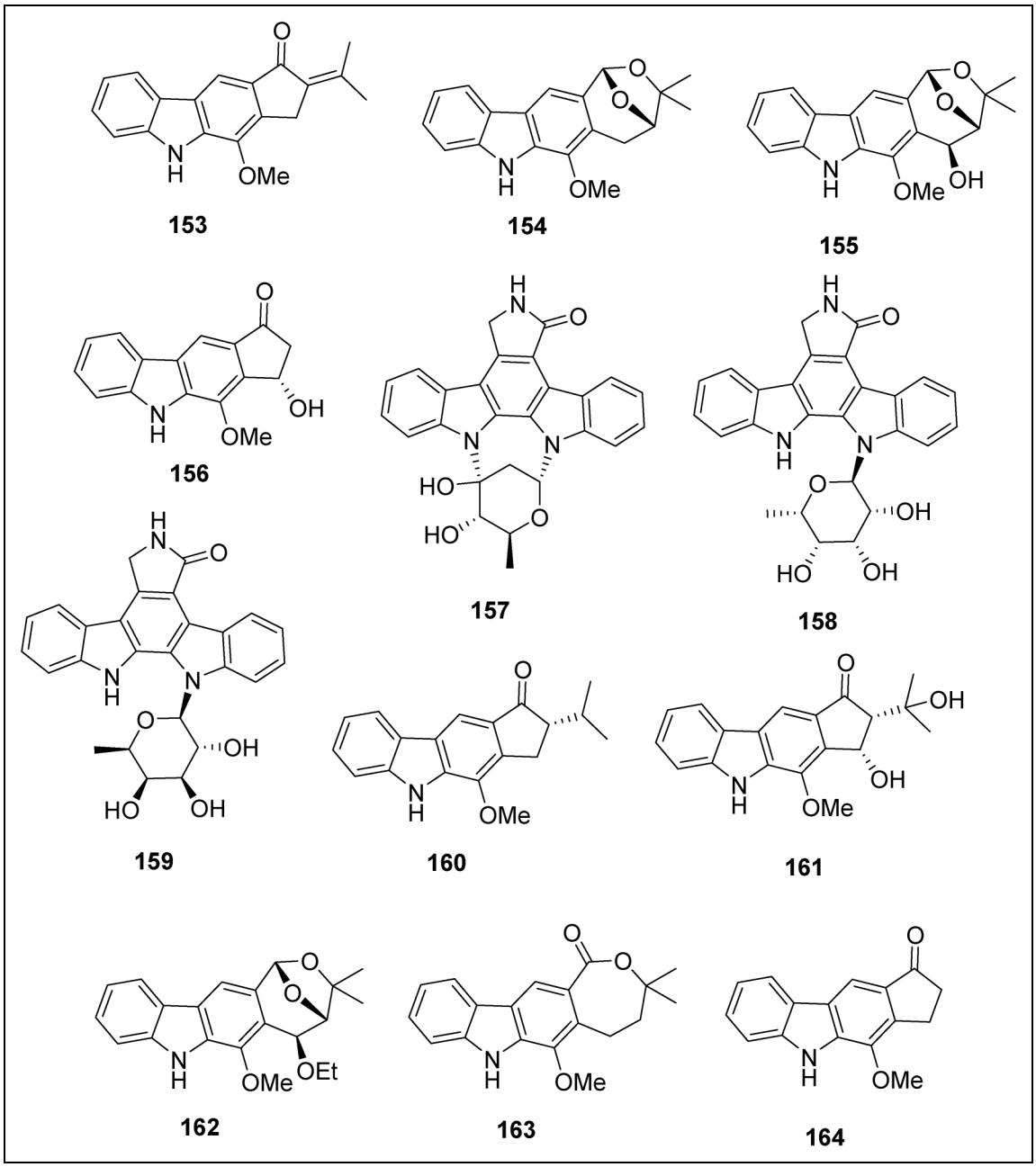

Figure 5. Isolated other fussed carbazole alkaloids. (continued)

were confirmed by x-ray crystallographic analysis.[40] Kim *et al* achieved three new carbazole glycosides, namely jejucarbazoles A-C (**69**-**71**), from *Streptomyces sp*. KCB15JA151 (Figure 2). Their absolute configurations were elucidated by ECD calculation.[41]

In 2023, 1-methoxy-3-formyl-8-isopentenyl carbazole (**72**) and *N*-methyl-1-hydroxyl carbazole (**73**) were achieved from *C. lansium* branch-leaves (Figure 2).[42] In the same year, antiostatin A7 (**74**), a carbazole alkaloid with long side chain, was obtained from a fermentation broth of the soil-derived *Streptomyces* sp. HS-NF-1322 strain (Figure 2).[43] The configuration of the OH group at the side chain remained unclear. Recently, four new 9*H*-carbazole derivatives (**75**-**78**) and four new natural carbazole alkaloids (**79**-**82**) were isolated from a fermented solid medium of the Thailand mangrove-derived *Streptomyces* strain, OUCMDZ-5511, under fluoride stress (Figure 2).[44] Carbazomycins I (**83**) and J (**84**), two novel carbazole alkaloids were isolated from the fermentation broth of *S. phattalungensis* DSM 45584 (Figure 2). Their structures were elucidated by analysis of HRESIMS and NMR spectroscopic data.[45] From the 95% ethanol aqueous extract of the roots of *C. lansium*, claulamine I (**85**) was isolated and identified based on spectroscopic data (Figure 2).[46]

