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Perspective

Advances in Development of Dopaminergic Aporphinoids

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1. Introduction

Aporphine alkaloids constitute one of the largest groups of isoquinolines, with more than 500 structures reported to date. Structures of these alkaloids include aporphines, proaporphines, secoaporphines, oxoaporphines, dehydroaporphines, 7-hydroxyaporphines, aporphine dimers, and aristolactams. They are widely distributed in plants including *Annonaceae*, *Lauraceae*, *Monimiaceae*, *Menispermaceae*, *Hernandiaceae*, *Ranunculaceae*, and others. Many natural aporphinoids have pharmacological activities, including antioxidant, antiplatelet, antitumor, anticonvulsant, antiplasmodial, antineoplastic, antimalarial, antiprotozoal, antipoliovirus, cytotoxic, and antiparkinsonian effects.[1,2] These natural products and their synthetic derivatives serve as leads for the development of potential treatments for a variety of diseases.[3−6] *R*-(−)-Apomorphine (**1**), the semisynthetic[7] or total[8] synthetic prototypical aporphine, is an *R*-(−)-10,11-catecholaporphine (chiral at carbon 6a) with dopamine (DA) receptor agonist activity that includes stimulation of locomotor behavioral activity, with application for the treatment of Parkinson's disease.[9,10] *S*-(+)-Bulbocapnine (**4**) is a naturally occurring aporphinoid[11] that has DA receptor antagonist activity that includes reduction of motor activity and induction of catalepsy.[12,13] The cytotoxic and antitumor potentialities of natural and synthetic aporphinoids were reviewed recently by Stevigny and co-workers,[5] and their structures have been reviewed annually by Bentley.[6] However, since the dopaminergic activities of aporphinoids have not been reviewed systematically since 1985,[4,5] we now report a review of progress in understanding the structure-activity relationships of naturally occurring and synthetic aporphinoids in 1990−2005, focusing on dopaminergic agents, structurally related to apomorphine (**1**) and bulbocapnine (**4**, Figure 1).

2. Naturally Occurring Aporphinoids

Shin et al.[14] found that bulbocapnine (**4**), the 1,2-(methylenedioxy) derivative of *S*-(+)apocodeine, reduced the content of DA in catecholamine-producing cultured pheochromocytoma (PC12) cells at an IC_{50} of 27 μM, without evidence of cell toxicity up to concentrations of 80 μM. This *S*-aporphine also inhibited tyrosine hydroxylase (TH), the rate-limiting step in DA biosynthesis at concentrations of 10−50 μM, without altering the expression of the mRNA for this enzyme.[15]

A large number of isoquinoline alkaloids have been obtained from various species of *Annonaceae*, *Fumariaceae*, and *Aristolochiaceae* and evaluated for the ability to inhibit neuronal transport of [^{3}H]DA and binding of DA (D_1-labeled with [^{3}H]-SCH 23390) and D_2 ([^{3}H]raclopride) receptor binding sites in rat brain tissue.[16−19] Aporphine analogues **5**−**14** (Figure 2) displayed weak to moderate activities at both DA transporters (DAT[a]) and receptors (Table 1). Noraporphines **5** and **6** with substituents on ring A have the highest affinity at DAT sites, with IC_{50} values of 800 and 1400 n M, respectively, and

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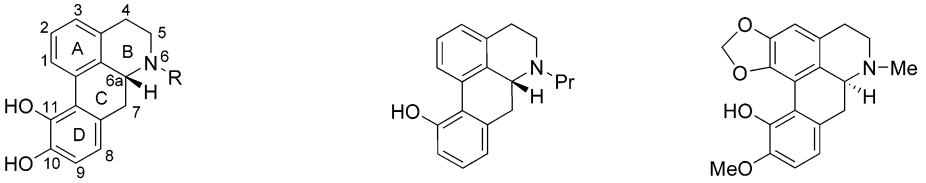

Figure 1. Structures of apomorphine (**1**) and bulbocapnine (**4**).

