# 1
# Introduction

## 1.1 Preview

From its early isolation by Baeyer from the reaction of indigo with a mixture of sulfuric acid and sulfuric anhydride [1], indole—*in*digo + *ol*eum—has a remarkable history and has made a huge impact on society, as we will see in this chapter. The reader is referred to several general reviews on the chemistry and synthesis of indoles [2–11] and their role in society [12]. Reviews devoted solely to indole ring synthesis are tabulated in Section 7 in this chapter.

## 1.2 Indole-Containing Natural Products

Indole (**1**) itself has several interesting natural sources, the most familiar of which is mammalian feces [13, 14], although its toxicity is low ($LD_{50}$ = 1,100 kg/mg in rats) [15]. Indole has also been identified in significant amounts in flowers (jasmine, narcissus, lilac, Easter lily, lemon flower, tuberose, and honeysuckle) and in trace amounts in other flowers and foods (clove, orchid, gardenia, coffee flower, *Daphne odora*, tomato, molasses, sesame seed, rye bread, cheese, aged casein, and aging fish) [15]. Despite its objectionable and pervasive odor at high concentration, at low levels indole as been used by perfumers to augment fragrances. The odor threshold of indole is 140 parts per billion, significantly higher than, for example, methyl mercaptan (0.02 ppb) and dimethyl sulfide (0.30–1.00 ppb) [15]. Indole is also a component of human sweat [16] and breath [17]. Indeed, almost 30% of the volatile head space of sweat is due to indole [16]. Along with several other odorants, indole is attractive to mosquitos (*Anopheles gambiae*) [18].

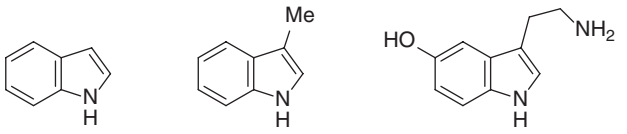
Other well-known indoles that have various natural sources are skatole (3-methylindole) (**2**), serotonin (**3**), L-tryptophan (**4**), tryptamine (**5**), the plant growth hormones 3-indoleacetic acid (**6**) and 4-chloro-3-indoleacetic acid (**7**) [19], the mushroom hallucinogen psilocin (**8**), and the indole-derived ancient dyes indigo (**9**) [20] and Tyrian Purple (**10**) [19] (Scheme 1).

The vast marine environment, which covers 70% of Earth's surface, provides a wealth of naturally occurring indoles, and several reviews are available [21–24]. According to Hamann, 95% of the marine tropical biosphere accounts for 34 of the 36 phyla of life on Earth [24]. Some recently discovered marine indoles are depicted in Scheme 2. Several eusyntyelamides (e.g., D (**11**)) were isolated from the Arctic bryozoan *Tegella* cf. *spitzbergensis* [25], and the indole **12** was discovered in the marine fungus *Aspergillus sydowii* [26]. A New Zealand ascidian *Didemnum* sp. has furnished the β-carboline alkaloid didemnidine B (**13**) [27], and the toxin, bunodosine 391 (**14**) is part of the venom of the sea anemone *Bunodosoma cangicum* [28]. The Arctic hydrozoan *Thuiaria breitfussi* has yielded the novel breitfussin B (**15**) [29]. Tribromoindole (**16**) was found in the red alga *Laurencia similis* collected from Hainan Island, China, along with two other tribromoindoles [30].

Our terrestrial environment also contains a wealth of naturally produced indoles, and some recent examples are shown in Scheme 3 [31–38]. The novel thiazolylindole barakacin (**17**) was found in the ruminal bacterium *Pseudomonas aeruginosa* strain Z10 [31]. Spirobacillene A (**18**) was isolated from a culture of *Lysinibacillus fusiformis* KMC003 derived from coal mine acidic drainage [32]. The Chinese plant *Alocasia*

COPYRIGHTED MATERIAL

*Indole Ring Synthesis: From Natural Products to Drug Discovery*, First Edition. Gordon W. Gribble.
© 2016 John Wiley & Sons, Ltd. Published 2016 by John Wiley & Sons, Ltd.



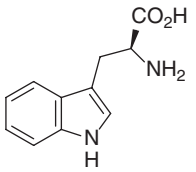
Indole (**1**)



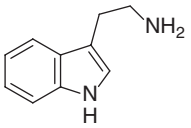
Skatole (**2**)



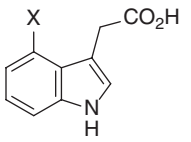
Serotonin (**3**)



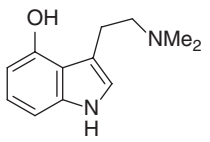
L-Tryptophan (**4**)



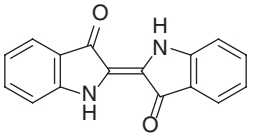
Tryptamine (**5**)



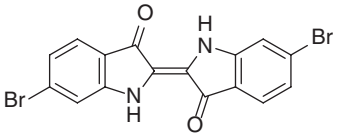
Indoleacetic acid (**6**, X = H)
4-Chloro-3-indoleacetic acid (**7**, X = Cl)



Psilocin (**8**)

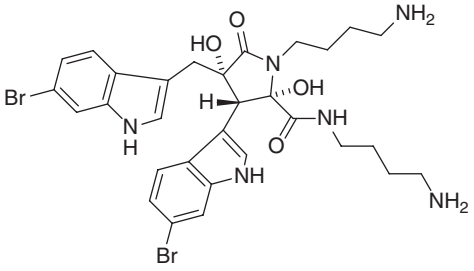


Indigo (**8**)

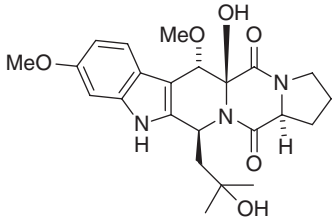


Tyrian Purple (**9**)

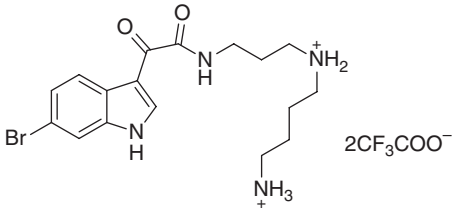
***Scheme 1*** *Well-Known Common Natural Indoles*



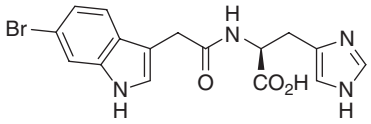
Eusynslyelamide D (**11**) [25]



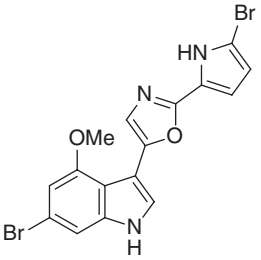
**12** [26]



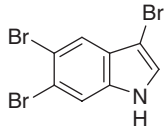
Didemnidine B (**13**) [27]



Bunodosine 391 (**14**) [28]

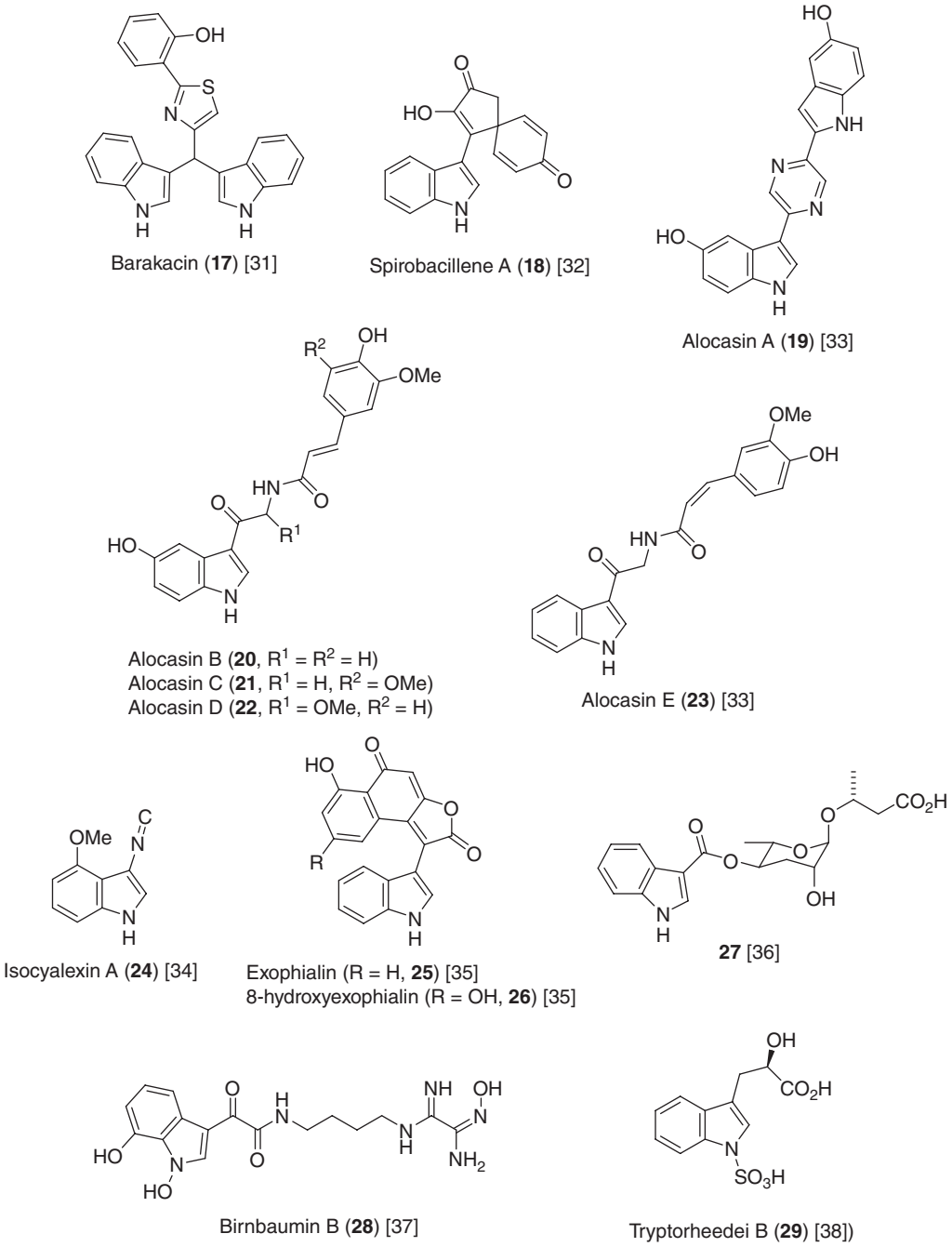


Breitfussin B (**15**) [29]



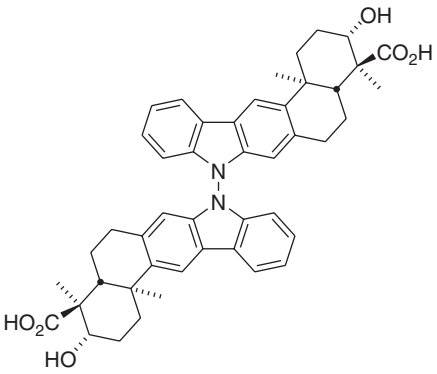
**16** [30]

***Scheme 2*** *Representative Newly Discovered Marine Indoles*

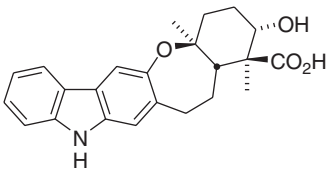



***Scheme 3*** *Representative Recently Discovered Terrestrial Indoles*

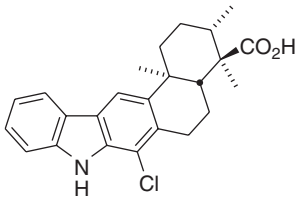
*macrorrhiza* has yielded the five new indole alkaloids alocasins A–E (**19–23**) [33]. Isocyalexin A (**24**) is the first plant-derived isocyanide to be discovered, isolated from rutabaga roots (*Braesica napobrassica*) [34]. The human pathogenic fungus *Exophiala dermatitidis* generates exophialin (**25**), and 8-hydroxyexophialin (**26**) is found in cultures of the mutant strain Me1-1 of *Exophiala dermatitidis* [35]. A component of the dauer larval stage pheromone of the nematode *Caenorhabditis elegans* is indole **27** [36]. The novel tryptorheedei B (**29**) is found in the seeds of *Entada rheedei*, a large woody liana growing in tropical Africa and Southeast Asia [38]. The corresponding *N*-sulfonyl-L-tryptophan (tryptorheedei A) accompanies **29**.



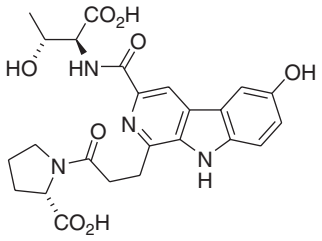
Dixiamycin A (**30**) [39]
Dixiamycin B (**31**, atropodiastereomer) [39]



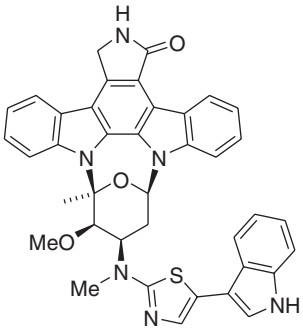
Oxiamycin (**32**) [39]



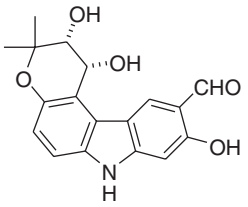
Chloroxiamycin (**33**) [39]



6-Hydroxymetatacarboline D (**34**) [40]



Fradcarbazole A (**35**) [41]



Clausenawalline K (**36**) [42]

***Scheme 4*** *Representative Recently Discovered Carbazoles, Carbolines, and Indolocarbazoles*

Carbazoles and the related indolocarbazoles represent a huge collection of natural products, and some recently discovered examples are shown in Scheme 4. A marine *Streptomyces* sp. SCSIO02999 has yielded four new carbazolo-sesquiterpenes, dixiamycins A (**30**), B (**31**), oxiamycin (**32**), and chloroxiamycin (**33**) [39]. The novel β-carboline **34** is found in the mushroom *Mycena metata* [40], and the extraordinary fradcarbazole A (**35**) is one of three related indolocarbazoles produced by the marine *Streptomyces fradiae* [41]. A series of new carbazole alkaloids, clausenawallines G–K (e.g., **36**), was isolated from twigs of *Clausena wallichii*, a folk medicine plant distributed throughout Southeast Asia [42].

## 1.3 Biological Activity of Indoles

All indoles probably have some biological activity. Kumar and colleagues have briefly tabulated the range of activities that indoles possess [43]. More generally, Rosén and colleagues compare the chemical space that is occupied by natural products and bioactive compounds as a strategic starting point for drug discovery [44]. Section 3 presents biological activities of indoles, and Section 4 covers those bona fide indole-containing pharmaceuticals.

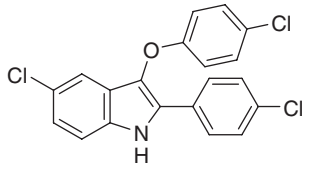
A growing worldwide problem is drug resistance to disease-inflicting bacteria, such as MRSA (methicillin-resistant *Staphylococcus aureus*) [45, 46]. Several indoles

show promise in treating these bacterial infections, such as aryloxyindole **37** [47], 2-aryl-5-nitroindole **38** [48], cationic peptide **39** [49], and pacidamycin D (**40**) [50]. Biofilm infections cause 17 million new cases and up to 550,000 fatalities per year in the United States. Menthyl indole **41** is very active against biofilm formation induced by several strains of *S. aureus* [51] (Scheme 5).

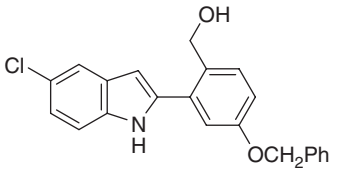
Marine biofouling is a major problem to the shipping industry, but not to sponges, many of which produce antifouling compounds that inhibit settlement and smothering by barnacle larvae (*Balanus improvisus*). Some of these indole compounds are shown in Scheme 6. The novel cyclopeptide bromobenzisoxalone barettin **42** was isolated from the marine sponge *Geodia barretti* [52], and the marine ascidian *Stomoza murrayi* contains several brominated indole-3-carbaldehydes such as tribromoindole **43**, both of which prevent larval settlement or overgrowth by other marine species [53]. The physostigmine-like alkaloid urochordamine A (**44**) from the tunicate *Ciona savignyi* has potent larval settlement and metamorphosis-promoting activity at 2 μg/mL [54]. The Mediterranean gorgonian *Paramuricea clavata* contains several antifouling indoles, such as 2-bromo-*N*-methyltryptamine (**45**) [55].

Antifungal activity is seen with indole RWJ-61907 (**46**), which inhibits the growth of *Saccharomyces cerevisiae* and *Candida albicans* [56]. The *N*-methylcryptolepine salt **47** shows activity against *Cryptococcus neoformans* and *C. albicans*, two fungi associated with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and *Aspergillus flavus* [57]. Antiparasitic activity is observed for several indole diamidines, such as **48**, which is active against *Trypanosoma brucei rhodesiense* and *Plasmodium falciparum* [58]. The glycosyl-isoindigo derivative **49** is active *in vitro* against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi Tulahuen* (Chagas disease), *Plasmodium falciparum* (malaria), and *Leishmania donovani* (leishmaniasis [59]) (Scheme 7).

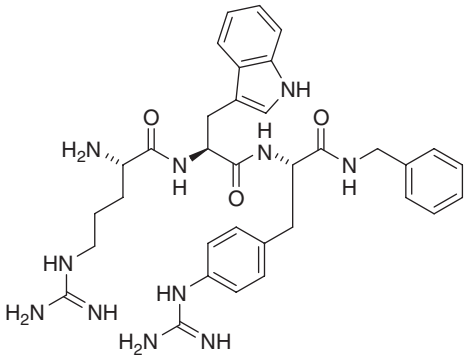
The final stage of HIV disease is AIDS. At the end of 2011 some 34 million people were living with HIV worldwide, and 1.7 million AIDS-related deaths were reported in 2011 [60]. Although these figures are lower than they were ten years ago, HIV drugs are still in great demand. Several indole derivatives show promise in this area (Scheme 8). Notably, indolyl aryl sulfones (e.g., **50** [61], **51** [62], **52** [63]), indole-3-sulfonamides (e.g., **53** [64]),



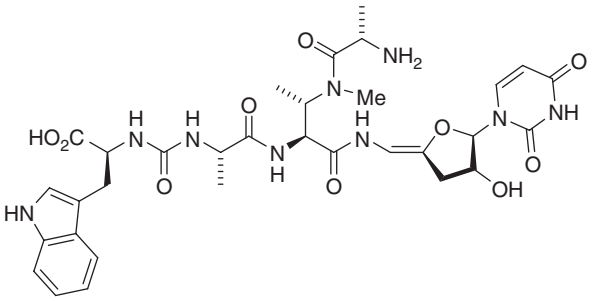

**37** [47]



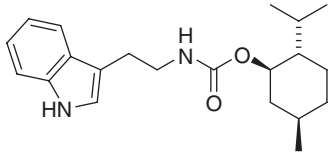

**38** [48]




**39** [49]

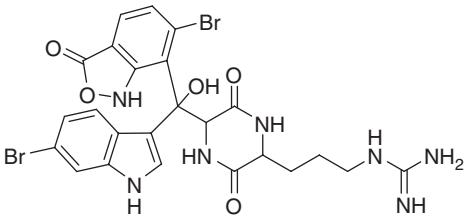



Pacidamycin D (**40**) [50]

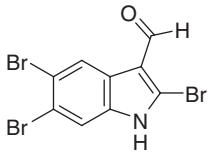



**41** [51]

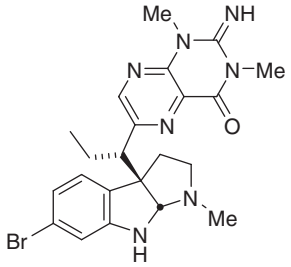
***Scheme 5*** *Representative Antibacterial Indoles*



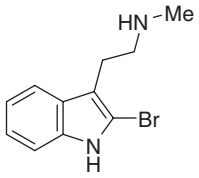
Bromobenzisoxazole barettin (**42**) [52]



**43** [53]

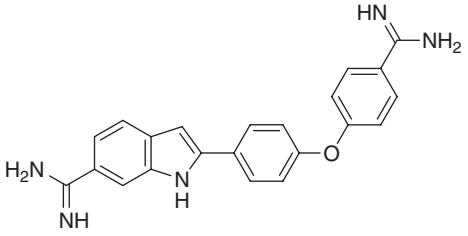


Urochordamine A (**44**) [54]

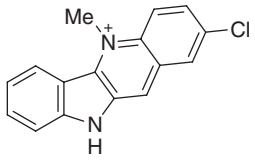


2-Bromo-*N*-methyltryptamine (**45**) [55]

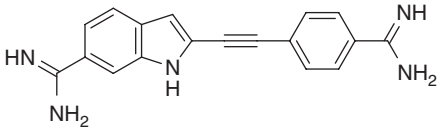
***Scheme 6*** *Representative Antifouling Indoles*



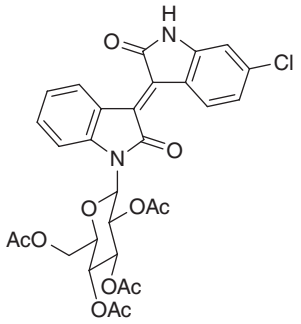
RWJ–61907 (**46**) [56]



**47** [57]



**48** [58]

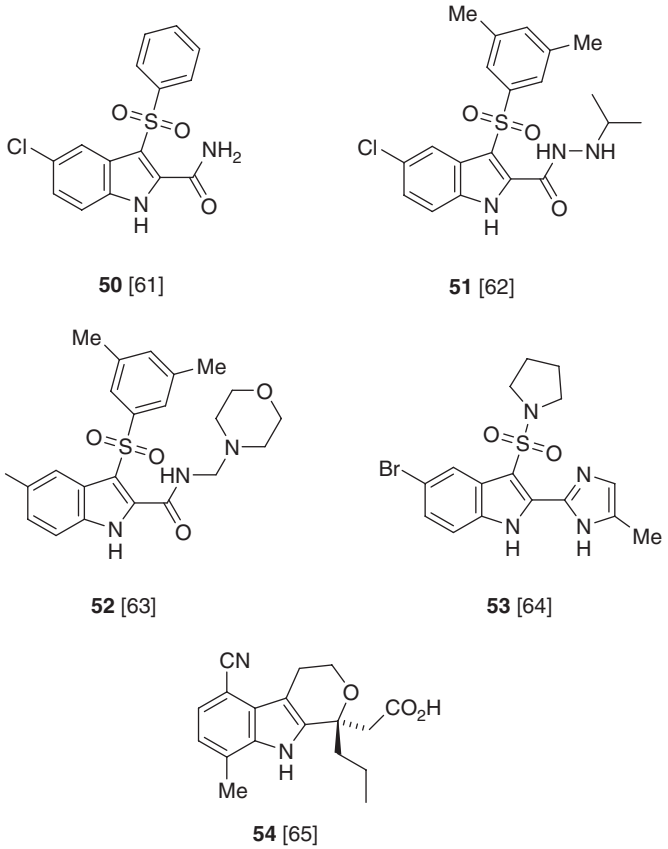


**49** [59]

***Scheme 7*** *Representative Antifungal and Antiparasitic Indoles*

and pyrano[3,4-*b*]indoles (e.g., **54** [65]), are active as potent non-nucleoside reverse transcriptase inhibitors (**50–53**), and **54** is a selective hepatitis C virus (HCV) RNA polymerase inhibitor. The development of predictive quantitative structure–activity relationship (QSAR) models for anti-HIV indolyl aryl sulfones has been described [66].

