2.04

Pyrroles and their Benzo Derivatives: Applications

GORDON W. GRIBBLE
Dartmouth College, Hanover, NH, USA

2.04.1 INTRODUCTION

Pyrroles, indoles, and, to a lesser extent, carbazoles comprise an immense group of natural products, medicinal agents, polymers, and other materials. According to Chemical Abstracts, during
the period from 1983 to early 1995, there were more than 74000 citations involving applications of these ring systems. Therefore, present coverage is severely limited, and, in some cases, is restricted to literature from the mid-1990s.

2.04.2 POLYMERS

2.04.2.1 Pyrolylres

Following the initial synthesis of polypyrrole (I) (PPy) \( \langle 68 \text{CR(C)}433 \rangle \), and the discovery of its conducting properties \( \langle 80 \text{SM}329 \rangle \), an enormous amount of work has been devoted to the study of this polymer and its possible applications. A number of reviews are available \( \langle 86 \text{CJC}76, \text{B-86MI} 204-01, 88 \text{CRV}183, 89 \text{ACR}249, 90 \text{MI} 204-01 \rangle \).

![Polypyrrole molecule](image)

Polypyrrole has been discussed as a possible electrochemical material \( \langle 83 \text{MI} 204-01 \rangle \), and this concept has been realized in the form of a PPy–Prussian blue composite as the oxidatively colored material \( \langle 92 \text{CM}1415, 94 \text{SM}17 \rangle \). PPy has also been used as a high-density information storage device \( \langle 85 \text{SM}255 \rangle \), a microwave absorber to weld thermoplastic materials \( \langle 93 \text{MI} 204-01 \rangle \), a precoat for the metallization of insulators, such as those on printed circuit boards \( \langle 93 \text{SM}3760 \rangle \), and a material for shielding electromagnetic radiation and for reducing or eliminating electromagnetic interference \( \langle 93 \text{AM} (5)281, 94 \text{MI} 204-01 \rangle \). In these applications, compared to standard metals, PPy films do not corrode, are flexible, and are lightweight.

The most intensively studied application of PPy has been in the manufacture of capacitor devices \( \langle 93 \text{MCLC}61, 94 \text{MI} 204-02 \rangle \). For example, a PPy–aluminum solid electrolyte capacitor exhibits good frequency and temperature characteristics and good thermal and moisture stabilities \( \langle 94 \text{SM}157 \rangle \). This capacitor can function continuously for more than 3600 h at 150 °C without deterioration. A PPy–Ta_{2}O_{5} capacitor has also been developed \( \langle 92 \text{MI} 204-01, 93 \text{BC}2449 \rangle \). Films of PPy function as cathodes in rechargeable lithium batteries, and are superior to conventional MnO_{2} cathodes \( \langle 91 \text{CC}986, 93 \text{SM}1495 \rangle \). PPy films have been considered as possible electrode material in supercapacitor devices and should have better performance with respect to sustained power \( \langle 94 \text{MI} 204-03 \rangle \). Polypyrrole has been incorporated in a lithographic structured conducting polymer \( \langle 90 \text{MI} 204-02 \rangle \).

The use of PPy electrodes in chemical sensor and enzyme-based biosensor devices has received extensive evaluation \( \langle 93 \text{SM}15 \rangle \). PPy film composites have been used to detect and measure ammonia \( \langle 84 \text{MI} 204-01 \rangle \), yeast metabolism \( \langle 94 \text{MI} 204-04 \rangle \), glucose levels \( \langle 86 \text{JCS(FI)1259}, 86 \text{ANC}2979 \rangle \), amino acids \( \langle 93 \text{MI} 204-02 \rangle \), ascorbic acid \( \langle 91 \text{JCS(FI)1115} \rangle \), flavin \( \langle 92 \text{MI} 204-02 \rangle \), proteins \( \langle 93 \text{MI} 204-03 \rangle \), and beer aroma components \( \langle 94 \text{MI} 204-05 \rangle \). Polypyrrole has been used as a switchable membrane to measure the permeation rates of gases from the liquid phase \( \langle 91 \text{SM}425, 92 \text{AM}4(4)428 \rangle \), and as mechanically stable and pinhole-free membranes for the electrochemical control of Na\(^{+}\)/K\(^{+}\) transport across these membranes \( \langle 94 \text{MI} 204-06 \rangle \). Related H\(^{+}\)-selective electrodes have also been developed based on PPy \( \langle 94 \text{MI} 204-07 \rangle \), and PPy has served as the reducing agent in the reduction of carcinogenic chromium(VI) \( \langle 93 \text{MI} 204-04 \rangle \). Strips of PPy have also been used as electrical muscles in various devices \( \langle 92 \text{AM}(4)277, 93 \text{MI} 204-05 \rangle \). Composite PPy materials can act as binders and releasers of cationic neuroleptic drugs \( \langle 92 \text{PI}106 \rangle \), and have also been used to bind cationic polypeptides \( \langle 91 \text{SM}979 \rangle \). Polypyrrole latex particles have been used as solid phase supports for immunoassays for the hepatitis B surface antigen, the AIDS antibody, and the pregnancy marker human chorionic gonadotropin \( \langle 92 \text{MI} 204-03 \rangle \). A nonconducting surface coated with polypyrrole serves as a sensor for ammonia and hydrazine \( \langle 90 \text{MI} 204-03 \rangle \), and a PPy-coated platinum electrode acts as a nitrate ion sensor \( \langle 90 \text{MI} 204-04 \rangle \). Silver ion can also be detected using a PPy-coated electrode \( \langle 90 \text{IEC}87 \rangle \). PPy doped with dodecylsulfate ion on a gold surface is an electrode that acts as a humidity sensor \( \langle 93 \text{SM}3671 \rangle \). A promising new composite for both sensor and electrochemical applications is PPy in montmorillonite clays \( \langle 94 \text{MI} 204-08 \rangle \).

Several simple substituted polypyrroles and polypyrrole copolymers have been prepared and studied \( \langle 83 \text{MI} 204-02, 94 \text{H(37)2069} \rangle \). For example, poly(3-alkylpyrroles) have been prepared by electrochemical polymerization and found to have conductivities comparable to that of PPy itself \( \langle 89 \text{CC}475, \ldots \rangle \).
89CC725). Likewise, the properties of a series of electrochemically polymerized 3-acylpyrroles have been reported (93SM1489). The polymerization of 3-ethylpyrrole on gold electrodes modified with pyrrole-containing alkanethiols affords a composite film that is better conducting than those from PPy (95L296, 95L302). Poly(3-methylpyrrole-4-carboxylic acid) silica composites have been used as HPLC stationary phases for protein separations (93JLC1023). Electrodes prepared from poly(N-oxaalkylpyrrole) and poly(N-butylpyrrole) have been used in solid state rechargeable lithium batteries (93MI 204-06). Novel conducting polymers consisting of bilayers with PPy and poly(N-methylpyrrole chloride) and poly(styrenesulfonate) exhibit dual ion transport depending on the potential (93CC258), and can serve as the cathode for a lithium battery (93MI 204-07). Poly(N-methylpyrrole) has been used to bind and release dopamine as a function of electrical potential (87MM1594). Novel conducting polymers made by the electrochemical polymerization of pyrroles (2)–(5) have been described (90BCJ1716). These interesting films have conductivity comparable to PPy and have distinguishable colors at different potentials and may find use in multicolor electrochromic devices. As a new, potential molecular recognition polymer, poly(3-crown ether pyrrole) has been prepared (94PP205), and a new lithium-rechargeable battery has been synthesized with the polymer from N-(3,6-dioxahexyl)pyrrole (6) as the electrolyte (91SM1147). Mixed polymers of PPy with 1,3-hexachlorobutadiene and poly(p-phenylenevinylene) have been prepared as novel electrochemical diodes and secondary batteries (91SM1495, 92CL2061). A PPy–lead dioxide composite electrode has been prepared for electroanalytical applications (92TAL481). Several polypyrroles, which are functionalized with amino acids and peptides, have been prepared and examined as enzyme recognition materials (94JA8813). An example of such a monomer is (7), the polymer from which interacts with carboxypeptidase. Oxidized PPy also forms complexes with DNA and this binding appears to be linked with the positive charge sites responsible for the observed conduction in the PPy films (92MI 204-04).