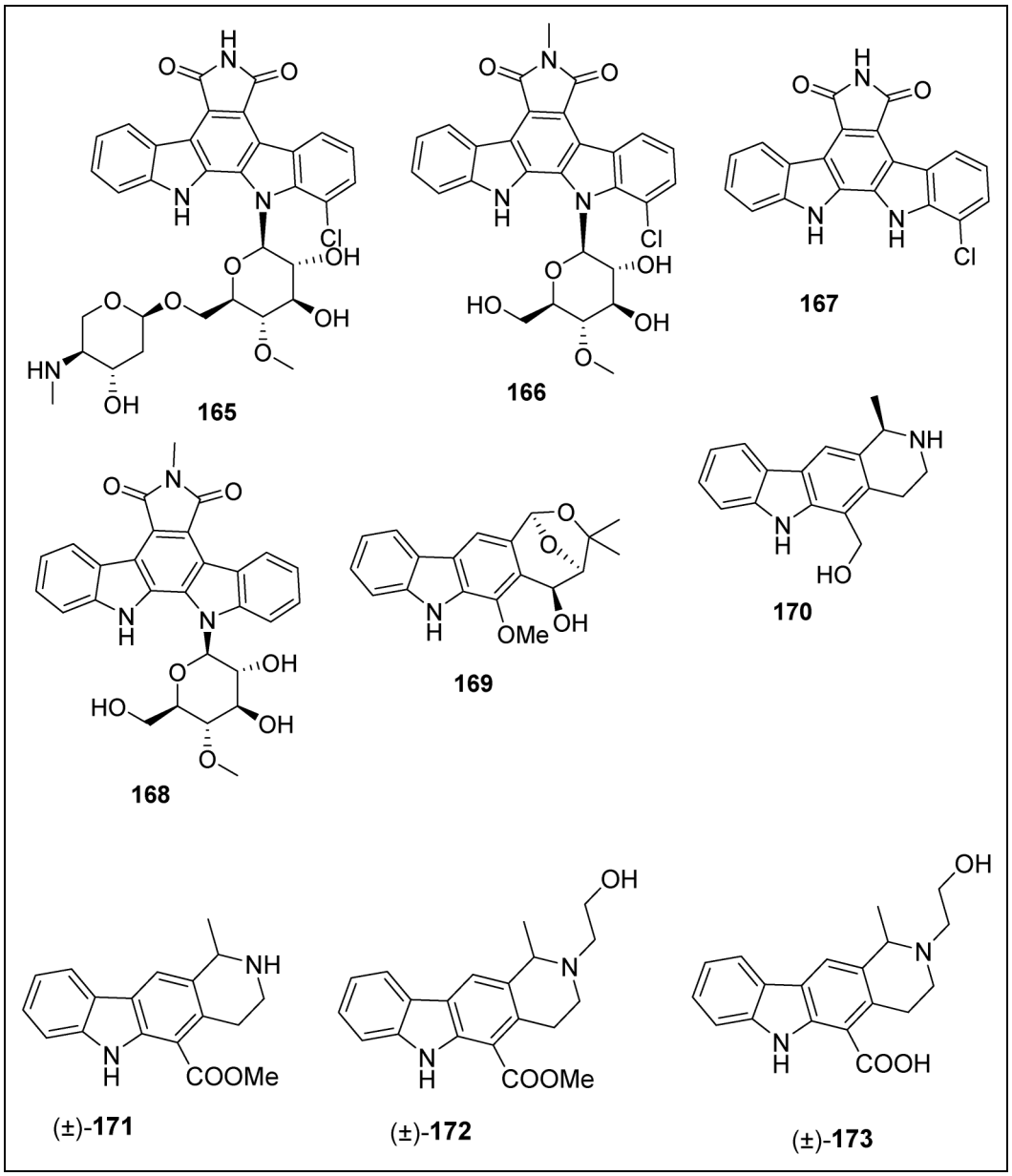

Figure 5. Continued.

Isolation of Furanocarbazole Alkaloids

Liu *et al* isolated claulansine D (**86**) from the stems of *C. lansium* (Figure 3). Its structure was elucidated by analyses of extensive spectroscopic and its absolute configuration was determined by ECD using the time-dependent density functional theory (TD-DFT) method.[7] Harmandianamine A (**87**) was isolated by Maneerat *et al* from the twigs of *C. harmandiana* (Figure 3).[10] Mafaicheenamine E (**88**) was afforded from the roots of *C. lansium* (Figure 3). Spectroscopic methods, including nuclear magnetic resonance (NMR), ultraviolet (UV), infared (IR), and mass spectrometry (MS) spectral data were used for structural characterization.[47] In 2014, Shen *et al* obtained clausenaline D (**89**) from the roots of *C. lansium* (Figure 3). Its structure was elucidated by mean of 2D-NMR spectroscopic analysis.[14] Du *et al* reported the isolation and structure determination of claulansine L from the stems of *Clausena lansium* (Figure 3). This compound was isolated as a racemic mixture which then was separated by semipreparative column to give two enantiomers, (+) claulansine L (**90**) and (-)-claulansine L (**91**). Configurations of these isomers were established based on CD spectrum.[18] Compound **90** also obtained by Deng *et al* and named as claulansine K (Figure 3).[48] Khan *et al* afforded two novel furocarbazole alkaloids including 3-formyl-6,7-dimethoxy-furo[1, 2]carbazole (**92**) and methyl-6,7-dimethoxy-furo[1, 2]carbazole-3-carboxylate (**93**) from the whole plant of *Lonicera quinquelocularis* (Figure 3).[49] (+)-(1'*R*,2'*R*)-claulansine D (**94**) was