A number of indoles and carbazoles possess antiinflammatory activity (Scheme 9). Thus, indoles **55–57** are three of several cyclooxygenase (COX) inhibitors based on the structure of thalidomide [67]. Whereas **55** shows no COX-1 activity and only weak COX-2 activity, indole **56** displays potent COX-1 activity and modest COX-2 activity. Indole **57** shows strong inhibition of both enzymes. Several




**50** [61] **51** [62]

**52** [63] **53** [64]

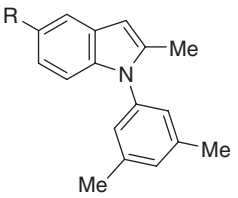
**54** [65]

***Scheme 8*** *Representative HIV Active Indoles*

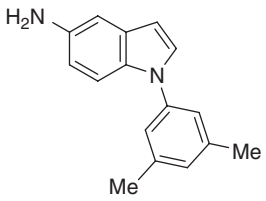
2-phenyl-3-(sulfonylphenyl)indoles (e.g., **58**) are potent and selective COX-2 inhibitors and possess higher activity than celecoxib [68]. Likewise, indole Schiff base **59** is a highly selective COX-2 inhibitor ($IC_{50} = 0.32\,\mu M$; COX-1, $IC_{50} > 100\,\mu M$) [69]. Furo[3,2-*b*]indole FI–302 (**60**) is a nonulcerogenic antiinflammatory compound with potency superior to that of the nonsteroidal antiinflammatory drugs (NSAIDs) mepirizole and tiaramide [70]. The carbazole carprofen (**61**) is a multitarget-directed ligand that inhibits COX-1, COX-2, and a fatty acid amide hydrolase (FAAH), and it is the starting point for the synthesis of many analogues [71]. Several indomethacin derivatives have been designed and synthesized to evaluate their inhibitory effects on COX, P-glycoprotein, and multidrug resistance [72]. Indole **62** is a potent inhibitor of matrix metalloproteinase–13 (MMP-13), a protein that functions in cartilage homeostasis [73]. The *Streptomyces* sp. HKI0231 indoles 0231A (**63**) and 0231B (**64**) are inhibitors of 3α-hydroxysteroid dehydrogenase, an enzyme involved in inflammatory processes [74, 75], and thus may be excellent lead structures as new antiinflammatory agents. The novel prostaglandin $D_2$ receptor antagonist **65** was developed for the treatment of allergic rhinitis, an inflammatory disease [76].

Cancer and cardiovascular disease not withstanding, obesity and diabetes are major global health problems. Several indoles have potential activity in this area (Scheme 10). Indoles **66** and **67** show significant antidyslipidemic activity and weight loss in hyperlipidemic rats, and these compounds represent a new class of hypolipidemic and antiobesity agents [77]. Tetracyclic indole **68** is a melanin-concentrating hormone receptor 1 (MCHR1) antagonist and is effective in reducing food intake in rats and monkeys [78]. *N*-Benzoylindole **69** is a potent liver X receptor (LXRβ) agonist and may exhibit antidiabetic activity of type 2 diabetes by reversing cholesterol accumulation and raising plasma high-density lipoprotein cholesterol (HDL) levels [79]. As a peptidomimetic agonist for the human orphan receptor BRS–3, indole **70** may find use in the treatment of obesity [80].

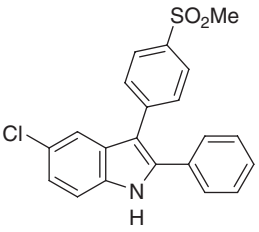
Serotonin (5-hydroxytryptamine [5-HT], **3**) receptors play an essential role in mediating neurotransmission and in so doing they influence memory, learning, sleep, aggression, anxiety, appetite, mood, and other neurological functions [81, 82]. These dozen or so receptors are targets for drugs to treat depression, pain, psychosis, sleep, learning disorders, insulin secretion, epilepsy, schizophrenia, and



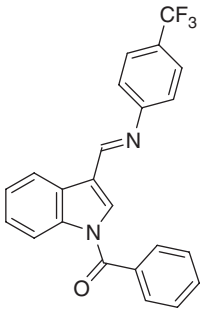
**55** [67], R = $NO_2$
**56** [67], R = $NH_2$



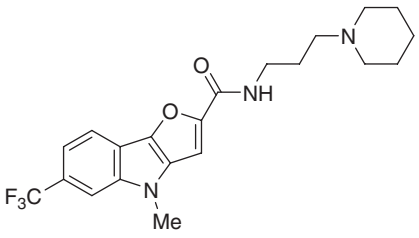
**57** [67]



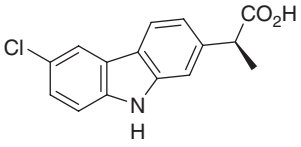
**58** [68]



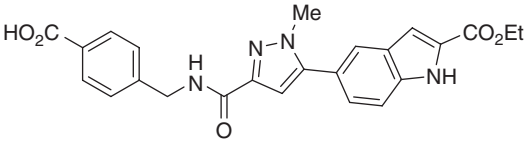
**59** [69]



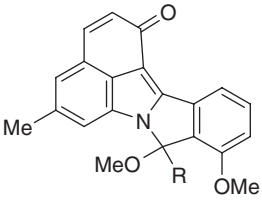
FI–302 (**60**) [70]



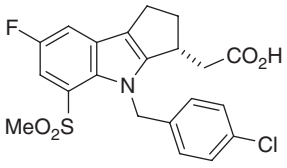
Carprofen (**61**) [71]



**62** [73]



0231A, R = OMe (**63**) [74], [75]
0231B, R = H (**64**) [74], [75]

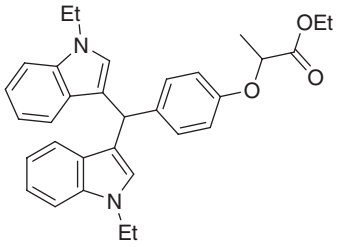


**65** [75]

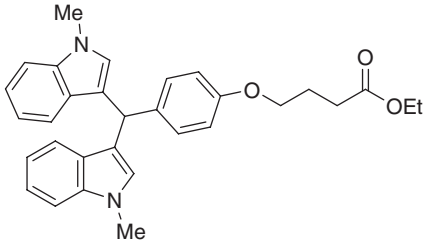
***Scheme 9*** *Representative Antiinflammatory Indoles*

other biological dysfunction. Several indoles bind to various 5-HT receptors (Scheme 11), including the drug sumatriptan (Section 4). A review of the 5-HT receptor subtype 5-$HT_6$ has appeared [83]. Indole **71** is remarkably selective as an agonist toward 5-$HT_{1D}$ versus 5-$HT_{1A}$ [84], and **72** is a potent and selective 5-$HT_6$ receptor antagonist having subnanomolar inhibition of the production of adenylate cyclase [85]. Indole **73** also has very high and selective affinity for 5-$HT_6$ as an agonist [86], and **74** is a selective antagonist for 5-$HT_6$ [87].

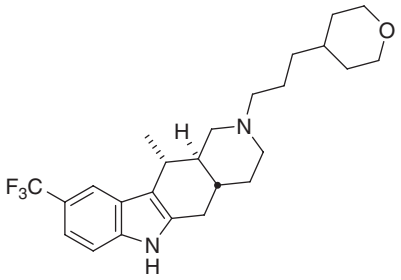
In addition to the anticancer indole alkaloids vinblastine and vincristine, discussed in the next section, many indoles display antitumor activity. Space does not allow complete coverage of these studies. Indole-3-carbinol (Scheme 12, **75**), found in vegetables of genus *Brassica* (kale, cauliflower, broccoli, turnip, collard, and others), its acid- and/or enzymatic-induced dimer, 3,3′-diindolylmethane (**76**), and its trimer, 2-(indol-3-ylmethyl)-3,3′-diindolylmethane (**77**), inhibit cancer cell proliferation and induce apoptosis in several cell lines [88–91]. However, one study reports that



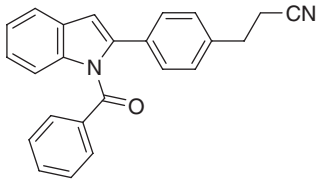

**66** [77]



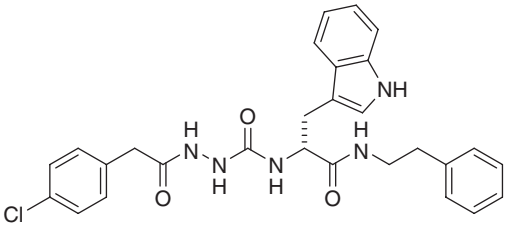

**67** [77]




**68** [78]

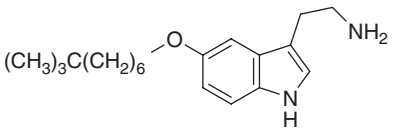



**69** [79]

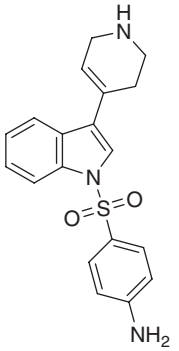



**70** [80]

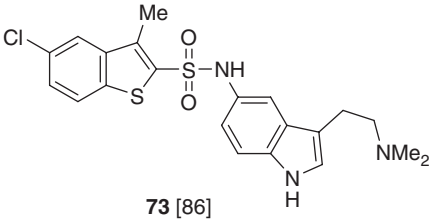
***Scheme 10*** *Representative Antiobesity Indoles*



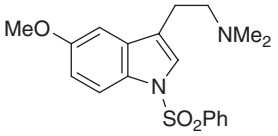

**71** [84]




**72** [85]

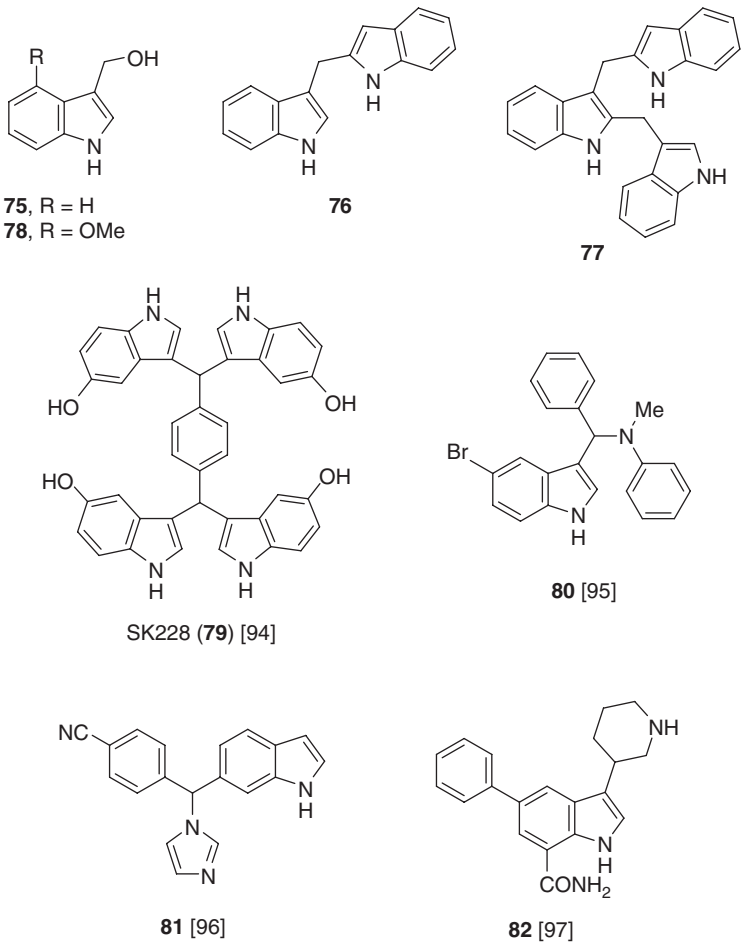



**73** [86]




**74** [87]

***Scheme 11*** *Representative Indoles that Bind to 5–HT Receptors with High Affinity*

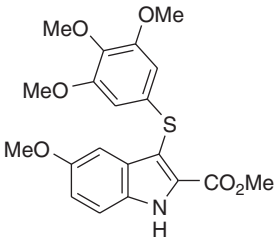



***Scheme 12*** *Representative Indoles with Antitumor Activity*

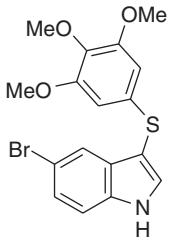
3,3′-diindolylmethane (**76**) is a liver carcinogen in trout by an estrogenic pathway [92]. A more potent inhibitor of human colon cancer cell proliferation than **75** is 4-methoxyindole-3-carbinol (**78**), which is a metabolite of 4-methoxyglucobrassicin formed during ingestion [93]. The novel 5-hydroxy tetraindole **79** (SK228) induces $G_2$ arrest and apoptosis in human breast cancer cells [94], and several indoles of type **80** inhibit cell proliferation of human colon cells (HT–29), human ovarian cells (SK–OV–5), and c-src kinase activity [95]. Indolyl imidazole **81** is a potent inhibitor of aromatase (CYP19) ($IC_{50}$ = 11.5 nM), suggesting activity against breast cancer [96]. Indole-7-carboxamide **82** is a potent inhibitor of the serine–threonine kinase (IKK-β), which regulates an important signaling pathway [97].

An important strategy for the treatment of cancer is the modulation of microtubule assembly either by preventing its disassembly or by blocking tubulin polymerization, and an excellent review is available that discusses several indole leads [98]. For example, Silvestri and colleagues report that arylthioindoles are potent inhibitors of tubulin polymerization [99–101]. For example, **84** inhibits the growth of MCF-7 cells at $IC_{50}$ = 13 nM [99], and **85** is the most potent antitubulin agent discovered thus far [101] (Scheme 13). A number of indole-3-carbaldehydes and their corresponding imines inhibit tubulin polymerization and inhibit the growth of breast cancer cells; for example, imine **86** (MCF-7, $IC_{50}$ = 27 nM; MDA-MB 231, $IC_{50}$ = 6 nM) [102]. 5′-Methoxyindirubin (**87**) induces cell death in human neuroblastoma cells (IMR-32, SK-N-SH, NB-39) without affecting normal cells (NHDF and HUVEC) [103].

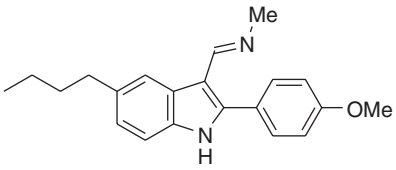
A large number of naturally occurring indoles display antitumor activity, but only a limited number can be illustrated here (Scheme 14). Cultures of *Aspergillus ochraceus* WC76466 produce stephacidins A (**88**) and B (not shown), both of which are selective inhibitors of prostate LNCaP cells, and they also show activity against a panel of other tumor cell lines [104]. The Panamanian soil microbe *Nocardia aerocolonigenes* (now reclassified as *Saccharothrix aerocolonigenes)* produces rebeccamycin (**89**) and 4′-deschlororebeccamycin (**90**), which have potent anticancer activity [105, 106] and an analogue is in human cancer trials (Section 4). A deepwater Palauan



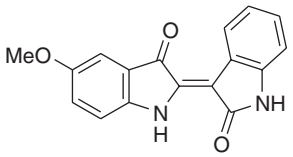
**84** [99]



**85** [101]

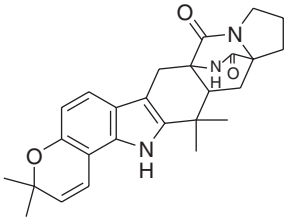


**86** [102]

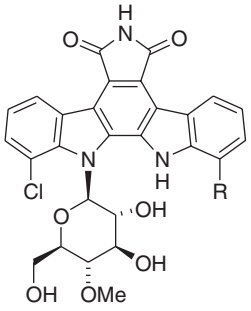


**87** [103]

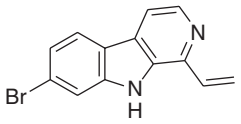
***Scheme 13*** *Representative Indoles with Tubulin Inhibitory Activity*



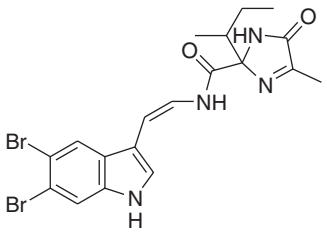
Stephacidin A (**88**) [104]



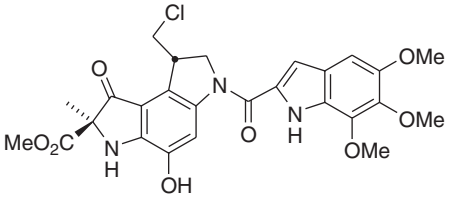
Rebeccamycin (**89**, R = Cl) [105]
Rebeccamycin (**90**, R = H) [106]



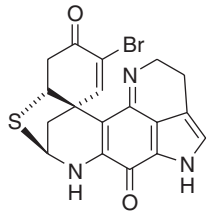
Plakortamine B (**91**) [107]



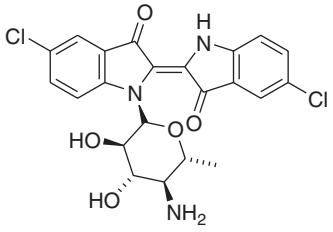
Kottamide D (**92**) [108]



Pyrindamycin A (**93**) [110]



Discorhabdin A (**94**) [112]



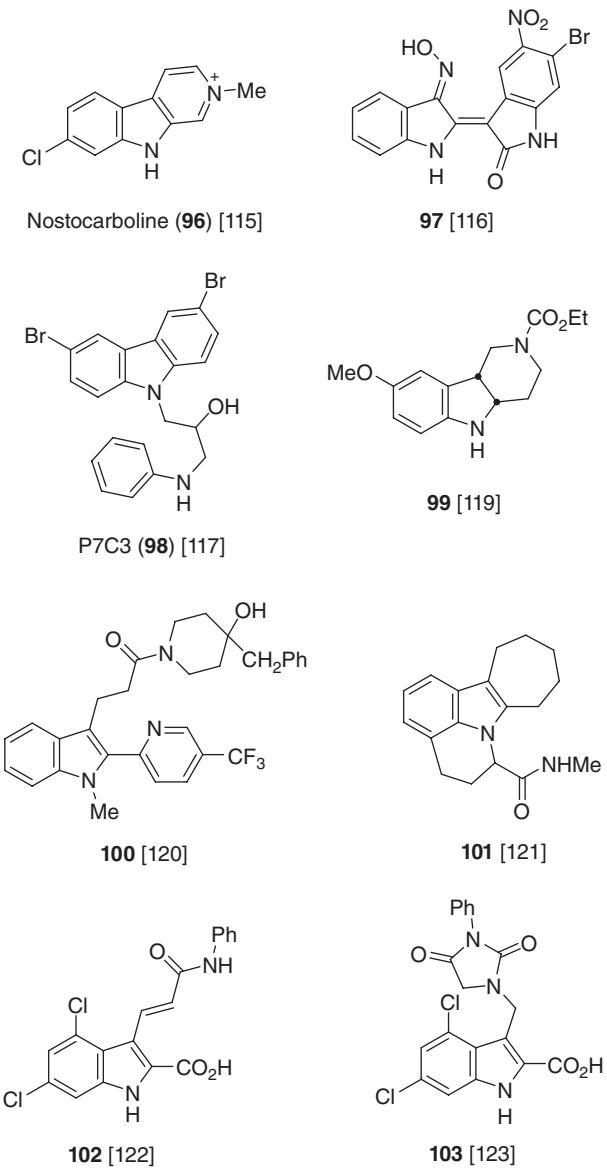
Akashin A (**95**) [113]

***Scheme 14*** *Representative Natural Indoles with Antitumor Activity*

sponge, *Plakortis nigra*, produces several plakortamines, the most active of which against HCT-116 human cancer cells is plakortamine B (**91**) [107]. The New Zealand ascidian *Pycnoclavella kottae* contains the indoles kottamides A–E [108, 109], one of which, kottamide D (**92**), inhibits the proliferation of HL60 cancer cells [108]. Pyrindamycin A (= duocarmycin $C_2$) (**93**) is a potent antitumor metabolite from *Streptomyces* SF2582 [110, 111]. The New Zealand sponge *Latruncula* sp. has yielded several discorhabdins, such as discorhabdin A (**94**), having potent cytotoxic activity [112]. A terrestrial *Streptomyces* sp. has furnished akashins A–C (e.g., **95**), which have antitumor activity against several human cancer cell lines [113].