![Structures](image)

A copolymer of pyrrole and N-methylpyrrole operates as a redox switching device (91SM241), and novel conducting copolymers have been prepared from pyrrole and N-methylpyrrole with N-vinylcarbazole (93SM1483). A copolymer of pyrrole and pyrrole-3-carboxylic acid has found application as a glucose biosensor by incorporating glucose oxidase in the film (94MI 204-09). The resulting biosensor expresses higher immobilized enzyme activity than earlier PPy composites based on this enzyme. A “self-doping” polymer of alternating pyrrole and benzoquinone monomers has been fashioned (91SM435), as has been the alternating PPy–benzene polymer (8), which is conducting when doped with iodine or AsF₅ (88CC1432). The electropolymerization of the corresponding monomer has afforded (9) (89SM199), and a series of novel pyrrole-fused polycyclic aromatic hydrocarbons have been synthesized for low band gap polymers, two of which are illustrated (10).
and (11) \(94CC1019\). Several pyrrole-based extended tetrathiafulvalene systems such as (12) have been designed as potential conducting charge-transfer complexes \(92JA5035, 92TL6457\). Novel multifunctional “photorefractive polymers” such as (13) have been devised \(93JA11735\).

Since the late 1980s several innovative syntheses of polypyrroles have been discovered. The photosensitized polymerization of pyrrole in aqueous solution and in polymer matrices using tris(2,2'-bipyridine)ruthenium(II) as a photosensitizer has been reported \(89CC132\), and PPy can be photochemically deposited on to any type of surface under visible light irradiation conditions \(89CC657, 90CC387\). The preparation and potential applications of surface-functionalized polypyrrole–silica nanocomposite particles have been discussed \(94PP217\).

The unique electronic properties of polypyrroles and the mechanism of their conductivity have been the object of many theoretical studies \(94MI204-10\). The future technical applications for conducting PPy polymers seems bright indeed \(94MI204-11\).

2.04.2.2 Indoles

Compared with the extensive investigations of polypyrrole, studies of indole polymers are in their infancy. A series of substituted indoles was electrooxidized and the conductivities of the resulting polymers were measured and compared \(84JPC4343\). Electropolymerized films of indole-5-carboxylic acid are stable and show rapid response to changes in solution pH. Therefore, these polymeric films are well suited for the fabrication of micro pH sensors \(92MI204-05\), and have been utilized in a modified glassy carbon electrode to measure ascorbate and NADH levels \(93CC1629\). The electropolymerization of indole-5-carboxylic acid leads to the initial formation of trimer (14) as a major product, the structure of which has been established by NMR \(94JCS(F1)1121, 94MRC559\). The novel
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2.04.2.3 Carbazoles

The carbazole polymer poly(N-vinylcarbazole) functions as a positive electrode material for a secondary lithium battery [85CC553], and as a memory photoreceptor [91MI 204-01]. The related poly[3-(3-bromocarbazol-9-yl)propyl]methylsiloxane (18) forms novel electrochromic films [89CC196]. Carbazole anions have been used to initiate the polymerization of acrylates and methacrylates [95CC275]. The novel polymeric pyrrolocarbazole (19) displays physical properties similar to those of polyanilines.

2.04.3 DRUGS

A number of new drugs have been approved for human therapeutic use since the early 1980s that contain pyrrole, indole, carbazole, and related ring systems.

The orally active antiinflammatory drug amtolmetin guacil (20) is used for the treatment of osteoarthritis, rheumatoid arthritis, and postoperative pain [B-94MI 204-12]. Etodolac (21) is also available for these ailments [B-86MI 204-02]. Ketorolac (22) is an antiinflammatory drug with both analgesic and antipyretic activity, with efficacy comparable to morphine for the management of moderate to severe postoperative pain [B-91MI 204-02]. The tryptamine derivative sumatriptan (23) is a highly selective 5-hydroxytryptamine receptor-1 (5-HT1D) agonist and a new drug for the treatment of migraine [B-92MI 204-06]. The first 5-HT1-receptor selective antagonist for the treatment of nausea and vomiting induced by cancer chemotherapy and radiotherapy to reach the market was...
ondansetron (24) \( \langle B\text{-}91\text{MI }204\text{-}02 \rangle \), and a further such drug, also a selective 5-HT\(_3\) antagonist, is tropisetron (25) \( \langle B\text{-}93\text{MI }204\text{-}08 \rangle \).

One of the few carbazole-containing drugs is carvedilol (26), a vasodilating beta-blocker useful in the treatment of hypertension and angina pectoris \( \langle B\text{-}92\text{MI }204\text{-}06 \rangle \). Bopindolol (27) is also a potent, long-acting \( \beta \)-adrenergic blocker used to treat hypertension, and related to the well known pindolol \( \langle B\text{-}86\text{MI }204\text{-}02 \rangle \). Pergolide (28) is a potent, long-acting dopamine agonist for Parkinson’s disease \( \langle B\text{-}89\text{MI }204\text{-}07 \rangle \). The dopamine \( \text{D}_2 \) receptor agonist cabergoline (29), which is potent, selective, and long-lasting, is used as a prolactin inhibitor and has undergone clinical trials for Parkinson’s disease and breast cancer \( \langle B\text{-}94\text{MI }204\text{-}12 \rangle \). The vasoconstrictor tinazoline (30) is useful as a nasal decongestant \( \langle B\text{-}89\text{MI }204\text{-}07 \rangle \).
The novel peptide histrelin (31) is a gonadotrophin-releasing hormone agonist for the treatment of central precocious puberty and is superior to gestational agents (B-94M 204-12). A mysterious and rare disease, cosinophilia myalgia syndrome, which has afflicted more than 1500 people with 27 deaths (90M 204-05, 90M 204-06), has been traced to the contaminant (32) in some batches of dietary L-tryptophan (33) (91TL99).

![Chemical structures](image)

2.04.4 MEDICINAL COMPOUNDS

For every newly approved drug, there are dozens more promising candidate drugs undergoing detailed examination and preclinical or clinical evaluation. Even if these candidate compounds never progress to the stage of human treatment, they often provide essential insight into biochemical and pharmacological mechanisms.

2.04.4.1 Antibacterials

Few new promising synthetic antibacterial compounds have been discovered. The fluoro derivative of the pyrrole-containing irloxacin (34), is known as E3604 (35) (B-88M 204-01), and pyrrole (36) is an inhibitor of DNA gyrase and is active against methicillin-resistant Staphylococcus aureus (B-90M 204-07).

2.04.4.2 Antitumor Agents

The less toxic synthetic CC-1065 analogue, U-71,184 (37), is in preclinical development (86TL4103, 86M 204-03), and the analogues (38) are 1000 times more active against KB cells in vitro (95M 204-01). For a review of CC-1065, see (86ACR230). The interesting dimeric compounds (39) and (40) show strong DNA affinity and cytotoxicity (89JA6428, 91JA8994). The former compounds display a good correlation of binding with cytotoxicity, with the best compounds having \( n = 3 \) and 5.
A number of synthetic analogues of distamycin and netropsin have been found to have excellent antitumor activity. For example, FCE 24517 (41), which is a nitrogen mustard–distamycin hybrid, is in clinical trials <B-93MI 204-09>. The distamycin derivative (42) has increased water solubility and enhanced cellular uptake <95H(41)337>, and (43) is one of several related antitumor compounds with
potent in vitro and in vivo activity \(94\text{BMC1467}\). The netropsin tryptophan composite (44) shows strong DNA binding \(93\text{BMC2623}\). Several simple pyrroles (45)–(47) have been designed and synthesized as novel DNA interstrand cross-linking agents, similar in mechanism to mitomycin \(93\text{JA3407}\). Pyrrole (45) has also been attached to distamycin to produce the DNA cross-linking agent (48) \(93\text{JA12633}\).

