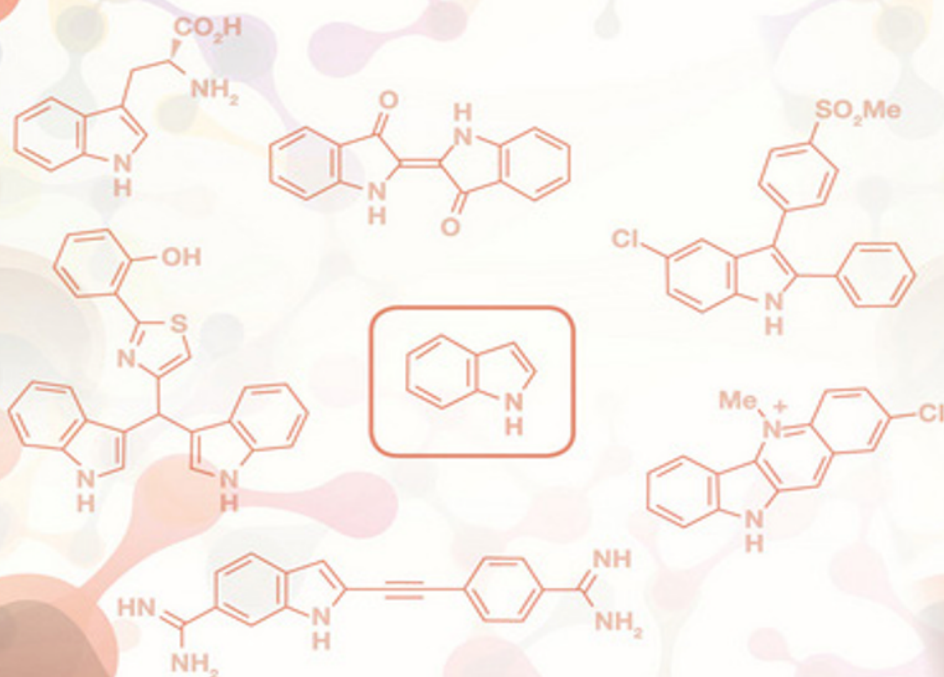




# Indole Ring Synthesis

From Natural Products to Drug Discovery



**Gordon W. Gribble**

**WILEY**



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From Natural Products to Drug Discovery

GORDON W. GRIBBLE

*Department of Chemistry, Dartmouth College, USA*

WILEY

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*Dedicated to the memory of my beloved brother, Alan Paul Gribble, 1944–2014.*





## About the Author

**Gordon W. Gribble** is a native of San Francisco, California, and completed his undergraduate education from the University of California at Berkeley in 1963. He earned his PhD in organic chemistry from the University of Oregon in 1967, working with Lloyd Dolby on indole chemistry as a National Institutes of Health predoctoral fellow. After his National Cancer Institute postdoctoral fellowship in 1967–1968 with Frank Anet at the University of California, Los Angeles, he joined the faculty of Dartmouth College in 1968 where he has been full professor of chemistry since 1980. His awards include the National Science Foundation Professional Development Award (1977), the American Cyanamid Academic Award (1988), the Dartmouth College Distinguished Teaching Award (1997), the University of Oregon Chemistry Alumni Achievement Award (1998), Abraham Lincoln High School “Wall of Fame” (2004), and the Dartmouth College Arts and Sciences Graduate Faculty Mentoring Award (2006). He served as department chair from 1988 to 1991. In 2005, he was named to the inaugural endowed chair as “The Dartmouth Professor of Chemistry.” He has been a visiting scholar/professor at Caltech; the University of Hawaii; the University of California, Santa Cruz; and Gettysburg College. He is a scientific adviser to the American Council on Science and Health and a member of the editorial boards of *Arkivoc* and *Current Organic Synthesis*. Dr. Gribble has published 370 papers on natural product synthesis, synthetic methodology, heterocyclic chemistry, polycyclic aromatic hydrocarbons, natural organohalogen compounds, organic chemical toxicity, and synthetic triterpenoids, one of which entered phase 3 clinical trials for the treatment of chronic kidney disease. He holds 34 patents. Since 1995 he has coedited the annual series *Progress in Heterocyclic Chemistry* and coauthored the second edition of *Palladium in Heterocyclic Chemistry*, published in 2007, along with Jack Li. He has written two monographs documenting more than 5000 naturally occurring organohalogen compounds. As a nationally ranked home winemaker for the past 38 years, he has a strong interest in the chemistry of wine and winemaking. He is a rated tournament chess player, enjoys scuba diving, and has a strong personal interest in the battles of Gettysburg and Iwo Jima, to which he has written about. He lives in Lebanon, New Hampshire, with his wife, and has two children, two grandsons, and two stepgrandsons.



# Preface

Given the enormous resurgence in indole ring synthesis over the past decade—highlighted by the power of transition-metal catalysis—there is a need for a comprehensive presentation of the myriad methods for constructing the indole ring: from the ancient to the modern and from the well-known to the obscure. The organization that I have adopted follows that in my two earlier reviews on indole ring synthesis,<sup>1,2</sup> beginning with an Introduction on the importance of indoles and their role in society. Given space limitations, with a few exceptions I do not explicitly cover the synthesis of indolines (2,3-dihydroindoles), oxindoles (indolin-2-ones), indoxyls (indole-3-ols), isatins (indoline-2,3-diones), and azaindoles (pyrrolo[2,3-*x*]pyridines). However, carbazoles, carbolines, and their fused ring derivatives are covered.

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<sup>1</sup> G.W. Gribble, *Contem. Org. Syn.*, 1994, 145–172.