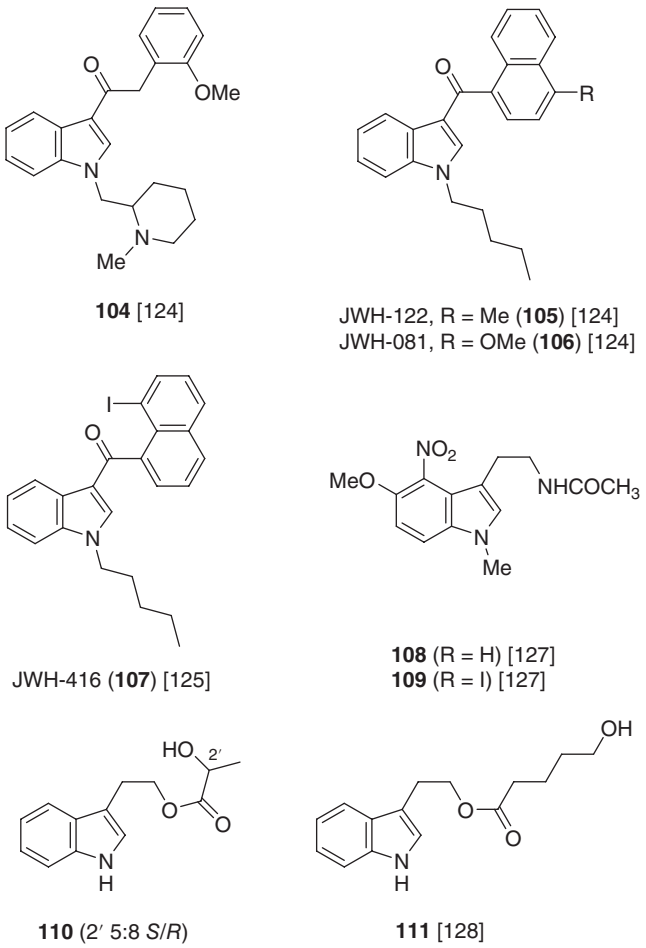
In addition to the major diseases we have discussed, numerous other disease conditions and biological syndromes are affected by indoles. For example, several β-carbolines show acetylcholinesterase activity [114], and the natural nostocarboline (**96**), from the freshwater cyanobacterium *Nostoc* 78-12A, has butyrylcholinesterase inhibitory activity comparable to that of galanthamine, a drug approved for the treatment of Alzheimer's disease (Scheme 15) [115]. Several synthetic indirubins are inhibitors of glycogen synthase kinase-3 (GSK-3), a kinase involved in abnormal hyperphosphorylation of proteins and the production of β-amyloid peptides and neurofibrillary tangles, a cascade of events thought to develop into Alzheimer's disease. One such active GSK-3 inhibitor is indirubin **97**. These indirubins also inhibit cyclin-dependent kinases (CDKI/cyclin B and CDK5/p25) [116]. Dibromocarbazole P7C3 (**98**) is a neuroprotective synthetic compound that could find utility in the protection of the hippocampus, the degeneration of which is associated with Alzheimer's disease [117, 118]. Thus, P7C3 and analogues protect newly born neurons from apoptosis, and thus they may represent a new therapy for Alzheimer's patients.

A new set of dihydroindoles, related structurally to the neuroprotective stobadine, has been developed that diminishes the toxicity of stobadine. For example, hexahydro-1*H*-pyrido[4,3-*b*]indole **99** displays improved neurological efficacy over that of stobadine [119]. A new human neurokinin-1 ($hNK_1$) receptor antagonist, 2-arylindole **100,** is one of several simple compounds that exhibit both good receptor-binding affinity and brain penetration. The $hNK_1$ receptor in the central nervous system is a potential target for the treatment of depression, anxiety, and drug-induced emesis [120]. A collection of tetracyclic indoles, such as **101**, possesses anticonvulsant activity [121], and 4,6-dichloroindole **102** inhibits convulsions induced by *N*-methyl-D-aspartate (NMDA) in mice. This potent *in vivo* antagonist acts at the strychnine-insensitive glycine-binding site [122]. A similar indole with excellent affinity for the glycine site of the NMDA receptor is 2-indolecarboxylic acid **103** [123].




***Scheme 15*** *Representative Biologically Active Indoles – 1*

The new cannabimimetic phenylacetylindole cannabipiperidiethanone (Scheme 16, **104**) is an adulterant found along with two other previously known synthetic cannabinoids, JWH-122 (**105**) and JWH-081 (**106**), in a Japanese herbal product [124]. These illegal designer drugs have potent affinity for the cannabinoid $CB_1$ and $CB_2$ receptors. Huffman and colleagues have developed structure–activity relationships at both of these receptors for 3-(1-naphthoyl) indoles [125]. For example, one compound, JWH-416 (**107**), has the desirable combination of very good $CB_2$ affinity but low $CB_1$ affinity, although many others are also selective for the former receptor [125]. A review of this area is available [126]. A study of the melatoninergic binding site $MT_3$ has found that 4-nitroindole melatonin




**104** [124]

JWH-122, R = Me (**105**) [124]
JWH-081, R = OMe (**106**) [124]

JWH-416 (**107**) [125]

**108** (R = H) [127]
**109** (R = I) [127]

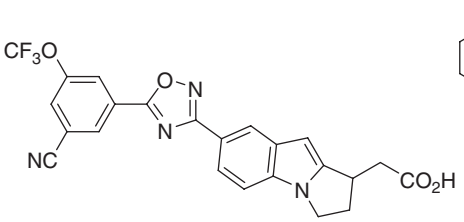
**110** (2′ 5:8 *S*/*R*)

**111** [128]

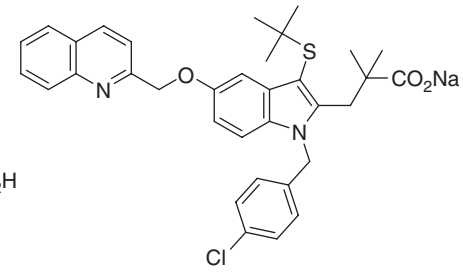
***Scheme 16*** *Representative Biologically Active Indoles—2*

derivative **108** is both potent and selective for the $MT_3$ receptor. The 2-iodo analogue **109** is also selective for $MT_3$, and the radiolabeled iodine-125 version might be used to characterize the $MT_3$ binding sites [127]. Indole esters **110** and **111** were isolated from the yeast *Pichia membranifaciens* living on the marine sponge *Halichondria okadai*. Both novel compounds have DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity [128].

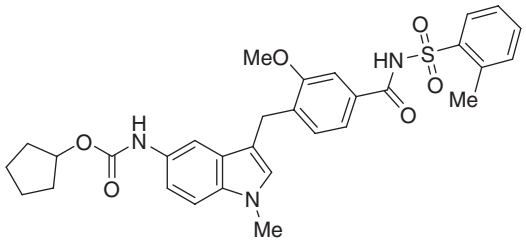
Several tricyclic indoles have been discovered to be potent and selective $S1P_1$ agonists. *In vivo* these compounds significantly reduce circulating lymphocytes, which in turn depresses the circulation of autoreactive immune cells. The net effect is to slow progression of multiple sclerosis. Indole **112** (Scheme 17) is the most potent compound tested that lowered the flowing lymphocytes in mice with autoimmune disease [129]. Such compounds may also act on astrocytes to reduce inflammation in the central nervous system. The antiinflammatory leukotriene modifier MK-0591 (**113**) is a FLAP (5-LO-activating protein) inhibitor that was efficacious in initial human asthma trials but was later withdrawn [130–132]. FLAP is a protein that is essential for the biosynthesis of leukotriene [133]. Zafirlukast (**114**) is a leukotriene receptor antagonist that has been marketed for the treatment of asthma since 1996 in the United States and is now available in at least 60 countries [132]. This drug reduces mucus buildup and constriction of the airways and lungs. Some *Nephila* spider polyamine toxins have an indole anchor, such as NPTX-8 (**115**) and NPTX-1 (**116**) secreted by *Nephila clavata*. These toxins are the most potent polyamine kainate receptor antagonists reported to date. Moreover, NPTX-1 (**116**) shows an extraordinary selectivity for GluK1 receptors over GluN1/2A type NMDA (>40,000 fold) and GluA1 type AMPA (>150 fold) receptors [134]. The indole headgroup is important for maximum inhibitory activity because other spider polyamines with a phenolic (resorcinol) headgroup are much less active. Inhibition of these ionotropic glutamate (iGlu) receptors is a promising tactic for the treatment of pain, stroke, and Alzheimer's disease [135–137]. Synthetic analogues of the indole alkaloid



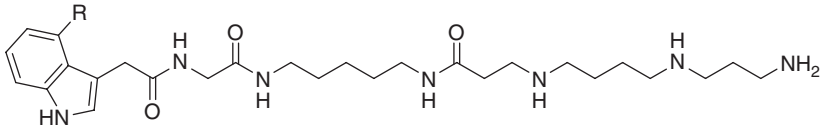
**112** [129]



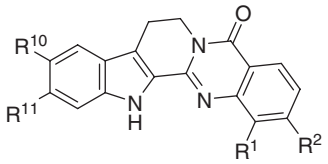
MK-0591 (**113**) [130], [131]

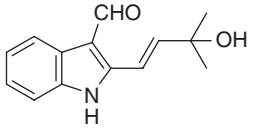


Zafirlukast (**114**) [133]



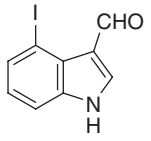
NPTX-8, R = H (**115**) [134]
NPTX-1, R = OH (**116**) [134]



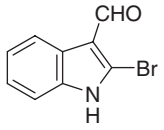


**121**

**117**, $R^1$ = OMe, $R^2$ = $R^{10}$ = $R^{11}$ = H
**118**, $R^1$ = $R^2$ = OMe, $R^{10}$ = $R^{11}$ = H
**119**, $R^{10}$ = OMe, $R^1$ = $R^2$ = $R^{11}$ = H
**120**, $R^{11}$ = OMe, $R^1$ = $R^2$ = $R^{10}$ = H



**122**



**123**

***Scheme 17*** *Representative Biologically Active Indoles—3*

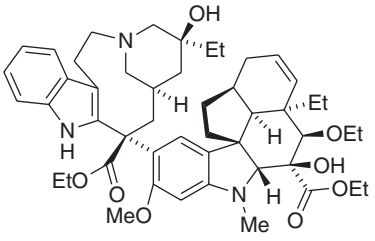
rutaecarpine are found to be potent and selective inhibitors of members of the human cytochrome P450-1 (CYP1) family of enzymes [138]. Thus, 1-methoxyrutaecarpine (**117**) and 1,2-dimethoxyrutaecarpine (**118**) are highly selective for CYP1A2, whereas 10- (**119**) and 11-methoxyrutaecarpine (**120**) are most selective for CYPB1 enzyme. These P450 enzymes play a critical role in the detoxification of foreign chemicals such as polycyclic aromatic hydrocarbons. The plant growth regulator indole-3-acetic acid (**6**) and synthetic derivatives have been employed by Somei to convert desert areas into green tracts of plants and grass as a means to combat global warming and prevent further deforestation (desertification). Three of these SOMRE (*Som*ei, *r*oot, and *e*longation) indoles are shown (**121–123**) that are intended for the greening of, for example, the Gobi desert in China. Applications of SOMRE

indoles to sword bean (*Cryptomeria japonica*) and Chinese medicine plants (*Forsythia viridissima* and *Glycyrrhiza*) are currently under way, and future target plants include sugar cane, rubber trees, and grasses [139].

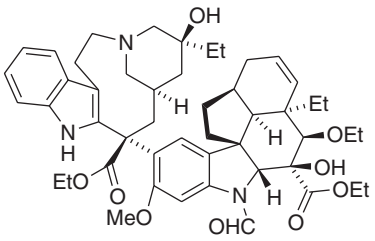
## 1.4 Indole-Containing Pharmaceuticals

A number of indoles are in current use as pharmaceuticals, and the number is certain to grow in the future, as indole remains a fundamental privileged scaffold [140].

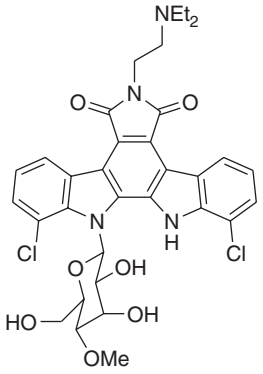
Several anticancer drugs are indoles, the most famous of which are the *Catharanthus roseus* plant alkaloids vinblastine (**124**) and vincristine (**125**) (Scheme 18), both of which continue to be important drugs for the treatment of Hodgkin's disease, childhood leukemia, and other cancers [141–143]. The rebeccamycin analogue NSC-655649 (**126**) is in phase II trials for the treatment of metastatic renal cell cancer [144]. An analogue of the antitumor CC-1065, bizelesin (**127**), is in human clinical trials for the treatment of solid tumors (kidney, stomach, colon, ovary, uterus, and others) [145]. One patient with advanced ovarian cancer



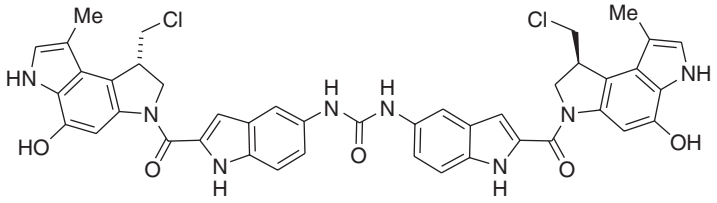

Vinblastine (Velban™) (**124**)



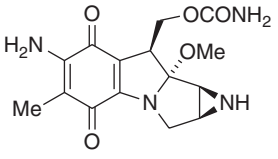

Vincristine (Oncovin™) (**125**)



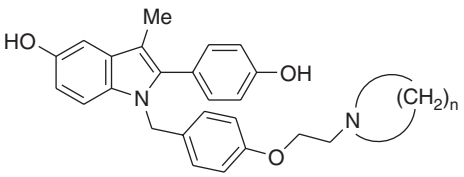

Becatecarin (**126**) [144]




Bizelesin (**127**) [145]




Mitromycin C (**128**)



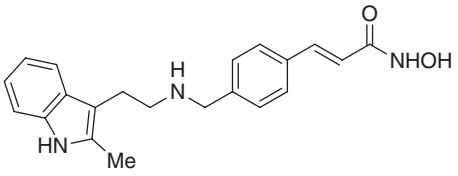

Bazedoxifene, n = 6 (**129**) [148]
Pipendoxifene, n = 5 (**130**) [149]

***Scheme 18*** *Anticancer Indole Drugs*

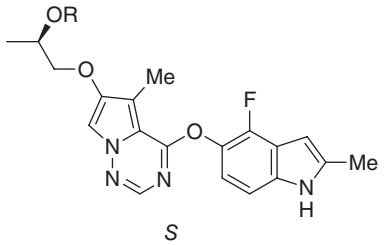
experienced a 40% reduction in her metastatic disease. Mitomycin C (**128**) is a widely used anticancer agent isolated from *Streptomyces caespitosus* and *S. lavendulae* [146, 147]. Bazedoxifene (**129**) [148] and pipendoxifene (**130**) [149] are related selective estrogen-receptor modulators (SERMs) and are being developed for osteoporosis and breast cancer, respectively. Pipendoxifene is in phase II trials for metastatic breast cancer [149, 150], and bazedoxifene is in final review by the U.S. Food and Drug Administration for the prevention and treatment of osteoporosis [150].

Panobinostat (Scheme 19, **131**) inhibits histone deacetylases (HDAC) and the proliferation of several tumors. It is in phase I/II trials for hematological cancers [150,151]. Brivanib (**132**) is a prodrug for BMS-540215 (**133**), and it inhibits the angiokinases VEGFR-2 and FGFR-1 [150,152]. The 4-fluoro-2-methylindole–related cediranib (**134**) is a tyrosine kinase inhibitor of all three VEGF receptors and is currently in phase II/III trials for advanced colorectal and non–small cell lung cancer [150, 153]. Poly(ADP-ribose) polymerase (PARP) is a protein involved in DNA repair and is elevated in some cancer patients. Indole AG-14699 (**135**) is an inhibitor of PARP and is currently in phase II studies for the treatment of ovarian and breast cancer and melanoma [150, 154]. The family of B-cell lymphoma-2 (Bcl-2) proteins is overexpressed in certain cancers such as non-Hodgkin's lymphoma. Obatoclax (**136**) inhibits Bcl-2 and is in phase II studies for the treatment of Hodgkin's lymphoma and related conditions [150, 155].