2.04.4.3 Antipsychotic Agents

Rimcazole (49) binds to sigma opiate sites in the brain \(B-87\text{MI204-01}\), and roxindole (50), which is in clinical trials, is a dopamine receptor agonist \(92\text{JMC4020}\). Pyrrole (51) is three times more
effective than sultopride as an antipsychotic agent, and pyrroles (52)-(54) represent new classes of sodium-independent dopamine receptor antagonists \( \langle B-88MI 204-02, B-93MI 204-10, B-94MI 204-13 \rangle \). Indole derivatives (55)-(57), especially terguride (55) have some activity against schizophrenia \( \langle B-92MI 204-07 \rangle \).
2.04.4 Analgesics

The simple indole derivative (58) is equipotent with morphine in analgesic tests but is devoid of opioid activity (B-85MI 204-01). Likewise, (59) was prepared as an indole analogue of a known analgesic, although it lacked the desired activity (86JMC1457). The adenosine receptor agonist UP 202-32 (60) is a potent analgesic (94JMC4307), and several fused indole and pyrrole opioid antagonists such as naltrindole (61) and norbinaltorphimine (62) have been synthesized (94JMC1495, 94JMC1882).

![Chemical structures](image)

2.04.4.5 Cannabinoids

Several pyrrole- and indole-based cannibinoids such as (63) and (64) are found to exhibit biological activity comparable to $\Delta^2$-THC (94BMC563, 95TL1401).

![Chemical structures](image)

2.04.4.6 Protein Kinase Inhibitors

Several natural and synthetic inhibitors of the family of enzymes known as protein kinases have been discovered, and many of these compounds have antitumor activity. The natural indolo-carbazole alkaloids are discussed separately.

Several indolylmaleimides (65)–(67) are strong inhibitors of protein kinase C (PKC), but not
of protein kinase A (PKA) \( \langle 94 \text{BMC}1303, 94 \text{BMC}2485, 95 \text{BMC}67 \rangle \). Likewise, the synthetic indolo[2,3-\( a \)]carbazole derivatives (68)--(71) are four of the dozens of potent and selective inhibitors of PKC that have been discovered \( \langle 93 \text{BMC}1537, 94 \text{BMC}1333, 94 \text{BMC}495, 95 \text{BMC}55 \rangle \). The indole disulfide (72) is a potent inhibitor of two types of tyrosine kinases \( \langle 94 \text{JMC}2033 \rangle \), and carbazole (73) is a potent, selective inhibitor of tyrosine kinase \( \langle 94 \text{JMC}2224 \rangle \).

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2.04.4.7 Serotonin Uptake Inhibitors

In view of the importance of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) in the etiology or treatment of numerous medical problems (anxiety, depression, stroke, migraine,
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hypertension, nausea, schizophrenia, and obsessive–compulsive disorders), an enormous effort has been made to develop selective inhibitors of the various 5-HT receptors.

Indoles RU 24969 (74), (75), EMD 56551 (76), and dimer (77) are potent agonists of the 5-HT$_{1A}$ receptor (B-87MI 204-02, B-92MI 204-08, 94JMC3263, 95BMC123). Isamoltane (78) is a potent 5-HT$_{1B}$ receptor agonist (B-89MI 204-02). One of several selective 5-HT$_{1C}$ receptor antagonists to be discovered is (79) (93JMC1104). In addition to (77), compounds (80)–(82) have 5-HT$_{1D}$ receptor affinity (93BMC993, 93JMC1529, 94JMC2509). Sumatripane (23), which is also a 5-HT$_{1D}$ receptor binder, is a drug for the treatment of migraine (B-92MI 204-08). Indole (83) (CC-263) is 15 times better than sumatripane (23) at binding to the 5-HT$_{1D}$ receptor (B-92MI 204-08).
Compounds (84) and (85) bind selectively to the 5-HT<sub>2</sub> receptor (B-92MI 204-08, 93JMC3073). Indole (86) is a 5-HT<sub>2A</sub> agonist and (87) is a 5-HT<sub>2C</sub> antagonist (B-94MI 204-14). Several indoles (88)–(90) have high affinity for the 5-HT<sub>3</sub> receptor (B-92MI 204-03), and (91), which is more potent than ondansetron (24), is in clinical trials (93JMC3693). Compound (92) is one of several related compounds that is a clinical candidate for depression because of its potent and selective inhibition of serotonin uptake (93JMC1194).

2.04.4.8 Angiotensin Receptor Antagonists

A few new nonpeptide angiotensin II receptor antagonists have been synthesized (93)–(95) (93JMC101, 93JMC2253, 93JMC4230).

2.04.4.9 Cholecystokinin Receptor Antagonists

Cholecystokinin (CCK) is an important peptide involved in anxiety. A number of highly selective antagonists for CCK receptors have been discovered. For example, devazepide (L-364,718) (96) is
active at the CCK-A receptor, and is comparable in affinity to CCK itself \(\text{B-88MI 204-03}\). Indoles (97) and (98) are also selective for the CCK-A receptor \(\text{B-91MI 204-03, 93BMC867}\), and antagonists (99) (Cl-988), (100), and others are selective for the CCK-B receptor \(\text{B-91MI 204-03, 93BMC2805}\).
2.04.4.10 Anti-HIV Agents

Delaviridine (101) and ateviridine (102), which are in clinical trials, are reverse transcriptase inhibitors and prevent the spread of HIV-1 in human lymphocytes. The simple indole (103) is also an inhibitor of this enzyme, while pyrrole (104), which is in clinical trials, inhibits the Tat regulator, which is a regulatory gene product required for HIV-1 replication and which is encoded by the HIV-1 virus. Pyrrole (105) (CE-0266) is a serine proteinase inhibitor.

\[
\text{(101)} \quad R^1 = \text{NHSO}_2\text{Me}, \quad R^2 = \text{i-Pr (delaviridine)} \\
\text{(102)} \quad R^1 = \text{OMe}, \quad R^2 = \text{Et (ateviridine)} \\
\text{(103)} \\
\text{(104)} \\
\text{(105) (CE-0266)}
\]

2.04.4.11 Cholesterol Lowering Agents

Several target enzymes in the cholesterol biosynthesis pathway have been targeted in attempts to lower blood cholesterol. The HMG-CoA reductase inhibitor (106) is 10 times more potent than lovastatin, and both SQ-33600 (107) and XU 62-320 (108) also inhibit this enzyme. The indole compound SaH 57-118 (109) inhibits acyl CoA cholesterol acyltransferase and lowers cholesterol absorption in rabbits by 65%.

\[
\text{(106)} \\
\text{(107) (SQ-33600)} \\
\text{(108) (XU 62-320)} \\
\text{(109) (SaH 57-118)}
\]
2.04.4.12 Melatonin Receptor Binders

Melatonin (110) is a neural hormone that is implicated in many disorders. Several melatonin receptor antagonists and agonists have been synthesized in order to study the pharmacology of melatonin and to map its receptor, including 6-chloromelatonin (111) and (112)–(114) \( ^{\langle B-86M1~204-04,~93JMC4069,~94BMC1555,~94BMC1559 \rangle} \). Glycosyl derivatives such as (115) have been prepared to effect the brain transport of melatonin \( ^{\langle 94BMC1485 \rangle} \).

2.04.4.13 Thromboxane Synthase Inhibitors

A number of compounds have been found to inhibit thromboxane synthase, an enzyme involved in the synthesis of thromboxane \( \text{A}_2 \), which is a potent pro-aggregatory and vasoconstrictor substance thought to play a role in vascular homeostasis. For example, (116)–(118) are inhibitors of this enzyme \( ^{\langle B-87M1~204-03,~B-90M1~204-08 \rangle} \) while (119) and (120) are thromboxane receptor antagonists \( ^{\langle B-90M1~204-08 \rangle} \). The structurally interesting (121) is dual acting \( ^{\langle 92BMC979 \rangle} \).

2.04.4.14 Antiinflammatory Agents

Several disease states result from tissue inflammation and the development of new anti-inflammatory agents continues to be an important focus of pharmaceutical companies.