<sup>2</sup> G.W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075.



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# 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—*indigo + oleum*—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.

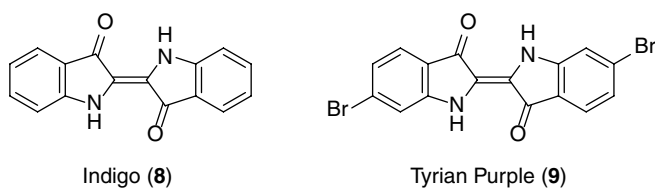
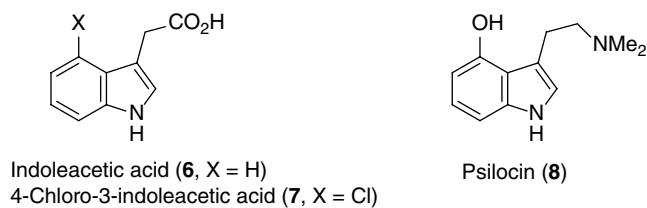
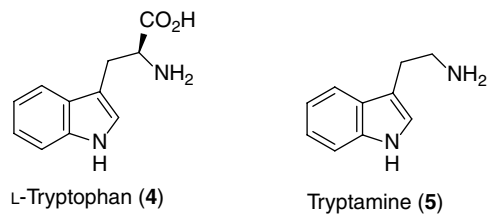
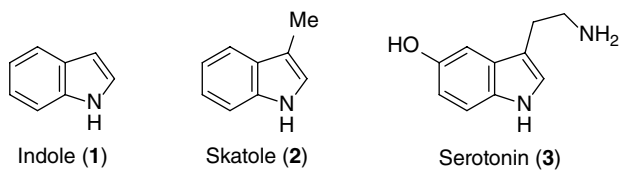
### 1.2 Indole-Containing Natural Products

Indole (**1**) itself has several interesting natural sources, the most familiar of which is mammalian feces [13, 14], although its toxicity is low ( $LD_{50} = 1,100 \text{ kg/mg}$  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 has 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].

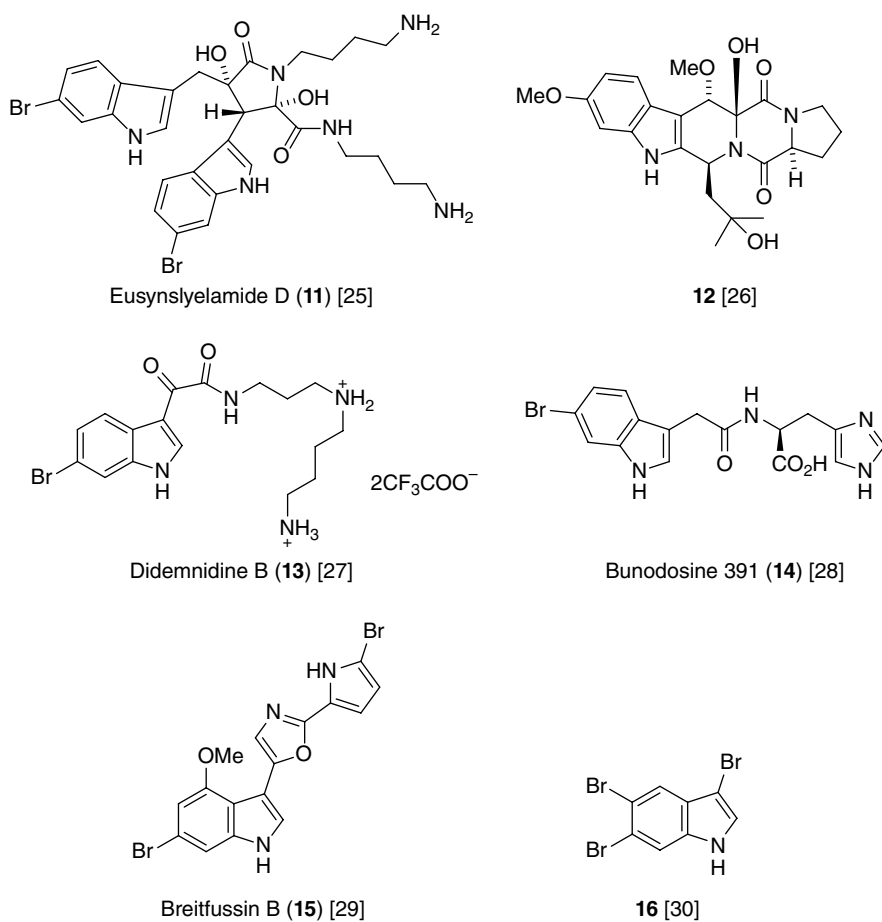
Other well-known indoles that have various natural sources are skatole (3-methylindole) (**2**), serotonin (**3**), L-tryptophan (**4**), tryptamine (**5**), the plant growth hormones 3-indoleacetic acid (**6**) and 4-chloro-3-indoleacetic acid (**7**) [19], the mushroom hallucinogen psilocin (**8**), 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 eusyntelamides (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  $\beta$ -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 breifussi* has yielded the novel breifussin B (**15**) [29]. Tribromoindole (**16**) was found in the red alga *Laurencia similis* collected from Hainan Island, China, along with two other tribromoindoles [30].