A major class of anticancer indoles is the indolocarbazoles, epitomized by the naturally occurring staurosporine (Scheme 20, **137**) and the earlier presented rebeccamycin (**89**) [156]. Indolocarbazoles typically inhibit members of the large family of protein kinase C (PKC) enzymes [157]. These serine–threonine kinases are involved in proliferation, differentiation, transcription, tumorigenesis, and angiogenesis, and overexpression of PKCs is implicated in numerous cancers. Staurosporine itself is too nonselective in its inhibition of PKCs, but the naturally occurring UCN-01 (7-hydroxystaurosporine) (**138**) is currently in phase II trials for the treatment of chronic lymphocytic leukemia (CLL). The related midostaurin (**139**) selectively inhibits the FLT-3 receptor tyrosine kinase and is currently in phase III trials for acute myelogenous leukemia (AML). Midostaurin is also broadly antiproliferative in other cancer cell lines [150]. A reduction product of the natural K-252a (not shown) is lestaurtinib (**140**), which is a

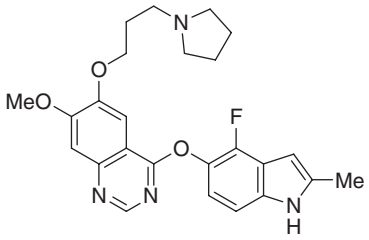



Panobinostat (**131**) [151]

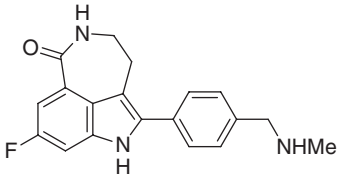



*S*

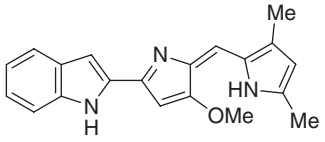
Brivanib, R = COCH(Me)$NH_2$ (**132**) [152]
BMS-540215, R = H (**133**) [152]




Cediranib (**134**) [153]

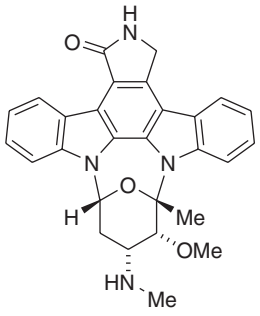



AG-14699 (**135**) [154]

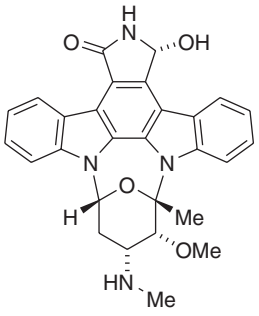



Obatoclax (**136**) [155]

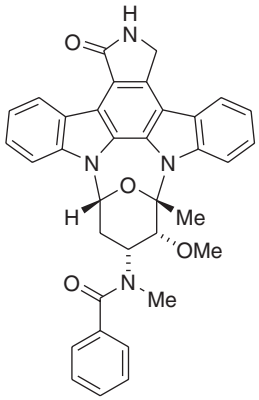
***Scheme 19*** *Anticancer Indole Drugs in Clinical Trials*



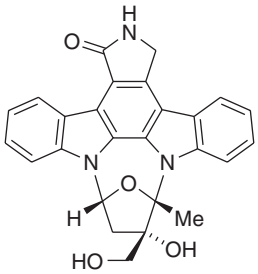
Staurosporine (**137**)



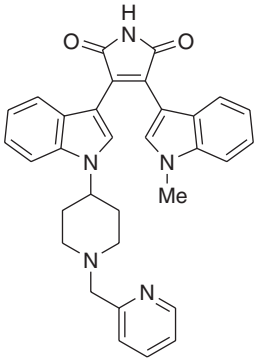
UCN-01 (**138**)



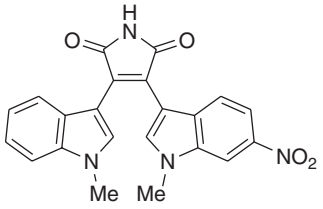
Midostaurin (**139**)



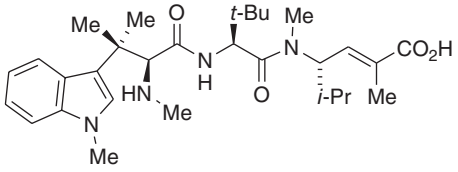
Lestaurtinib (**140**) [158]



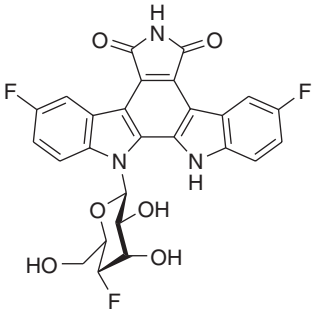
Enzastaurin (**141**) [159]



MKC-1 (**142**) [160]



Hemiasterlin (**143**) [161]



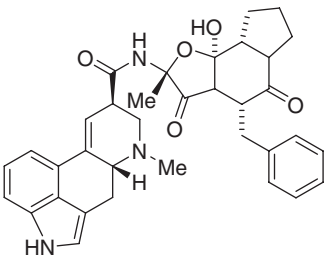
BMS-250749 (**144**) [163]

***Scheme 20*** *Anticancer Indolocarbazole and Related Drugs in Clinical Trials*

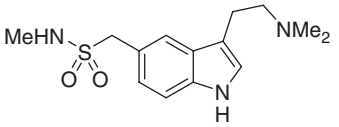
multiple tyrosine kinase inhibitor and is in phase III trials for several cancers [150, 158]. Enzastaurin (**141**) is an acyclic bisindolylmaleimide that is highly potent and selective toward protein kinase C β isoform (PKC β) and is currently in phase III trials for large B-cell lymphoma and in phase II trials for glioblastoma [150, 159].

Another bisindolylmaleimide, MKC-1 (**142**), induces cancer cell death (apoptosis) by targeting tubulin. This agent demonstrated activity in phase II trials against breast, ovarian, and non–small cell lung cancer and leukemia, but it was subsequently withdrawn from further study [150, 160].

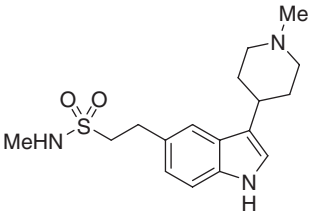
Another tubulin-binding indole is the tripeptide hemiasterlin (**143**), which was isolated from the South African sponge *Hemiasterella minor* [161]. Although toxic, **143** has served as a lead compound for nonindole analogues in clinical trials. By binding to tubulin, hemiasterlin and its derivatives prevent tubulin polymerization and cause cell death [162]. The difluoro indolocarbazole BMS-250749 (**144**) is a selective topoisomerase I (topo I) inhibitor and has entered phase I trials as a broad-spectrum anticancer agent, including showing curative antitumor activity against Lewis lung carcinoma [163].



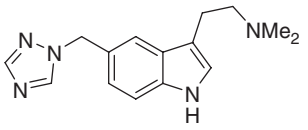
Ergotamine (Ergostat$^{TM}$) (**145**)



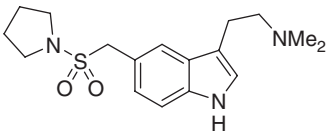
Sumatriptan (Imitrex$^{TM}$) (**146**)



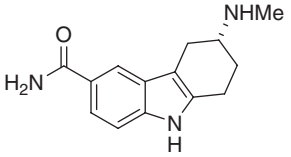
Naratriptan (Amerge$^{TM}$) (**147**)



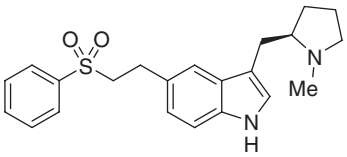
Rizatriptan (Maxalt$^{TM}$) (**148**)



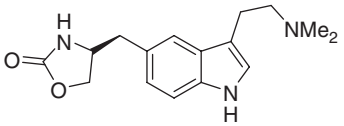
Almotriptan (Axert$^{TM}$) (**149**)



Frovatriptan (Frova$^{TM}$) (**150**)



Eletriptan (Relpax$^{TM}$) (**151**)



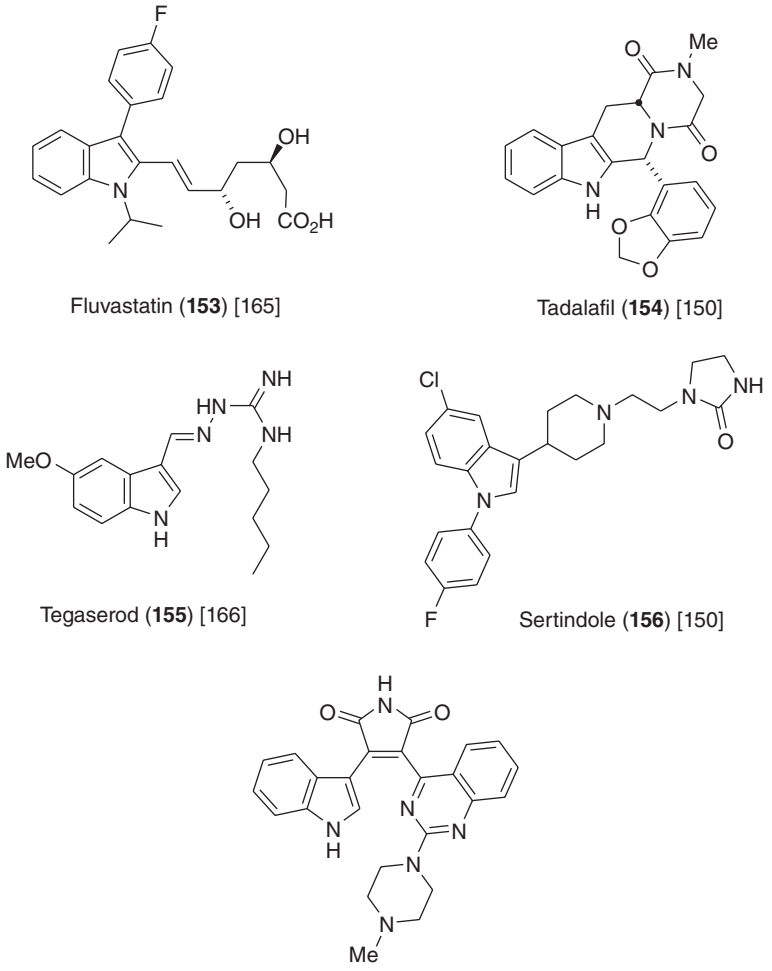
Zolmitriptan (Zomig$^{TM}$) (**152**)

***Scheme 21*** *Indole Triptans*

Several other diseases are prevented or managed using indole-based drugs. For example, the triptans are powerful antimigraine medicines, and several are known (Scheme 21) [150, 164]. These compounds are selective 5-$HT_{1B/10}$ agonists, and the ergot alkaloid ergotamine (**145**) provided a lead for the subsequent development of sumatriptan (**146**), naratriptan (**147**), rizatriptan (**148**), almotriptan (**149**), frovatriptan (**150**), eletriptan (**151**), and zolmitriptan (**152**). Sumatriptan was the first triptan to be approved in the United States (1991) as a drug to treat migraine.

Drugs that lower blood cholesterol by retarding its synthesis in the liver are called statins [165] and are epitomized by atorvastatin (Lipitor; a pyrrole, not an indole). These drugs function by inhibiting the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA), crucial for a step in the cholesterol biosynthesis pathway. The one indole statin is fluvastatin (**153**), a minor player in this arena [165] (Scheme 22). Tadalafil (Cialis) (**154**) is a drug for the treatment of erectile dysfunction by inhibiting type 5 phosphodiesterase (PDE5) and relaxing smooth muscle to increase blood flow [150]. The 5-$HT_4$ agonist tegaserod (**155**) is a drug for irritable bowel syndrome and constipation [166]. The relatively new antipsychotic sertindole (**156**) acts against the dopamine $D_2$, serotonin 5-$HT_2$, and $\alpha_1$-adrenergic receptors and is a drug for the treatment of schizophrenia [150]. The PKC inhibitor sotrastaurin (**157**) is under consideration as a transplant rejection preventive [167]. This indole acts synergistically with cyclosporine, a well-established immunosuppressive drug.

As mentioned earlier in Section 3, serotonin (**3**) activates a series of well-defined receptors in the central and peripheral nervous systems [81, 82]. The 5-$HT_3$ receptor comprises a



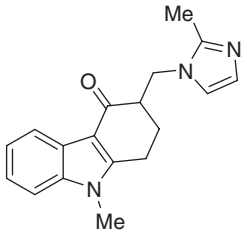

***Scheme 22*** *Miscellaneous Indole Pharmaceuticals*

superfamily of ion channels that regulate neuronal depolarization by increasing sodium, potassium, and calcium ion flux [168]. Several indole pharmaceuticals have been developed as antiemetics to prevent nausea and vomiting following chemotherapy (Scheme 23)[150]. They function by diminishing the role of the vagus nerve to trigger vomiting in the medulla oblongata, and they also obstruct serotonin receptors in the chemoreceptor activation region. One of these 5-$HT_3$ antagonists, alosetron (**162**), is used to treat severe diarrhea in women with irritable bowel syndrome (IBS).

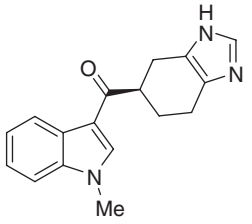
A few indole-based compounds are active against viruses (Scheme 24). The non-nucleoside reverse transcriptase inhibitor delaviridine (**163**) is used in antiretroviral therapy [150]. The blue-green alga *Dichothrix baueriana* has yielded bauerine B (**164**), a dichloro β-carboline active against herpes simplex virus type 1 [169]. Seeds of the plant *Solanum indicum* have yielded the new coumarinolignoid indicumine B (**165**), which possesses anti–hepatitis B activity [170]. Eudistomin K sulfoxide (**166**) displays activity against both herpes and polio viruses. This β-carboline was isolated from the New Zealand ascidian *Ritterella sigillinoides* [171]. Other marine indoles such as dragmacidin F, manzamine A, and microspinosamide have antiviral activity (HIV, herpes). The marine environment is a very promising source for new antiviral lead compounds [172].

Several natural and synthetic indole-containing cyclic peptides have pharmacological properties (Scheme 25). Daptomycin (**167**) was isolated from the soil microbe *Streptomyces roseosporus* and is used to treat gram-positive bacterial infections [150, 173]. The synthetic cyclic peptide eptifibatide (**168**) is a glycoprotein IIb/IIIa antagonist and platelet aggregation inhibitor. This drug is used to treat patients who have acute coronary syndrome (ACS) and are especially susceptible to blood clots [150,174].

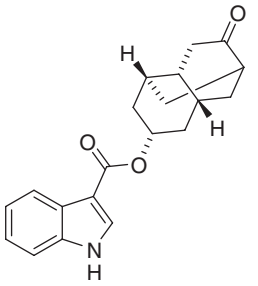
Several other human diseases are favorably affected by indole-based drugs (Scheme 26). Vilazodone (**169**) is a



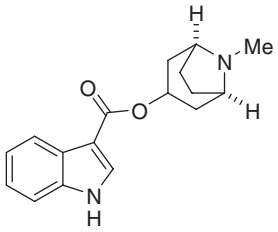
Ondansetron (Zofran$^{TM}$) (**158**)



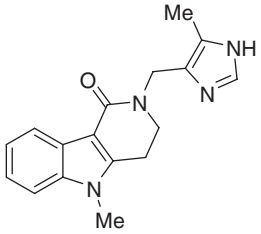
Romosetron (Nasea$^{TM}$) (**159**)



Dolasetron (Anzemet$^{TM}$) (**160**)

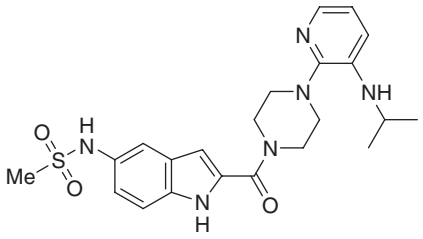


Tropisetron (Navoban$^{TM}$) (**161**)

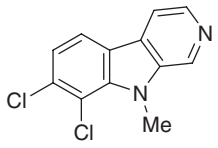


Alosetron (Lotronex$^{TM}$) (**162**)

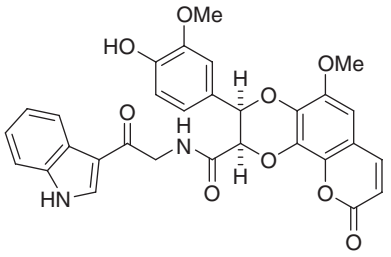
***Scheme 23*** *Indole 5-HT$_3$ Receptor Antagonist Pharmaceuticals*



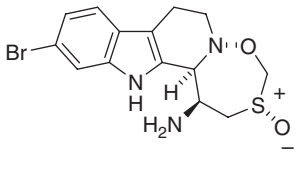
Delaviridine (**163**) [150]



Bauerine B (**164**) [169]

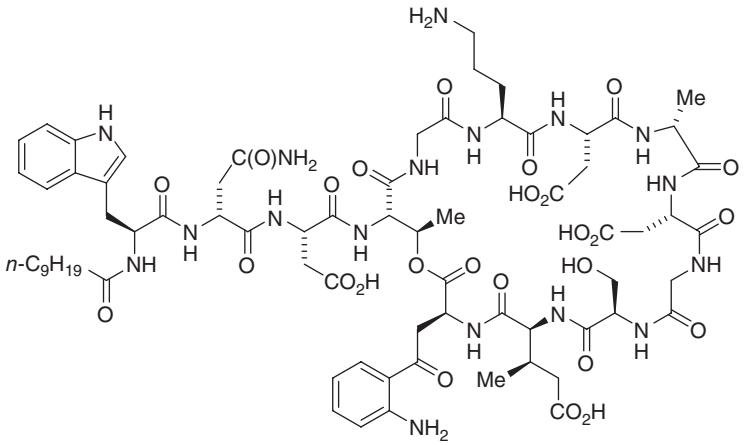


Indicumine B (**165**) [170]

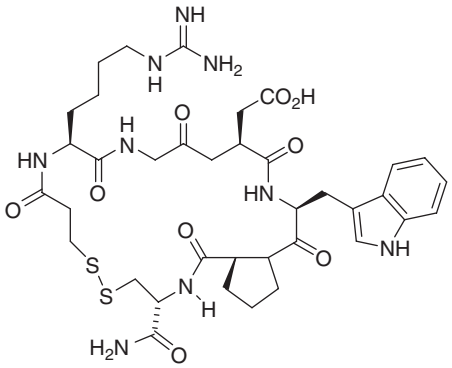


Eudistomin K Sulfoxide (**166**) [171]

***Scheme 24*** *Representative Antiviral Indoles*



Daptomycin (Cubicin™) (**167**) [173]



Eptifibatide (Integrilin™) (**168**) [174]

***Scheme 25*** *Indole-Based Cyclopeptides*

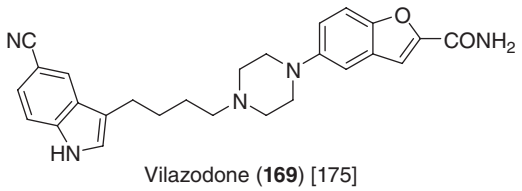
long-acting 5-$HT_{1A}$ partial agonist and selective serotonin reuptake inhibitor (SSRI) that is in phase III trials for the treatment of depression [175]. The highly specific 5-$HT_2$ receptor antagonist pruvanserin (**170**) is in phase II clinical trials for the treatment of insomnia [150]. Tiplaxtinin (**171**) is a potent and selective inhibitor of plasminogen activator inhibitor 1 (PAI-1) and has efficacy in preventing acute arterial thrombosis [176]. The cyclic bisindolylmaleimide ruboxistaurin (**172**) is an inhibitor of PKCβ and is under consideration for the treatment of diabetic retinopathy [177]. An inhibitor of human nonpancreatic secretory phospholipase A2 (hnpoPLA2), LY-311727 (**173**), is a potential treatment for sepsis [178], and the $M_4$ muscarinic antagonist **174** may find utility against Parkinson's disease [179]. The indole thiophene DG-041 (**175**) is an antagonist for the EP3 receptor for prostaglandin $E_2$ and is in clinical studies for the treatment of peripheral artery disease (PAD) [180]. Lastly, one of the most familiar indole drugs is indomethacin (**176**), which is a classic powerful nonsteroidal antiinflammatory drug. It has also found use in controlling fever in patients with liver metastases of solid tumors [181].

This brief survey of indole pharmaceuticals and indole candidate drugs is necessarily incomplete. Many more indoles are known that have excellent biological activity, but space does not permit coverage. For example, myriad indole alkaloids have a range of biological activities, and some, like the antihypertensive reserpine, are clinically useful. In addition, the many indoline- and oxindole-based pharmaceuticals could not be included in this chapter.

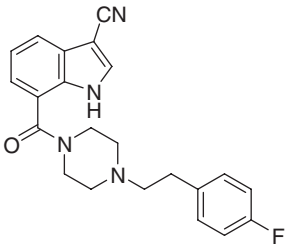
## 1.5 Indole-Containing Materials

The enormous resurgence in recent years of the chemistry of materials has had a significant indole component, and several applications of indole-based materials are presented. Section 6 covers indole-designed ligands.

