Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety

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Received June 3, 2009

Contents

1. Introduction

The marine environment has been explored in the search for new bioactive compounds over the last 50 years, becoming a highly important and rich source of potent molecules and drug leads reported to possess a wide scope of activities. Alkaloids constitute one of the largest classes of natural products and are synthesized by terrestrial and marine organisms on all evolutionary levels. Alkaloids are usually present in an organism as a mixture consisting of several major and a few minor compounds of the same biosynthetic origin and differing only in functional groups. This group of compounds has apparently evolved as a defense mechanism against predators and as a result alkaloids are often highly potent and toxic molecules.[1] Marine invertebrates have proven to be an outstanding source of active molecules, one of the most promising being indole alkaloids. Although many of these marine alkaloids closely resemble the endogenous amines (serotonin, dopamine, or histamine), their potential affinity to various neurological targets and consequential impact on animal behavior is virtually unexplored.

Indole alkaloids, their activity, synthesis, and potential use in medicine have been already reviewed in several articles.[2] In this review, we provide information on current and potential pharmaceuticals including small molecule natural indole alkaloids, their biological properties, structure−activity relationship studies, and especially their potential for the treatment of neurological disorders.

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1.1. Indole Moiety in Drugs

The indole moiety is present in a number of drugs currently on the market. Most of these belong to triptans which are used mainly in the treatment of migraine headaches (Figure 1). All members of this group are agonists of migraine associated $5HT_{1B}$ and $5HT_{1D}$ serotonin receptors. Sumatriptan (Imitrex) was developed by Glaxo for the treatment of migraines and introduced into the market as the first member of the triptan family.[3] Relative to the second generation triptans, sumatriptan has lower oral bioavailability and a shorter half-life. Frovatriptan (FROVA) was developed by Vernalis for the treatment of menstruation associated headaches. Frovatriptan's affinity for migraine specific serotonin receptors $5HT_{1B}$ is believed to be the highest among all triptans.[4] In addition, frovatriptan binds to $5HT_{1D}$ and $5HT_7$ receptor subtypes.[5] Zolmitriptan marketed by AstraZeneca is used to treat acute migraine attacks and cluster headaches. GlaxoSmithKline's naratriptan (Amerge) is also used in the treatment of migraines and some of its side effects include dizziness, tiredness, tingling of the hands and feet, and dry mouth. All available triptans are well tolerated and effective.[6] The highest incidence of central nervous system (CNS) related side effects (dizziness, drowsiness) was reported for zolmitriptan (5 mg), rizatriptan (10 mg), and eletriptan (40 mg, 80 mg).[7] The differences in side-effect profiles for triptans are not likely caused by their different affinity toward serotonin receptors or other neurological receptors in the CNS. There is a positive correlation between the lipophilicity coefficient and CNS side effects; these undesired effects are also dose-dependent.

1.2. Serotonin Receptors: Possible Targets for Neurologically Active Marine Indole Alkaloids

Given that depression affects approximately 18 million Americans annually,[8] it is crucial to develop new effective treatments for this disorder. Intensive studies are being conducted in the area of new targets for antidepressant drugs,[9,10] but most antidepressant drugs still target the neurotransmitter systems, mainly serotonin, dopamine, and noradrenaline.

Serotonin is one of the neurotransmitters present in the central and peripheral nervous system, which plays an important role in normal brain function and regulates sleep, mood, appetite, sexual function, memory, anxiety, and many others.[11] Serotonin exerts its effects through seven families of receptors ($5HT_1$−$5HT_7$) further divided into several subclasses. Except for the $5HT_3$ receptor which is a ligand-gated ion channel, the serotonin receptors belong to the

10.1021/cr900211p
Published on Web 04/09/2010

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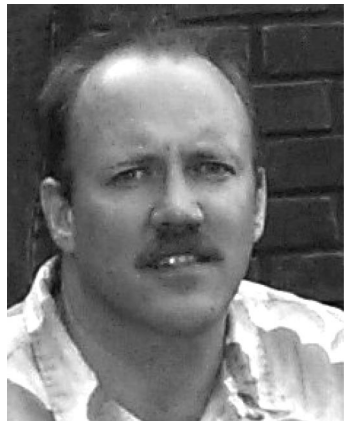

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G-protein coupled receptor family. Because of a lack of selective ligands, there is still little known about several 5HT receptor subclasses.[12] Marine monoindole alkaloids, sharing structure similarities with serotonin, are certain to become useful tools to facilitate the understanding of serotonin receptor function and generate new drug leads for the treatment of depression, anxiety, migraines, and other 5HT receptor related disorders.

2. Natural Indole Alkaloids of Marine Origin

A growing number of indole alkaloids are being reported from various marine organisms. Because of the presence of specific enzymes, haloperoxidases, in the marine environment a large group of alkaloids isolated from sponges, seaweeds, ascidians, and mollusks are halogenated.

The structural similarity of indole alkaloids to endogenous amines and neurotransmitters has led researchers to postulate the possible neurological activity of these molecules. Several compounds carrying an indole moiety have been reported to possess affinity toward different serotonin receptors: barettin, 8,9-dihydrobarettin,[13] tris-indole alkaloids gelliusine A and B,[14] and σ-conotoxin.[15] Methylaplysinopsin (**1**) (Figure 2) isolated from *Aplysinopsis reticulata* by Baird-Lambert et al. was reported to inhibit monoamine oxidase (MAO) and to displace serotonin from its receptors.[16] Other molecules from this group: 6-bromo-2′-de-*N*-methylaplysinopsin (**2**), 6-bromoaplysinopsin (**3**), and *N*-3′-ethylaplysinopsin (**4**) (Figure 2) isolated from *Smenospongia aurea* were reported to displace high-affinity antagonist binding for human $5HT_{2C}$ and $5HT_{2A}$ receptors.[17] *N*-3′-ethylaplysinopsin did not display selectivity to either of these two receptors ($K_i = 3.5$ and 1.7 μM for $5HT_{2C}$ and $5HT_{2A}$ receptors, respectively). 6-Bromoaplysinopsin showed only low selectivity toward $5HT_{2C}$ receptors ($K_i = 0.33$ and 2.0 μM for $5HT_{2C}$ and $5HT_{2A}$ receptor, respectively); however 6-bromo-2′-de-*N*-methylaplysinopsin exhibited strong (40-fold) selectivity to $5HT_{2C}$ receptors ($K_i = 2.3$ μM for $5HT_{2C}$ and >100 μM for $5HT_{2A}$). In addition to neurological activity, 6-bromoaplysinopsin also showed significant activity against *Plasmodium falciparum*.