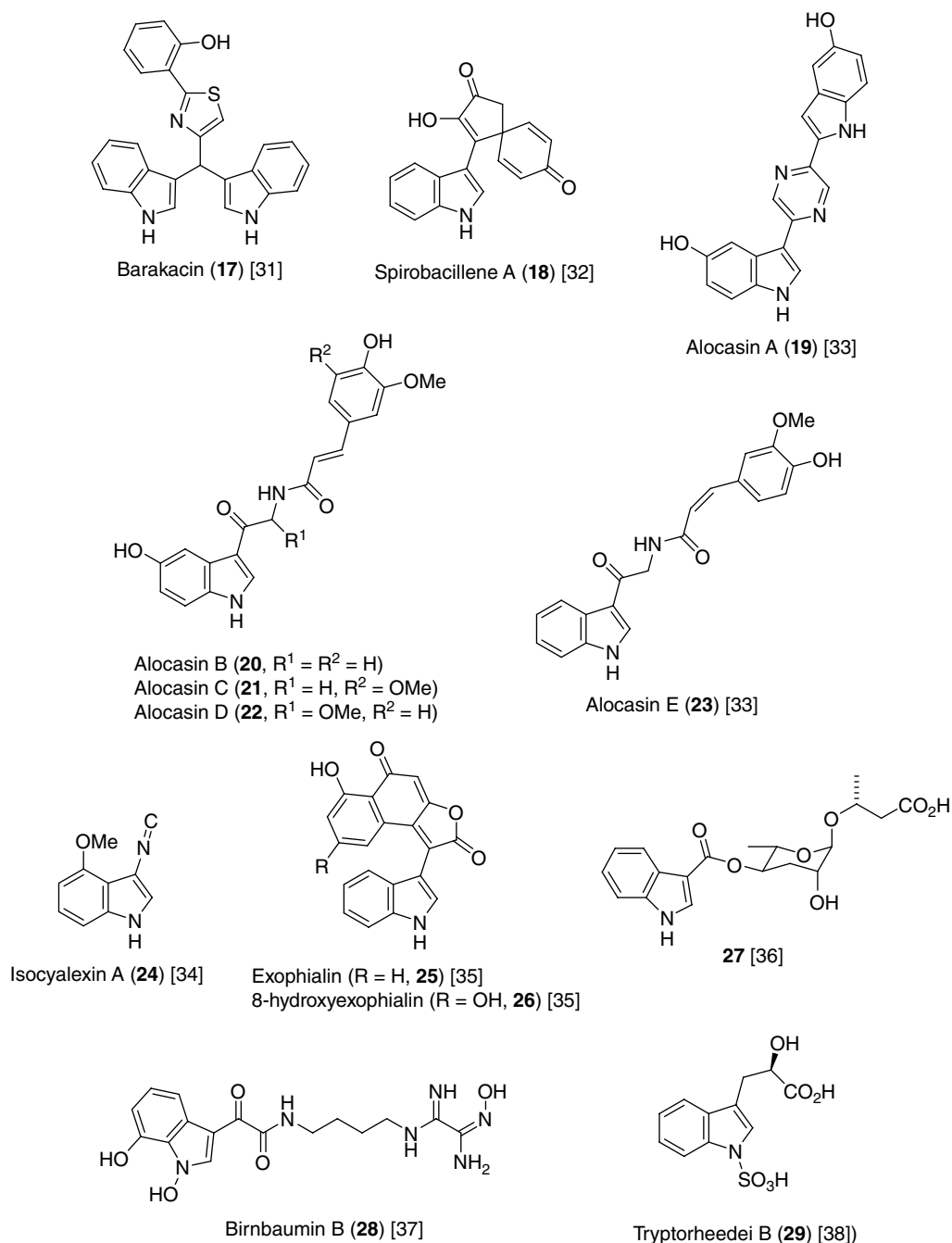
Our terrestrial environment also contains a wealth of naturally produced indoles, and some recent examples are shown in Scheme 3 [31–38]. The novel thiazolyl-indole barakacin (**17**) was found in the ruminal bacterium *Pseudomonas aeruginosa* strain Z10 [31]. Spirobacillene A (**18**) was isolated from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



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



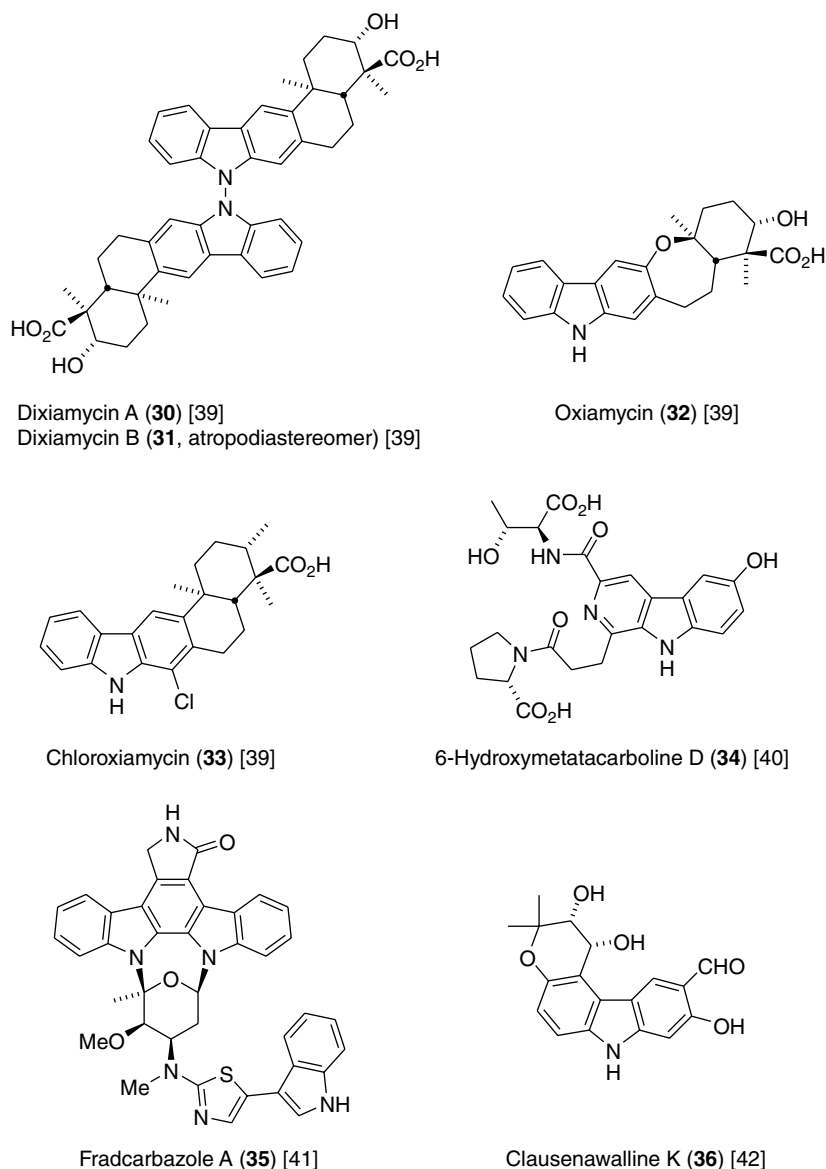
**Scheme 2** Representative Newly Discovered Marine Indoles