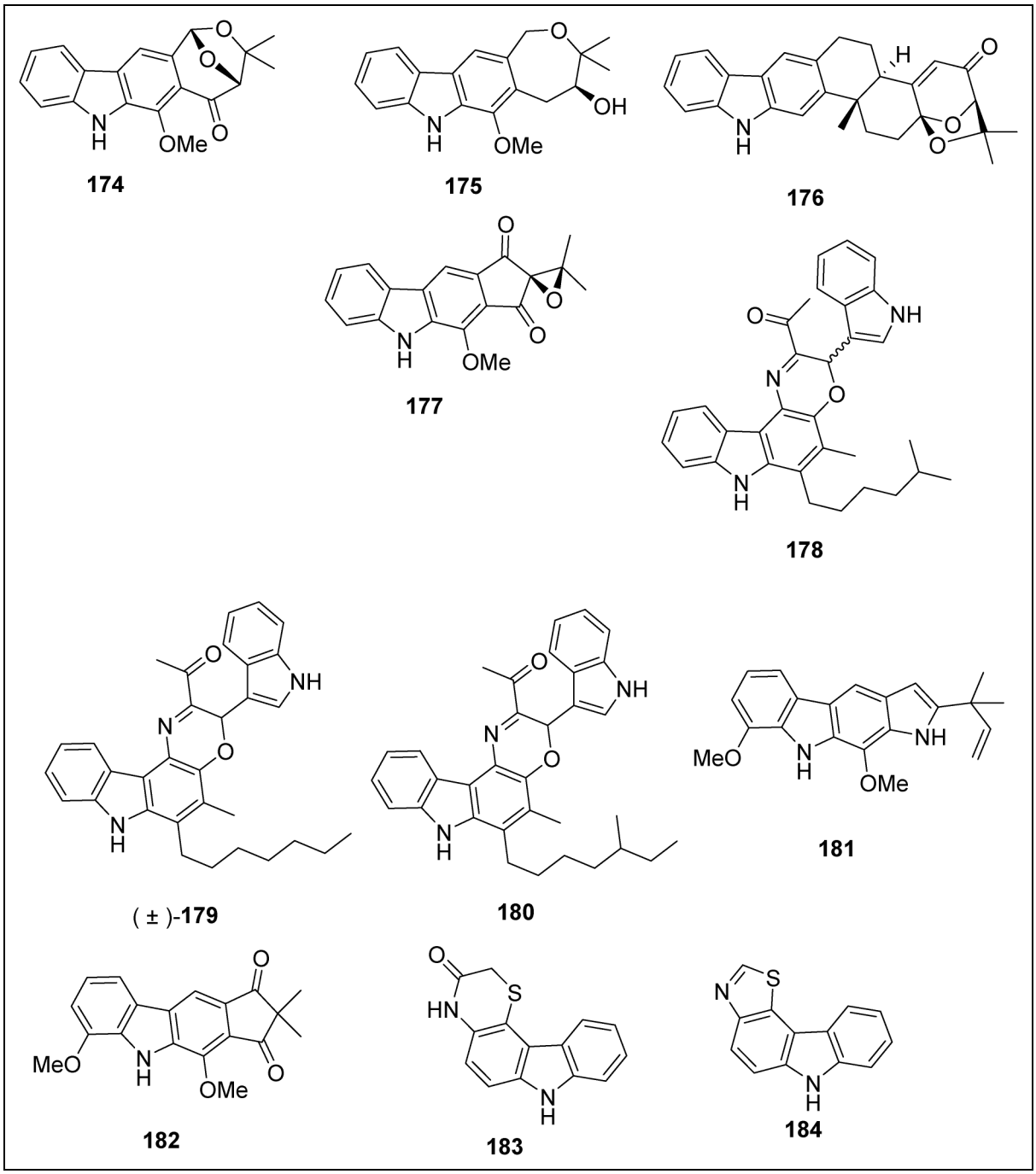

Figure 5. Continued.

discovered from the stems of *C. lansium* (Figure 3).[50] Mycrophyline K (**95**) was isolated from the leaves and stems of *M. microphylla* as a racemic mixture and further separated by semipreparative HPLC using a Chiralpak AD-H column (Figure 3).[51] In 2020, Liu *et al* obtained clausenanisine A (**96**) from the fresh ripe fruits of *C. anisum-olens*.[37] Ma *et al* discovered a pair of new carbazole alkaloid enantiomers, namely microphylines R (**97**) from the leaves and stems of *M. microphylla* (Figure 3). The chirally pure isomers were isolated by chiral HPLC separation and their absolute configurations were established by analysis of the CD spectra and calculated ECD data.[52]

Isolation of Pyranocarbazole Alkaloids

Liu *et al* isolated two novel pyranocarbazole alkaloids, claulansine C (**98**) and F (**99**), from the stems of *C. lansium* (Figure 4). Their structures were determined by means of