5,6-Dibromo-*N,N*-dimethyltryptamine (**5**)[18] and 5-bromo-*N,N*-dimethyltryptamine (**6**)[19] (Figure 3) exhibited antimicrobial activity as reported by Tymiak.[20] The dibrominated compound was significantly more active over the monobromotryptamine. Both of the compounds were also found to possess neurological activity: 5,6-dibromo-*N,N*-dimethyltryptamine showed antidepressant action in forced swim test and tail suspension test,[21,22] and 5-bromo-*N,N*-dimethyltryptamine exhibited strong sedative effect in the locomotor activity test.[22]

The dibromotryptamine (**5**) was also found to display significant activity in an MTT assay using HCT-116 colon carcinoma cell lines (IC_{50} values: $p53^{+/+}$ 12.6 μM, $p53^{-/-}$ 85 μM, $p21^{+/+}$ 85 μM, and $p21^{-/-}$ 63 μM, where +/+ indicates parental cell line and −/− indicates knockouts).[23]

A new and interesting marine metabolite, sharing structure similarities with indoles and cannabinoids (Figure 4) was recently reported to possess promising antidepressant activity in the forced swim test.[22] Veranamine (**7**) isolated from *Verongida rigida* is an example of an unusual structure and supports the importance of isolation often being the only method that offers access to structurally new and unique molecules, which could not be readily synthesized for biological evaluation.

Many naturally occurring indole alkaloids have not been tested for neurological activity. Their structures, however, indicate possible affinity to serotonin, dopamine, or adrenergic receptors. As reported by Fahy et al.,[24] a fraction containing 6-bromotryptamine (**8**) showed antibacterial and antifungal actvity in vitro; however there is no data for the pure natural product. Another derivative of tryptamine, N_b-acetyltryptamine (**9**), was isolated from an unidentified fungus growing on the surface of the marine red alga *Gracilaria verrucosa*.[25] The same compound, together with its diacetylated derivative (**10**), was reported from marine bacterium *Roseivirga echinicomitans* $KMM6058^T$ associated with the sea urchin *Strongylocentrotus intermedius*.[26] Both compounds were found to be weakly cytotoxic toward Erlich

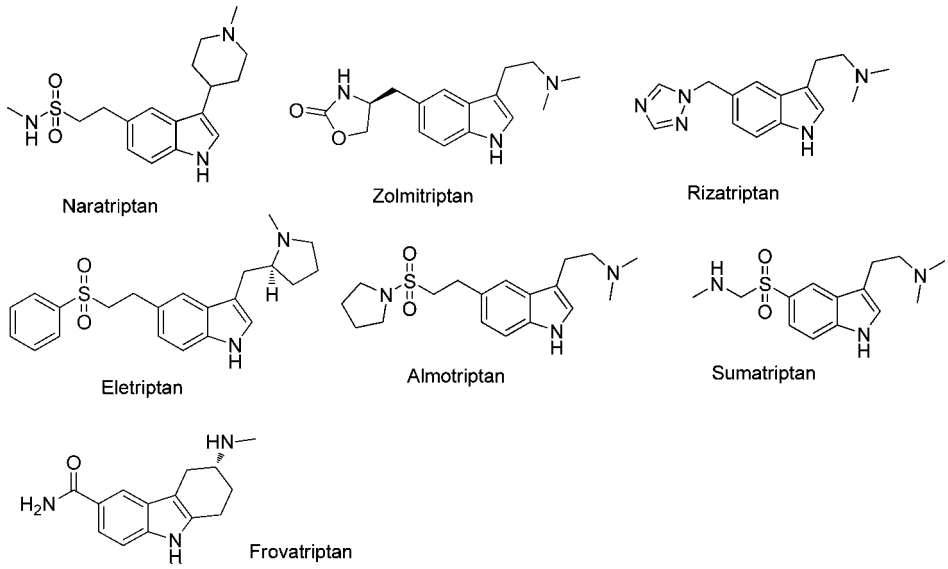
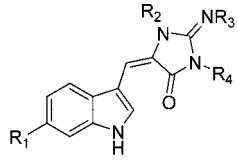
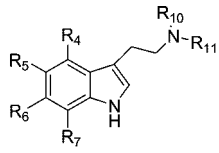


Figure 1. Currently available drugs from the triptan group.



Methylaplysinopsin (**1**): R_1=R_3=H, R_2=R_4=CH_3
6-bromo-2`-de-*N*-methylaplysinopsin (**2**): R_1=Br, R_2=R_3=H, R_4=CH_3
6-bromoaplysinopsin (**3**): R_1=Br, R_2=R_4= CH_3, R_3=H
N-3`-ethylaplysinopsin (**4**): R_1=H, R_2=R_4=CH_3, R_3=CH_2CH_3

Figure 2. Aplysinopsin derivatives.



5,6-dibromo-*N,N*-dimethyltryptamine (**5**): R_4=R_7=H, R_5=R_6=Br, R_{10}=R_{11}=CH_3
5-bromo-*N,N*-dimethyltryptamine (**6**): R_4=R_6=R_7=H, R_5=Br, R_{10}=R_{11}=CH_3
6-bromotryptamine (**8**): R_4=R_5=R_7=R_8=R_{10}=R_{11}=H, R_6=Br
N_b-acetyltryptamine (9): R_4=R_5=R_6=R_7=R_{10}=H, R_{11}=$COCH_3$
Diacetyltryptamine (**10**): R_4=R_5=R_6=R_7=H, R_{11}=R_{10}=$COCH_3$
5,6-dibromo-3-(2-methylaminoethyl)indole (**11**): R_4=R_7=R_{10}=H, R_5=R_6=Br, R_{11}=CH_3
5,6-dibromo-3-(2-aminoethyl)indole (**12**): R_4=R_7=R_{10}=R_{11}=H, R_5=R_6=Br

Figure 3. Tryptamine derivatives.