**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**.



**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  $\beta$ -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.

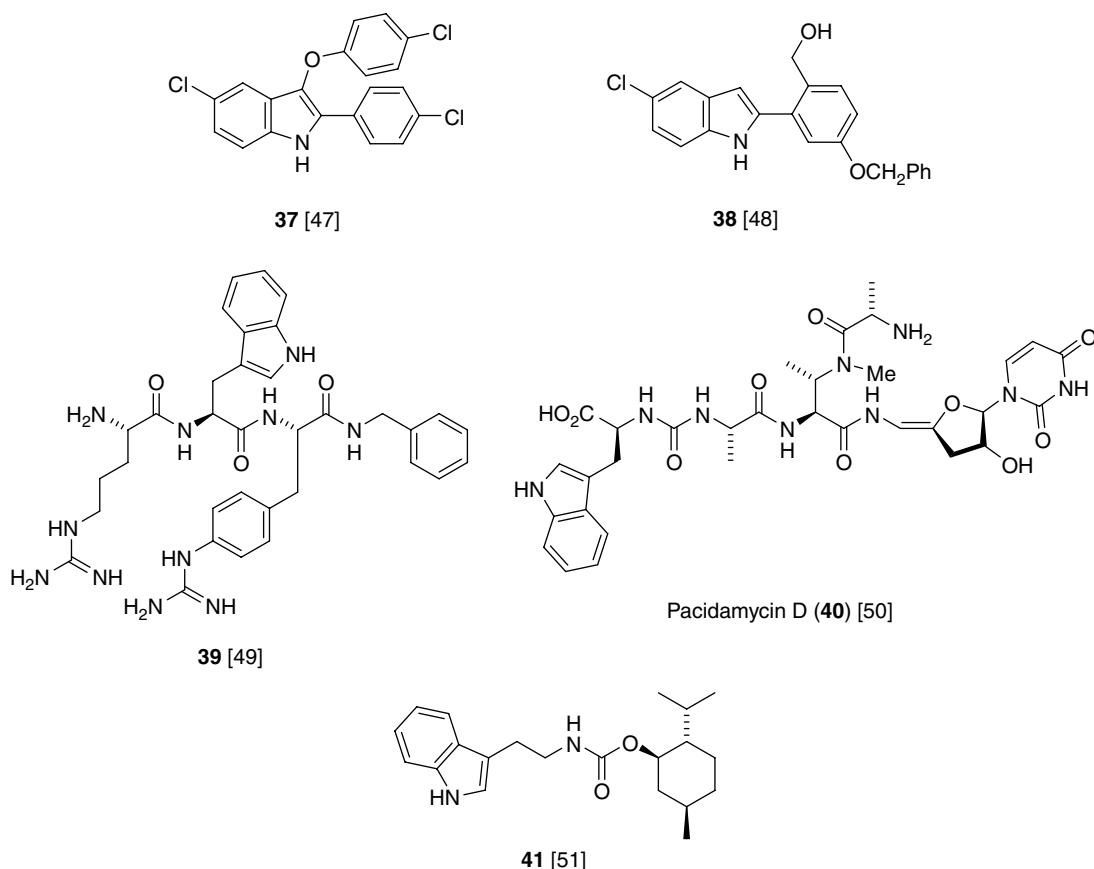
A growing worldwide problem is drug resistance to disease-inflicting bacteria, such as MRSA (methicillin-resistant *Staphylococcus aureus*) [45, 46]. Several indoles

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).