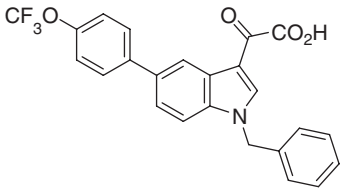
A major thrust in the area of indole materials has been anion complexation and sensing by indole-, carbazole-, biindole-, and indolocarbazole-designed receptors. An excellent feature article by Gale [182] precisely covers this literature to 2008, so the treatment here begins with 2009. d'Ischia



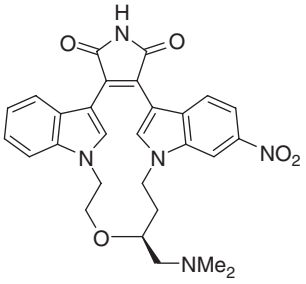

Vilazodone (**169**) [175]



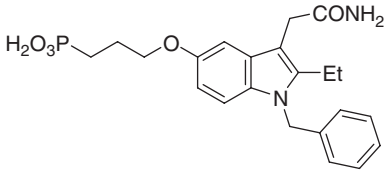

Pruvanserin (**170**) [150]



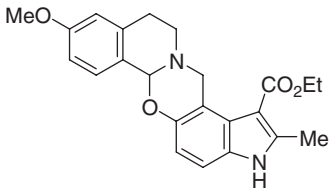

Tiplaxtinin (**171**) [176]



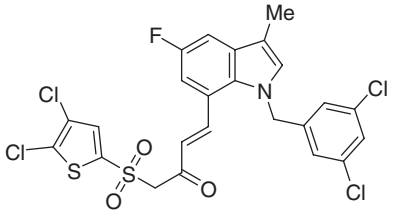

Ruboxistaurin (Arxxant™) (**172**) [177]



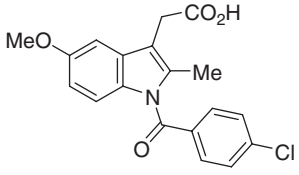

LY-311727 (**173**) [178]




PD-102,807 (**174**) [179]




DG-041 (**175**) [180]

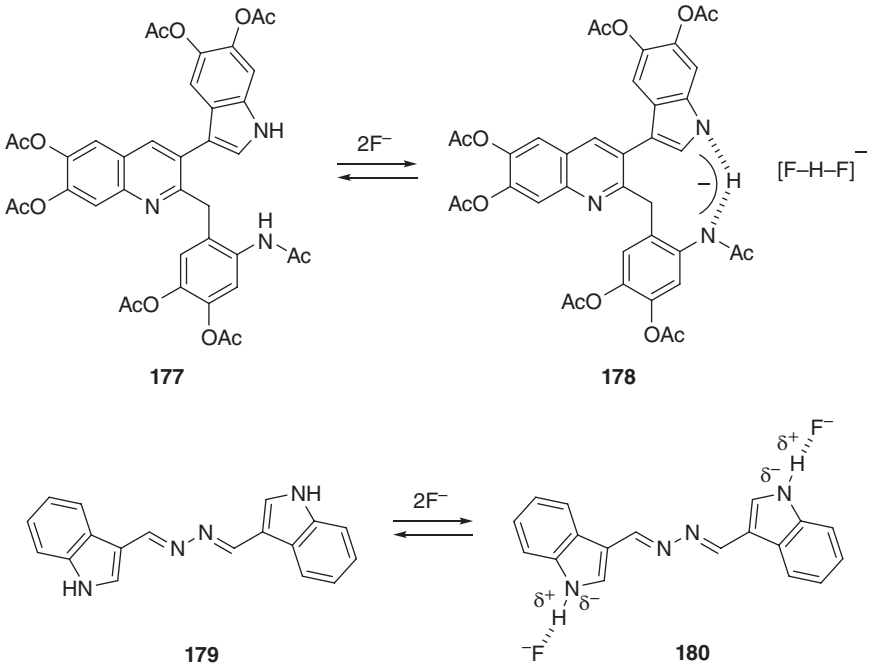



Indomethacin (**176**) [181]

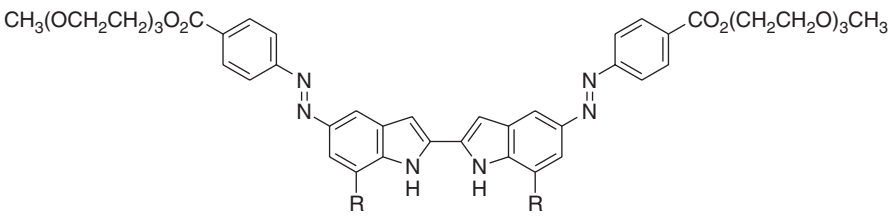
***Scheme 26*** *Other Indoles with Pharmacological Activity*

and colleagues have synthesized the novel acetyl trimer **177** by acid-promoted trimerization of 5,6-dihydroxyindole followed by acetylation [183]. Compound **177** is a selective fluoride-sensing compound, as illustrated in **177–178** (Scheme 27). This fluoride-sensing scaffold displays marked fluorescence enhancement at 489 nm that is selective for fluoride. Other anions, including chloride, bromide, iodide, acetate, nitrite, and bisulfate, show no significant changes in the fluorescence spectra. A different fluoride-sensing system was described by Shiraishi involving indole-azadiene **179–180**, in a H-bonding 1:2 stoichiometry [184]. This system is highly sensitive for fluoride in both colorimetric and fluorometric analyses, but not for chloride, bromide, iodide, acetate, perchlorate, bisulfate, biphosphate, nitrate, and thiocyanate. Indole **179** was readily prepared by condensing indole-3-carbaldehyde with hydrazine.

Jeong and colleagues have synthesized the biindole–diazo conjugates **181** and **182** as new anion sensors (Scheme 28) [185].

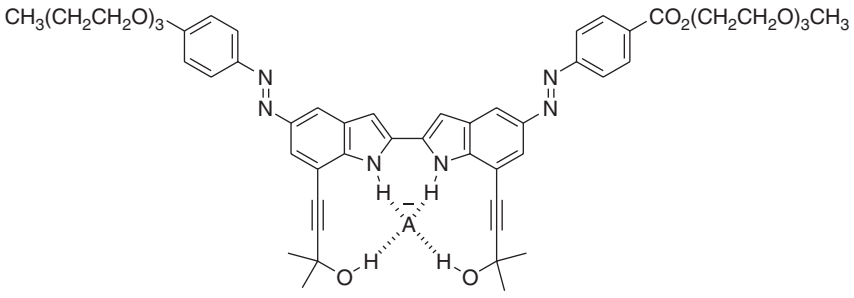



***Scheme 27*** *Indole Fluoride Sensors*

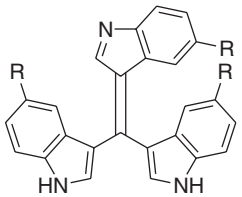



**181**, R = I

**182**, R = ≡— C(OH)$(CH_3)_2$




**183**



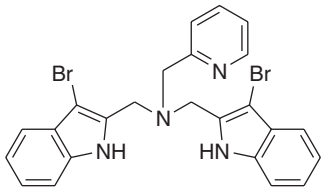

**184**, R = H
**185**, R = OMe
**186**, R = $NO_2$

***Scheme 28*** *Indole Anion Sensors*

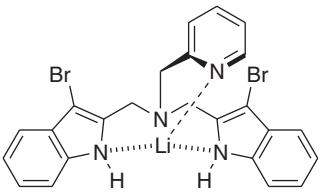
Both compounds bind basic anions, but the binding of anions with **182** is up to 100 times stronger given the extensive hydrogen bonding as shown in **183**. Shao and colleagues prepared tris(indolyl)methanes **184–186** as anion receptors and colorimetric chemosensors as a function of R [186]. Thus, whereas all three systems show strong binding of fluoride, **184** and **185** show much higher binding affinity for biphosphate than for acetate, and **186** shows the strongest binding for fluoride. Other anions such as chloride, bromide, iodide, perchlorate, and bisulfate are much less bound to **186**.

The novel ion-pair indole-pyridine-amine–based receptor **187** binds both anions and cations [187]. For example, both lithium and chloride bind simultaneously to this molecule as shown in **188** and **189** (Scheme 29). The authors propose for chloride binding a weak H-bond to the C-3H on pyridine in addition to two strong H-bonds to the two indole nitrogen hydrogens. Hof and Whiting have developed a series of indole-derived hosts that bind various ammonium cations (e.g., **190**, **191**). Binding results from a combination of electrostatic attraction, cation–π interaction, and hydrophobicity [188]. Host **190** was designed as a mimic of tryptophan-endowed protein-binding cavities.

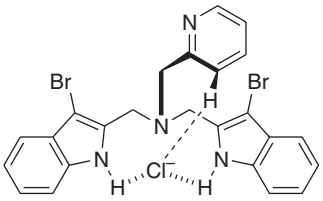
Several novel indole-formulated fluorescence devices have been described (Scheme 30). Müller has developed metal-selective luminescence sensors **192** that exhibit selective halochromic fluorescence of zinc and magnesium over calcium [189]. Whereas these 2,4-diarylpyrano[2,3-*b*]indoles display no fluorescence as the free base, halochromic green fluorescence results upon protonation, methylation, or selective metal cation complexation [189]. Ahn and colleagues synthesized LipidGreen (**193**), a fluorescent probe for *in vivo* lipid imaging in zebrafish. LipidGreen stains lipid droplets in 3T3L1 preadipocyte cell lines and zebrafish fat deposits. It also can be employed as a lipid marker in drug screening [190]. Manderville and colleagues show that indole-deoxyguanosine **194** is a fluorescent reporter of hydrogen-bonding specificity. Thus, the fluorescence in **194** is quenched on Watson–Crick hydrogen bonding to deoxycytosine, but the fluorescence is amplified upon hydrogen bonding to guanosine in Hoogsteen base pairing. The fluorescence of indole **194** is about ten times brighter than that of the corresponding pyrrole–deoxyguanosine [191]. Yao has prepared several novel pyrrolocoumarin fluorescent dyes



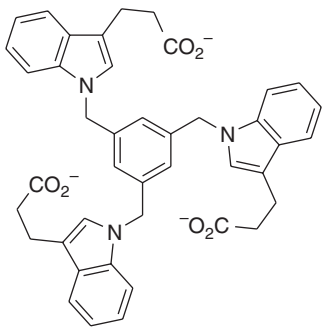

**187** [187]



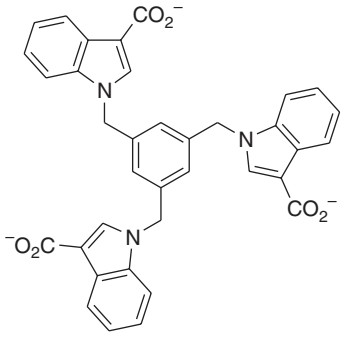

**188** [187]




**189** [187]

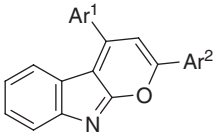



**190** [188]

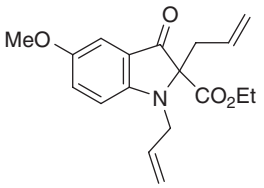



**191** [188]

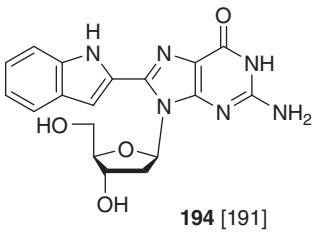
***Scheme 29*** *Indole-Based Receptors*



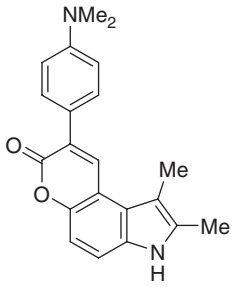
**192** [189]



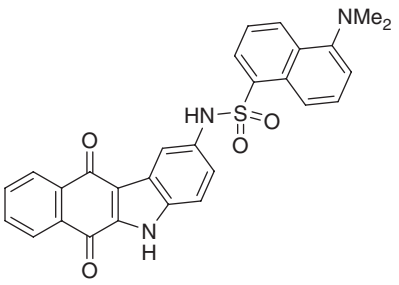
LipidGreen (**193**) [190]



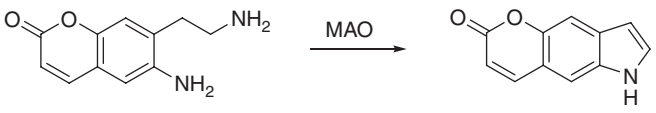
**194** [191]



**195** [192]

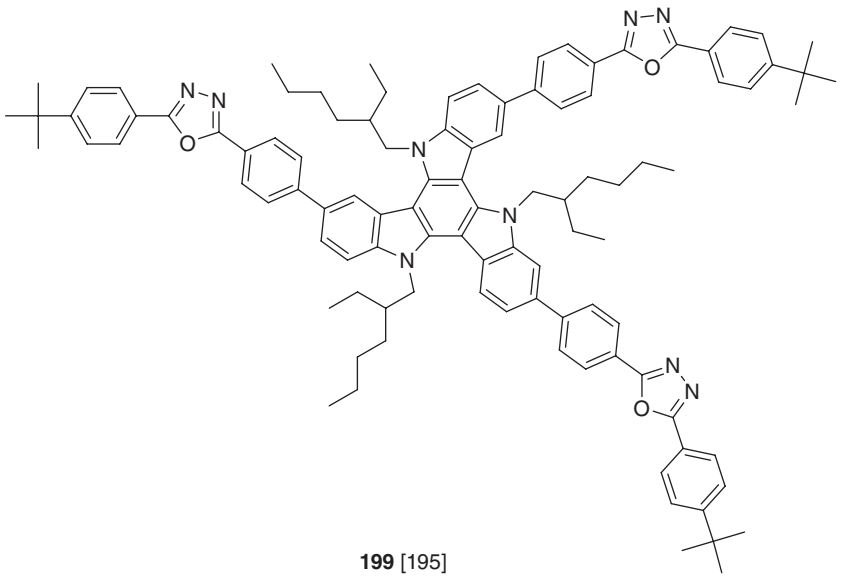


**196** [193]

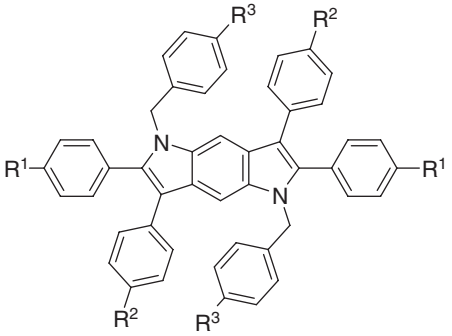


**197** [194]

**198**



**199** [195]



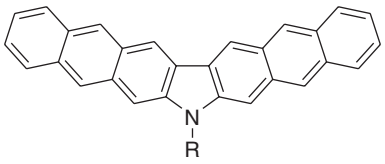
**200** [196], $R^1$ = H, $NPh_2$; $R^2$ = H, $NPh_2$, CN;
$R^3$ = *n*-hexyl

***Scheme 30*** *Indole-Based Fluorescence Probes*

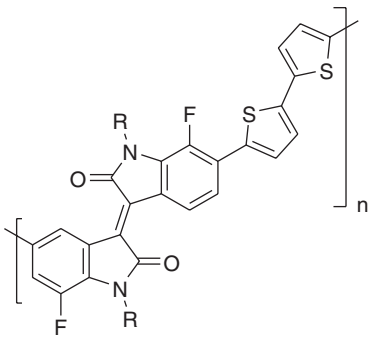
with large Stokes shifts (e.g., **195**) as possible biological imaging agents [192]. Bittner and colleagues have developed benzocarbazole quinone **196** as a fluorescent molecular switch (quinone–hydroquinone) for possible use in molecular electronics and recognition. The switching can be induced both chemically and electrochemically [193]. Sames designed a fluorescent reporter for monoamine oxidase (MAO) enzymes. Thus, nonfluorescent aminocoumarin **197** is switched (oxidized) to fluorescent indolocoumarin **198** upon exposure to MAO A and B [194]. Hiyoshi and colleagues prepared the donor-π-acceptor 1,3,4-oxadiazole triindole **199**. This material has good film-forming capability and shows promise as an electroluminescence device in a single-layer OLED (organic light-emitting diode) [195]. Another candidate molecule for an OLED is benzodipyrrole **200**, which was synthesized by Nakamura and represents a new class of organic electronic materials [196].

Indole-containing materials are used as organic field-effect transistors (OFET) (Scheme 31). Wudl and colleagues synthesized dinaphthocarbazoles (azaheptacenes) **201** and used them in solution-processed OFETs. These azaheptacenes are more robust than the standard heptacene and other polyacene derivatives [197]. Pei and colleagues find that the fluoro-substituted isoindigo polymer **202** has both improved stability and high performance over the nonfluorinated analogue. Fluorination lowers the LUMO level of the polymer and greatly amplifies electron mobility in this novel isoindigo-crafted donor-acceptor conjugated polymer [198]. The venerable natural dye indigo (**203**) has found use as an OFET by Irimia-Vladu and colleagues. By virtue of its planar structure, cross-conjugated π-system, and strong intermolecular interactions, indigo possesses excellent charge-transporting properties. Furthermore, the property of this compound to be oxidized and reduced reversibly provides transport ambipolarity [199]. Yao found that indigo carmine (**204**) is a positive-electrode material for rechargeable lithium batteries [200].

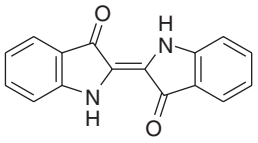
Wang, Andersson, and colleagues designed and synthesized the novel isoindigo-terthiophene copolymer **205** for use as a donor-acceptor polymer in a high-performance solar cell (Scheme 32). The 6.3% power conversion efficiency observed for **205** is the highest yet reported for an isoindigo-based polymer solar cell [201]. Fulgimide **206** undergoes photochromic fluorescence switching



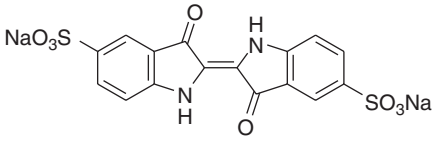

**201** [197], R = benzyl, *n*-dodecyl




**202** [198], R = $(CH_2)_3CH(C_{14}H_{29})_2$

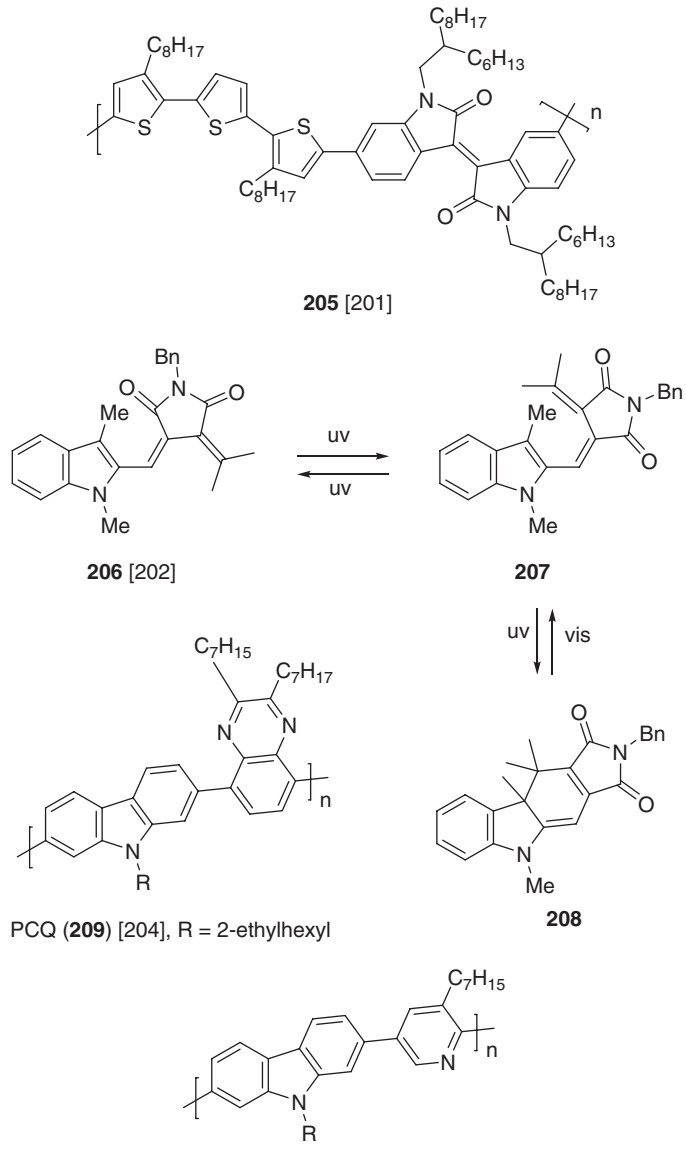



Indigo (**203**) [199]




**204** [200]

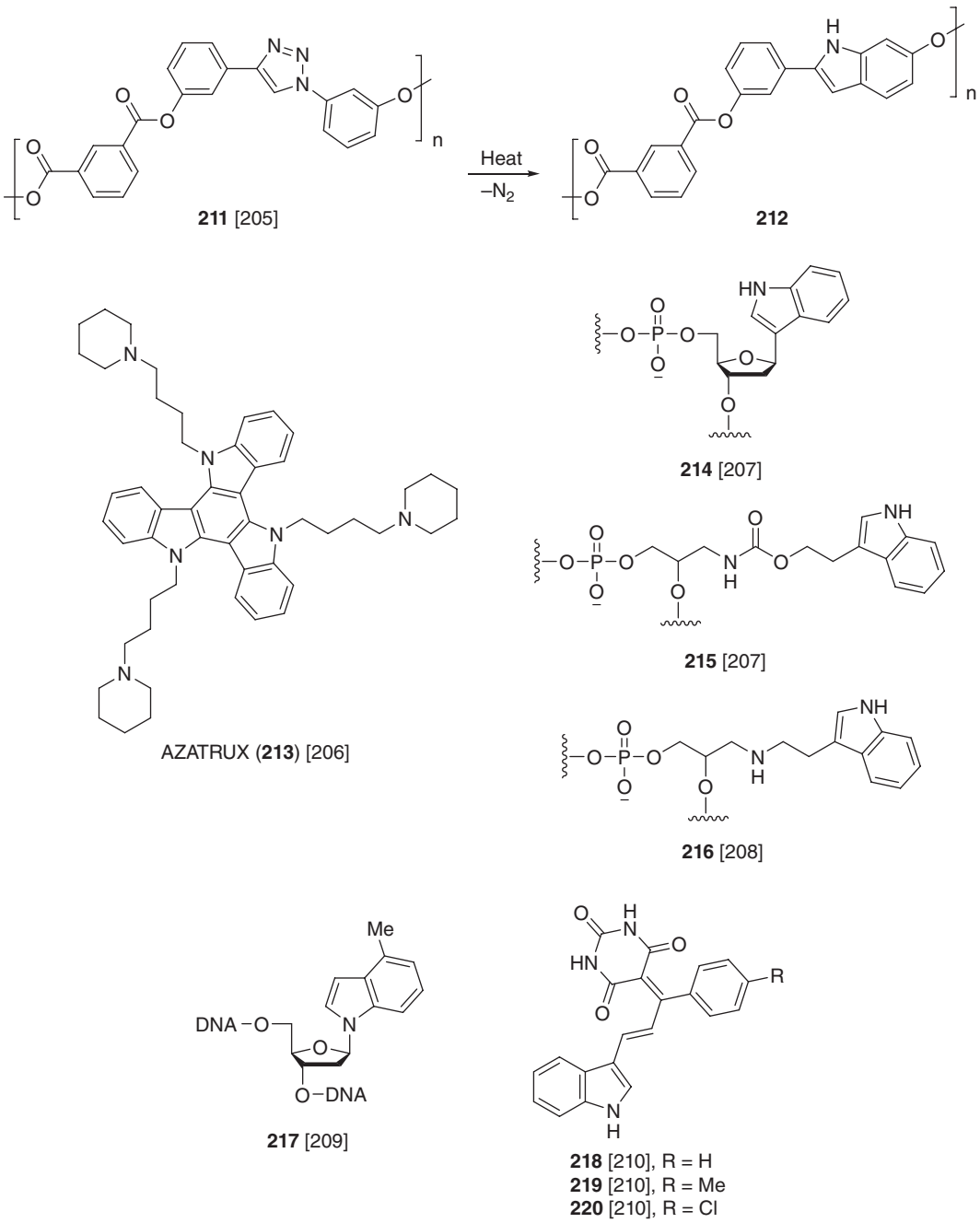
***Scheme 31*** *Indole-Based Transistors*




***Scheme 32*** *Indole-Based Electronic Devices*

(**206–207–208**) as shown by Andréasson and Pischel [202]. Leclere and colleagues have devised new blue, green, and red light-emitting conjugated poly(*N*-substituted-2,7-carbazole) derivatives. For example, PCQ (**209**) emits green light and PCPy (**210**) emits blue light. These materials are thermally stable, show good optical properties, and will soon be tested in light-emitting devices [203, 204].