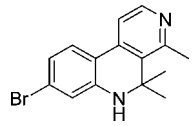


Figure 4. Structure of veranamine (**7**).

carcinoma tumor cells; diacetyltryptamine exhibited higher helmolytic activity and caused 50% destruction of membrane of sperm and egg cells at the concentrations of 7.5 and 15 μg/mL, respectively. At the concentration of 50 μg/mL, compound **10** caused 100% inhibition of embryo development, while compound **9** did not show any inhibition. Neither of the compounds showed any activity toward yeast-like fungi and gram-positive or gram-negative bacteria. Dibrominated compounds **11** and **12** were reported for the first time by Van Lear et al. as antibacterial metabolites from a marine sponge *Polyfibrospongia maynardii*.[27] The same alkaloids were later isolated from a *Hyrtios erecta* sponge and found to be selective inhibitors of neuronal isoform of nitric oxide synthase (nNOS).[28]

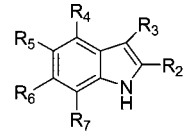
Three bromoindoles (**13**−**15**) isolated from the midintestinal gland of the gastropod *Drupella fragum* were reported to have antioxidative acitivites.[29] 6-Bromo-5-hydroxyindole (**13**) exhibited stable antioxidative activity higher than α-tocopherol. An additional two compounds, 6-bromoindole-3-carbaldehyde and its debrominated derivative, were obtained from an *Acinetobacter* sp. associated with the ascidian *Stomozoa murrayi*.[30] The brominated metabolite (**16**) showed antimicrobial activity and inhibited the settlement of cyprid larvae of *Balanus amphitrite* with EC_{50} of 5 μg/mL. Debrominated indole-3-carbaldehyde did not exhibit antimicrobial activity, and its antifouling effect was weaker (EC_{50} of 28 μg/mL). Davyt et al. reported a new indole derivative, 3-indoleacrylamide (**18**), possessing in vitro anthelmintic activity.[31] The compound was isolated from the red alga *Chondria atropurpurea*, together with several other known bisindole and indole alkaloids (**19**). Another antibacterial indole (**20**) was isolated from *Distaplia regina,* an ascidian collected from Palau.[32] Interesting, sulfur-containing polybrominated indoles were isolated from *Laurencia brongniartii*; these compounds did not show any cytotoxicity toward HT-29 and P-388 cell lines.[33] Monoindole alkaloids have also been found to regulate the process of plant growth; this type of activity was reported for 3-(hydroxyacetyl)indole (**24**)[34] and indole-3-acetamide (**25**) (Figure 5).[35]

Table 1 lists other natural tryptamine derivatives isolated from marine organisms with no activity reported.

3. Synthetic Indole Alkaloids

The literature reports numerous efforts to synthesize selective serotonin receptor ligands. Various structures have been reported as potent and selective agents for serotonin receptors; some of which share structural similarities with compounds isolated from sponges. EMDT (2-ethyl-5-methoxy-*N,N*-dimethyltryptamine) was synthesized as the first selective $5HT_6$ agonist.[36] Tables 2−6 present the reported synthetic tryptamine related structures.

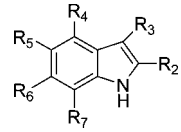
Several structure−activity relationship studies have been published outlining the best possible structures for agonists and antagonists of serotonin receptors. Dukat et al. reported



6-bromo-5-hydroxyindole (**13**):R_2=R_3=R_4=R_7=H, R_5=OH, R_6=Br
6-bromo-4,5-dihydroxyindole (**14**): R_2=R_3=R_7=H, R_4=R_5=OH, R_6=Br
6-bromo-4,7-dihydroxyindole (**15**): R_2=R_3=R_5=H, R_4=R_7=OH, R_6=Br
6-bromoindole-3-carbaldehyde (**16**): R_2=R_4=R_5=R_7=H, R_3=CHO, R_6=Br
Indole-3-carbaldehyde (**17**): R_2=R_4=R_5=R_6=R_7=H, R_3=CHO
3-indoleacrylamide (**18**): R_2=R_4=R_5=R_6=R_7=H, R_3= $CHCHCONH_2$
3-indoleacrylic acid (**19**): R_2=R_4=R_5=R_6=R_7=H, R_3= CHCHCOOH
3,6-dibromoindole (**20**): R_2=R_4=R_5=R_7=H, R_3=R_6=Br
2-methylsulfinyl-3-methylthio-4,5,6-tribromoindole (**21**): R_2=$SOCH_3$, R_3=SCH_3, R_4=R_5=R_6=Br, R_7=H
3-methylsulfinyl-2,4,6-tribromoindole (**22**): R_2=R_4=R_6=Br, R_3=$SOCH_3$, R_5=R_7=H
4,6-dibromo-2,3-di(methylsulfinyl)indole (**23**): R_2=R_3=$SOCH_3$, R_4=R_6=Br, R_5=R_7=H
3-(hydroxyacetyl)indole (**24**): R_2=R_4=R_5=R_6=R_7=H, R_3=$CONH_2$
Indole-3-acetamide (**25**): R_2=R_4=R_5=R_6=R_7=H, R_3=$COCH_2OH$

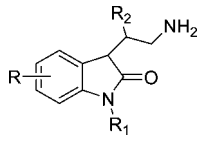
Figure 5. Indole derivatives.

Table 1. Natural Marine Tryptamine Derivatives



compound	R_2	R_3	R_4	R_5	R_6	R_7	refs, activity if reported
26	Cl	Cl	H	H	H	Cl	Brennan and Erickson.[63] Antifungal
27	Cl	Cl	H	H	H	Br	activity of crude extract.
28	Br	Cl	H	H	H	Br	
29	Br	Br	H	H	H	Br	
30	Cl	Cl	Cl	H	H	Cl	
31	Cl	Cl	Br	H	H	Br	
32	Br	Br	Br	H	H	Br	
33	Cl	Cl	Cl	H	H	H	
34	H	$COCH_2OH$	H	H	Br	H	Guella et al.[64]
35	H	H	Br	H	Br	H	Higa, T. et al.[65]
36	CH_3	H	Br	H	Br	H	
37	H	CHO	H	OH	Br	H	Cafieri et al.[66]
38	Br	H	Br	H	Br	H	Tanaka and Higa[67]
39	Br	Br	Br	H	Br	H	
40	SCH_3	H	Br	H	Br	H	
41	$SOCH_3$	SCH_3	Br	H	Br	H	
42	SCH_3	$SOCH_3$	Br	H	Br	H	
43	H	CH_2CH_2OH	H	OH	H	H	Salmoun et al.[68]
44	H	Br	H	Br	Br	H	Ji et al.[69]
45	Br	Br	H	Br	Br	H	
46	Br	Br	H	H	Br	H	

Table 2. Oxindole Derivatives



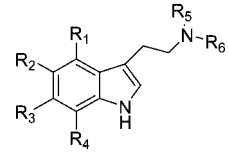
compound	R	R_1	R_2	ref
47	6-CH_3O	H	H	Daisley and Walker[40]
48	H	H	CH_3	
49	5-CH_3O	CH_3	CH_3	
50	H	CH_3	CH_3	
51	H	H	H	
52	5-CH_3O	H	H	
53	H	CH_2CH_3	CH_3	
54	H	$CH_2CH_2CH_3$	CH_3	

structure-affinity relationship (SAFIR) and quantitative structure−activity relationship (QSAR) of several tryptamine derivatives toward the $5HT_{1E}$ receptor subtype.[37] According to these findings, the two-atom chain which separates the indole from terminal amine group is crucial for the binding of tryptamines to the receptor. Also, branching of this chain reduces the affinity. The indole moiety seems important for the affinity and any changes (benzene ring, replacement of NH by S) reduce the affinity. The substitution at the amine group, as long as the substituents remain small, does not affect affinity.