The indomethacin derivative cinmetacin (122) has been studied, and the indomethacin prodrugs
acemetacin (123) and proglumetacin (124) exhibit fewer gastroduodenal lesions than indomethacin in humans (B-88MI 204-04). The antiarthritis indole (125) suppresses the secondary response in rat adjuvant arthritis (B-86MI 204-05), and pyrrole (126) and carbazole (127) also display anti-inflammatory properties (B-88MI 204-04, 94JMC988).

2.04.4.15 Phospholipase Inhibitors

Compounds (128) and (129) inhibit human phospholipase A and the latter compound displays antiinflammatory activity (B-93MI 204-14).
2.04.4.16 Lipoygenase Inhibitors

Several compounds, such as (130)–(133), have been discovered to be potent inhibitors of 5-lipoygenase, an enzyme involved in the synthesis of leukotrienes from arachidonic acid. Of these agents, (133) also inhibits cyclooxygenase 〈91MI 204-04, 92BMC1655, B-93MI 204-14, 94JMC1153〉. Compound (130) (MK 591), which is also a potent inhibitor of leukotriene B₄ (LTB₄) biosynthesis, is currently in clinical evaluation 〈92BMC1395〉.

2.04.4.17 Leukotriene Synthesis Inhibitors

Compound ICl 204,219 (134) is a potent selective antagonist of leukotriene D₄ (LTD₄) and has clinical activity against antigen-induced bronchoconstriction in asthmatic patients, and Cl 949 (135) is a mediator release inhibitor which protects against allergen-induced anaphylaxis 〈B-89MI 204-04〉. Compound (136), which is very similar to (134), is a potent and selective antagonist of the peptidoleukotrienes 〈93JMC394〉.

2.04.4.18 Miscellaneous Medicinal Compounds

The simple 2-indolecarboxylic acid (137) and 1-carbazolecarboxylic acid (138) inhibit parathyroid hormone stimulated bone resorption 〈B-87MI 204-04〉. A new class of calcium ion channel activators is FPL 64176 (139) 〈93JMC2739〉, and nitropyrole (140) is related to the potassium ion channel activator cromakalin and has smooth muscle relaxant properties 〈92BMC1595〉. Pyrrole (141) is a reversible potassium ion competitive inhibitor of the gastric H⁺/K⁺-ATPase 〈B-90MI 204-09〉. Ali-
prosin (142) and aptazepine (143) are two antagonists of the \( \alpha \)-2-adrenoreceptor (B-88MI 204-05, B-89MI 204-05). Class I antiarrhythmic properties have been discovered in McN-4130 (144) (B-86MI 204-06), and two tachykinin antagonists are (145) (FK 888) and (146) (B-93MI 204-15).
Indole DPI 201,106 (147) has positive inotropic and vasodilator activity, is bradycardic and prolongs the action potential \( <B-87M204-05> \), and (148) is a cerebrovasodilator \( <B-88M204-06> \). BW A575C (149) is an angiotensin converting enzyme inhibitor-β-blocker \( <B-89M204-06> \). Several tryptophan derivatives like (150) are inhibitors of metalloproteinases \( <B-90M204-10> \) and (151) is a nonpeptide mimic of somatostatin \( <92M135> \). Indole amide derivatives of type (152) are inverse agonists at the benzodiazepine receptor \( <92JMC2214> \).

\[
\text{(147) (DPI 201, 106)}
\]

\[
\text{(148)}
\]

\[
\text{(149) (BW A575C)}
\]

\[
\text{(150)}
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\[
\text{(151)}
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\[
\text{(152)}
\]

Indole funnel web spider metabolites, such as (153), are potent NMDA antagonists \( <B-91M204-05> \), and the related synthetic (154) is a polyamine antagonist \( <B-94M204-16> \). Several antagonists at the glycine site of the NMDA receptor have been discovered, such as (155) and related indole-2-carboxylic acids \( <92M1627, B-94M204-16> \). Indole derivative (156) is an inhibitor of 5α-reductase \( <B-94M204-17> \), and the newly discovered (157) is a substance P receptor antagonist \( <95M204-02> \). Substance P is a peptide neurotransmitter implicated in the transmission of pain and in the initiation of inflammatory responses. The drug candidate GR 159897 (158) is a highly potent, orally active nonpeptide neurokinin NK₂ receptor antagonist \( <94M1951> \).

Several novel compounds have been discovered to have potential utility in the treatment of the effects of ischemia following stroke. For example, indoramin (159) increases the rate of ATP synthesis in the brain and may be useful in treating ischemia \( <B-86M204-07> \). Isatin oxime NS257 (160), which is an AMPA receptor antagonist, is a candidate for the treatment of stroke \( <94M371> \). The generation of superoxide anion, which is associated with injury to the central nervous system,
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is inhibited by OPC-1561 (161) <91JAN53>. A new inhibitor of endothelin converting enzyme (ECE) has been uncovered in indole (162) <93BMC1953>. The production of neurosteroids is linked to the mitochondrial DBI receptor complex, and several new ligands have been discovered for this complex, including indole (163) <93JMC2908>. Biindolyl (164), which is prepared from indigo, is a potent inhibitor of ATP binding to DNA A protein <94BMC1771>. This protein is involved in DNA replication. The non-peptide neurotensin (NT) mimetic (165) binds strongly to NT receptors <94BMC1241>.
The simple N-carboalkoxyisatins (166) are inhibitors of chymotrypsin \(<95BMC89\)\>, and N-alkyl-indoles (167), which form stable vesicles, serve as models for studying transmembrane proteins and, in particular, the role of tryptophan in the insertion and anchoring of membrane-spanning proteins \(<95JA1265\>\). Several compounds, (168)–(170), are potent platelet activating factor antagonists \(<B-93MI204-16, 94JMC2011, 94JMC4423\>\), and ABT-299 (169) is actually the prodrug (—AcOCH₂Cl) of an agent that is in clinical trials for the treatment of sepsis. This compound is one of the most potent antagonists of platelet activating factor yet described. The nitropyrrrole sugar (171) has been designed and synthesized to function as a universal replacement for any of the natural nucleosides in DNA \(<95JA1201\>\), and the novel tryptophan phosphoric acid analogue (172) has been described \(<92SL708\>\).

The novel biindolyl (173) and others have been constructed as possible urea binders \(<93JA12601\>\),
and "homorubin" (174) has been synthesized for study and comparison with natural bilirubin and related tetrapyrroles <94TL673>. Likewise, the pyrrole-based cryptand L (175) has been designed to act as a dicopper ligand <94CC649>.

2.04.5 DYES

Several pyroles, indoles, and carbazoles have found use both as laser dyes and textile dyes. For example, a number of pyromethene-BF₂ complexes such as (176) show broadband laser activity in the region 530–580 nm under flashlamp excitation <90HAC389>. Indoloanthraquinone (177) is an efficient laser dye in the 500–550 nm region <91BCJ3417>. Pyridocarbazole (178) is a new visible or near-IR color-former, depending on oxidation state and metal chelate complexation <92CC1114>.

Interest in indigo chemistry remains strong. Thus, the novel indigoid \textit{para}-quinodimethanes, such as (179), are known <92AG(E)1202>. The historically famous indophenine dye of von Baeyer has been reinvestigated and the product from \textit{N}-heptylisatin is found to be a mixture of several geometric
isomers, one of which is (180). The simpler compound (181), formed from only one unit of thiophene, was also reported for the first time \(<93JA11512>\).