Emrick and Ryu have used the thermolysis of diphenyl-1,2,3-triazoles to give phenylindoles as novel monomers leading to polymers **211** → **212** that possess low flammability (Scheme 33) [205]. Franceschin and colleagues prepared azatrux (**213**) as a selective binder to G-quadruplex DNA [206]. This family of nucleic acid secondary structures is stabilized by coplanar quartets of guanines, called G-quadruplexes, held together by hydrogen bonding (Hoogsteen bonding). Binding to G-quadruplex DNA may offer a novel anticancer strategy by forming telomeric G-quadruplexes, thus blocking telomerase, an enzyme that is overexpressed in most cancer cells and whose substrate is telomeric single-strand DNA. Indole has been incorporated into DNA as an artificial DNA base, as illustrated for the indole nucleoside of β-2′-deoxyribofuranoside **214** as well as the tetered analogues **215** and **216**. All three modified




***Scheme 33*** *Miscellaneous Indole-Based Materials*

DNA duplexes are less stable than the natural DNA duplex [207, 208]. David and colleagues find that the DNA repair system adenine glucosylase MutY easily recognizes 4-methylindole β-deoxynucleoside (**217**) when it is opposite 7,8-dihydro-8-oxo-2′-deoxyguanosine and guanosine in DNA [209]. Biradar and colleagues designed the indole–barbitone compounds **218–220** and find that they exhibit antioxidant and DNA cleavage activity [210].

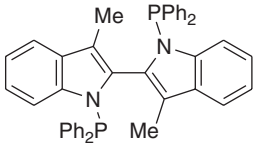
## 1.6 Indole-Containing Ligands

With the incredible increase in research devoted to metal-catalyzed coupling reactions, which we will encounter in subsequent chapters, and the necessity of employing specialized ligands for this chemistry, it is no surprise that numerous indole-based ligands have been invented. In this regard Bandini and Eichholzer published an excellent

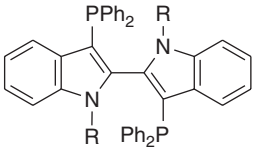
review, "Catalytic Functionalization of Indoles in a New Dimension," which emphasizes the advancements and triumphs in the selective catalytic carbon–carbon bond-forming reactions of indoles from 2005 to 2008 [211].

A very large number of indole-based ligands have been developed to facilitate palladium- and rhodium-catalyzed cross-coupling reactions. The research groups of Sannicolo, Benincori, Beller, Reek, Koskinen, Heo, Mino, Sarkar, Franzén, and Kwong have made enormous contributions in this area.

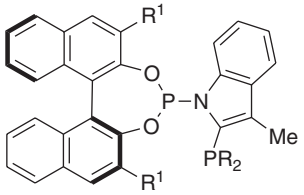
Sannicolo, Benincori, and colleagues have designed biindole-phosphine ligands BISCAP (**221**) [212] and 2-BINPO (**222**) (Scheme 34) [213]. Both are chiral, and **222** has been resolved into enantiomers. Reek and colleagues designed the phosphine–phosphoramidite ligand IndolPHOS (**223**), which is an excellent ligand for rhodium-catalyzed asymmetric hydrogenation and rhodium-catalyzed hydroformylation [214, 215]. This research team later designed INDOLPhospholes (**224**) as a novel catalyst for allylic alkylation [216]. Beller and colleagues synthesized




BISCAP (**221**) [212]

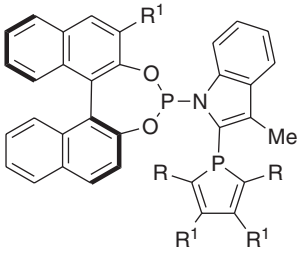



2-BINPO (**222**), R = Me, $CH_2OMe$ [213]



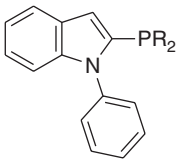

INDOLPHOS (**223**) [214], [215]

| R | $R^1$ |
|---|---|
| Ph | H |
| *i*-Pr | H |
| Cy | H |
| *o*-Tol | H |
| Ph | $SiMe_3$ |
| *i*-Pr | Me |

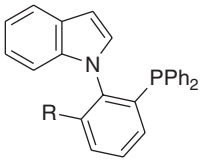



INDOLPhosphole (**224**) [216]

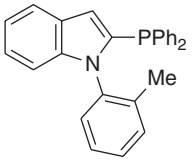
| R | $R^1$ |
|---|---|
| Ph | H |
| H | Me |



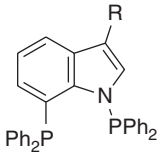

**225** R = *t*-Bu, adamantyl [217]



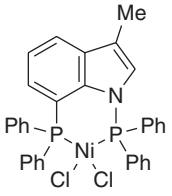

**226** R = OMe, Me, $CF_3$ [219]




**227** [219]




**228** R = H [220], [221]
**229** R = Me [222]



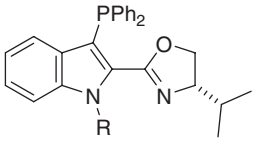

**230** [222]

***Scheme 34*** *Indole-Phosphine Ligands*

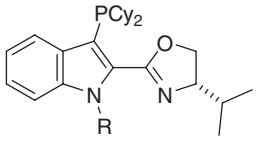
indole–phosphine ligands **225** for the efficient palladium-catalyzed amination of aryl chlorides [217]. Heo used this ligand in Suzuki cross-coupling reactions of arylboronic acids and aryl halides [218]. Mino and colleagues synthesized the new indole–phosphine ligands **226** (chiral) and **227** for palladium-catalyzed allylic allylation [219]. Sarkar and colleagues prepared indole–phosphine ligands **228** and **229**, both of which are air stable. Ligand **228** was used to effect Suzuki cross-coupling of arylboronic acids and aryl/allyl chlorides [220] and the amination of allylic alcohols [221], and ligand **229** is a ligand for nickel-catalyzed Kumada coupling of aryl Grignards with aryl chlorides [222]. The nickel–phosphine complex **230** was isolated and characterized by x-ray crystallography.

Franzén and coworkers described a series of indole-phosphine-oxazoline (IndPHOX) ligands, **231–238** (Scheme 35). The power of these ligands is demonstrated by the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate with 98% enantioselectivity [223]. These IndPHOX ligands have also been used in palladium-catalyzed asymmetric allylic amination with enantioselectivities of as high as 99% [224]. Subsequent work by this group led to the new ligands **239–245** [225]. The *N*-MOM and *N*-THP groups in these ligands afforded improved enantioselectivity of the palladium-catalyzed allylic amination reaction, with **243** giving higher percentage of enantiomeric excess than **244** (97% vs. 80%).

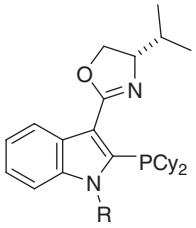
Another leader in this area of indole-based ligands is Kwong (Scheme 36). He and his colleagues have prepared the new ligands **246–251**, which are very efficient in Suzuki couplings [226]. Subsequent research by this group led to the preparation and evaluation of indole–phosphine ligands **251** (CM-Phos) [227], **253** [228], **254** [229], **255** [229], and **256–263** [230]. Of this large collection of Kwong ligands, CM-Phos (**251**) has seen the most extensive use in palladium-catalyzed cross-coupling reactions, particularly for Suzuki reactions involving aryl tosylates and mesylates [229, 231, 232], but also for Hiyama couplings



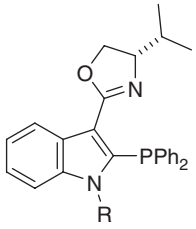

**231** (R = Me)
**232** (R = $CH_2OMe$)



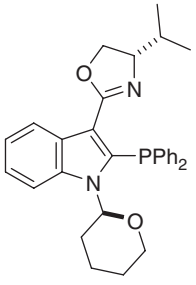

**233** (R = Me)
**234** (R = $CH_2OMe$)



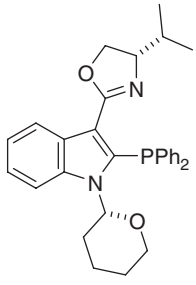

**235** (R = Me)
**236** (R = $CH_2OMe$)



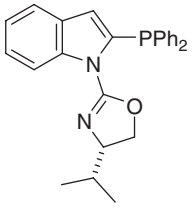

**237** (R = Me)
**238** (R = $CH_2OMe$)
**239** (R = Bn)
**240** (R = $CON(iPr)_2$)
**241** (R = Ph)
**242** (R = Pr)




**243**

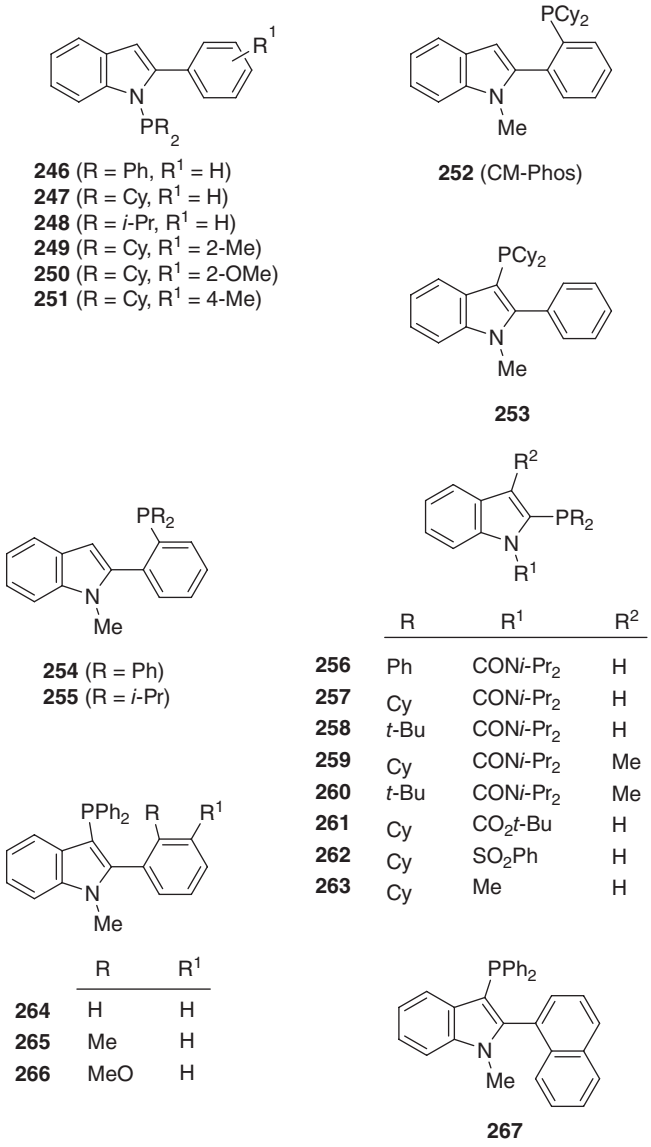



**244**




**245**

***Scheme 35*** *Franzén Indole-Phosphine Ligands [223–225]*




**246** (R = Ph, $R^1$ = H)
**247** (R = Cy, $R^1$ = H)
**248** (R = *i*-Pr, $R^1$ = H)
**249** (R = Cy, $R^1$ = 2-Me)
**250** (R = Cy, $R^1$ = 2-OMe)
**251** (R = Cy, $R^1$ = 4-Me)

**252** (CM-Phos)

**253**

**254** (R = Ph)
**255** (R = *i*-Pr)

| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **256** | Ph | CON*i*-$Pr_2$ | H |
| **257** | Cy | CON*i*-$Pr_2$ | H |
| **258** | *t*-Bu | CON*i*-$Pr_2$ | H |
| **259** | Cy | CON*i*-$Pr_2$ | Me |
| **260** | *t*-Bu | CON*i*-$Pr_2$ | Me |
| **261** | Cy | $CO_2$*t*-Bu | H |
| **262** | Cy | $SO_2$Ph | H |
| **263** | Cy | Me | H |

| | R | $R^1$ |
|---|---|---|
| **264** | H | H |
| **265** | Me | H |
| **266** | MeO | H |

**267**

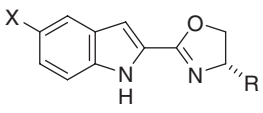
***Scheme 36*** *Kwong Indole-Phosphine Ligands [226–235]*

[233], amination [227], and cyanation of aryl chlorides in yields up to 96% [234]. Ligand **264** is a member of the new group of indole–phosphine ligands, **264–267**, developed by Kwong [235, 236]. For example, **266** is effective for the palladium-catalyzed borylation of aryl chlorides [235].

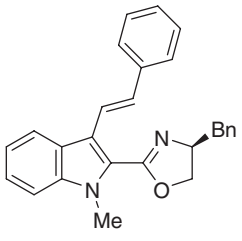
The group of Koskinen and Franzén prepared and used a series of indole–oxazoline ligands (Scheme 37). Koskinen and colleagues synthesized **268–273** [237], and Franzén made and evaluated the indole–olefin–oxazoline ligands **274–279** [238]. These last ligands are very effective in the rhodium-catalyzed asymmetric conjugate addition of enones with boron reagents, affording enantioselectivities of up to 94%.

Given the voluminous effort by several groups to design, synthesize, and implement ligands based on indole, it is clear that these remarkable ligands will continue to find important use in asymmetric metal-catalyzed synthesis.

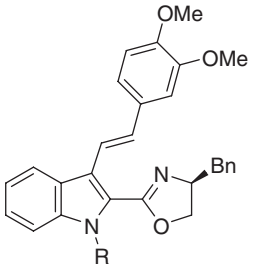
A different type of indole material is Nindigo (**280**), a set of derivatives formed from anilines reacting with indigo [239]. These new materials represent binucleating ligands with twin β-diketiminate-type metal binding sites, illustrated in **281** (Scheme 38). Another novel indole compound is the 1,2-dimethyl-3-sulfonyl group (MIS) **282**, which finds utility as a protecting group for the side chain of arginine [240]. Thus, the corresponding sulfonyl chloride reacts with arginine to give **283**. The MIS group is compatible with tryptophan-containing peptides and is easily removed with mild acid.



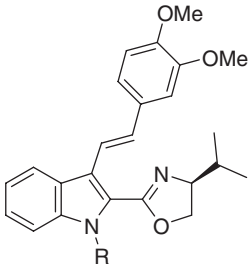
| | R | X |
|---|---|---|
| **268** | *t*-Bu | H |
| **269** | Bn | H |
| **270** | (*R*)-Ph | H |
| **271** | *i*-Bu | H |
| **272** | *t*-Bu | MeO |
| **273** | *t*-Bu | Cl |



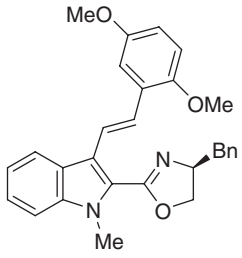
**274**



**275** (R = Me)
**276** (R = $OCH_2OMe$)

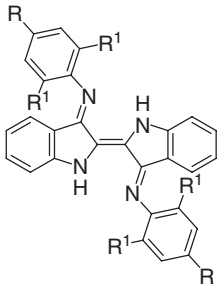


**277** (R = Me)
**278** (R = $OCH_2OMe$)

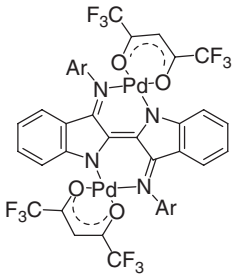


**279**

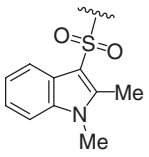
***Scheme 37*** *Indole-Oxazoline Ligands [237, 238]*



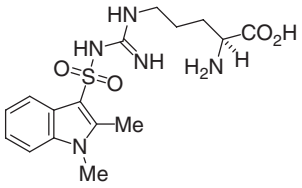
**280** (R = H, Me; $R^1$ = H, Me, *i*-Pr) [239]



**281** [239]



**282** [240]



**283** [240]

***Scheme 38*** *Novel Indole Materials*

## 1.7 Reviews of Indole-Ring Synthesis

Before beginning coverage of the synthesis of the indole ring, it is important to cite the numerous outstanding previous reviews in this area. They are arranged below from general to specialized reviews in descending chronological order. Some reviews of indole-ring analogues follow these. Additional specialized reviews of particular indole ring syntheses are cited within the appropriate chapter.

### 1.7.1 General Reviews on Indole Ring Synthesis

M. Inman and C.J. Moody, Indole Synthesis – Something Old, Something New, *Chem. Sci.*, 2013, **4**, 29–41. An excellent review that focuses on a monosubstituted arene starting point by a leading practitioner of indole chemistry and synthesis (Moody).

D.F. Taber and P.K. Tirunahari, Indole Synthesis: A Review and Proposed Classification, *Tetrahedron*, 2011, **67**, 7195–7210. A concise, modern review that proposes a useful classification system for constructing the indole ring.

R. Vicente, Recent Advances in Indole Synthesis: New Routes for a Classic Target, *Org. Biomol. Chem.*, 2011, **9**, 6469–6480. A review that covers the most recent developments and innovations.

G.R. Humphrey and J.T. Kuethe, Practical Methodologies for the Synthesis of Indoles, *Chem. Rev.*, 2006, **106**, 2875–2911. A comprehensive review covering both classic and modern indole ring syntheses.

J.A. Joule, Indole and Its Derivatives (2000), in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, Category 2, vol. **10** (ed. E.J. Thomas), George Thieme Verlag, Stuttgart, Germany; Chapter 10.13. An outstanding, comprehensive review written by a leading heterocyclic chemist.

G.W. Gribble, Recent Developments in Indole Ring Synthesis – Methodology and Applications, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075. A review covering the 1994–1999 literature.

R.J. Sundberg, *Indoles* (1996), Academic Press, London. An excellent review covering the gamut of methods, including selective experimental procedures.

G.W. Gribble, Recent Developments in Indole Ring Synthesis – Methodology and Applications, *Contemp. Org. Synth.*, 1994, 145–172. A review covering the 1990–1993 literature.

### 1.7.2 Specialized Reviews

#### *1.7.2.1 Solid-Phase Indole Ring Synthesis*

S.A Patil, R. Patil, and D.D. Miller, Solid Phase Synthesis of Biologically Important Indoles, *Curr. Med. Chem.*, 2009, **16**, 2531–2565. A recent review with a strong focus on the solid-state synthesis of biologically active indoles.

J. Tois, R. Franzén, and A. Koskinen, Synthetic Approaches Towards Indoles on Solid Phase Recent Advances and Future

Directions, *Tetrahedron*, 2003, **59**, 5395–5405. An excellent complement to the review by Patil, Patil, and Miller.

K. Knepper, R.E. Ziegert, and S. Bräse, Solid Phase Indole Synthesis, *PharmaChem*, 2003, **2**, 4–7. A brief review illustrating the utility of solid-phase synthesis of indoles.

S. Bräse, C. Gil, and K. Knepper, The Recent Impact of Solid-Phase Synthesis on Medicinally Relevant Benzoannelated Nitrogen Heterocycles, *Bioorg. Med. Chem.*, 2002, **10**, 2415–2437. A comprehensive review covering the solid-phase synthesis of not only indoles but also several other nitrogen-containing aromatic heterocycles.

S. Cacchi and G. Fabrizi, Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions – Update 1, *Chem. Rev.*, 2011, **111**, PR215–PR283. An outstanding review and update of their 2005 paper (cited below).

J.J. Song, J.T. Reeves, D.R. Fandrick, *et al.*, Construction of the Indole Nucleus Through C–H Functionalization Reactions, *Arkivoc*, 2010, **1**, 390–449. This very nice review also covers nitrene approaches to indoles.

J. Barluenga, F. Rodríguez, and F.J. Fañanás, Recent Advances in the Synthesis of Indole and Quinoline Derivatives Through Cascade Reactions, *Chem. Asian J.*, 2009, **4**, 1036–1048. This review covers cascade reactions mainly involving the metals palladium, copper, gold, and platinum.

S. Cacchi and G. Fabrizi, Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions, *Chem. Rev.*, 2005, **105**, 2873–2920. The title says it all.