Agents binding to $5HT_6$ receptors were also extensively investigated.[38] Glennon et al. found that *N*-mono- or *N,N*-dimethylation of serotonin derivatives resulted in a slight increase in affinity. The primary amine moiety of serotonin derivatives may be rapidly metabolized by oxidative deamination. This is likely to cause problems by reducing the ability of a molecule to cross the blood−brain barrier. Replacing a primary amine with secondary or tertiary amines increases the lipophilicity of the molecule and makes it less prone to metabolism, hence increasing its chance to become a useful drug.

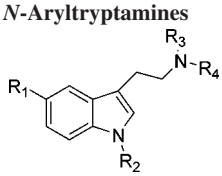
Oxindoles were reported to possess antidepressant activity in the early 1970s, and according to structure activity relationship studies, the optimal side chain for oxindoles was $(CH_2)_3NHCH_3$ or any other group providing an equivalent metabolic product. Any branching of the side chain caused

Table 3. Synthetic Tryptamine Derivatives



compound	R_1	R_2	R_3	R_4	R_5	R_6	refs
56	H	$C(CH_3)_3$	H	H	CH_3	H	Xu et al.[42]
57	H	$C(CH_3)_3$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	
58	H	Br	H	H	H	H	
59	H	$C(CH_3)_3$	H	H	$CH_2CH_2CH_3$	H	
60	H	$C(CH_3)_3$	H	H	CH_3	CH_3	
61	H	c-pentane	H	H	H	H	
62	H	c-pentan-1-ene	H	H	Bn	Bn	
63	H	CH_3	H	H	H	H	
64	H	C_2H_5	H	H	H	H	
65	H	i-Pr	H	H	H	H	
66	H	t-Bu	H	H	H	H	
67	H	c-hexyl	H	H	H	H	
68	H	Br	H	H	Bn	Bn	
69	H	H	F	H	CH_2CH_3	CH_2CH_3	Blair et al.[44]
70	H	OCH_3	H	H	CH_3	CH_3	
71	OH	H	F	H	CH_3	CH_3	
72	OH	H	H	F	CH_3	CH_3	
73	H	OCH_3	F	H	CH_3	CH_3	
74	F	OCH_3	H	H	CH_3	CH_3	
75	H	H	H	H	CH_2CH_3	CH_2CH_3	
76	H	OCH_3	H	H	H	CH_2PhOPh	Chen et al.[45]
77	H	OPh	H	H	H	CH_2PhOPh	
78	H	N_2O	H	H	H	CH_2PhOPh	
79	H	H	Br	H	H	H	
80	H	H	Cl	H	H	$CH_2PhOCH_2CF_2CHF_2$	
81	H	Cl	H	H	H	$CH_2PhOCH_2CF_2CHF_2$	
82	H	H	H	F	H	$CH_2PhOCH_2CHF_2$	
83	H	CH_3	H	Cl	H	H	Audia et al.[46]
84	H	H	CH_3	Cl	H	H	
85	H	H	CH_3	H	H	H	
86	H	H	CH_3	CH_3	H	H	
87	H	H	H	Cl	H	H	
88	H	H	H	F	H	H	
89	H	H	CH_3	Br	H	H	
90	H	H	H	OCH_3	H	H	Audia et al.[47]
91	H	CH_3	H	Br	H	H	
92	H	H	H	Cl	H	H	
93	H	H	H	F	H	H	
94	H	CH_3	H	Cl	H	H	
95	H	H	CH_3	Cl	H	H	
96	H	H	CH_3	H	H	H	
97	H	H	CH_3	CH_3	H	H	
98	H	H	CH_3	Br	H	H	
99	H	C_2H_5	H	H	H	H	
100	H	i-Pr	H	H	H	H	
101	H	t-Bu	H	H	H	H	
102	H	Br	H	Br	H	H	
103	H	F	H	F	H	H	
104	H	CH_3	CH_3	H	H	H	
105	H	H	H	Cl	H	H	Audia et al.[48]
106	H	H	H	Br	H	H	
107	H	H	CH_3	Br	H	H	
108	H	Cl	H	H	H	$COPhOCH_3$	Cao et al.[49]
109	H	H	H	H	H	$COOC_2H_5$	
110	H	Cl	H	H	H	COPh	

Table 4. Substituted *N*-Aryltryptamines

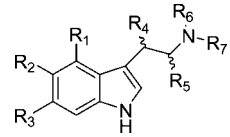


compound	R_1	R_2	R_3	R_4	refs
111	OCH_3	CH_3	CH_3	CH_3	Vermeulen et al.[50]
112	Cl	Ac	H	Ac	Cao et al.[49]
113	Cl	H	H	Ac	

reduction in activity. The substituent at the heterocyclic nitrogen atom should be a phenyl and the group substituted at position 3 on indolinone should be small to retain the antidepressive effects of the oxindoles.[39] Following these findings, a series of oxindole tryptamine derivatives, shown in Table 2, was prepared by Daisley and Walker.[40] As shown in this study, compounds **47**−**50** given orally at the dose of 100 mg/kg caused hyperthermia in mice. The same dose (100 mg/kg) of compounds **47** and **50** delivered subcutaneously had moderate activity in the hot-plate assay, while **53** and **54** showed significant, but not consistent activity. Compound **54** caused slight suppression of appetite.