The carbazole azo dye (182) is used for dying polyester fabrics \(<94CA(120)32867>\), and the related \(\gamma\)-carboline (183) represents a new class of dyes that is very light stable in a nylon-6 matrix \(<91DP83>\). The thiophene pyrrole derivative (184) is a novel polyester dye \(<93MI204-17>\). Diindole (185) is a new dye for instant photography \(<91JOC4576>\). In connection with possible use as light-fast dyes for wool, a series of calix[3]indoles and indole oligomers have been synthesized as novel metal ligands \(<93CC819, 93SL246>\). Examples include (186) and (187). In this regard, the novel pyrrole complex (188) has been designed and synthesized to complex uranyl ion \(<92IC529>\).
2.04.6 AGROCHEMICALS

Surprisingly, there are relatively few examples of agrochemicals or other pesticides that incorporate pyrrole, indole, or carbazole units. However, a few examples of insecticidal and herbicidal pyrrole compounds are known. Indeed, discovery of the potent antibacterial activity of the naturally produced pyoluteorin has led to several synthetic analogues of potential commercial importance. Bromopyrrole (189) proved to have the greatest herbicidal activity of 20 related pyroles \( \langle 90 \text{MI 204-11} \rangle \), and pyrrole (190) has both pre- and postemergence herbicidal activity \( \langle 90 \text{MI 204-12} \rangle \). Dibromopyrrole (191) shows strong herbicidal efficacy \( \langle 94 \text{MI 204-18} \rangle \), and cyanopyrroles (192) and (193) (fenpiclonil) are important new fungicides for cereal seed treatment \( \langle B-91 \text{MI 204-06} \rangle \). Pyrrole (194) is in commercial development as a broad spectrum insecticide and miticide \( \langle B-91 \text{MI 204-07, 94MI 204-19} \rangle \).

2.04.7 NATURAL PRODUCTS

It is impossible to cover in this short chapter the myriad natural products discovered between 1983 and 1995 that contain a pyrrole, indole, or carbazole ring. Therefore, coverage is limited to the literature since 1990 and highlights from 1983 to 1990.

2.04.7.1 Bacterial Products

A number of extraordinarily complex and biologically potent metabolites have been discovered in bacteria. Despite the existence of an estimated three million species of bacteria, only a small percentage have thus far been examined for their chemical content. A variety of structurally fascinating and biologically important compounds have been isolated from *Streptomyces* sp. For
example, a *Streptomyces* sp. produces the simple 2-acetylpyrrole (195), a compound with hepatoprotective properties (91ABC2117). Pimprinethine (196) is produced by several microorganisms, such as *S. cinnamomeus* (82JAN549), and the related WS-30581-A (197) and -B (198) are metabolites of *Streptoverticillium waksmanii* (84JAN1153). All three are similar to pimprinine (199). Pyrrolostatin (200), which inhibits lipid peroxidation in the brain, is produced by *Streptomyces chromomyceticus* (93JAN892), and glycerinopyrin (201) has been identified from cultures of *S. violaceus* (91LA77). Another *Streptomyces* sp. has yielded the antitumor BE-18591 (202) (93JAN1799). The interesting diolymics A1 (203) and A2 (204) are products of *Streptomyces* sp. (93JAN762), and hydroxytryptophan is present in aborycin, a tricyclic 21-peptide from *S. griseoflavus* (94LA741). Chromoxymycin (205) is a novel pyrrole metabolite found in cultures of *S. rubropurpureus* (85TL3273).

\[
\begin{align*}
(195) & \quad (196) \quad (197) \quad (198) \quad (199) \\
(196) & = \text{Et (primprinethine)} \\
(197) & = \text{R = n-Pr (WS-30581-A)} \\
(198) & = \text{R = n-Bu (WS-30581-B)} \\
(199) & = \text{R = Me (pimprinine)} \\
(200) & = \text{HO}_2\text{C} \\
(201) & = \text{N (pyrrolostatin)}
\end{align*}
\]

Not unlike the potent antitumor compound CC-1065, several structurally and mechanistically related compounds, the duocarmycins, such as (206), are produced by *Streptomyces* sp. These metabolites display exceptionally potent cytotoxicity activity (91JAN1045). Since the late 1980s, a series of carbazole derivatives have been found that are potent free radical scavengers. Thus, *S. chromofuscus* produces carazostatin (207) (89JAN1879), and *Streptomyces* sp. has afforded neo-carazostatins A–C (208)–(210) (91JAN903), all of which are antioxidants and inhibit lipid peroxidation. Epocarbozolins A (211) and B (212) are produced by *S. anulatus* (93JAN25), and a series of aminoacarbazoles, such as antiostatin A1 (213), is found in cultures of *S. cyaneus* (90JAN1337). Carquinoestatin A (214) is a potent neuronal cell protecting substance and radical scavenger from *S. exfoliatus* (93TL4943).

A number of related carbazoles are secreted by *Streptoverticillium ehimense*. For example, at least eight carbazomycins (e.g., (215) and (216)) have been isolated from cultures of this microbe (87JAN157, 88JAN602). Cytoblastin (217), which is related to indolactam V and the telecicins, is produced by *S. eurocidicum* (91MI 204-08), and *S. blastomycteticum* has provided blastmycin F (218) and the strong tumor promoter (-)-7-geranylindolactam V (219) (94MI 204-20). The similar pendolymics (220) and (221) are produced by *Nocardiospsis* sp., and (221) inhibits phorbol ester binding to protein kinase C (88MI 204-07, 91MI 204-09).

The interesting sulfur-containing indoles (222) and (223) have been isolated from the hyper-
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201) Glycerinopyrin

202) (BE-18591)

203) R = αOH (diolmycin A1)
204) R = βOH (diolmycin A2)

206) (duocarmycin SA)

207) (carazostatin)

208) R = OH (neocarazostatin A)
209) R = H (neocarazostatin B)
210) R = OMe (neocarazostatin C)

211) R = Me (epocarbozolin A)
212) R = Et (epocarbozolin B)

213) (antiostatin A1)

214) (carquinostatin A)
thermophilia archaea *Thermococcus tadjuricus* and *T. acidaminovorans* (93LA871). The topoisomerase II inhibitor BE 10988 (224), which contains a thiazole ring, is produced by an unidentified organism (91TL2791). The novel pyrroles cycloprodigiosin (225) and (226) are produced by the marine bacteria *Beneckea gazogenes* and *Alteromonas rubra* (83TL2701, 83TL2797, 91JAN187). Isatin (227), which is also produced by *Alteromonas* sp., protects embryos of the shrimp *Palaeomon macrodactylus* from the pathogenic fungus *Lagenidium callinectes* (89SC1116). Several related metabolites, such as chromopyrrolic acid (228) and violacein (229), have been isolated from *Chromobacterium violaceum* (93MI 204-18). The cofactor tryptophan tryptophylquinone (TTQ), which is present in bacterial methylamine dehydrogenases (*Paracoccus denitrificans*), has structure (230) (95JA1485).

Species of *Streptomyces* also produce an array of halogenated metabolites. Thus, cultures of *Streptomyces* sp. have yielded pyroxamycin (231) (87JAN961) and the optically active neopyrrolomycin (232) (90JAN1192). The novel metabolite roseophelin (233) from *S. griseoviridis* has significant cytotoxicity activity (92TL2701). Complestatin (234), from *S. lavendulae* (89TL4987), is closely related to the kistamicins found in cultures of *Microtetraspora parvosata* (93JAN1812). Complestatin is a potent inhibitor of the complement system and the kistamicins are active against
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The influenza Type A virus. Another strain of Streptomyces produces chloropeptin I, which is identical to complestatin except for the attachment of the indole ring (94JAN1173). Halogenated pyroles are also produced by Pseudomonas bacteria. Pyrrolnitrin (235), known since 1965, has been found in P. cepacia along with related pyroles (90MI204-13). Pyrrolomycins C-E (236)–(238) are produced by Actinosporangium vitaminophilum (83JAN1263, 83JAN1483). Thiazohalostatin (239), which was isolated from cultures of Actinomadura sp., has a cytoprotective effect and prevents cell death caused by calcium overload (93JAN1638). The microbe A. mellauria produces indolocarbazoles AT2433-A1 (240) and -A2 (241), which have strong antitumor and antibiotic activity (89JAN1784). The Panamanian soil microorganism Nocardia aerocolonigenes (renamed Saccharothrix aerocolonigenes) has afforded the related rebeccamycin (242) and (243) (85TL4011, 87JAN668). A Microspora sp. produces the novel cochinmicins I–III (e.g., (244)) (92JAN1709).

2.04.7.2 Fungal Products

Like bacteria, the 1.5 million estimated species of fungi are abundant on Earth and produce a multitude of secondary metabolites, many of which contain heterocyclic ring systems.