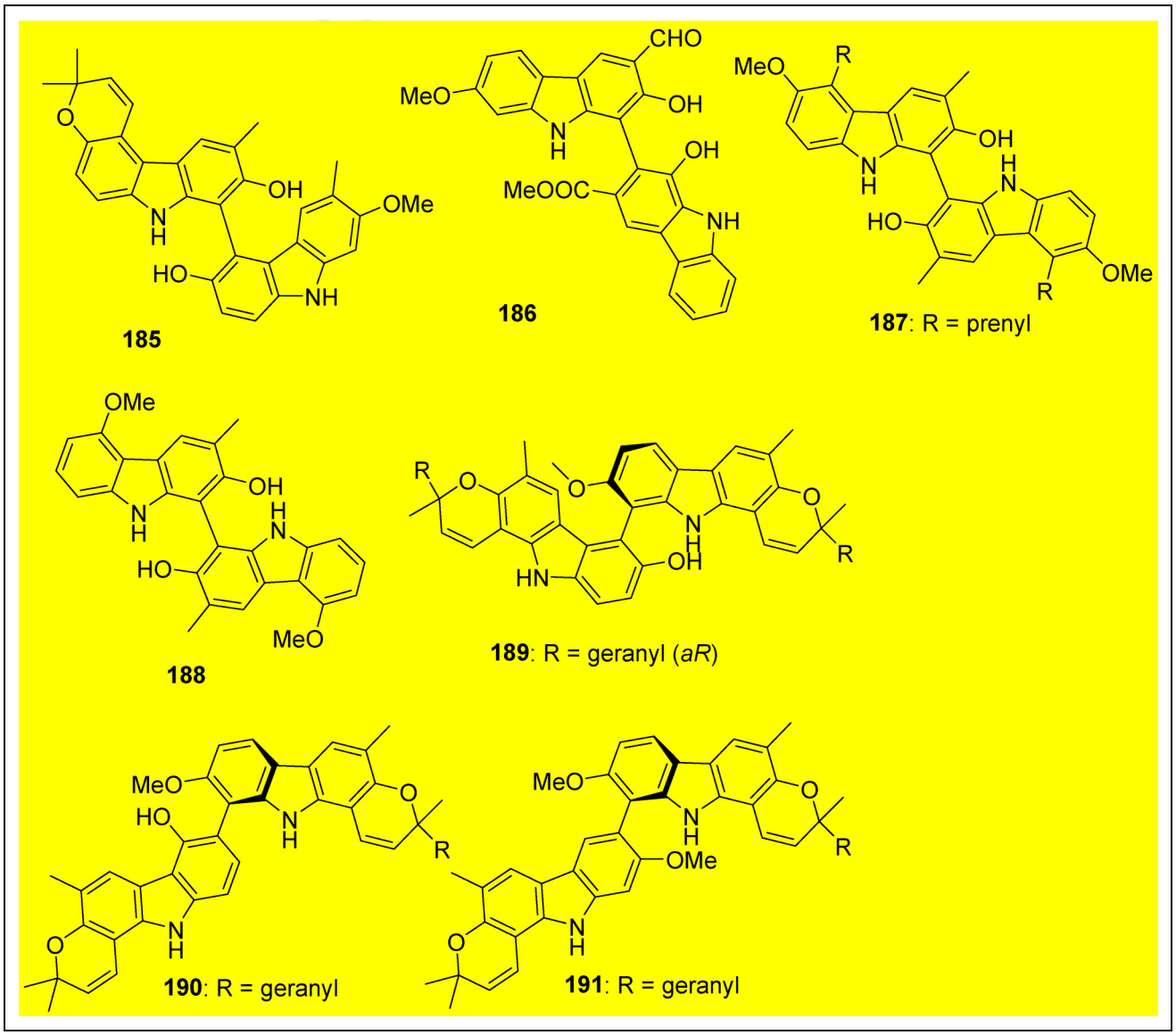

Figure 6. Isolated dimeric carbazole alkaloids.

extensive spectroscopic. Furthermore, the absolute configuration of **98** was determined by ECD using the time-dependent-DFT method.[7] The isolation and structure determination of clausenawalline C (**100**) from the roots of *C. wallichii* was accomplished by Maneerat *et al* (Figure 4).[8] Shen *et al* obtained claulamine A (**101**) from the stems of *C. lansium* (Figure 4). Its structure and configuration were determined by analyses of spectroscopic data and CD analysis.[53] Harmandianamine B (**102**) was isolated by Maneerat *et al* from the twigs of *C. harmandiana* (Figure 4).[10] Nakamura *et al* discovered karapinchamine B (**103**) from the leaves of *M. koenigii* collected in Sri Lanka (Figure 4).[11] Ma *et al* described the isolation and structure determination of four new carbazole alkaloids including *N*-benzyl carbazole-A (**104**), *N*-benzyl carbazole-B (**105**), iso-koenidine (**106**), and iso-koenigine (**107**) from *M. koenigii* (Figure 4). All of them belong to pyranocarbazole alkaloids.[54] Sriphana *et al* obtained one novel carbazole alkaloid, clauraila E (**108**), from the methanol extract of the roots of *C. harmandiana* (Figure 4).[55] Maneerat *et al* isolated three new carbazole alkaloids, clausenawallines I-K (**109**-**111**) from the twigs of *C. wallichii* (Figure 4). Their structures were elucidated by mean of spectroscopic methods.[13]

In 2014, Shen *et al* obtained three new carbazole alkaloids including claulamines C-E (**112**-**114**) from the roots of *C. lansium* (Figure 4). Their structures were elucidated by mean of 2D-NMR spectroscopic analysis and their absolute configurations were established from their ECD spectra.[14] Two novel carbazole alkaloids, guillauminines A (**115**) and B (**116**), were afforded and identified from the acetone extract of *C. guillauminii* roots (Figure 4). Their structures were elucidated by

spectroscopic methods.[56] Tan *et al* achieved four new pyranocarbazole alkaloids including murrastinines A-C **(117-119)** and murrayatanine A **(120)** from the bark and leaves of *M. koenigii* (Linn.) (Figure 4).[16] Unfortunately, configurations of **117** and **120** were not elucidated. Du *et al* reported the isolation and structure determination of claulansine M (**121**) from the stems of *C. lansium* (Figure 4).[18] Glycosmisine A (**122**), a new carbazole–indole hybrid dimeric alkaloid, was isolated from the stems of *G. pentaphylla* by Chen *et al* (Figure 4) and its structure was elucidated by mean of spectroscopic methods.[22] Nalli *et al* demonstrated the isolation and structure elucidation of three new carbazole alkaloids including murrayakonines B-D (**123**-**125**) from the stem and the leaves of *M. koenigii* (Figure 4).[57] The configuration of murrayakonine B was not provided.

Cao *et al* isolated dunnine D (**126**) from the stems of *C. dunniana* as a racemic mixture which then was separated by chiral HPLC to obtain the optically pure enantiomers (Figure 4). The absolute configurations of these isomers were established based on ECD data.[58] Two new polyprenylated pyranocarbazole alkaloid derivatives, namely mycrophylines L (**127**) and M (**128**) were isolated from the leaves and stems of *M. microphylla* (Figure 4). Structures of isolated compounds were determined by analysis of spectroscopic data but configurations at chiral carbons were not characterized.[51] In their phytochemical investigation of *M. microphylla*, 12 novel pyranocarbazole alkaloid including microphylines A-J (**129**, **131**, **133**-**140**) and epimicrophylines A (**130**) and B (**132**) were discovered by Ma *et al* from the leaves and stems (Figure 4). Microphylines D-F were obtained as pairs of enantiomers and then were further separated by chiral-phase HPLC resolution to give pure enantiomers. Their structures were elucidated based on spectroscopic analysis. The absolute configuration of microphyline A was confirmed by x-ray crystallographic data analysis and other compounds by calculated ECD data.[59] Compounds **136–140** are new thujane-carbazole alkaloids while the other are new menthene-carbazole alkaloids. Clausenalansine A (**141**) was isolated by Liu *et al* from the fruits of *C. lansium* (Figure 4).[27] From the stems and leaves of *C. lansium*, Lin *et al* achieved two new geranylated pyranocarbazole alkaloids, clauselansiumines A (**142**) and B (**143**) (Figure 4).[60] The complete absolute configuration of **143** was not assigned. Zanthoaustrone C (**144**) was isolated and identified by Fu *et al* from the roots of *Z. austrosinense* Huang (*Rutaceae*) (Figure 4).[33] In 2020, Liu *et al* demonstrated the isolation and structure elucidation of clausenanisine B (**145**) from the fresh ripe fruits of *C. anisum-olens* (Figure 4).[37]