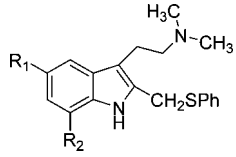
In 1967, Ostrovskaya published a report on the pharmacological activity of 2-substituted tryptamines. Among the tested compounds, 2-(2-methyl-2-amino)propylindole hy-

Table 5. Tryptamine Derivatives



compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	refs
114	H	H	H	H	CH_3	H	H	Nichols et al.[51]
115	OCH_3	H	H	H	CH_3	H	H	
116	H	OCH_3	H	H	CH_3	H	H	
117	H	H	OCH_3	H	CH_3	H	H	
118	OH	H	H	H	CH_3	H	H	
119	H	OH	H	H	CH_3	H	H	
120	H	F	H	H	H	H	$COCH_3$	Yang et al.[52]
121	H	H	F	H	H	H	$COCH_3$	
122	H	H	H	OH	H	H	$COCH_3$	
123	H	F	H	OH	H	H	$COCH_3$	
124	H	H	F	OH	H	H	$COCH_3$	
125	H	OH	H	H	H	H	$COCH_3$	
126	H	OH	H	H	CH_3	H	H	Young E.[53]
127	H	OH	H	H	C_2H_5	H	H	
128	H	OCH_3	H	H	CH_3	H	H	
129	H	H	H	H	C_2H_5	H	H	

Table 6. Arylthioether Tryptamine Derivatives



compound	R_1	R_2	refs
130	F	H	Ramakrishna et al.[54]
131	F	F	
132	Cl	H	
133	OCH_3	H	

drochloride (**55**) was found to cause "motor excitation, tremor of the limbs and tail, stereotyped spasm of the head" when tested in mice and rats and administered i.v at doses 10−30 mg/kg (Figure 6).[41]

More recent synthetic and medicinal chemistry oriented research is focused on the preparation of ligands for specific types and subtypes of serotonin receptors. Xu et al.[42] evaluated a series of 5-alkyltryptamine derivatives to find out which substituents were crucial for the affinity of the molecule toward $5HT_{1D}$ receptors. In the case of 1,5-alkyltryptamines, increasing the size of the 5-alkyl substituent resulted in increased affinity toward $5HT_{1D}$ receptor. They also found that the substituent in position 5 did not have to possess hydrogen bonding properties to exhibit strong affinity toward this receptor type because it is the size of the group that dictates the affinity. 5-Tert-butyltryptamines showed the highest affinity for the $5HT_{1D}$ receptor with compound **56** being the most potent agonist (K_i = 0.45 nM).

Research completed by Blair and co-workers[43] on thieno[3,2-*b*]- and thieno[2,3-*b*] pyrrole bioisosters of *N,N*-dimethyltryptamine revealed that thiophene cannot serve as a replacement for the phenyl ring in the indole moiety of tryptamines which bind to $5HT_2$ receptors. However, thiophene can be a suitable bioisostere for compounds possessing

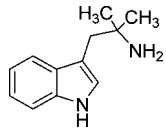


Figure 6. Structure of 2-(2-methyl-2-amino)propylindole (**55**).

affinity for the $5HT_{1A}$ receptor. Another paper by Blair et al. reports the effect of ring fluorination on the activity of hallucinogenic tryptamines.[44] According to their findings, fluorination of tryptamines in positions 4−7 reduces hallucinogenic activity. Introducing fluorine at the 6 position of 5-methoxy-*N,N*-dimethyltryptamine decreases the $5HT_{1A}$ receptor binding affinity. For example, compound **73** exhibited a K_i of 84.5 nM, while compound **70** exhibited a K_i of 1.7 nM. In the case of *N,N*-dimethyltryptamine, fluorination at position 6 caused a 5 fold decrease in affinity toward the $5HT_{1A}$ receptor (compound **69** versus **75**).

Fluorination of 5-methoxy-*N,N*-dimethyltryptamine at position 4 (compound **74**) led to increased affinity toward the $5HT_{1A}$ receptor with a K_i of 0.23 nM (compared to a K_i of 1.7 nM for compound **70**). In the case of $5HT_{2A}$ and $5HT_{2C}$ receptors, fluorination at position 6 has only insignificant effects on the affinity to these receptors. Chen et al. described the process of preparation of *N*-(2-arylethyl)benzamines and tryptamine derivatives (compounds **76**−**82**) as antagonists of $5HT_6$ receptors.[45] The authors discussed using of these antagonists to treat cognitive dysfunction and any disorders associated with $5HT_6$ receptors: age-related cognitive disorders, anxiety, schizophrenia, Parkinson's disease, epilepsy, convulsions, migraine, and sleep disorders.

In 1998, Audia et al. presented several 8-substituted tetrahydro-β-carboline compounds and tryptamine-like intermediates possessing high affinity toward all the subtypes of $5HT_2$ receptors.[46] Compounds **83**−**89** were prepared to serve as molecular tools to develop selective therapeutic $5HT_{2A}$ and $5HT_{2C}$ agents, as well as to become effective drugs by themselves. Another patent publication by Audia et al. describes compounds **90**−**104** with affinity toward $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$, which could be useful in the treatment of various disorders associated with these receptors, including tachygastria, ichlasia, dyspepsia, schizophrenia, anxiety, depression, and migraines.[47] Indole derivatives **105**−**107** and their affinity to $5HT_2$ receptors were the subject of a patent published in 1995 by Audia et al.[48] This publication claimed the use of the aforementioned compounds to protect or to treat mammals suffering from $5HT_2$ receptor related disorders such as hypertension, depression and anxiety. Compounds **108**−**110**, **112**, and **113** were

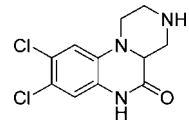


Figure 7. Structure of WAY-161503.

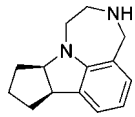


Figure 8. Antiobesity, antidepressant, and antipsychotic compound, WAY-163909.

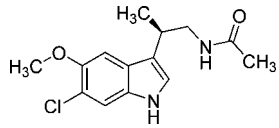


Figure 9. PD-6735, a drug candidate for sleep disorders.

disclosed as inhibitors of angiogenesis, which plays a crucial role in the pathogenesis of cancer, immune and inflammatory disorders.[49]

Another subtype of serotonin receptors, $5HT_7$, has been recently linked to psychiatric disorders like depression and schizophrenia, but their function still remains largely unknown. Vermeulen et al. presented a comprehensive study of inverse agonists of these receptors and determined that tryptamine derivatives like compound **111** without additional aromatic rings exhibit only poor affinity toward these receptors.[50]

A series of enantiomeric pairs of α-methyltryptamines was investigated by Nichols et al.[51] The authors tested tryptamine analogues in $5HT_{1B}$ and $5HT_2$ receptor binding assays and showed that enantioselectivity at both binding sites varied depending on the aromatic substituents. At both receptor subtypes, the order of affinity for the α-methyltryptamines was 5-substituted (**116**) > 4-substituted (**115**) > unsubstituted (**114**) > 6-substituted (**117**). In the case of 5-hydroxy-α-methyltryptamine (**119**), an *S* isomer had higher affinity to both receptors over the *R* isomer. For compounds **115** and **118**, the *R* isomers exhibited higher affinity at the $5HT_{1B}$ receptor but not at the $5HT_2$.