The fungus Penicillium crustosum produces an array of stunningly complex penitremes A–F, for example (245) (83JCS(P1)1857, 90CPB3473), and P. nigricans has yielded pennigritrem (246) (92JCS(P1)23). The okaramines A–F, such as (247), are produced by P. simplicissimum (91ABC3143).
The fungus *Emericella desertorum* contains several related indoles such as emindole DA (248) \(^{88\text{JCS(P1)1689}}\), and *E. nivea* has yielded the isomeric pollen growth inhibitor emeniveol \(^{92\text{TL}6987}\). Emenide PA (249) was found in *E. purpurea* from an Egyptian desert soil sample \(^{94\text{JCS(P1)1673}}\).

Species of *Aspergillus* fungi produce many different structural types such as the ochrindoles A–D, for example (250) from *A. ochraceus* \(^{94\text{MI}204-21}\), and (251) from *A. flavipes* \(^{94\text{MI}204-22}\). Several related metabolites, such as (252), which have insect antifeedant activity, were isolated from *A. flavus* \(^{88\text{JOC}5457}\). The carbazole, aflavazole, which is related to (252), is also produced by this fungus \(^{90\text{JOC}5299}\), as are the aflatremes, such as (253) \(^{92\text{MI}204-09}\). Tubingensin B (254) is produced by *A. tubingensis* \(^{89\text{TL}5965}\). A wide variety of ergot alkaloids are produced by *Claviceps* fungi, including two new fructosides of chanoclavin e (255) from *C. fusiformis* \(^{90\text{MI}204-14}\).

The fungus *Thielavia minor* contains OPC-15161 (256), which is an inhibitor of superoxide anion generation by guinea pig macrophages \(^{91\text{JAN}52}\). Fiscalin B (257) is found in *Neosartorya fischeri* \(^{93\text{JAN}545}\), and terezine D (258) is a metabolite of *Sporothrix teretispora* \(^{95\text{MI}204-03}\). The potent inhibitor of squalene synthase, viridiofungin C (259), is found in cultures of *Trichoderma viride* \(^{93\text{TL}5235}\). The fungus *Auxarthron umbrinum* produces rumbrin (260), which prevents membrane
lipid peroxidation and calcium overload, and, thus, may be useful in the treatment of myocardial and cerebral ischemia \( \langle 93\text{JAN888} \rangle \). The slime mold *Lycogala epidendrum* secretes lycogarubins A–C, for example, (261), which display some anti-HSV-1 virus activity \( \langle 94\text{TL2559} \rangle \).

### 2.04.7.3 Marine Natural Products

Since the mid-1980s there has been an explosion of activity in the area of marine natural products isolation and characterization.
Marine sponges have furnished a rich collection of pyrroles, indoles, and a few carbazoles—many of which are halogenated. The simple pyrroles (262) and (263) have been isolated from *Agelas oroides* (94MI 204-23), from which oridon had earlier been isolated. Another *Agelas* sp. afforded
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Midpacamide (267) and (268) are found in *A. mauritiana* (88CL803). Kermadine (269) is produced by an Okinawan *Agelas* sponge and is a novel antagonist of serotonergic receptors (84TL2475). Another study of an Okinawan *Agelas* sp. revealed the anti-leukemic agelasine G (270) (92CPB766). The Fijian *A. mauritiana* contains (267) as well as mauritamide A (271) (94TL1375), and the Caribbean *A. clathrodes* produces clathrodin (272) (3-debromohymenidin) (91MI 204-10). A set of dimeric sceptrins, such as (273) and ageliferins, such as (274), have been isolated from *A. sceptrum* and *A. conifera* (89PAC525, 91JOC2965). Some of these metabolites are potent actomyosin ATPase activators (90T5579).

\[
\begin{align*}
&\text{(256) (OPC-15161)} \\
&\text{(257) (fiscalin B)} \\
&\text{(258) (terezine D)} \\
&\text{(259) (viridiofungin C)} \\
&\text{(260) (rumbrin)} \\
&\text{(261) (lycogarubin A)}
\end{align*}
\]
Hymenodin (275), which is an antagonist of serotonergic receptors, is found in an Okinawan *Hymeniacidon* sp. (86El176). This sponge also produces manzacidins A–C (e.g., 276) (91JOC4574), as well as several new cyclic heptapeptides that contain tryptophan (93T2391). The Sri Lankan sponge *Lissodendoryx* sp. contains the simple pyrrole (277) (85MI 204-02), and the novel chlorinated phorbazoles A–D (e.g., 278) are produced by *Phorbas aff clathrata* sponge (94TL2589). Species of the sponge *Trikentriion* have yielded several novel pyrrole and indole metabolites, including trikentramine (279) from *T. loeve* (90TL2979), and a series of trikentrins (e.g., 280) from *T. flabelliforme* (86T6545). The Western Australian sponge *Axinella* sp. produces the related herbindoles A–C, such as (281), which have cytotoxic and antifeedant activity (90T3089). The Western Indian ocean *Axinella cf. carteri* sponge produces the cytotoxic tryptophan-containing cyclic peptide axinstatin 4 (93H(35)711). The three brominated indoles (282)–(284) are released by the sponge *Oceanapia bartschi* (92ZN(B)408), and (283) is also found in the sponges *Pleroma menoui* (89ZN914), *Plocamissma igzo* (93MI 204-19), and *Pseudosuberites hyalinus* (93MI 204-20), as well as in the coral *Dendrophyllia* sp. (89HCA1444). The deep water sponge *Pseudosuberites hyalinus* also contains 6-bromoindoles (285)–(288) (93MI 204-20), and *Pleroma menoui* from the Coral Sea produces (289) and (290) (93MI 204-20). Penaresin (291), which is 10 times more potent than caffeine as a calcium inducer, is found in the Okinawan sponge *Penares* sp. (90H(31)2205). The New Caledonian sponge *Corallistes undulatus* produces serotonin and acrylate derivatives (292)–(294) (93MI 204-21). An *Ircinia* sp. from Okinawa contains indole-3-acrylic acid (debmopopensin) and the novel cytotoxic tryptophan derivative.
konbamidin (295) (94MI 204-24). The sponge Plocamissma igzo has also yielded igzamide (296) (93MI 204-19).

Several tryptamines are also found in marine sponges. Thus, (297) and (298) have been identified in Smenospongia aurea (85T1039), and d-6-bromohaphtorine (299) is found in Aplysina sp. (94MI 204-25). The Palauan sponge Chelonaplysilla sp. is the source of chelanon A (300) and B (301) (91JOC4403). The sponge Discodermia polydiscus, collected in deep Bahamian waters, contains the cytotoxic (302) (91JOC4307). A number of related sponge metabolites having two indole rings have been discovered since the late 1980s, only a few of which are shown here. For example, topsentin B2 (303) has been found in the Mediterranean sponge Topsentia genitrix (87CJC2118), the deep water Caribbean sponge Spongostorites sp. (88JOC5446, 91JOC4304), and the British Columbian sponge Hexadella sp. (90T715). The latter study also identified dragmacidon A (304) and related metabolites.
A deep-water Caledonian sponge (Gellius or Orina sp.) produces the novel tris-indoles gelliusines A and B (306) as a pair of diastereomers \(94\text{MI} 204-26\). The sponge *Tedania ignis* contains a series of simple indoles (307)–(310) and carbazole (311), although some of the former may be isolation artifacts \(91\text{MI} 204-11\). A large number of imidazolinyln-indoles have been discovered in sponges and soft corals—including isoplysin A (312) from *Aplysina* sp. \(94\text{MI} 204-25\); for a leading reference, see \(94\text{T224}\). The photochemical isomerization of these metabolites has been investigated \(89\text{HCA1444}\). The unique tripeptide hemiasterlin (313) has been isolated from *Hemieasterella minor* \(94\text{TL4453}\). The sponge *Dictyodendrilla* sp. produces three reductose inhibitors such as (314), which contains the unique pyrrolo[2,3-\(c\)]carbazole spirolactone ring system \(93\text{JOC7632}\).