#### *1.7.2.2 Specific Indoles*

M. d'Ischia, A. Napolitano, and A. Pezzella, 5,6-Dihydroxyindole Chemistry: Unexplored Opportunities Beyond Eumelanin, *Eur. J. Org. Chem.*, 2011, 5501–5516. A unique microreview on the building blocks of eumelanin polymers.

L.F. Silva, Jr., M.V. Craveiro, and I.R.M. Tébéka, Total Syntheses of Trikentrins and Herbindoles, *Tetrahedron*, 2010, **66**, 3875–3895. Excellent summary of the different syntheses of these novel indole natural products.

O.V. Serdyuk, V.M. Muzalevskiy, and V.G. Nenajdenko, Synthesis and Properties of Fluoropyrroles and Their Analogues, *Synthesis*, 2012, **44**, 2115–2137. An excellent review by a leader of fluorine in heterocycles (Nenajdenko).

V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, *et al.*, Synthesis of Trifluoromethyl Pyrroles and Their Benzo Analogues, *Synthesis*, 2009, 3905–3929. A complementary review to Serdyuk, Muzalevskiy, and Nenajdenko (2012) cited above.

D.A. Horton, G.T. Bourne, and M.L. Smythe, The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures, *Chem. Rev.*, 2003, **103**, 893–930. A review dealing with indoles and many other aromatic and nonaromatic heterocycles.

A.M. Lobo and S. Prabhakar, Recent Developments in the Synthesis of Biologically Active Indole Alkaloids, *J. Heterocycl. Chem.*, 2002, **39**, 429–436. A short review of indole alkaloid synthesis.

M. Somei, 1-Hydroxyindoles, *Heterocycles*, 1999, **50**, 1157–1211. A nice review by the leading authority on 1-hydroxyindoles.

H.M. Hugel and D.J. Kennaway, Synthesis and Chemistry of Melatonin and of Related Compounds. A Review, *Org. Prep. Proc. Int.*, 1995, **27**, 1–31. An excellent review of this important group of biologically significant compounds.

#### *1.7.2.3 Microwave-Promoted Indole Ring Synthesis*

S.A. Patil, R. Patil, and D.D. Miller, Microwave-Assisted Synthesis of Medicinally Relevant Indoles, *Curr. Med. Chem.*, 2011, **18**, 615–637. An excellent review highlighting the utility of microwave heating in indole ring synthesis.

#### *1.7.2.4 Specific Reactions for Indole Ring Synthesis*

G. Palmisano, A. Penoni, M. Sisti, *et al.*, Synthesis of Indole Derivatives with Biological Activity by Reactions Between Unsaturated Hydrocarbons and *N*-Aromatic Precursors, *Curr. Org. Chem.*, 2010, **14**, 2409–2441. An excellent recent review focusing primarily on the synthesis of biologically active indoles and starting with a nitrogen-substituted arene.

S.K. Bur and A. Padwa, The Pummerer Reaction: Methodology and Strategy for the Synthesis of Heterocyclic Compounds, *Chem. Rev.*, 2004, **104**, 2401–2432. This review by a leading heterocyclic chemist (Padwa) has a short section on indole alkaloids.

S.P. Gromov, Ring Transformation of Pyridines and Benzo Derivatives Under the Action of C-Nucleophiles, *Heterocycles*, 2000, **53**, 1607–1630. This specialized review covers mostly the excellent indole work of the author, much of which is available only in Russian.

A. Godard, F. Marsais, N. Plé, *et al.*, Connection Between Metalation of Azines and Diazines and Cross-Coupling Strategies for the Synthesis of Natural and Biologically Active Molecules, *Heterocycles*, 1995, **40**, 1055–1091. An excellent account of the work by Quéguiner and his colleagues on the synthesis of azacarbazoles.

### 1.7.3 Name Reactions

Several outstanding books on name reactions in organic chemistry are available. These typically briefly cover the classic indole name reactions with examples, references, and, in some cases, experimental procedures.

J. Li and J.M. Cook (2005) Indoles, in *Name Reactions in Heterocyclic Chemistry* (ed. J.-J. Li), Wiley-Interscience, Hoboken, New Jersey, Chapter 3, pp. 99–158.

B.P. Mundy, M.G. Ellerd, and F.G. Favaloro, Jr. (2005) *Name Reactions and Reagents in Organic Synthesis*, 2nd Edn., Wiley-Interscience, Hoboken, New Jersey.

E. Kruiswijk (2005) *The Comprehensive e-Book of Name Organic Reactions and Their Mechanisms*, 2nd edn. link.springer.com/content/pdf/10.2478/BF02479284.pdf

J.J. Li (2002) *Name Reactions*, Springer, Berlin.

A. Hassner and C. Stumer (2002) *Organic Syntheses Based on Name Reactions*, 2nd edn, Pergamon, Amsterdam.

A.R. Surrey (1954) *Name Reactions in Organic Chemistry*, Academic Press, New York.

### 1.7.4 Miscellaneous Reviews

In addition to the references 4–10 in the Preview, other treatments of indole ring synthesis are available.

T.L. Gilchrist, Synthesis of Aromatic Cycles, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2491–2515. This review by a leading heterocyclic chemist has a short section on indoles.

C.J. Moody, "Oxidation by Nitrene Insertion" (1991), in *Comprehensive Organic Synthesis*, vol. **7** (eds. B.M. Trost, I. Fleming, and S.V. Ley), Pergamon Press, Oxford, pp. 21–38.

J.T. Kuethe, A General Approach to Indoles: Practical Applications for the Synthesis of Highly Functionalized Pharmacophores, *Chimia*, 2006, **60**, 543–553.

M. Shiri, M.A. Zolfigol, H.G. Kruger, and Z. Tanbakouchian, Bis- and Trisindolylmethanes (BIMs and TIMs), *Chem. Rev.*, 2010, **110**, 2250–2293.

### 1.7.5 Synthesis of Carbazoles, Carbolines, and Indolocarbazoles

J. Roy, A.K. Jana, and D. Mal, Recent Trends in the Synthesis of Carbazoles: An Update, *Tetrahedron*, 2012, **68**, 6099–6121. An excellent recent review spanning 2008–2011.

H.-J. Knölker and K.R. Reddy, Isolation and Synthesis of Biologically Active Carbazole Alkaloids, *Chem. Rev.*, 2002, **102**, 4303–4427. An outstanding review by a leading practitioner in the field (Knölker).

J. Bergman, T. Janosik, and N. Wahlström, Indolocarbazoles, *Adv. Heterocycl. Chem.*, 2001, **80**, 1–71. An excellent survey of these (fused) carbazoles, which possess enormous biological activity, by a pioneer in this field (Bergman).

G.W. Gribble and S.J. Berthel A Survey of Indolo[2,3-*a*]carbazoles and Related Natural Products (1993), in *Studies in Natural Products Chemistry,* Volume 12, Structure and Chemistry, Elsevier, Amsterdam, pp. 365–409.

D.P. Chakraborty and S. Roy, Carbazole Alkaloids. III, *Prog. Chem. Org. Nat. Prod.*, 1991, **57**, 71–152. This review and the previous two are excellent accounts of this area of natural products.

U. Pindur, Recent Developments in the Syntheses of Carbazole Alkaloids, *Chimia*, 1990, **44**, 406–412. A short review on the synthesis of biologically active carbazoles.

J.A. Joule, Recent Advances in the Chemistry of 9*H*-Carbazoles, *Adv. Heterocycl. Chem.*, 1984, **35**, 83–198. An excellent review on the chemistry and synthesis of carbazoles.

R.A. Abramovitch and I.D. Spenser, The Carbolines, *Adv. Heterocycl. Chem.*, 1964, **3**, 79–207. A specialized review on these azacarbazoles.

N. Campbell and B.M. Barclay, Recent Advances in the Chemistry of Carbazole, *Chem. Rev.*, 1947, **40**, 359–380; An early review that is a segue to Joule (1984), cited above.

### 1.7.6 Reviews of Indole Analogues

Although I do not cover the synthesis of indolines, oxindoles, isatins, and azaindoles in this monograph, some excellent reviews on the synthesis of these indole analogues are available [241–243].

All of this rich chemistry on indole ring synthesis puts the question, "Why do we need another review?" My answer is that despite these wonderful voluminous reviews, there is no single monograph covering indole ring synthesis *in toto*. My intent in the present volume is to present all methods for constructing the indole ring that are available to the practicing chemist.

## References


[1] A. Baeyer, *Chem. Ber.*, 1880, **13**, 2254–2263.
[2] R.B. Van Order and H.G. Lindwall, *Chem. Rev.*, 1942, **30**, 69–96.
[3] R.J. Sundberg (1970) *The Chemistry of Indoles*, Academic Press, New York.
[4] R.J. Sundberg (1996) *Indoles*, Academic Press, London.
[5] R.J. Sundberg (1984) *Comprehensive Heterocyclic Chemistry*, vol. **4** (eds A.R. Katritzky, C.W. Rees, C.W. Bird, and G.W.H. Cheeseman), Pergamon, Oxford, pp. 313–376.
[6] G.W. Gribble (1996) *Comprehensive Heterocyclic Chemistry II*, vol. **2** (eds A.R. Katritzky, C.W. Rees, E.F.V. Scriven, and C.W. Bird), Pergamon Press, Oxford, pp. 207–257.
[7] J. Bergman and T. Janosik (2008) *Comprehensive Heterocyclic Chemistry III*, vol. **3** (eds A.R. Katritzku, C.A. Ramsden, E.F.V. Scriven, and R.J.K. Taylor), Elsevier, Amsterdam, pp. 269–351.
[8] R.K. Brown (1972) *Indoles*, Part I (ed.W.J. Houlihan), Wiley, New York, pp. 385–396.
[9] G.W. Gribble and J.A. Joule (eds) (2012) *Progress in Heterocyclic Chemistry*, vol. **24**, Chapter 5.2, Pergamon Press, Oxford (and previous volumes in this annual series).
[10] For two excellent introductions to indoles, see (a) J.A. Joule and G.F. Smith (2010) *Heterocyclic Chemistry*, 5th edn, Wiley, New York; (b) T.L. Gilchrist (1997) *Heterocyclic Chemistry*, 3rd edn, Longman, Essex.
[11] M. Ishikura, T. Abe, T. Choshi, and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694–752 and previous reviews in this series.
[12] A.F. Pozharskii, A.T. Soldatenkov, and A.R. Katritzky (2011) *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry, and Applications*, 2nd edn, Wiley, West Sussex.
[13] C.A. Herter, *J. Amer. Med. Assoc.*, 1907, **48**, 985–992.
[14] W. Bergeim, *J. Biol. Chem.*, 1917, **32**, 17–22.
[15] G.S. Clark, *Perf & Flav*, 1995, **20**, 21–31.
[16] J. Meijerink, M.A.H. Braks, A.A. Brack, *et al.*, *J. Chem. Ecol.*, 2000, **26**, 1367–1382.
[17] J.G. Kostelc, G. Preti, P.R. Zelson, *et al.*, *J. Periodontal Res.*, 1980, **15**, 185–192.
[18] A.F. Carey, G. Wang, C.-Y. Su, *et al.*, *Nature*, 2010, **464**, 66–72.
[19] For reviews of halogenated indoles, see (a) G.W. Gribble (2012) Occurrence of halogenated alkaloids, in *The Alkaloids*, vol. **71** (ed. H.-J. Knölker), Elsevier, London, UK, pp. 1–165; (b) G.W. Gribble, *Heterocycles*, 2012, **84**, 157–207.
[20] E.D. Glowacki, G. Voss, L. Leonat, *et al.*, *Israel J. Chem.*, 2012, **52**, 540–551.
[21] U. Pindur and T. Lemster, *Curr. Med. Chem.*, 2001, **8**, 1681–1698.
[22] A. Aygün and U. Pindur, *Curr. Med. Chem.*, 2003, **10**, 1113–1127.
[23] C.-G. Yang, H. Huang, and B. Jiang, *Curr. Org. Chem.*, 2004, **8**, 1691–1720.
[24] W. Gul and M.T. Hamann, *Life Sci.*, 2005, **78**, 442–453.

[25] M. Tadesse, J.N. Tabudravu, M. Jaspars, *et al.*, *J. Nat. Prod.*, 2011, **74**, 837–841.
[26] F. He, Y.-L. Sun, K.-S. Liu, *et al.*, *J. Antibiot.*, 2012, **65**, 109–111.
[27] R. Finlayson, A.N. Pearce, M.J. Page, *et al.*, *J. Nat. Prod.*, 2011, **74**, 888–892.
[28] A.J. Zaharenko, G. Picolo, W.A. Ferreira, Jr., *et al.*, *J. Nat. Prod.*, 2011, **74**, 378–382.
[29] K.Ø. Hanssen, B. Schuler, A.J. Williams, *et al.*, *Angew. Chem. Int. Ed.*, 2012, **51**, 12238–12241.
[30] N-Y. Ji, X-M. Li, L-P. Ding, and B-G. Wang, *Helv. Chim. Acta*, 2007, **90**, 385–391.
[31] I. Zendah, K.A. Shaaban, E. Helmke, *et al.*, *Zeit. Naturforsch.*, 2012, **67b**, 417–420.
[32] H.B. Park, Y.-J. Kim, J.K. Lee, *et al.*, *Org. Lett.*, 2012, **14**, 5002–5005.
[33] L. Zhu, C. Chen, H. Wang, *et al.*, *Chem. Pharm. Bull.*, 2012, **60**, 670–673.
[34] M.S.C. Pedras and E.E. Yaya, *Org. Biomol. Chem.*, 2012, **10**, 3613–3616.
[35] B.L.J. Kindler, H.-J. Krämer, S. Nies, *et al.*, *Eur. J. Org. Chem.*, 2010, 2084–2090.
[36] R.A. Butcher, J.R. Ragains, and J. Clardy, *Org. Lett.*, 2009, **11**, 3100–3103.
[37] A. Bartsch, M. Bross, P. Spiteller, *et al.*, *Angew. Chem. Int. Ed.*, 2005, **44**, 2957–2959.
[38] L.K. Nzowa, R.B. Teponno, L.A. Tapondjou, *et al.*, *Fitoterapia*, 2013, **87**, 37–42.
[39] Q. Zhang, A. Mándi, S. Li, *et al.*, *Eur. J. Org. Chem.*, 2012, 5256–5262.
[40] R.J.R. Jaeger, M. Lamshöft, S. Gottfried, *et al.*, *J. Nat. Prod.*, 2013, **76**, 127–134.
[41] P. Fu, Y. Zhuang, Y. Wang, *et al.*, *Org. Lett.*, 2012, **14**, 6194–6197.
[42] W Maneerat, W. Phakhodee, S. Cheenpracha, *et al.*, *Phytochemistry*, 2013, **88**, 74–78.
[43] V. Sharma, P. Kumar, and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491–502.
[44] J. Rosén, J. Gottfries, S. Muresan, *et al.*, *J. Med. Chem.*, 2009, **52**, 1953–1962.
[45] M. Segarra-Newnham and T.J. Church, *Annals Pharmacother.*, 2012, **46**, 1678–1687.
[46] I.C. Sutcliffe, *Proc. Natl. Acad. Sci.*, 2012, **109**, 18637–18638.
[47] S. Daly, K. Hayden, I. Malik, *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4720–4723.
[48] S. Samosorn, J.B. Bremner, A. Ball, and K. Lewis, *Bioorg. Med. Chem.*, 2006, **14**, 857–865.
[49] R. Karstad, G. Isaksen, B.-O. Brandsdal, *et al.*, *J. Med. Chem.*, 2010, **53**, 5558–5566.
[50] K. Okamoto, M. Sakagami, F. Feng, *et al.*, *J. Org. Chem.*, 2012, **77**, 1367–1377.
[51] R.J. Worthington, J.J. Richards, and C. Melander, *Org. Biomol. Chem.*, 2012, **10**, 7457–7474.
[52] E. Hedner, M. Sjögren, S. Hodzic, *et al.*, *J. Nat. Prod.*, 2008, **71**, 330–333.
[53] I. Moubax, N. Bontemps-Subielos, B. Banaigs, *et al.*, *Environ. Toxicol. Chem.*, 2001, **20**, 589–596.
[54] S. Tsukamoto, H. Hirota, H. Kato, and N. Fusetani, *Tetrahedron Lett.*, 1993, **34**, 4819–4822.
[55] N. Pénez, G. Culioli, T. Pérez, *et al.*, *J. Nat. Prod.*, 2011, **74**, 2304–2308.
[56] R.J. Deschenes, H. Lin, A.D. Ault, and J.S. Fassler, *Antimicrob. Agents Chemother.*, 1999, **43**, 1700–1703.
[57] S.Y. Ablordeppey, P. Fan, S. Li, *et al.*, *Bioorg. Med. Chem.*, 2002, **10**, 1337–1346.
[58] A.A. Farahat, A. Kumar, M. Say, *et al.*, *Bioorg. Med. Chem.*, 2010, **18**, 557–566.
[59] F. Bouchikhi, F. Anizon, R. Brun, and P. Moreau, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6319–6321.
[60] www.unaids.org.
[61] T.M. Williams, T.M. Ciccarone, S.C. MacTough, *et al.*, *J. Med. Chem.*, 1993, **36**, 1291–1294.
[62] R. Ragno, A. Coluccia, G. La Regina, *et al.*, *J. Med. Chem.*, 2006, **49**, 3172–3184.
[63] G. La Regina, A. Coluccia, A. Brancale, *et al.*, *J. Med. Chem.*, 2011, **54**, 1587–1598.
[64] Z. Zhao, S.E. Wolkenberg, M. Lu, *et al.*, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 554–559.
[65] A. Gopalsamy, K. Lim, G. Ciszewski, *et al.*, *J. Med. Chem.*, 2004, **47**, 6603–6608.
[66] K. Roy and A.S. Mandal, *J. Enzym. Inhib. Med. Chem.*, 2008, **23**, 980–995.
[67] H. Sano, T. Noguchi, A. Yanatani, *et al.*, *Bioorg. Med. Chem.*, 2005, **13**, 3079–3091.
[68] W. Hu, Z. Guo, X. Yi, *et al.*, *Bioorg. Med. Chem.*, 2003, **11**, 5539–5544.
[69] J. Kaur, A. Bhardwaj, Z. Huang, and E.E. Knaus, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2154–2159.
[70] T. Kameyama, F. Amanuma, S. Okuyama, *et al.*, *J. Pharmacobio-Dyn.*, 1985, **8**, 477–486.
[71] A.D. Favia, D. Habrant, R. Scarpelli, *et al.*, *J. Med. Chem.*, 2012, **55**, 8807–8826.
[72] M. Arisawa, Y. Kasaya, T. Obata, *et al.*, *J. Med. Chem.*, 2012, **55**, 8152–8163.
[73] S.J. Taylor, A. Abeywardane, S. Liang, *et al.*, *J. Med. Chem.*, 2011, **54**, 8174–8187.
[74] T. Komoda, Y. Shinoda, and S. Nakatsuka, *Biosci. Biotechnol. Biochem.*, 2003, **67**, 659–662.
[75] T. Komoda and S. Nakatsuka, *Heterocycl. Commun.*, 2003, **9**, 119–122.
[76] K.R. Campos, M. Journet, S. Lee, *et al.*, *J. Org. Chem.*, 2005, **70**, 268–274.
[77] K.V. Sashidhara, M. Kumar, R. Sonkar, *et al.*, *J. Med. Chem.*, 2012, **55**, 2769–2779.
[78] J.T. Mihalic, X. Chen, P. Fan, *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7001–7005.
[79] S. Kher, K. Lake, I. Sircar, *et al.*, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4442–4446.
[80] D. Weber, C. Berger, P. Eickelmann, *et al.*, *J. Med. Chem.*, 2003, **46**, 1918–1930.
[81] N.M. Barnes and T. Sharp, *Neuropharmacology*, 1999, **38**, 1083–1152.
[82] D. Hoyer, J.P. Hannon, and G.R. Martin, *Pharmacol. Biochem. Behav.*, 2002, **71**, 533–554.
[83] M.L. Woolley, C.A. Marsden, and K.C.F. Fone, *Curr. Drug Targets – CNS Neurological Disorders*, 2004, **3**, 59–79.
[84] R.A. Glennon, S.-S. Hong, M. Bondarev, *et al.*, *J. Med. Chem.*, 1996, **39**, 314–322.
[85] D.C. Cole, J.W. Ellingboe, W.J. Lennox, *et al.*, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 379–383.
[86] J. Holenz, R. Mercè, J.L. Díaz, *et al.*, *J. Med. Chem.*, 2005, **48**, 1781–1795.
[87] M.G.N. Russell, R.J. Baker, L. Barden, *et al.*, *J. Med. Chem.*, 2001, **44**, 3881–3895.