(-)-(2′*R*)-claulamine A (**146**) was isolated from the stems of *C. lansium* by Sun *et al* (Figure 4).[36] In their phytochemical investigation on *M. microphylla*, Ma *et al* discovered four pairs of new carbazole alkaloid enantiomers, namely microphylines N-Q (**147**-**150**), from the leaves and stems (Figure 4). The chirally pure isomers were isolated by chiral HPLC separation and their absolute configurations were established by analysis of the CD spectra and calculated ECD data.[52] Sakunpak *et al* afforded 8-hydroxymahanimbine (**151**), a new naturally occurring pyranocarbazole alkaloid from *C. cambodiana* Guill leaves (Figure 4).[61] Optical rotation and absolute configuration of this alkaloid were not provided. Recently, from the 95% ethanol aqueous extract of the roots of *C. lansium*, a pair of enantiomeric alkaloids, (+) (2′*R*, 6′*S*)-claulamine H and (-) (2′*S*, 6′*R*)-claulamine H (**152**), was obtained and separated by chiral-phase separation (Figure 4).[46]

Isolation of Other Fused Carbazole Alkaloids

Mafaicheenamine D (**153**) was isolated from the roots of *C. lansium* (Figure 5).[47] Liu *et al* isolated four novel carbazole alkaloids, claulansines A (**154**), B (**155**), E (**156**), and G from the stems of *C. lansium* (Figure 5). Claulansine G has the same structure as mafaicheenamine D. Their structures were elucidated by analyses of extensive spectroscopic. Furthermore, absolute configurations of compounds **154–156** were determined by ECD using the TD-DFT method.[7] Shen *et al* isolated two new carbazole alkaloids, clausenaline A and claulamine B, from the stems of *C. lansium* (Figure 5). Again, clausenaline A has the same structure as mafaicheenamine D and claulamine B has the same structure as claulansine B.[53] Zhou *et al* achieved three novel indolocarbazoles alkaloids, namely streptocarbazoles C (**157**), 3′-*epi*-K252d (**158**), and 2′,4′-*epi*-K252d (**159**), from the rice solid fermentation of the marine-derived *Streptomyces* sp. A65 (Figure 5). Structures of these alkaloids were elucidated by mean of spectroscopic and spectrometric methods. The absolute configurations of compounds **157** and **158** were confirmed by single-crystal x-ray crystallographic analysis, while the absolute configuration of **159** was deduced based on calculated ECD spectra.[62] Shen *et al* obtained clausenalines B (**160**) and C (**161**) from the roots of *C. lansium* (Figure 5).[14]

Du *et al* reported the isolation and structure determination of claulansine P (**162**), from the stems of *C. lansium* (Figure 5).[18] This compound is ethyl ether of **155**. Xia *et al* achieved two novel carbazole alkaloids named clauemarazoles C (**163**) and D(**164**) from the stems of *C. emarginata* (Figure 5).[20] Shaaban *et al* demonstrated the isolation and structure elucidation of the four new indolocarbazole alkaloids, AT2433-A3, A4, A5, and B3 (**165**-**168**), from *actinomadura melliaura* ATCC 39691, a strain isolated from a soil sample collected in Bristol Cove, California (Figure 5).[63] (+)-(1′*R*,2′*R*,6′*R*)-claulansine B (**169**) was discovered from the stems of *C. lansium* (Figure 5). Its structure was elucidated based on spectroscopic and chemical methods and its configurations was established based on ECD calculation spectra.[50] Ndongo *et al* obtained janetinine (**170**) from the stem bark of *Pleiocarpa pycnantha* (Figure 5). The absolute configuration of this compound was confirmed by comparison of its experimental and computed ECD curves.[64] Three new racemic pyridocarbazole alkaloids, namely (±)-stritidas A-C (**171**-**173**), were afforded by Li *et al* from the twigs of *S. nitida* and their structures were elucidated by mean of spectroscopic methods (Figure 5).[65]

Two new carbazole alkaloids, claulansiums A (**174**) and B (**175**) were yielded from the methanol extract of the branches and leaves of *C. lansium* (Figure 5).[66] Ariantari *et al* obtained shearilicine (**176**), a novel carbazole alkaloid from the EtOAc extract of *Penicillium sp* (Figure 5). This compound features a new type of indole diterpenoid scaffold with a rare 6/5/6/6/6/6/5 heterocyclic system. The absolute configuration of this alkaloid was established based on the TDDFT-ECD approach and single-crystal x-ray determination.[67] Two unreported carbazole alkaloids, namely claulansines U and V (**177**), were obtained from the stems of *C. lansium*. Their structures were demonstrated by spectroscopic experiments (Figure 5).[36] Claulansine U has the same structure as claulansiums A. Zhang *et al* demonstrated the isolation and structure elucidation of (±)-morindolestatin (**178**) with a novel [1, 4]oxazino[2,3- *c*]carbazole skeleton from a new soil-derived *Streptomyces sp* (Figure 5).[35] (±)- Morindolestatin B (**179**) and morindolestatin C (**180**) were obtained from a fermentation broth of the soil-derived *Streptomyces* sp. HS-NF-1322 strain (Figure 5).[43] Two new alkaloids, 1,7-dimethoxy-2′-prenyl-1′,9-dihydropyrrolocarbazole (**181**) and 1,7-dimethoxy-4′,5′-dimethylcyclopentacarbazole-1′,3′-dione (**182**), were isolated from the $CHCl_3$ extraction of *Corydalis decumbens* (Figure 5).[68] Two new 9*H*-carbazole derivatives (**183**, **184**) were isolated from a fermented solid medium of the Thailand mangrove-derived *Streptomyces* strain, OUCMDZ-5511, under fluoride stress (Figure 5).[44]