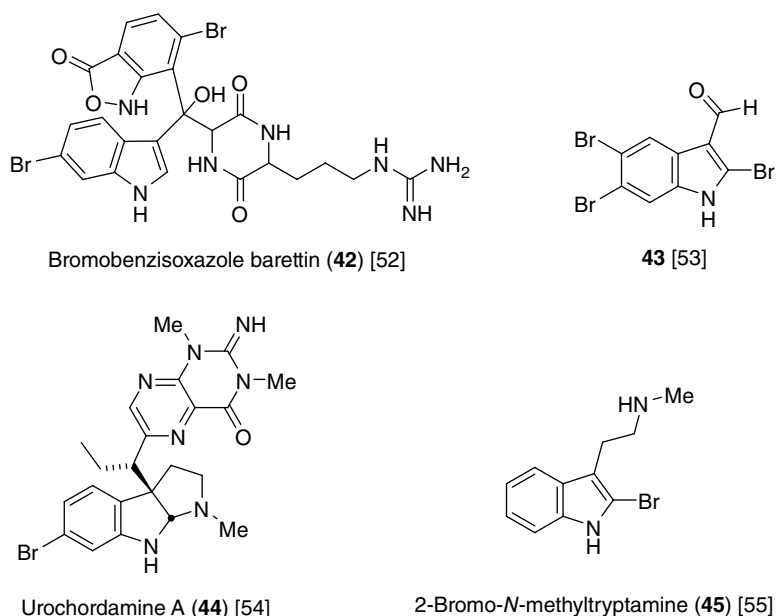
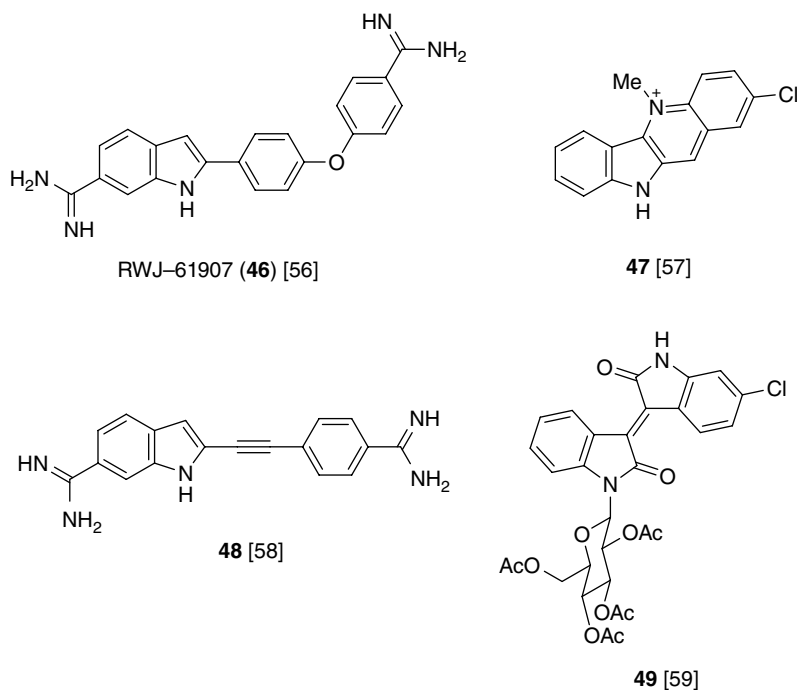
Marine biofouling is a major problem to the shipping industry, but not to sponges, many of which produce antifouling compounds that inhibit settlement and smothering by barnacle larvae (*Balanus improvisus*). Some of these indole compounds are shown in Scheme 6. The novel cyclopeptide bromobenzisoxalone baretin **42** was isolated from the marine sponge *Geodia barretti* [52], and the marine ascidian *Stomozia 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  $\mu\text{g/mL}$  [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-isouindigo 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]),



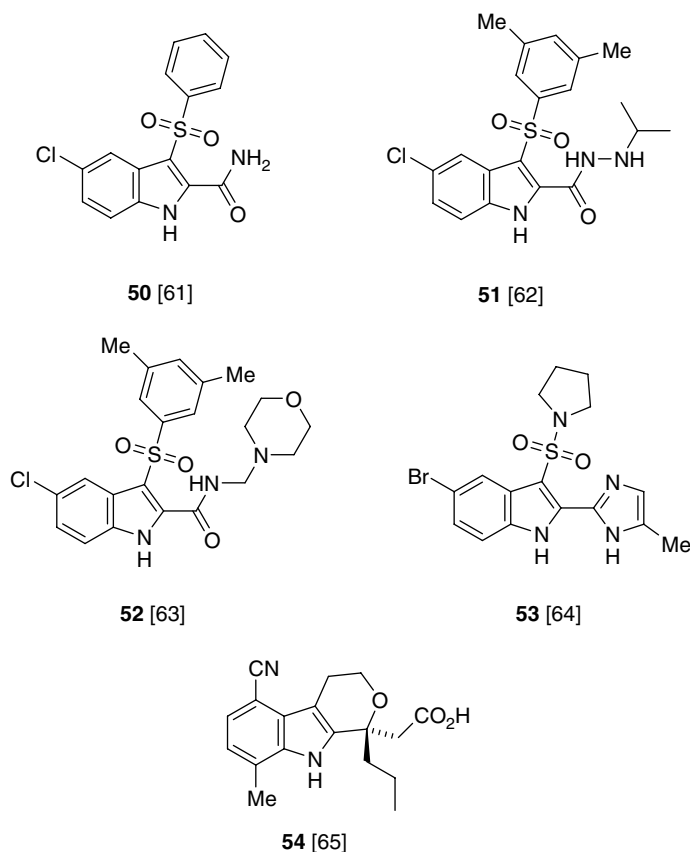
**Scheme 5** Representative Antibacterial Indoles