Several indole-containing cyclic peptides are found in sponges. For example, *Jaspis johnstoni* produces jaspadine (315), which contains the rare 2-bromotryptophan amino acid and which is a potent antitumor, antifungal, and insecticidal compound \(86\text{JA3123, 86TL2797, 87MI 204-06}\). The Okinawan sponge *Theonella* sp. has yielded several structurally similar peptides, such as orbicularamide A (316) \(91\text{JA7811}\), and keramamides A–H, J (e.g., 317) \(91\text{JA7812, 95T2525}\). The deep-sea sponge *Discoderma* sp. contains several novel peptides, such as polydiscamid A (318) \(92\text{JOC1767}\) and discobahamins A and B \(94\text{MI} 204-27\).

Marine tunicates have also afforded several indole- and pyrrole-containing natural products of structural and biological interest. For example, the Brittany tunicate *Dendrodoa grossularia* has furnished several novel indoles, such as grossularine-1 (319) and (320) \(86\text{TL2621, 89T3445}\). The Gulf
of California tunicate *Didemnum candidum* produces 6-bromotryptamine (321) and the bis-indole (322) (91MI 204-12), while a tunicate from Fiji (*Polycitorea mariae*) contains citorellamine (323) (87TL749). The solitary ascidian *Halocynthia roretzi* produces halocymamines A (324) and B, which inhibit the growth of fish viruses and marine bacteria (90B159). The Philippine ascidian *Polyandrocarpa* sp. produces polyandrocarpamides A–D, (such as (325) and (326)) (90TL2521), and *Eusynstelya misakiensis* has yielded the novel eusynstelyamide (327) (94MI 204-28). An ascidian *Polycitor* sp. produces the novel polycitrins A (328) and B (329), and polycitone A (330) (94JOC999). When disturbed, the marine ciliate *Pseudokeronopsis rubra* secretes the four chemical defense agents keronopsins (331)–(334) (94AG(E)1495).

The marine ascidian *Atapozoa* sp. produces the new tambjamine E (335) and F (91ES04), and wakayin (336) is the first pyrroloiminoquinone from an ascidian (*Clavelina* sp.) (91JOC4596). This
compound is cytotoxic and exhibits topoisomerase II inhibitory activity. The Caribbean ascidian *Lissoclinum fragile* has furnished the novel eudistomin U (337) and isoeudistomin U (338) (94MI 204-28). The ascidian *Diazena chinensis* contains the potent cytotoxic diazonamides A (339) and B (340) (91JA2303). Bryozoans, or “moss animal,” have yielded a rich array of novel metabolites, ranging from the simple indoles (341)-(343) from *Zoobotryon verticillatum* (93MI 204-22) to the extraordinarily intricate chartellines A-C (e.g., 344) (85JA4542) and chartellamides A (345) and B (87JOC5638). The bryozoan *Sessibugula translucens* and their predatory nudibranchs *Tambjeello* and *T. abdere* contain tambjamine B (346) and others (83JOC2314). The bryozoan *Bugula dentata* also contains tambjamines G-J (94AJC1625), similar in structure to (346), and the blue pigment (347) (86E84).

Marine acorn worms have proven to be a rich source of natural indoles, most of which were isolated prior to 1983 (B-83MI 204-03). More recent examples include (348)-(350) from *Ptychodera* sp. (87T1063) and *Glossobalanus* sp. (85E1487). The marine worm *Polphysia crassa* produces the antibacterial and labile 2,3,4-tribromopyrrole (351) (90MI 204-15). An *Aplysia* sp. sea hare contains bromoindoles (352) and (353) (89IC(B)322). The long and fascinating history of the ancient royal indigoid dyes from *Murex* molluscs (74MI 204-01, B-83MI 204-03) continues in 1992 with the isolation for the first time of 6-bromoindigotin (354) from *M. trunculus* (92MI 204-10). The Japanese Ivory shell, *Babydosia japonica*, produces several highly toxic compounds, including prosurugatoxin (355) (85CPB2890), although it now appears that bacteria associated with this animal actually produces these toxins (85CPB3059). Likewise, bacteria (*Vibrio parahaemolyticus*) from the toxic mucus of the boxfish *Ostracion cubicus* produce vibrindole A (356) and (357) (94MI 204-29). The mollusc *Monodonta labio* from Japan produces monodontamides D (358) and E (359) (94T6805).
Seaweeds produce an array of novel compounds including those that contain the indole or pyrrole ring. For example, the red alga *Gracilariopsis lemaneiformis* from Oregon contains the simple pyrroles (360) and (361) <91MI 204-13>, and nostodione A (362) is a mitotic arrestor from a blue-green alga <94MI 204-30>, which is related to the dimeric scytomenin (363), the structure of which has been determined <93E825>. This blue-green algal metabolite is a photoprotective pigment present in many fresh water algae. The seaweed *Martensia denticulata* produces denticins A–C (e.g., 364),
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which have antiphotooxidative activity \(\langle94\text{MI} 204-31\rangle\). The novel sulfur-containing itomanindoles A and B \((365)\), the bis-indole \((366)\), and several other brominated sulfur-containing indoles are found in the red alga \textit{Laurencia bronziartii} \(\langle88\text{TL}6091, 89\text{TL}7301\rangle\). The bis-indole \((367)\) is the latest of several such metabolites to be found in the blue-green alga \textit{Rivularia firma} \(\langle91\text{MI} 204-14\rangle\). The blue-green alga \textit{Polypothrix tjipanasensis} is the source of 15 new indolo[2,3-a]carbazoles, the tjipanazoles, which include \((368)-(370)\) \(\langle91\text{TL}7739\rangle\).

A large number of chlorinated indoloisonitriles and related indoles have been isolated from the
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(335) (tambjamine E)

(336) (wakayin)

(337) (eudistomin U)

(338) (isoeudistomin U)

(339) $X = \text{H, } R = \text{COCH(NH$_2$)CHMe}_2$
(340) $X = \text{Br, } R = \text{H}$ (diazonamide B)

(341) $R = \text{CH}_2\text{NMe}_2$
(342) $R = \text{CH}_2\text{N(O)Me}_2$
(343) $R = \text{CHO}$

(344) (chartelline A)

(345) (chartellamide A)

(346) (tambjamine B)

(347)

(348) $X = \text{Br, } Y = \text{H}$
(349) $X = \text{Y = H}$
(350) $X = \text{H, } Y = \text{Me}$

(351)

(352) $X = \text{H}$
(353) $X = \text{Br}$
blue-green alga *Hapalosiphon fontinalis* (87JOC1036). Two of these hapalindoles are shown as (371) and (372). The terrestrial blue-green alga *Fischerella muscicola* has yielded fischerindole L (373) (92TL3257), while *F. ambiguа* produces ambiguous isonitrile F (374) along with other similar metabolites (92JOC857). The oxindole (375) has also been cultured from *Hapalosiphon fontinalis* (89P1565), and *H. welwitschia* and *Westiella intricata* produce several complex indoles, the major metabolite of which is (376) (94JA9935). The blue-green alga *Lyngbya majuscula* contains lyngbyatoxins B (377) and C in addition to teleocidins (90MI204-16). The compound responsible for the bioluminescence of krill (*Euphausia pacifica*), which was isolated in 1968, has been shown to be (378) (93TL2779), and is similar to the dinoflagellate (*Pyrocystis lunula*) luciferin (89JA7607).
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(363) (sytonemin)

(364) (denticin A)

(365) (itomanindole B)

(366)

(367)

(368) (tijpanazole A1)

(369) (tijpanazole I)

(370) (tijpanazole J)

(371) (hapalindole A)

(372) (hapalindole E)

(373) (fischerindole L)
2.04.7.4 Plant Products

The myriad indole-containing plant alkaloids of the indoloquinolizidine type and other types are not covered. The list of simple indole, pyrrole, and carbazole plant alkaloids, which is discussed here, is far shorter.