Isolation of di- and Trimeric Carbazole Alkaloids

The isolation and structure determination of two dimeric carbazole alkaloids named clausenawallines E (**185**) and F (**186**) from the roots of *C. wallichii* was accomplished by Maneerat *et al* (Figure 6).[8] Yang *et al* obtained two previously undescribed dimeric carbazole derivatives, bisglybomine B (**187**) and biscarbalexine A (**188**), from the stems of *G. pentaphylla* (Figure 6).[9] In these two articles, no information about resolution of these compounds to pure enantiomers and configurations of enantiomers were given. Uvarani *et al* reported the isolation and structure determination of bisgerayafolines A-C (**189**-**191**), three new dimeric carbazole alkaloids, from the blue-violet-colored *M. koenigii* ripened fruits collected in India (Figure 6). Configurations of these compounds were defined as *a*R. These alkaloids have geranyl side chain at the pyran ring.[69] These are geranylated carbazole alkaloids. Uvarani *et al* discovered two new dimeric carbazole alkaloids, bisgerayafoline D (**192**) and bismahanimbinol (**193**) from the fruit pulp of *M. koenigii* (Figure 6). The structures of these chiral bispyranocarbazoles were established by analysis of spectroscopic data and the absolute configurations of bisgerayafoline D (**192**) and bismahanimbinol (**193**) were assigned as (*a*S) and (*a*R), respectively using a combination of computational CD and experimental ECD spectroscopic data.[70] Lv *et al* isolated two unique trimeric carbazole alkaloids, murratrines A (**194**) and B (**195**), and eleven new dimeric carbazole alkaloids, murradines A-K (**196**-**206**), from the leaves and stems of *M. tetramera* (Figure 6). Their structures and absolute configurations were determined based on NMR spectroscopy methods and ECD data analysis.[71] The absolute configurations of murradines I (**204**) and J (**205**) were defined as (*a*R) and (*a*S), respectively.

Tan *et al* afforded bismahanimboline **(207)** from the bark and leaves of *M. koenigii* (Linn.) (Figure 6).[16] The absolute configuration of this compound was not determined. From the aerial parts of this species, Naz *et al* isolated and identified bikoeniquinonine (**208**) (Figure 6).[17] Nalli *et al* demonstrated the isolation and structure elucidation of murrayakonine A (**209**) from the stem and the leaves of *M. koenigii* (Figure 6).[57] In 2018, Wei *et al* obtained 6,7′-dimethoxy-3,3′,13,13′,14,14′-hexamethyl-9,9′-dihydro-[5,5′-bipyrano-carbazole]-6′,7-diol (**210**) from the whole plant of *C. sanki* (Figure 6).[25] Unfortunately, there was no information about resolution of enantiomers and absolute configuration from the study. Through their phytochemical investigation of *C. dunniana*, Cao *et al* isolated three undescribed dimeric carbazole alkaloids, namely dunnines A-C (**211**-**213**), from the stems (Figure 6). All of them were obtained as racemic mixture which then were separated by chiral HPLC to obtain the optically pure enantiomers, **211** (*a*S), **211** (*a*R), **212** (*a*S), **212** (*a*R), **213** (*a*S), **213** (*a*R). Structures of isolated compounds were determined by mean of spectroscopic methods, and the absolute configurations were established based on ECD data.[58] In their phytochemical investigation on the traditional Chinese medicine *M. kwangsiensis*, Chen *et al* achieved 14 undescribed biscarbazole alkaloids including kwangsines A-M (**215**-**227**) and (±)-bispyrayafoline C (**214**) from the leaves and stems (Figure 6). Compounds **214**–**217** were obtained as racemic mixtures which then separated by chiral HPLC separation to obtain **214** (*a*S), **214** (*a*R), **215** (*a*S), **215** (*a*R), **216** (*a*S), **216** (*a*R), **217** (*a*S), and **217** (*a*R). Their structures were determined by analysis of spectroscopic data. Their absolute configurations were established by ECD exciton coupling method, as well as comparison of experimental and calculated ECD data.[72] Cao *et al* isolated five dimeric carbazole alkaloids including integerrines B-F (**228**-**232**) from the dried leaves and stems of *Micromelum integerrimum* (Figure 6). Integerrines B-E are racemic biscarbazoles. The racemic compounds were then further resolved using chiral-phase HPLC and configurations of enantiomerically pure compounds, **228** (*a*S), **228** (*a*R), **229** (*a*S), **229** (*a*R), **230** (*a*S), **230** (*a*R), **231** (*a*S), and **231** (*a*R) were established by comparison of experimental and calculated ECD data.[32] Compound **232** was isolated as an enantiomerically pure compound and the (*a*R) configuration was deduced from ECD spectrum. Recently, a new dimeric carbazole alkaloid, 3,3′,5,5′,8-pentamethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-10,10′-bipyrano[3,2-*a*]carbazole (**233**), was isolated from the hexane extract of leaves of *M. koenigii* (L.) Sprengel (Figure 6).[73] The structure was elucidated based on 13C and 1H NMR, HRMS, and 2D NMR data.

Bioactivities of Isolated Carbazole Alkaloids

Antimicrobial Activity

Compounds **6**, **87**, **102** showed weak antibacterial activity against *E. coli* TISTR 780, *S. typhimurium* TISTR 292, *S. aureus* TISTR 1466 and *S. aureus* (MRSA) SK1.[10] Similarly, compound **28** isolated from the leaves and stem bark extracts of *C. anisata* exhibited weak antibacterial activity against various bacterial strains.[21] Murrayakonines A-D (**209**, **123**-**125**) obtained from the stem and the leaves of *M. koenigii* also displayed weak antimicrobial activities when tested with various bacterial strains.[57] Clausenawalline E obtained from the roots of *C. wallichii* displayed remarkable antibacterial activity against methicillin-resistant *S. aureus* SK1 (MRSA SK1) and *S. aureus* TISTR 1466 with MIC values of 8 μg/mL.[8] Clauraila E (**108**), claulansine A **(154**), and mafaicheenamine E **(88)** displayed different degrees of antifungal activity against *Botryosphaeria dothidea* with EC_{50} values ranging from 54.18 to 129.83 μg/mL.[55] Chlocarbazomycin C (**67**) displayed moderate antimicrobial activities (MIC, 32 μg/mL) against *M. smegmatis*, *B. mycoides* and *C. albicans*.