**Scheme 6** Representative Antifouling Indoles**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



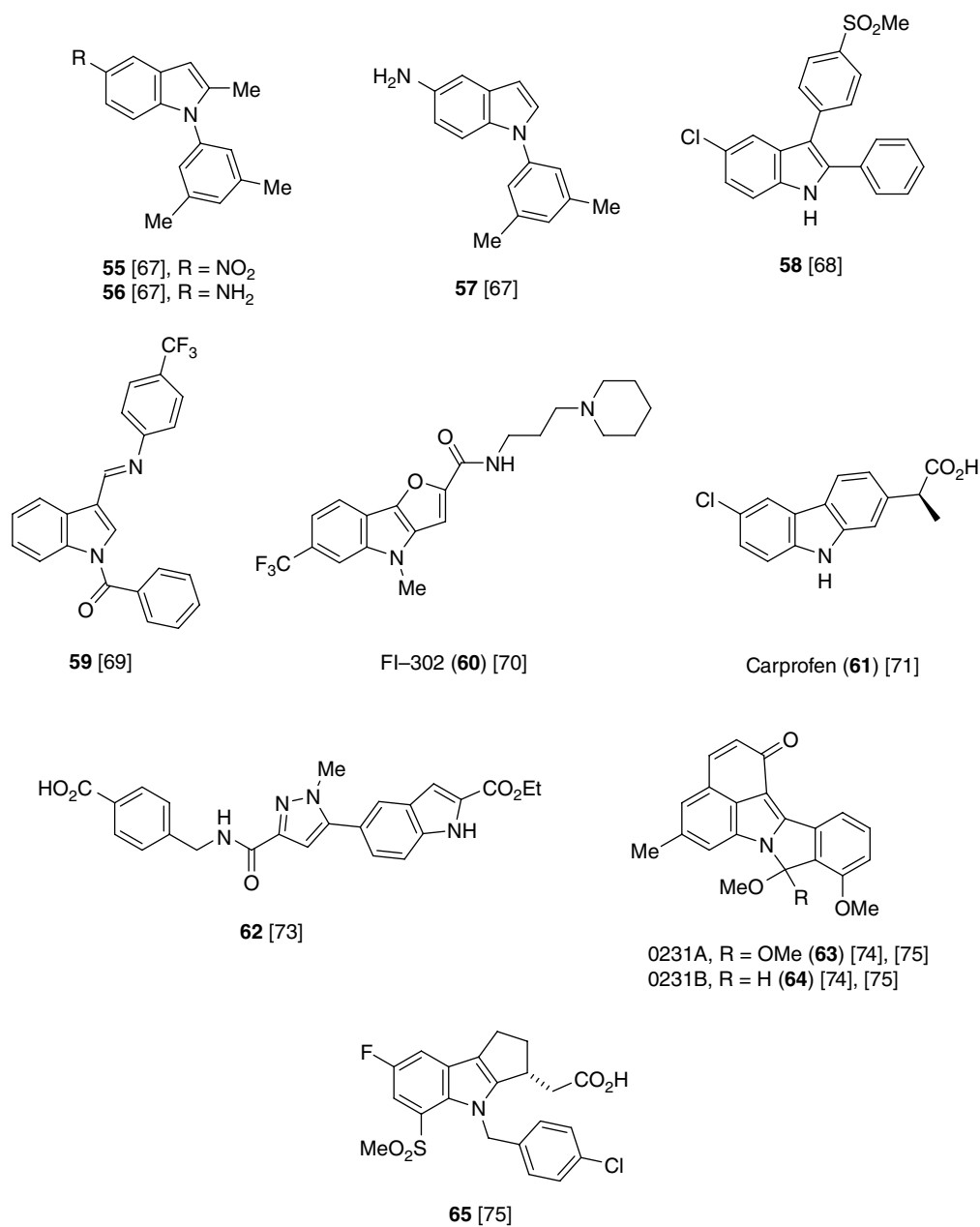


**Scheme 8** Representative HIV Active Indoles

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  $3\alpha$ -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 notwithstanding, 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 (LXR $\beta$ ) 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].

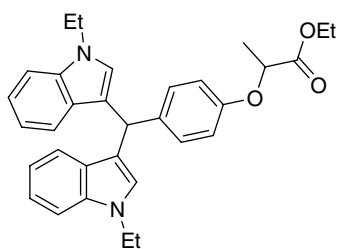
Serotonin (5-hydroxytryptamine [5-HT], **3**) receptors play an essential role in mediating neurotransmission and in so doing they influence memory, learning, sleep, aggression, anxiety, appetite, mood, and other neurological functions [81, 82]. These dozen or so receptors are targets for drugs to treat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



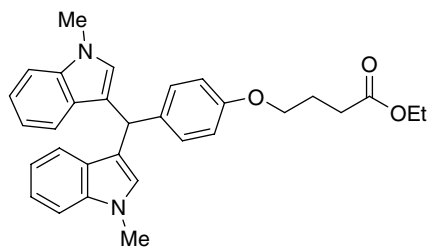
**Scheme 9** Representative Antiinflammatory Indoles

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<sub>6</sub> has appeared [83]. Indole **71** is remarkably selective as an agonist toward 5-HT<sub>ID</sub> versus 5-HT<sub>1A</sub> [84], and **72** is a potent and selective 5-HT<sub>6</sub> receptor antagonist having subnanomolar inhibition of the production of adenylyl cyclase [85]. Indole **73** also has very high and selective affinity for 5-HT<sub>6</sub> as an agonist [86], and **74** is a selective antagonist for 5-HT<sub>6</sub> [87].