Several simple pyroles have been discovered in plants. For example, the poisonous mushroom *Clytocybe acromelalga* contains pyrrole amino acid (379) \( \langle 91\text{CL}1541 \rangle \), and *Aster tataricus* produces the pyrrole-containing peptides asterinins A–C (e.g., 380) \( \langle 94\text{P}945 \rangle \). The Chinese herbal medicine *Pseudostellaria heterophylla* has yielded (381) \( \langle 88\text{MI}204-08 \rangle \). The interesting metabolite (382) of zeatin riboside from tobacco crown gall cells has been identified \( \langle 90\text{TL}1419 \rangle \). The Mexican folk plant *Quararibea funebris* has yielded several novel pyroles, including funebrine (383), funebral, and funebradiol (384) \( \langle 90\text{M}1204-17 \rangle \). The epilupinine derivative (385), and a related compound, are found in the plants *Virgilia divaricata* and *V. oroboides* \( \langle 91\text{P}1891 \rangle \). The complex 9,21-didehydroryanodine (386) is produced by *Ryania speciosa* \( \langle 84\text{CC}1265 \rangle \).

Several terrestrial plants utilize methyl 4-chloroindole-3-acetate (387) and acid (388) as growth hormones, including peas and beans. Studies in the late 1980s have involved *Vicia faba* (fava bean) \( \langle 87\text{ABC}3081 \rangle \), *V. amurensis* \( \langle 87\text{MI}204-07 \rangle \), and *Pinus sylvestris* \( \langle 86\text{MI}204-08 \rangle \). Green peas (*Pisum sativum*) also contain (S)-4-chlorotryptophan (389) and malonyl derivatives (390) and (391) \( \langle 93\text{TL}1057 \rangle \), and *V. faba* contains (389) and 4-chloro-6-methoxyindole (392) \( \langle 92\text{P}2327 \rangle \).
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(383) (funerbiline)

(384) (funerbadiol)

(385)

(386)

(392)

(393) (monatin)

(394)

(393), which is 1400 times sweeter than sucrose, is produced by Schlerochiton ilicifolius \( \langle 92 \text{JCS(P1)3095} \rangle \). The simple enone (394) is found in Pamburis missionis \( \langle 94 \text{P879} \rangle \), and indolone (395) has been isolated from the edible mushroom Pleurotus salmonostramineus \( \langle 94 \text{A8849} \rangle \). This labile compound may play a very important part in the photochemical generation of oxygen from water. Paniculidin A (396) and B (397) and paniculol (398) have been characterized from Murraya paniculata \( \langle 85 \text{CPB1770, 90 \text{JCS(P1)2047} \rangle \), and M. gleniei has yielded the novel bis-indole (399) \( \langle 90 \text{TL5217} \rangle \). Another bis-indole, sciodelol (400), is found in Tricholoma sciodes \( \langle 94 \text{M1204-32} \rangle \), and the fruit bodies of this plant as well as those of \( T. \) virgatum produce simple indoles (401)-(403) \( \langle 94 \text{T3571} \rangle \).

The novel indole dimers peronatin A (404) and B and two related oxygenated compounds are...
found in *Collybia peronata* and *Tricholoma scalpturatum*, respectively, and (<94MI 204-33>). Several indole derivatives have been isolated from the roots of *Esenbeckia leiocarpa*, including *leiocarpatriol A* (<405>) and *leiocarpane* (<406>) (<90G387>). In view of their suspected anticancer properties, cruciferous vegetables have been extensively examined for their chemical content. For example, kale, broccoli, collards, and brussels sprouts contain varying amounts of indoles (<407>)–(<409>) (<88MI 204-09), and Chinese cabbage (*Brassica campestris*) when inoculated with *Pseudomonas cichorii* produces the phytoalexins brassinin (<410>) and (<411>) (<86CC1077, 90PI499), and several brassicanals (<412>)–(<415>) (<91E304>). White cabbage (*B. oleracea*) produces similar compounds when provoked by *Pseudomonas cichorii* (<90PI499). Dithyreanitrile (<416>) is an insect antifeedant produced by *Dithyrea wislizenii* (<91E304), and camalexin (<417>) forms in the leaves of *Camelina sativa* (false flax) following elicitation by the fungus *Alternaria brassicae* (<91T3909>.

Yuehchukene (<418>) is a biogenetically novel alkaloid produced by *Murraya paniculata* (<85CC47>), as is spermacoecine (<419>) (*Borreria verticillata*) (<91P997>). Caulerpinic acid (<420>) is the latest of several similar indole alkaloids to be found in *Caulerpa racemosa* (<91P3041>). The acetylcholinesterase inhibitor, crooksidine (<421>), was isolated from *Haplophyton crooksii* (<93P217>), and *Evodia rutaecarpa* contains (<422>) (<88MI 204-10). In addition to containing aspidochibine, *Aspidosperma quebracho*
blanco has yielded (423), a compound that has apparently been formed by indole ring cleavage \( \langle 91\text{TL4949} \rangle \). Monomargine (424), which also contains a novel structure, is found in Monocarpia marginalis and has cytotoxicity activity \( \langle 93\text{TL1795} \rangle \). Also of biogenetic interest is the growing group of alkaloids from Aristotelia and several examples are known. Thus, \( A. \text{chilensis} \) contains (425) \( \langle 90\text{P1354} \rangle \), \( A. \text{fruticosa} \) has yielded aristofruticosin (426) \( \langle 88\text{TL3355} \rangle \), and \( A. \text{australasica} \) has provided the new 17-hydroxyhobartine (427) \( \langle 90\text{ML}204-18 \rangle \). Several novel tryptophan-containing cyclic peptides have been identified in orange (\( \text{Citrus sinensis} \)) \( \langle 91\text{ABC2923} \rangle \).

Over the years, numerous carbazole-containing alkaloids have been discovered in plants, and several examples have been reported. Glycozolid (428) is found in Glycosmis pentaphylla \( \langle 85\text{MI}204-03 \rangle \), and several carbazoles, such as (429)-(431), are produced by Clausena excavata \( \langle 92\text{CPB1069}, 93\text{P449}, 94\text{BMC2395} \rangle \), by \( C. \text{harmandiana} \) (e.g., 432) \( \langle 88\text{MI}204-11 \rangle \), and by \( C. \text{lansium} \) (e.g., 433) \( \langle 91\text{P343} \rangle \).
Species of *Murraya* are also rich sources of carbazole alkaloids, such as the cytotoxic koenoline (434) and (435) from *M. koenigii* ⟨85P3041, 94P1073⟩, and the novel (436)–(438) from *M. siamensis* ⟨90MI 204-19⟩. Several carbazoles related to (438) have been isolated from *M. euchrestifolia*, such as murrayamine A (439) ⟨91P1048⟩, eustifoline A (440), furostifoline (441), and others ⟨90CPB1548⟩. In addition, this Taiwanese plant contains several novel binary carbazole alkaloids, such as mur-rastifoline B (442), chrestifoline B (443), and oxydimurrayafoline (444) ⟨87CPB450, 90CPB1143⟩. Dimer (445) was identified in *M. exotica* ⟨92MI 204-11⟩. In 1995, clausenal (446) was isolated from *Clausena heptaphylla* ⟨95P787⟩.

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2.04.7.5 Miscellaneous Natural Products

A few instances of pyrrole-, indole-, carbazole-containing natural products are known from insects and higher animals, in addition to tryptophan-containing peptides.

The funnel-web spider *Argiope* sp. produces argiotoxins 659 (447) and the related 673 (B-89MI 204-08). These compounds exhibit excitatory amino acid antagonism. The ladybird beetle *Exochomus quadripustulatus* contains exochomine (448) (92TL1281), and a very similar compound chilocorine is secreted by the ladybird beetle *Chilocorus cacti* (94T2365). The Amazonian frog *Phylomedusa bicolor* produces a tryptophan-containing peptide that interacts with an adenosine receptor and which is used by the natives as a stimulant for “hunting magic” (92PNA(89)10960). Another indole

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peptide, spinorphin, first isolated from the bovine spinal cord, is a natural inhibitor of enkephalin-degrading enzymes. The first carbazole of any type to be isolated from mammals was 3-chlorocarbazole (449), a compound that exhibits potent monoamine oxidase inhibition and is present in bovine urine. Isatin (227) has been shown to be identical with “tribulin” and is present in human urine and rat brain and heart. This compound is a monoamine oxidase inhibitor and is a normal constituent of tissues and body fluids of both humans and rats.