Anti-Inflammatory Activity

Some carbazole alkaloids exhibited considerable anti-inflammatory activity by different method. Two carbazole alkaloid dimer, murradines B (**197**) and H (**203**), isolated from the leaves and stems of *M. tetramera* exhibited inhibition of NO production stimulated by lipopolysaccharide in BV-2 microglial cells with IC_{50} values of 11.4 and 19.3 μM, respectively.[71] The prenylated carbazole alkaloid clausevestine (**45**) displayed remarkable inhibitory effects on NO (nitric oxide) production with IC50 value of 19.3 μM.[28] Dimeric carbazole murrayakonine A (**209)** showed good anti-inflammatory activities, using both *in vitro* and *in vivo* experiments, against the key inflammatory mediators TNF-α and IL-6.[57] Zanthoaustrones A-C (**52**, **53**, **144**, respectively) isolated from the roots of *Z. austrosinense* Huang (*Rutaceae*) displayed significant inhibitory activities on NO production with IC50 values in range of 0.89 to 1.59 μM, which is better than the positive control (hydrocortisone) with an IC50 value of 4.06 μM.[33] 1-ethoxy-2-hydroxy-3-methylcarbazole (**48**) and 1,7-dimethoxy-8-formyl-2-hydroxy-3-methylcarbazole (**49**) exhibited moderate inhibitory effects on NO production in LPS-stimulated BV-2 microglial cells with IC_{50} values of 7.7 and 15.1 μM, respectively.[31]

Anticancer Activity

Many natural carbazole alkaloids displayed strong anticancer activity. Mafaicheenamine E (**88**) exhibited cytotoxicity against MCF-7 cell line with IC_{50} value of 3.1 μg /mL.[47] Murrastinine C (**119**) and murrayatanine A (**120**) obtained from the bark and leaves of *M. koenigii* (Linn.) showed moderate cytotoxic activity against HL-60 and HeLa cell lines ($CD_{50} < 20$ μg/mL) *via* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[16] Two carbazole–indole-type dimeric alkaloids, glycosmisines A (**122**) and B (**29**), displayed good cytotoxicity against three human cancer cell lines including A549, HepG-2 and Huh-7.[22] Clausevestine (**45**) displayed excellent antiproliferative activities against five human cancer cell lines, including HL-60, SMMC-7721, A-549, MCF-7 and SW480 by means of the MTT method, with the IC50 values ranging from 0.32 ± 0.04 to 3.86 ± 0.12 μM.[28] Clausemargine A (**47**) exhibited significant neuroprotective activities against five human cancer cell lines, HL-60, SMMC-7721, A-549, MCF-7 and SW480 using the MTT method with IC_{50} values ranging from 0.28 to 1.08 μM, better than doxorubicin, the reference drug.[30] Five new carbazole alkaloids named clausehainanines A-E (**35**-**39**) displayed remarkable anticancer activity against various human cancer cell lines including HL-60, SMMC-7721, A-549, MCF-7 and SW480 with IC50 values ranging from 0.36 to 1.36 μM.[26] 6-Methoxymukonidine (**31**) exhibited moderate cytotoxicity to HuCCA-1, MOLT-3 and HepG2 cancer cell lines with IC_{50} values ranging from 15.09 to 28.50 μg/mL, but none to A549 cell line.[23] Zanthoaustrones A-C (**52**, **53**, **144**, respectively) showed significant antiproliferative activities against diverse human cancer cell lines including HL-60, SMMC-7721, A-549, MCF-7, and SW480, with IC50 values in range of 0.85 to 29.56 μM, which is equivalent to the positive control (cisplatin) (IC50 values ranging from 1.58 to 28.69 μM).[33] 3′-*epi*-K252d (**158**) and 2′,4′-*epi*-K252d (**159**) displayed moderate cytotoxic activity against the PC3 cells with IC_{50} values of 9.67 and 6.79 μM, respectively.[62] Janetinine (**170**) showed cancer chemopreventive properties through either quinone reductase induction (CD = 30.7 μM).[64] Shearilicine (**176**) was shown to be possess strong cytotoxic activity toward L5178Y cells, with an IC_{50} value of 3.6 μM, and an IC_{50} against A2780 cells of 8.7 μM.[67] Excavatine A (**8**) displayed good cytotoxicity against A549 and HeLa cell lines with the IC_{50} values of 5.25 and 1.91 mg/ml *via* SRB assay, respectively.[12] Clausenawalline F (**18)** displayed potent cytotoxicity against oral cavity cancer (KB) and small-cell lung cancer (NCI-H187) with IC_{50} values of 10.2 and 4.5 μM, respectively.[8] 6-methoxy-9*H*-carbazole-3-carboxylic acid (**13**) exhibited moderate cytotoxicity against MCF-7, H1299 and SMMC-7721 tumor cell lines.[15] Claulansine W (**58**) displayed remarkable cytotoxicities against four human cancer cell lines including MCF-7, HCT-116, HepG2, and Capan-2 cell lines *in vitro* by the MTT method, with IC_{50} values ranging from 2.16 to 4.94 μM.[36]