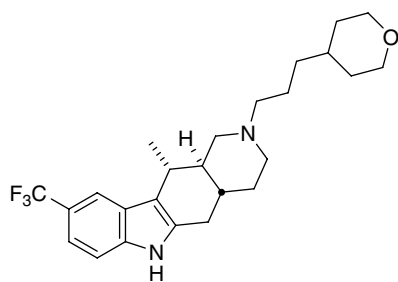
In addition to the anticancer indole alkaloids vinblastine and vincristine, discussed in the next section, many indoles display antitumor activity. Space does not allow complete coverage of these studies. Indole-3-carbinol (Scheme 12, **75**), found in vegetables of genus *Brassica* (kale, cauliflower, 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



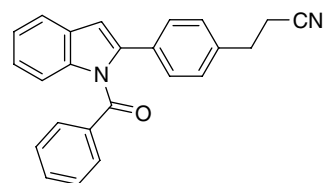
66 [77]



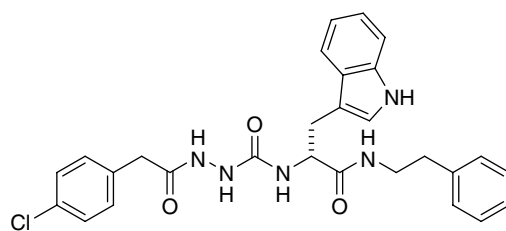
67 [77]



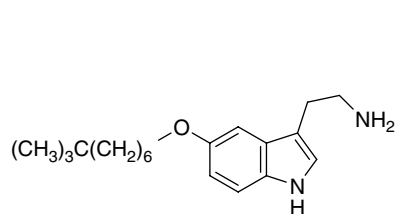
68 [78]



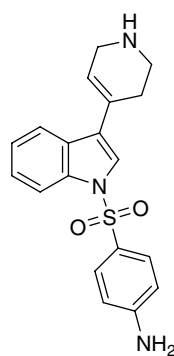
69 [79]



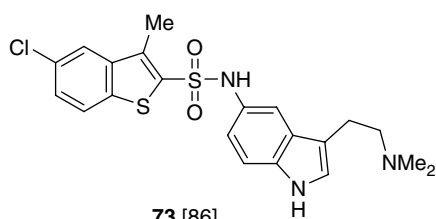
70 [80]

**Scheme 10** Representative Antiobesity Indoles

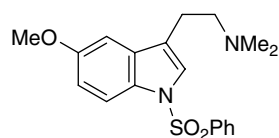
71 [84]



72 [85]

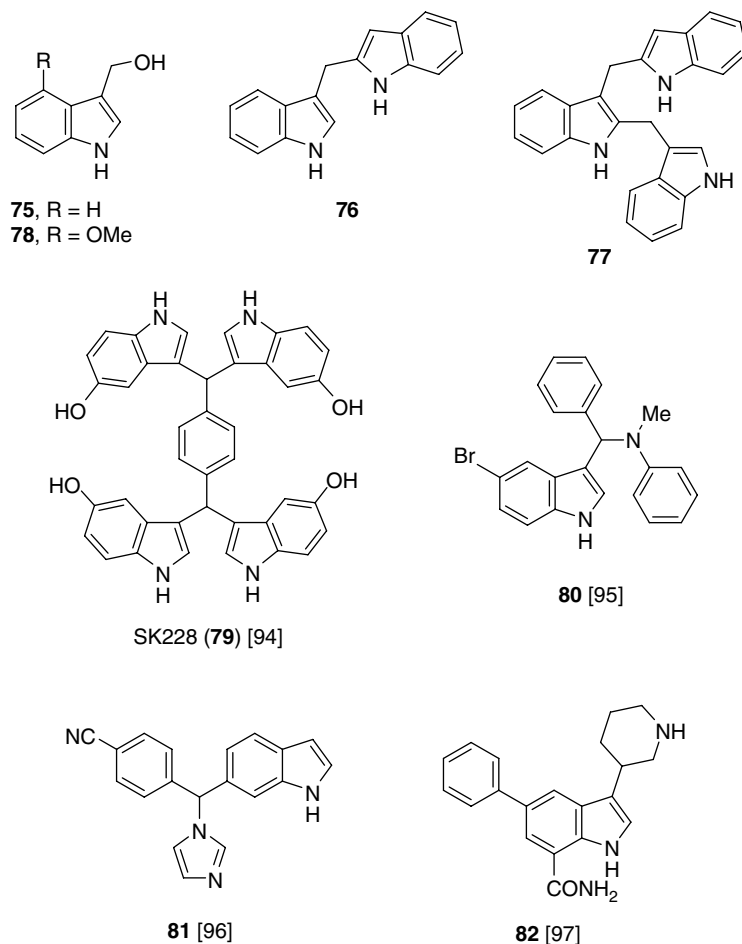


73 [86]



74 [87]

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



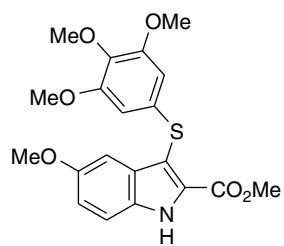
**Scheme 12** Representative Indoles with Antitumor Activity

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<sub>2</sub> 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<sub>50</sub>=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].

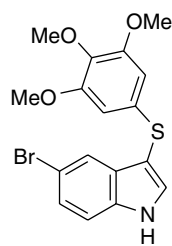
An important strategy for the treatment of cancer is the modulation of microtubule assembly either by preventing its disassembly or by blocking tubulin polymerization, and an excellent review is available that discusses several indole leads [98]. For example, Silvestri and colleagues report that arylthioindoles are potent inhibitors of tubulin polymerization [99–101]. For example, **84** inhibits the

growth of MCF-7 cells at IC<sub>50</sub>=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<sub>50</sub>=27 nM; MDA-MB 231, IC<sub>50</sub>=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].