Three new indole alkaloids were produced by microbial transformation using *Streptomyces staurosporeus*. Yang and Cordell fed the bacterial cultures with tryptamine hydrochloride, 5-fluorotryptamine hydrochloride, and 6-fluorotryptamine, then extracted the culture, and obtained β-hydroxy-N_b-acetyltryptamine (**122**), 5-fluoro-β-hydroxy-N_b-acetyltryptamine (**123**), and 6-fluoro-β-hydroxy-N_b-acetyltryptamine (**124**), respectively.[52]

Methods of preparation and insecticidal activity of several simple indole alkaloids were described in a patent by Young (compounds **126**−**129**).[53]

Stereoisomers, salts, methods of preparation, and medicines containing the arylthioether tryptamine derivatives (**130**−**133**) shown in Table 6 are claimed for possible use in central nervous system disorders related to the function of $5HT_6$ receptors (anxiety, depression, motor disorders).[54]

4. In the Pipeline: Novel Tryptamine- and Indole-Derived Structures

One of the new molecules reported in the past few years sharing structure similarities with indole alkaloids is the Wyeth compound, WAY-161503 (Figure 7), a selective $5HT_{2C}$ receptor agonist. According to a recent report, research conducted on the action of WAY-161503 confirms that $5HT_{2C}$ receptors may play an inhibitory role in the regulation of reward-related behavior.[55] WAY-161503 is covered by several patents and is claimed to be useful for the treatment or prevention of urinary incontinence,[56−58] as well as for depressive disorders.[59]

Another compound, WAY-163909 (Figure 8), a selective $5HT_{2C}$ receptor agonist, was found to be of potential utility in obesity treatment. The same compound exhibited antidepressant and antipsychotic activity in preclinical animal models.[60]

A melatonin receptor agonist that has recently completed phase II clinical trials for sleep disorders in blind individuals, PD-6735 (Figure 9), also contains an indole moiety. The drug was not only efficient in re-establishing the right day/night cycle but also displayed an excellent safety profile.

5. Conclusions

A summary of structure−activity relationship studies reported for monoindole and tryptamine derivatives is shown in Figure 10. Naturally occurring tryptamine derivatives possess a number of structural features not found in the reported synthetic molecules. For example, compounds **5**, **11**, **12**, and **26**−**46** possess two or more halogens. In addition halogen substituents at position 2 of the indole moiety (compounds **22**, **26**−**33**, **38**, **39**, **45**, **46**) are also unique to marine natural products. In marine tryptamine derivatives, the substituent at the amine nitrogen, if any, is usually methyl or acetyl (compounds **5**, **6**, **9** and **10**), while in synthetic compounds this position is substituted with larger moieties

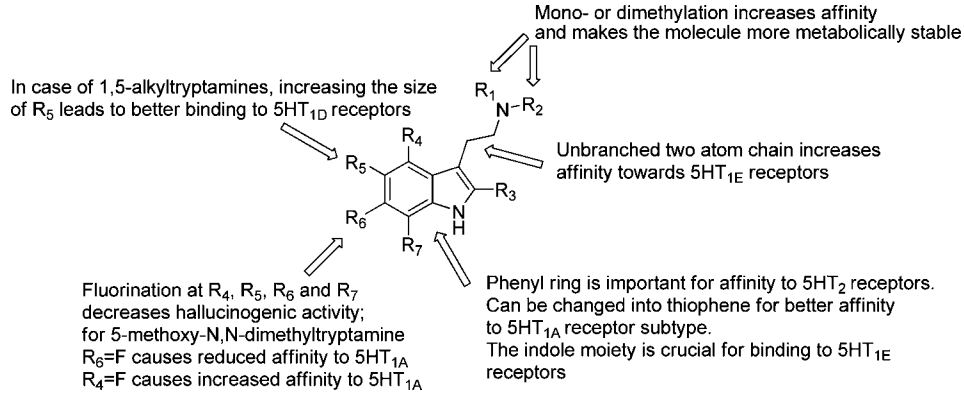


Figure 10. Summary of structure−activity relationship studies for tryptamine derivatives.

(compounds **57**, **62**, **68**, **76**−**82**, **108**−**110**). The indole nitrogen of marine monoindoles is usually not alkylated, in contrast to synthetic indole alkaloids (compounds **49**, **50**, **53**, **54**, **111**, **112**). Branching of the side chain is uncommon in natural marine indole alkaloids, while it is present quite frequently in synthetic molecules (compounds **48**−**50**, **53**, **54**, **114**−**119**, **122**−**128**). Halogenation in position 4 of the indole ring is frequently reported in natural monoindole alkaloids (compounds **21**, **22**, **23**, **30**−**42**), while it is rather rare in the synthetic molecules. In this review, we have discussed 46 natural indole alkaloids of marine origin and 87 synthetic molecules. The synthesis of monoindole alkaloids was in many cases inspired by the naturally occurring molecules and their similarity to serotonin. Some of the above-mentioned natural indole alkaloids are not readily available by current synthetic methods, and as a result provide access to new and unusual chemotypes not previously investigated. When obtained in good yields, marine indole alkaloids can serve as starting materials for the preparation of a number of analogs providing preliminary structure activity relationship information. Marine natural products clearly provide valuable access to chemical diversity and regiochemistry that would otherwise require development of methodologies without preliminary evidence of biological activity. As a result there are interesting opportunities for marine natural products to inspire the development of novel ligands for neurological receptors.

According to the World Health Organization, major depression will become the second leading cause of death by the year 2020 because of the complications arising from cardiovascular system and stress.[61] There is a tremendous unmet need for new, safer, and more effective antidepressant drugs since currently used antidepressants have significant side effects and about 30% of the population does not respond to these current treatments.[62] Marine natural products have been overlooked as potent neurologically active molecules, considered primarily as anticancer and antimicrobial leads.

Marine indole alkaloids represent a rich group of natural compounds and have tremendous potential to become new drug leads for various psychiatric disorders, as well as to provide better insights into the understanding of serotonin receptor function. These molecules are reasonable synthetic targets, which further enhances their value as possible drug leads; however, few, if any, have been prepared as part of synthetic or medicinal chemistry studies designed to generate optimized leads for depression and anxiety.