[88] Y.-C. Chang, J. Riby, G.H.-F. Chang, *et al.*, *Biochem. Pharmacol.*, 1999, **58**, 825–834.
[89] X. Ge, F.A. Fares, and S. Yannai, *Anticancer Res.*, 1999, **19**, 3199–3204.
[90] J.-R. Weng, C.-H. Tsai, S.K. Kulp, and C.-S. Chen, *Cancer Lett.*, 2008, **262**, 153–163.
[91] H. Mori, K. Niwa, Q. Zheng, *et al.*, *Mutation Res.*, 2001, **480-481**, 201–207.
[92] A.D. Shilling, D.B. Carlson, S. Katchamart, and D.E. Williams, *Toxicol. Appl. Pharmacol.*, 2001, **170**, 191–200.
[93] R. Kronbak, F. Duus, and O. Vang, *J. Agric. Food Chem.*, 2010, **58**, 8453–8459.
[94] W.-S. Li, C.-H. Wang, S. Ko, *et al.*, *J. Med. Chem.*, 2012, **55**, 1583–1592.
[95] V.K. Rao, B.S. Chhikara, A.N. Shirazi, *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3511–3514.
[96] M.-P. Lézé, A. Palusczak, R.W. Hartmann, and M. Le Borgne, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4713–4715.
[97] D.D. Miller, P. Bamborough, J.A. Christopher, *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2255–2258.
[98] A. Brancale and R. Silvestri, *Med. Res. Rev.*, 2007, **27**, 209–238.
[99] G. De Martino, G. La Regina, A. Coluccia, *et al.*, *J. Med. Chem.*, 2004, **47**, 6120–6123.
[100] G. De Martino, M.C. Edler, G. La Regina, *et al.*, *J. Med. Chem.*, 2006, **49**, 947–954.
[101] G. La Regina, M.C. Edler, A. Brancale, *et al.*, *J. Med. Chem.*, 2007, **50**, 2865–2874.
[102] D. Kaufmann, M. Pojarová, S. Vogel, *et al.*, *Bioorg. Med. Chem.*, 2007, **15**, 5122–5136.
[103] H. Saito, K. Tabata, S. Hanada, *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5370–5373.
[104] J. Qian-Cutrone, S. Huang, Y.-Z. Shu, *et al.*, *J. Am. Chem. Soc.*, 2002, **124**, 14556–14557.
[105] D.W. Nettleton, T.W. Doyle, B. Krishnan, *et al.*, *Tetrahedron Lett.*, 1985, **26**, 4011–4014.
[106] J.A. Bush, B.H. Long, J.J. Catino, *et al.*, *J. Antibiot.*, 1987, **40**, 668–678.
[107] J.S. Sandler, P.L. Colin, J.N.A. Hooper, and D.J. Faulkner, *J. Nat. Prod.*, 2002, **65**, 1258–1261.
[108] D.R. Appleton, M.J. Page, G. Lambert, *et al.*, *J. Org. Chem.*, 2002, **67**, 5702–5704.
[109] D.R. Appleton and B.R. Copp, *Tetrahedron Lett.*, 2003, **44**, 8963–8965.
[110] K. Ohba, H. Watabe, T. Sasaki, *et al.*, *J. Antibiot.*, 1988, **41**, 1515–1519.
[111] S. Ishii, M. Nagasawa, Y. Kariya, *et al.*, *J. Antibiot.*, 1989, **42**, 1713–1717.
[112] N.B. Perry, J.W. Blunt, and M.H.G. Munro, *Tetrahedron*, 1988, **44**, 1727–1734.
[113] R.P. Maskey, I. Grün-Wollny, H.H. Fiebig, and H. Laatsch, *Angew. Chem. Int. Ed.*, 2002, **41**, 597–599.
[114] N. Khorana, K. Changwichit, K. Ingkaninan, and M. Utsintong, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2885–2888.
[115] P.G. Becher, J. Beuchat, K. Gademann, and F. Jüttner, *J. Nat. Prod.*, 2005, **68**, 1793–1795.
[116] P. Polychronopoulos, P. Magiatis, A.-L. Skaltsounis, *et al.*, *J. Med. Chem.*, 2004, **47**, 935–945.
[117] K.S. MacMillan, J. Naidoo, J. Liang, *et al.*, *J. Am. Chem. Soc.*, 2011, **133**, 1428–1437.
[118] A. Mahapatra, *ACS Chem. Neurosci.*, 2010, **1**, 589.
[119] S. Štolc, V. Šnirc, M. Májeková, *et al.*, *Cell. Mol. Neurobiol.*, 2006, **26**, 1495–1504.
[120] K. Dinnell, G.G. Chicchi, M.J. Dhar, *et al.*, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1237–1240.
[121] J.L. Stanton and M.H. Ackerman, *J. Med. Chem.*, 1983, **26**, 986–989.
[122] M.-J. Don, D.F.V. Lewis, S.-Y. Wang, *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2535–2538.
[123] M. Jansen and G. Dannhardt, *Eur. J. Med. Chem.*, 2003, **38**, 855–865.
[124] N. Uchiyama, R. Kikura-Hanajiri, and Y. Goda, *Chem. Pharm. Bull.*, 2011, **59**, 1203–1205.
[125] J.L. Wiley, V.J. Smith, J. Chen, *et al.*, *Bioorg. Med. Chem.*, 2012, **20**, 2067–2081.
[126] R.K. Razdan, V.K. Vemuri, A. Makriyannis, and J.W. Huffman (2009) *Cannabinoid Receptor Ligands and Structure-Activity Relationships*, Part 1 (ed. P.H. Reggio), Humana Press, New York, pp. 3–94.
[127] V. Leclerc, S. Yous, P. Delagrange, *et al.*, *J. Med. Chem.*, 2002, **45**, 1853–1859.
[128] Y. Sugiyama, Y. Ito, M. Suzuki, and A. Hirota, *J. Nat. Prod.*, 2009, **72**, 2069–2071.
[129] D.J. Buzard, S. Han, L. Lopez, *et al., Bioorg. Med. Chem. Lett.,* 2012, **22**, 4404–4409.
[130] P. Prasit, M. Belley, M. Blouin, *et al.*, *J. Lipid Mediat.*, 1993, **6**, 239–244.
[131] Z. Diamant, M.C. Timmers, H. van der Veen, *et al.*, *J. Allergy Clin. Immunol.*, 1995, **95**, 42–51.
[132] C.D. Funk, *Nature Rev., Drug Discovery*, 2005, **4**, 664–672.
[133] J.F. Evans, C. Léville, J.A. Manchini, *et al.*, *Mol. Pharmacol.*, 1991, **40**, 22–27.
[134] S. Lucas, M.H. Poulsen, N.G. Nørager, *et al.*, *J. Med. Chem.*, 2012, **55**, 10297-10301.
[135] H. Bräuner-Osborne, J. Egebjerg, E.Ø. Nielsen, *et al.*, *J. Med. Chem.*, 2000, **43**, 2609–2645.
[136] R. Planells-Cases, J. Lerma, and A. Ferrer-Montiel, *Curr. Pharm. Des.*, 2006, **12**, 3583–3596.
[137] S.F. Traynelis, L.P. Wollmuth, C.J. McBain, *et al.*, *Pharmacol. Rev.*, 2010, **62**, 405–496.
[138] M.-J. Don, D.F.V. Lewis, S.-Y. Wang, *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2535–2538.
[139] M. Somei, *Heterocycles*, 2011, **82**, 1007–1027.
[140] M.E. Welsch, S.A. Snyder, and B.R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361.
[141] I.S. Johnson, J.G. Armstrong, M. Gorman, and J.P. Burnett Jr., *Cancer Res.*, 1963, **23**, 1390–1427.
[142] P.G. Goppi, C. Broglia, F. Merli, *et al.*, *Cancer*, 2003, **98**, 2393–2401.
[143] G.M. Cragg, P.G. Grothaus, and D.J. Newman, *Chem. Rev.*, 2009, **109**, 3012–3043.
[144] M. Hussain, U. Vaishampagan, L.K. Heilbrun, *et al.*, *Invest. New Drugs*, 2003, **21**, 465–471.

[145] G.H. Schwartz, A. Patnaik, L.A. Hammond, *et al.*, *Ann. Oncology*, 2003, **14**, 775–782.
[146] T. Hata, Y. Sato, R. Sugawara, *et al.*, *J. Antibiot. Ser. A*, 1956, **9**, 141–146.
[147] M. Tomasz, *Chem. Biol.*, 1995, **2**, 575–579.
[148] C.P. Miller, H.A. Harris, and B.S. Komm, *Drugs Fut.*, 2002, **27**, 117–121.
[149] L.A. Sorbera, J. Castaner, and J.S. Silvestre, *Drugs Fut.*, 2002, **27**, 942–947.
[150] Y.-J. Wu, *Prog. Heterocycl. Chem.*, 2012, **24**, 1–42.
[151] P. Revill, N. Mealy, N Serradell, *et al.*, *Drugs Fut.*, 2007, **32**, 315–322.
[152] H. Huynh and J. Fargnoli, *Drug Fut.*, 2009, **34**, 881–895.
[153] L.A. Sorbera, N. Serradell, E. Rosa, *et al.*, *Drugs Fut.*, 2007, **32**, 577–589.
[154] Y. Wang, *Drugs Fut.*, 2009, **34**, 177–182.
[155] Y. Wang, N. Serradell, J. Bolos, and E. Rosa, *Drugs Fut.*, 2007, **32**, 228–233.
[156] G.W. Gribble and S.J. Berthel, *Stud. Nat. Prod. Chem.*, 1993, **12**, 365–409.
[157] M. Prudhomme, *Curr. Pharm. Des.*, 1997, **3**, 265–290.
[158] P.R. Revill, N. Serradell, J. Bolos, and E. Rosa, *Drugs Fut.*, 2007, **32**, 215–222.
[159] L.A. Sorbera, N. Serradell, J. Bolos, and E. Rosa, *Drugs Fut.*, 2007, **32** 297–309.
[160] C. Dulsat and R. Castaner, *Drugs Fut.*, 2009, **34**, 270–275.
[161] R. Talpir, Y. Benayahu, Y. Kashman, *et al.*, *Tetrahedron Lett.*, 1994, **35**, 4453–4456.
[162] L.-C. Hsu, D.E. Durrant, C.-C. Huang, *et al.*, *Invest. New Drugs*, 2012, **30**, 1379–1388.
[163] M.G. Saulnier, B.H. Long, D.B Frennesson, *et al.*, *J. Med. Chem.*, 2005, **48**, 2258–2261.
[164] J.J. Li, D.S. Johnson, D.D. Sliskovic, and B.D. Roth (2004) Triptans for migraine, in *Contemporary Drug Synthesis*, John Wiley & Sons, Hoboken, NJ, Chapter 12.
[165] J.J. Li (2009) *Triumph of the Heart*, Oxford University Press, New York.
[166] A. Graul, J. Silvestre, and J. Castaner, *Drugs Fut.*, 1999, **24**, 38–44.
[167] M. McCall, S. Merani, C. Toso, and A.M.J. Shapiro, *Drugs Fut.*, 2009, **34**, 618–623.
[168] C.N. Eid, Jr., Y.J. Wu, and G. Kenny (2002) Cognition enhancers, in *Burger's Medicinal Chemistry and Drug Discovery* (ed. D.J. Abraham), John Wiley & Sons, New York, Chapter 12, pp. 779–835.
[169] L.K. Larsen, R.E. Moore, and G.M.L. Pattersen, *J. Nat. Prod.*, 1994, **57**, 419–421.
[170] H.-L. Yin, J.-H. Li, J. Li, *et al.*, *Fitoterapia*, 2013, **84**, 360–365.
[171] R.J. Lake, M.M. Brennan, J.W. Blunt, *et al.*, *Tetrahedron Lett.*, 1988, **29**, 4971–4972.
[172] S. Sagar, M. Kaur, and K.P. Minneman, *Mar. Drugs*, 2010, **8**, 2619–2638.
[173] J.R. Woodworth, E.H. Nyhart, G.L. Brier, *et al.*, *Antimicrob. Agents Chemother.*, 1992, **36**, 318–325.
[174] R.M. Scarborough, *Drugs Fut.*, 1998, **23**, 585–590.
[175] L.A. Sorbera, X. Rabasseda, J. Silvestre, and J. Castaner, *Drugs Fut.*, 2001, **26**, 247–252.
[176] H. Elokdah, M. Abou-Gharbia, J.K. Hennan, *et al.*, *J. Med. Chem.*, 2004, **47**, 3491–3494.
[177] L.A. Sorbera, J. Silvestre, X. Rabasseda, and J. Castaner, *Drugs Fut.*, 2000, **25**, 1017–1026.
[178] R.W. Schevitz, N.J. Bach, D.G. Carlson, *et al.*, *Nature Struct. Biol.*, 1995, **2**, 458–465.
[179] M.C. Oliancis and P. Onali, *Life Sci.*, 1999, **65**, 2233–2240.
[180] S. Heptinstall, D.I. Espinosa, P. Manolopoulos, *et al.*, *Platelets*, 2008, **19**, 605–613.
[181] A.B. Bredt and G.J.D. Girey, *Cancer*, 1982, **50**, 1430–1433.
[182] P.A. Gale, *Chem. Commun.*, 2008, 4525–4540.
[183] L. Panzella, A. Pezzella, M. Arzillo, *et al.*, *Tetrahedron*, 2009, **65**, 2032–2036.
[184] Y. Shiraishi, H. Maehara, and T. Hirai, *Org. Biomol. Chem.*, 2009, **7**, 2072–2076.
[185] G.W. Lee, N.-K. Kim, and K.-S. Jeong, *Org. Lett.*, 2010, **12**, 2634–2637.
[186] L. Wang, X. He, Y. Guo, *et al.*, *Org. Biomol. Chem.*, 2011, **9**, 752–757.
[187] K.N. Skala, K.G. Perkins, A. Ali, *et al.*, *Tetrahedron Lett.*, 2010, **51**, 6516–6520.
[188] A.L. Whiting and F. Hof, *Org. Biomol. Chem.*, 2012, **10**, 6885–6892.
[189] J. Schönhaber, W. Frank, and T.J.J. Müller, *Org. Lett.*, 2010, **12**, 4122–4125.
[190] J.H. Lee, J.-H. So, J.H. Jeon, *et al.*, *Chem. Commun.*, 2011, **47**, 7500–7502.
[191] K.M. Schlitt, A.L. Millen, S.D. Wetmore, and R.A. Manderville, *Org. Biomol. Chem.*, 2011, **9**, 1565–1571.
[192] L. Chen, T.-S. Hu, and Z.-J. Yao, *Eur. J. Org. Chem.*, 2008, 6175–6182.
[193] R.A. Illos, D. Shamir, L.J.W. Shimon, *et al.*, *Tetrahedron Lett.*, 2006, **47**, 5543–5546.
[194] G. Chen, D.J. Yee, N.G. Gubernator, and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 4544–4545.
[195] H. Hiyoshi, T. Aoyama, T. Wada, *et al.*, *Heterocycles*, 2009, **77**, 595–602.
[196] H. Tsuji, Y. Yokoi, C. Mitsui, *et al.*, *Chem. Asian J.*, 2009, **4**, 655–657.
[197] T.V. Pho, J.D. Yuen, J.A. Kurzman, *et al.*, *J. Am. Chem. Soc.*, 2012, **134**, 18185–18188.
[198] T. Lei, J.-H. Dou, Z.-J. Ma, *et al.*, *J. Am. Chem. Soc.*, 2012, **134**, 20025–20028.
[199] M. Irimia-Vladu, E.D. Glowacki, P.A. Troshin, *et al.*, *Adv. Mater.*, 2012, **24**, 375–380.
[200] M. Yao, M. Araki, H. Senoh, *et al.*, *Chem. Lett.*, 2010, **39**, 950–952.

[201] E. Wang, Z. Ma, Z. Zhang, *et al.*, *J. Am. Chem. Soc.*, 2011, **133**, 14244–14247.
[202] P. Remón, M Bälter, S. Li, *et al.*, *J. Am. Chem. Soc.*, 2011, **133**, 20742–20745.
[203] J.-F. Morin, S. Beaupré, M. Leclerc, *et al.*, *Appl. Phys. Lett.*, 2002, **80**, 341–343.
[204] J.-F. Morin and M. Leclerc, *Macromolecules*, 2001, **34**, 8413–8417.
[205] B.-Y. Ryu and T. Emrick, *Angew. Chem. Int. Ed.*, 2010, **49**, 9644–9647.
[206] L. Ginnari-Satriani, V. Casagrande, A. Bianco, *et al.*, *Org. Biomol. Chem.*, 2009, **7**, 2513–2516.
[207] J. Barbaric, C. Wanninger-Weiß, and H.-A. Wagenknecht, *Eur. J. Org. Chem*., 2009, 364–370.
[208] C. Wanninger and H.-A. Wagenknecht, *Synlett*, 2006, 2051–2054.
[209] C.L. Chepanoske, C.R. Langelier, N.H. Chmiel, and S.S. David, *Org. Lett.*, 2000, **2**, 1341–1344.
[210] J.S. Biradar, B.S. Sasidhar, and R. Parveen, *Eur. J. Med. Chem.*, 2010, **45**, 4074–4078.
[211] M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9608–9644.
[212] T. Benincori, E. Brenna, F. Sannicolo, *et al.*, *J. Organometal. Chem.*, 1997, **529**, 445–453.
[213] T. Benincori, O. Piccolo, S. Rizzo, and F. Sannicolo, *J. Org. Chem.*, 2000, **65**, 8340–8347.
[214] J. Wassenaar and J.N.H. Reek, *Dalton Trans.*, 2007, **34**, 3750–3753.
[215] J. Wassenaar, M. Kuil, and J.N.H. Reek, *Adv. Synth. Catal.*, 2008, **350**, 1610–1614.
[216] J. Wassenaar, S. van Zutphen, G. Mora, *et al.*, *Organometallics*, 2009, **28**, 2724–2734.
[217] F. Rataboul, A. Zapf, R. Jackstell, *et al.*, *Chem. Eur. J.*, 2004, **10**, 2983–2990.
[218] Y.L. Choi, C.-M. Yu, B.T. Kim, and J.-N. Heo, *J. Org. Chem.*, 2009, **74**, 3948–3951.
[219] T. Mino, S. Komatsu, K. Wakui, *et al.*, *Tetrahedron Asym.*, 2010, **21**, 711–718.
[220] R. Ghosh, N.N. Adarsh, and A. Sarkar, *J. Org. Chem.*, 2010, **75**, 5320–5322.
[221] R. Ghosh and A. Sarkar, A., *J. Org. Chem.*, 2011, **76**, 8508–8512.
[222] R. Ghosh and A. Sarkar, A., *J. Org. Chem.*, 2010, **75**, 8283–8286.
[223] Y. Wang, A. Hämäläinen, J. Tois, and R. Franzén, *Tetrahedron: Asym.*, 2010, **21**, 2376–2384.
[224] Y. Wang, M.J.P. Vaismaa, A.M. Hämäläinen, *et al.*, *Tetrahedron: Asym.*, 2011, **22**, 524–529.
[225] Y. Wang, M.J.P. Vaismaa, K. Rissanen, and R. Franzén, *Eur. J. Org. Chem.*, 2012, 1569–1576.
[226] C.M. So, C.P. Lau, and F.Y. Kwong, *Org. Lett.*, 2007, **9**, 2795–2798.
[227] C.M. So, Z. Zhou, C.P. Lau, and F.Y. Kwong, *Angew. Chem. Int. Ed.*, 2008, **47**, 6402–6406.
[228] H.W. Lee, F.L. Lam, C.M. So., *et al.*, *Angew. Chem. Int. Ed.*, 2009, **48**, 7436–7439.
[229] C.M. So, C.P. Lau, A.S.C. Chan, and F.Y. Kwong, *J. Org. Chem.*, 2008, **73**, 7731–7734.
[230] C.M. So, C.C. Yeung, C.P. Lau, and F.Y. Kwong, *J. Org. Chem.*, 2008, **73**, 7803–7806.
[231] W.K. Chow, C.M. So, C.P. Lau, and F.Y. Kwong, *J. Org. Chem.*, 2010, **75**, 5109–5112.
[232] P.Y. Wong, W.K. Chow, K.H. Chung, *et al.*, *Chem. Commun.*, 2011, **47**, 8328–8330.
[233] C.M. So, H.W. Lee, C.P. Lau, and F.Y. Kwong, *Org. Lett.*, 2009, **11**, 317–320.
[234] P.Y. Yeung, C.M. So, C.P. Lau, and F.Y. Kwong, *Org. Lett.*, 2011, **13**, 648–651.
[235] W.K. Chow, O.Y. Yuen, C.M. So, *et al.*, *J. Org. Chem.*, 2012, **77**, 3543–3548.
[236] C.M. So, W.K. Chow, P.Y. Choi, *et al.*, *Chem. Eur. J.*, 2010, **16**, 7996–8001.
[237] M.J. Oila, J.E. Tois, and M.P. Koskinen, *Synth. Commun.*, 2008, **38**, 361–370.
[238] N. Kuuloja, J. Tois, and R. Franzén, *Tetrahedron: Asym.*, 2011, **22**, 468–475.
[239] S.R. Oakley, G. Nawn, K.M. Woldie, *et al.*, *Chem. Commun.*, 2010, **46**, 6753–6755.
[240] A. Isidro, D. Latassa, M. Giraud, *et al.*, *Org. Biomol. Chem.*, 2009, **7**, 2565–2569.
[241] D. Liu, G. Zhao, and L. Xiang, *Eur. J. Org. Chem.*, 2010, 3975–3984.
[242] F. Zhou, Y.-L. Liu, and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381–1407.
[243] C. Marti and E.M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209–2219.