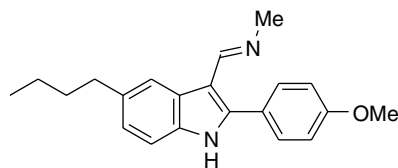
A large number of naturally occurring indoles display antitumor activity, but only a limited number can be illustrated here (Scheme 14). Cultures of *Aspergillus ochraceus* WC76466 produce stephacidins A (**88**) and B (not shown), both of which are selective inhibitors of prostate LNCaP cells, and they 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



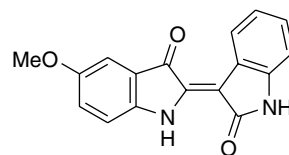
**84** [99]



**85** [101]

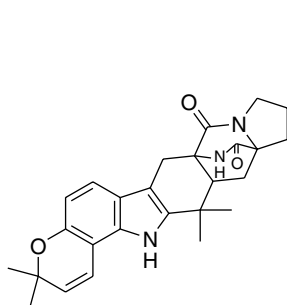


**86** [102]

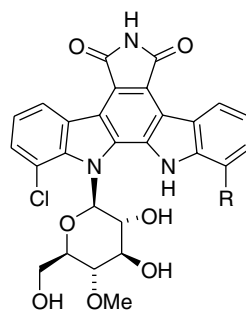


**87** [103]

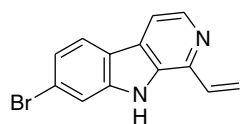
**Scheme 13** Representative Indoles with Tubulin Inhibitory Activity



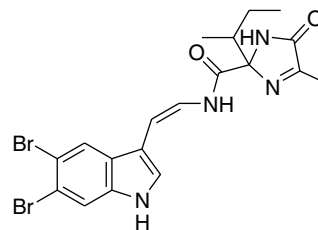
Stephacidin A (**88**) [104]



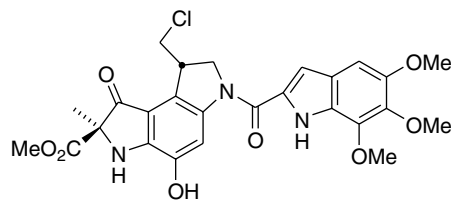
Rebeccamycin (**89**, R = Cl) [105]  
Rebeccamycin (**90**, R = H) [106]



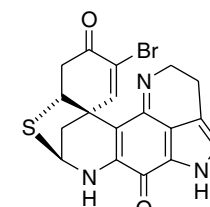
Plakortamine B (**91**) [107]



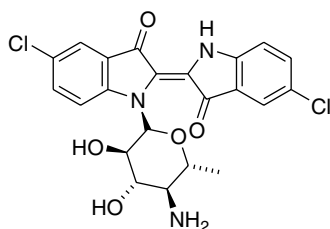
Kottamide D (**92**) [108]



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



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



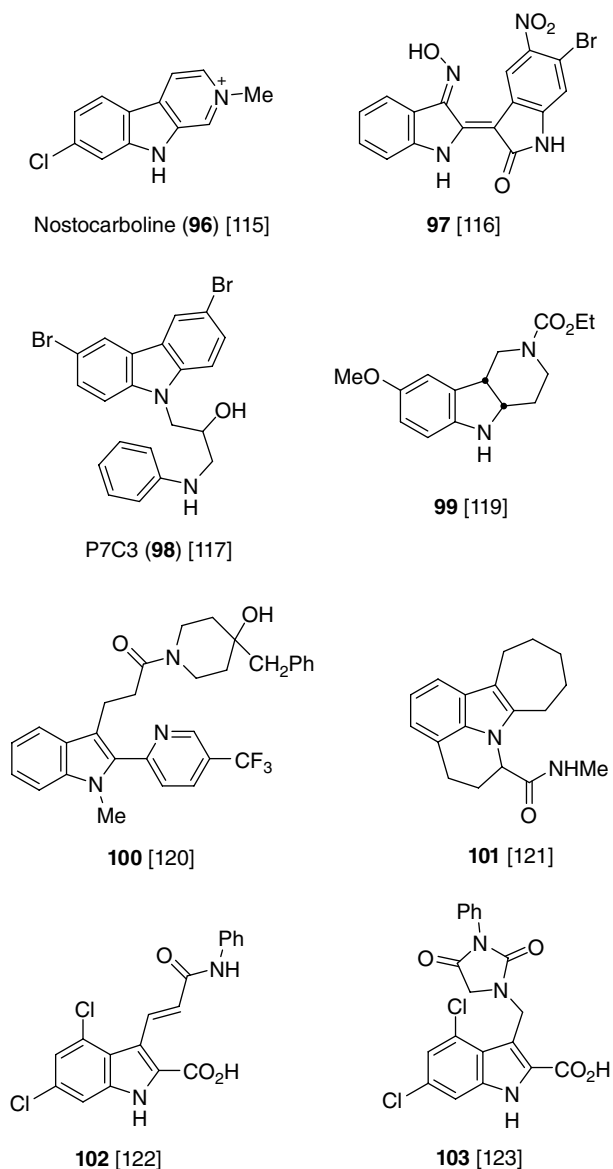
Akashin A (**95**) [113]

**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<sub>2</sub>) (**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  $\beta$ -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  $\beta$ -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<sub>1</sub>) receptor antagonist, 2-arylindole **100**, is one of several simple compounds that exhibit both good receptor-binding affinity and brain penetration. The hNK<sub>1</sub> 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<sub>1</sub> and CB<sub>2</sub> 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<sub>2</sub> affinity but low CB<sub>1</sub> affinity, although many others are also selective for the former receptor [125]. A review of this area is available [126]. A study of the melatonergic binding site MT<sub>3</sub> has found that 4-nitroindole melatonin