6. Acknowledgments

The authors would like to thank Ms. Naomi Montalvo from the laboratory of Dr. Russell Hill, Center of Marine Biotechnology, University of Maryland Biotechnology Institute for the photograph used in the cover art and NIH for financial support.

7. References

(1) Fattorusso, E.; Taglialatela-Scafati, O., Eds. *Modern Alkaloids. Structure, Isolation, Synthesis and Biology*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008.
(2) (a) Aygun, A.; Pindur, U. *Curr. Med. Chem.* **2003**, *10*, 1113. (b) Gupta, L.; Talwar, A.; Chauhan, M. S. *Curr. Med. Chem.* **2007**, *14*, 1789. (c) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442.
(3) Sheftell, F. D.; Bigal, M. E.; Tepper, S. J.; Rapaport, A. M. *Expert Rev. Neurother.* **2004**, *4*, 199.
(4) Markus, F.; Mikko, D. K. *Expert Opin. Pharmacother.* **2007**, *8*, 3029.
(5) Balbisi, E. A. *Int. J. Clin. Pract.* **2004**, *58*, 695.
(6) Ferrari, M. D.; Goadsby, P. J.; Roon, K. I.; Lipton, R. B. *Cephalgia* **2002**, *22*, 633.
(7) Dodick, D. W.; Martin, V. *Cephalgia* **2004**, *24*, 417.
(8) National Institutes of Health. *Invisible Disease: Depression*; NIH publication 01-4591; National Institutes of Health: Washington, DC, 2001; www.nimh.nih.gov/publicat/invisible.cfm.
(9) Holden, C. *Science* **2003**, *302*, 810.
(10) Krishnan, V.; Nestler, E. J. *Nature* **2008**, *455*, 894.
(11) Nichols, D. E.; Nichols, C. D. *Chem. Rev.* **2008**, *108*, 1614.
(12) Fantegrossi, W. E.; Murnane, K. S.; Reissig, C. J. *Biochem. Pharmacol.* **2008**, *75*, 17.
(13) Hedner, E.; Sjogren, M.; Frandberg, P.-A.; Johansson, T.; Goransson, U.; Dahlstrom, M.; Jonsson, P.; Nyberg, F.; Bohlin, L. *J. Nat. Prod.* **2006**, *69*, 1421.
(14) Bifulco, G.; Bruno, I.; Minale, L.; Riccio, R.; Calignano, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1294.
(15) England, L. J.; Imperial, J.; Jacobsen, R.; Craig, A. G.; Gulyas, J.; Akhtar, M.; Rivier, J.; Julius, D.; Oliviera, B. M. *Science* **1998**, *281*, 575.
(16) Baijrd-Lambert, J.; Davis, P. A.; Taylor, K. M. *Clin. Exp. Pharmacol. Physiol.* **1982**, *9*, 203.
(17) Hu, J. F.; Schetz, J. A.; Kelly, M.; Peng, J.; Ang, K. K. H.; Flotow, H.; Leong, C. Y.; Ng, S. B.; Buss, A. D.; Wilkins, S. P.; Hamann, M. T. *J. Nat. Prod.* **2002**, *65*, 476.
(18) Djura, P.; Stierle, D. B.; Sullivan, B.; Faulkner, D. J.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1435.
(19) Debitus, C.; Laurent, D.; Pais, M. *J. Nat. Prod.* **1988**, *51*, 799.
(20) Tymiak, A. A.; Rinehart, K. L., Jr.; Bakus, G. J. *Tetrahedron* **1985**, *41*, 1039.
(21) Diers, J. A.; Ivey, K. D.; El-Alfy, A.; Shaikh, J.; Wang, J.; Kochanowska, A. J.; Stocker, J. F.; Hamann, M. T.; Matsumoto, R. R. *Pharmacol., Biochem. Behav.* **2008**, *89*, 46.
(22) (a) Kochanowska, A. J.; Rao, K. V.; Childress, S.; El-Alfy, A.; Matsumoto, R. R.; Kelly, M.; Stewart, G. S.; Sufka, K.; Hamann, M. T. *J. Nat. Prod* **2008**, *71*, 186. (b) Hamann, M. T.; Kochanowska, A. J.; El-Alfy, A.; Matsumoto, R. R.; Boujos, A. WO 2009049030, 2009;*Chem. Abstr.*, **2009**, *150*, 414288.
(23) Tasdemir, D.; Bugni, T. S.; Mangalindan, G. C.; Concepcion, G. P.; Harper, M. K.; Ireland, C. M. *Z. Naturforsch. C.* **2002**, *57*, 914.
(24) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564.
(25) Li, Y.; Li, X. F.; Kim, D. S.; Choi, H. D.; Son, B. W. *Arch. Pharm. Res.* **2003**, *26*, 21.
(26) Oleinikova, G. K.; Ivchuk, O. I.; Denisenko, V. A.; Chaikina, E. L.; Menzorova, N. I.; Nedashkovskaya, O. I.; Kuznetsova, T. A. *Chem. Nat. Compd.* **2006**, *42*, 713.
(27) Van Lear, G. E.; Morton, G. O.; Fulmor, W. *Tetrahedron Lett.* **1973**, *14*, 299.
(28) Aoki, S.; Ye, Y.; Higuchi, K.; Takashima, A.; Tanaka, Y.; Kitagawa, I.; Kobayashi, M. *Chem. Pharm. Bull.* **2001**, *49*, 1372.
(29) Ochi, M.; Kataoka, K.; Ariki, S.; Iwatsuki, C.; Kodama, M.; Fukuyama, Y. *J. Nat. Prod.* **1998**, *61*, 1043.
(30) Olguin-Uribe, G.; Abou-Mansour, E.; Boulander, A.; Debard, H.; Francisco, C.; Combaut, G. *J. Chem. Ecol.* **1997**, *23*, 2507.
(31) Davyt, D.; Entz, W.; Fernandez, R.; Mariezcurrena, R.; Mombru, A. W.; Saldana, J.; Dominiguez, L.; Coll, J.; Manta, E. *J. Nat. Prod.* **1998**, *61*, 1560.
(32) Quereshi, A.; Faulkner, D. J. *Nat. Prod. Lett.* **1999**, *13*, 59.
(33) El-Gamal, A. A.; Wang, W.-L.; Duh, C.-Y. *J. Nat. Prod.* **2005**, *68*, 815.
(34) Bernart, M.; Gerwick, W. H. *Phytochemistry* **1990**, *29*, 3697.
(35) (a) Kishi, Y.; Goto, T.; Inoue, S.; Sugiura, S.; Kishimoto, H. *Tetrahedron Lett.* **1966**, *7*, 3445. (b) Cardellina, J. H., II; Nigh, D.; Van Wagenen, B. C. *J. Nat. Prod.* **1986**, *49*, 1065.
(36) Holenz, J.; Merce, R.; Diaz, H. L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B.; Hernandez, S.; Monroy, X.; Sanchez, E.; Hernandez, E.; Perez, R.; Cubi, R.; Sanfeliu, O.; Buschmann, H. *J. Med. Chem.* **2005**, *48*, 1781.
(37) Dukat, M.; Smith, C.; Herrick-Dacis, K.; Teitler, M.; Glennon, R. A. *Bioorg. Med. Chem.* **2004**, *12*, 2545.
(38) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufeisen, S.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011.
(39) Canas-Rodriguez, A.; Leeming, P. R. *J. Med. Chem.* **1972**, *15*, 762.
(40) Daisley, R. W.; Walker, J. *Eur. J. Med. Chem.* **1979**, *14*, 47.
(41) Ostrovskaya, R. U. *Bull. Exp. Biol. Med.* **1967**, *63*, 82.
(42) Xu, Y. C.; Schaus, J. M.; Walker, C.; Krushinski, J.; Adham, N.; Zgombick, J. M.; Liang, S. X.; Kohlman, D. T.; Audia, J. E. *J. Med. Chem.* **1999**, *42*, 526.
(43) Blair, J. B.; Marona-Lewicka, D.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1999**, *42*, 1106.