Neuroprotective Activity

Neuroprotective activity is a valuable biological activity of carbazole alkaloids. Clausenalansines A-F (**141** and **40**-**44**) isolated from the fruits of *C. lansium* exhibited excellent neuroprotective effects with the EC_{50} values ranging from 0.86 to 2.58 μM indicating that the fruits of this species may help people prevent the

occurrence of Parkinson's disease.[27] Claulansine X (**63**) was shown to be moderate inhibition effect on PC12 cells induced by serum withdrawal at the concentration of 10 μM.[38] Clausenalenine A (**64**) obtained from the stems and leaves of *C. lenis* displayed remarkable neuroprotective effect with EC_{50} value of 0.68 μM compared to the standard drug curcumine (EC_{50} value of 5.98 μM).[39] Clauselansiumines A (**142**) and B (**143**) exhibited excellent neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells *in vitro* with the EC_{50} values of 0.48 and 0.98 μM, respectively.[60] Dunnines A-D (**211**-**213** and **126**) showed good inhibition of the apoptosis of PC12 cell induced by 6-hydroxydopamine with IC_{50} values in the range of 14.7–47.2 μM.[58] (+)-(1′*R*,2′*R*)-claulansine D (**94**) inhibited PC12 cell damage induced by okadaic acid, and increased cell viability from 70.5 ± 5.4% to 89.7 ± 4.8% at 10 mM.[50] Claulansines U (**174**) and V (**177**) protected PC12 cells against serum deprivation injury at 10μM - an increase of cell survival rates from 47.4 ± 4.3% (model) to 67.8 ± 6.6% and 63.3 ± 8.2%, respectively.[36] Antiostatin A7 (**74**), (±)-morindolestatin B (**179**), and morindolestatin C (**180**) possessed neuroprotective effects on PC12 and HT-22 neuronal cells by inhibiting ferroptosis, especially, antiostatin A7, which significantly increased cell viability greater than the positive drug deferoxamine at a concentration of 10 μM.[43]

Antidiabetic Activity

Ma *et al* reported that microphylines A-J (**129**, **131**, **133**-**140**) and epimicrophylines A (**130**) and B (**132**) promoted insulin secretion in the HIT-T15 cell line, 1.9–3.1-fold higher than the gliclazide control at 100 μM.[46] Claulansine K exhibited *in vitro* α-glucosidase inhibitory activity (IC_{50} value of 10 μM) with the IC_{50} value of 0.11 μM.[48] Dunnines A-D (**211**-**213** and **126**) could remarkably promote insulin secretion in HIT-T15 cell line (1.9-3.1-fold of the control, phorbol 12-myristate 13-acetate) at 40 μM.[58] Liu *et al* reported that clausenanisines A-C (**96**, **145**, and **59**, respectively) and clausenanisines D-F **(60-62)** isolated from the fresh ripe fruits of *C. anisum-olens* exhibited remarkable *α*-glucosidase inhibitory activities with IC_{50} values ranging from 0.58 to 38.48 μM.[37] Carbazomarin C (**46**) showed strong inhibition on yeast α-glucosidase in a dose-dependent manner with IC_{50} value of 0.22 μM.[29] Bisgerayafolines A-C (**189**-**191**) exhibited anti-α-glucosidase activity with IC_{50} values ranging from 41.2–69.0 μM using acarbose as the reference.[69] Compound **233** showed excellent α-amylase inhibitory activity (IC_{50} = 30.32 ± 0.34 μM) and α-glucosidase inhibitory activity (IC_{50} = 30.91 ± 0.36 μM).[73]

Other Bioactivities

Bisgerayafolines A-C were moderately active *via in vitro* antioxidant bioassays including FRAP, metal chelating, $ABTS^{+\bullet}$, $DPPH^{\bullet}$, $OH^{\bullet}$, and $NO^{\bullet}$.[69] Clausenanisines A-F (**96**, **145**, and **59-62**) displayed significant PTP1B inhibitory activities with IC_{50} values ranging from 0.58 ± 0.05 to 38.48 ± 0.32 μM.[37] Dunnines A-D (**211**-**213** and **126**) could inhibit the apoptosis of PC12 cell induced by 6-hydroxydopamine with IC_{50} values in the range of 14.2–47.2 μM.[58] Claulansines N, P, and Q (**17**, **162**, **19**) exhibited good hepatoprotective activities against APAP-induced toxicity in HepG2 cells, which are comparable to bicyclol, the positive control.[18] Jejucarbazoles B (**70**) and C **(71)** displayed strong inhibition of indoleamine 2,3-dioxygenase 1 with IC_{50} values of 9.17 and 8.81 μM, respectively, while jejucarbazole A (**69**) exhibited a moderate activity with IC_{50} value of 18.38 μM.[41] 8-hydroxymahanimbine (**151**) showed potent inhibitory activity against pancreatic cholesterol esterase, with IC_{50} value of 48.56 μM.[61] Clauolenzole A (**54**) exhibited anti-HIV activity with an EC_{50} value of 2.4 μg/mL and SI of 7.1.[34] Compound **73** significantly reduced the level of violacein production and biofilm formation in *C. violaceum*, highlighting its potential as a novel quorum sensing inhibitor.[44] In antidepressant assay, 1,7-dimethoxy-2′-prenyl-1′,9-dihydropyrrolo-carbazole (**181**) and 1,7-dimethoxy-4′,5′-dimethylcyclopenta-carbazole-1′,3′-dione (**182**) could significantly inhibit the reuptake of 5-HT and NE, which was equivalent to fluoxetine hydrochloride and desipramine, respectively.[68]

Conclusion

In conclusion, in this review article, we have described the isolation and bioactivity of carbazole alkaloids. We have summarized more than 60 studies on isolation and bioactivity of carbazole alkaloids in the literature. More than 230 carbazole alkaloids with different skeletons have been isolated and identified. Majority of isolated carbazole alkaloids are from *Clausena* and *Murraya* plants. These carbazole alkaloids possess a wide range of bioactivities such as antimicrobial, anti-inflammatory, anticancer, neuroprotective, and antidiabetic activities. Due to time constrain, details about structure elucidation and bioactivities were not described. In the future, construction of carbazole skeleton and total syntheses of carbazole alkaloids will be discussed and reported.

Author Contributions

Chung Nguyen-Thi collected materials. Dung Vo-Cong prepared figures. Duc Dau-Xuan wrote the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval is not applicable to the article.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

ORCID iD

Duc Dau-Xuan https://orcid.org/0000-0002-3538-8565

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