(44) Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4701.
(45) Chen, Z.; Cohen, M. P.; Fisher, M. J.; Giethlen, B.; Gillig, J. R.; Ronald, J.; McCowan, J. R.; Miller, S. C.; Schaus, J. M. Int. Patent WO 2002078693, 2002; *Chem. Abstr.*, **2002**, *137*, 294763.
(46) Audia, J. E.; Droste, J. J.; Evrard, D. A.; Fludzinski, P.; Murdoch, G. L.; Nelson, D. L. U.S. Patent 5760051, 1998; *Chem. Abstr.* **1998**, *129*, 54355.
(47) Audia, J. E.; Droste, J. J.; Evrard, D. A.; Fludzinski, P.; Murdoch, G. L.; Nelson, D.; Lloyd, G. Eur. Patent EP 620222, 1994; *Chem. Abstr.* **1994**, *122*, 31501.
(48) Audia, J. E.; Cohen, M. L. Gidda, J. S.; Nelson, D. L. G.; Baker, S. R.; Ezquerra-Carrera, J.; Lamas-Peteira, C.; Pedregal-Tercero, C. Int. Patent WO 9524200, 1995; *Chem. Abstr.* **1995**, *128*, 39584.
(49) Cao, L.; Choi, S.; Moon, Y.-C.; Tamilarasu, N.; Qi, H.; Lennox, W. J.; Hwang, S. Int. Patent WO 2006058088, 2006; *Chem. Abstr.* **2006**, *145*, 27846.
(50) Vermeulen, E. S.; Van Smeden, M.; Schmidt, A. W.; Sprouse, J. S.; Wikstrom, H. V.; Grol, C. J. *J. Med. Chem.* **2004**, *47*, 5451.
(51) Nichols, D. E.; Lloyd, D. H.; Johnson, M. P.; Hoffman, A. J. *J. Med. Chem.* **1988**, *31*, 1406.
(52) Yang, S. W.; Cordell, G. A. *J. Nat. Prod.* **1997**, *60*, 230.
(53) Young, E. Brit. Patent GB 807877, 1959; *Chem. Abstr.* **1959**, *53*, 67751.
(54) Ramakrishna, V. S. N.; Kambhampati, R. S.; Shirsath, V. S.; Deshpande, A. D.; Vishwakarma, S.; Jasti, V. Int. Patent WO 2007046112, 2007;*Chem. Abstr.* **2007**, *146*, 462134.
(55) Hayes, D. J.; Clemens, R.; Greenshaw, A. J. *Psychopharmacology* **2008**, *203*, 579.
(56) Kamo, I.; Hashimoto, T. Int. Patent WO 2006022420, 2006; *Chem. Abstr.* **2006**, *144*, 226351.
(57) Hildebrand, K. R. U.S. Patent US 2007253995, 2007; *Chem. Abstr.* **2007**, *147*, 474862.
(58) McMurray, G.; Miner,W. D. Int. Patent WO 2004096196, 2004; *Chem. Abstr.* **2004** *141*, 388769.
(59) Wolfgang, C. D.; Polymeropoulos, M. H. Int. Patent WO 2007137227, 2007; *Chem. Abstr.* **2007**, *148*, 1117.
(60) Dunlop, J.; Marquis, K. L.; Lim, H. K.; Leung, L.; Kao, J.; Cheesman, C.; Rosenzweig-Lipson, S *CNS Drug Rev* **2006**, *12*, 167.
(61) http://www.who.int/mental_health/management/depression/definition/en/ (accessed February 9, 2009).
(62) Isometsa, E. T.; Henriksson, M. M.; Aro, H. M.; Heikkinen, M. E.; Kuoppasalmi, K. I.; Lonnqvist, J. K. *Am. J. Psychiatry* **1994**, *151*, 530.
(63) Brennan, M. R.; Erickson, K. L. *Tetrahedron Lett.* **1978**, *19*, 1637.
(64) Guella, G.; Mancini, I.; Duhet, D.; Richer de Forges, B.; Pietra, F. *Z. Naturforsch. C.* **1989**, *44*, 914.
(65) Higa, T.; Ichiba, T.; Okuda, R. K. *Cell. Mol. Life Sci.* **1985**, *41*, 1487.
(66) Cafieri, F.; Fattorusso, E.; Mahajnah, Y.; Mangoni, A. *Z. Naturforsch B.* **1993**, *48*, 1408.
(67) Tanaka, J.; Higa, T. *Tetrahedron* **1989**, *45*, 7301.
(68) Salmoun, M.; Devijver, C.; Daloze, D.; Braekman, J.-C.; van Soest, R. W.M. *J. Nat. Prod.* **2002**, *65*, 1173.
(69) Ji, N.-Y.; Li, X.-M.; Ding, L.-P.; Wang, B.-G. *Helv. Chim. Acta* **2007**, *90*, 385.

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