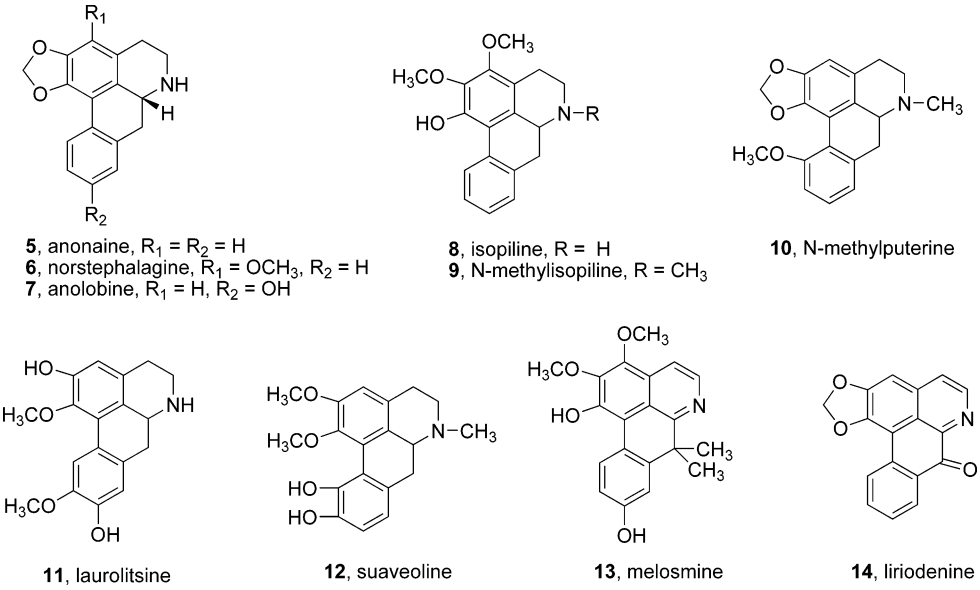

Figure 2. Naturally occurring aporphinoids (**5**−**14**).

substitution with 9-OH (**7**), 11-methoxy (**10**), or *N*-methyl (**9**) groups, as well as addition of substituents on ring D (**11**,**12**), substantially decreased DAT affinity.[19] The 10,11-catecholaporphine **12** showed more than 6-fold lower DAT affinity than its 9,10-substituted congener **11**. The 7,7-dimethylaporphine and 7-oxoaporphine **13** and **14** also displayed poor DAT affinity. In contrast, substitution on ring D, as with compounds **11** and **12**, yielded agents with some affinity for D_1 and D_2 DA receptors. Notably, 10,11-dihydroxy compound **12** showed 126-fold preference for D_2 over D_1 receptors (Table 1). Compound **13** displayed low affinity (IC_{50} = 12 500 μM) for D_1 receptors but 6-fold selectivity over D_2 receptors. The 3-methoxy substituted aporphine **9** showed some D_2 receptor affinity (IC_{50} = 2800 nM) and 6-fold selectivity over the D_1 receptor (Table 1).

A series of *cularine* derivatives (**15**−**19**, Figure 3) were also assayed under the same conditions.[16,19] These compounds generally possess poor affinity for DA reuptake inhibition with IC_{50} values of >40 μM. However, their bisphenyl ether functionality instead of a biphenyl component improved affinity at DA receptors, with some preference for 9,10- over 8,9-substitution patterns (compounds **15**, **16**, and **19** vs **17** and **18**) and especially for the 9-OH/10-MeO combination in compound **19** (D_1 and D_2 DA receptor IC_{50} of 60 and 30 nM, respectively). The 6-MeO substituted compound **18** had less D_1 receptor affinity than the 6-OH congener **17** and 25-fold greater affinity at D_2 (IC_{50} = 2000 nM) than at D_1 sites.

S-(+)-Boldine (**20**, Figure 4) is a major alkaloid of the leaves and bark of the Chilean boldo tree (*Peumus boldus* Molina, Monimiaceae).[20] It has antioxidant activity that effectively protects against free radical induced lipid peroxidation or enzyme inactivation. In addition, **20** has α_{1A}-adrenergic antagonist activities in vascular tissue,[21] and it has also been reported to have hepatoprotective, cytoprotective,[22,23] antipyretic, and anti-inflammatory effects.[24] Boldine (**20**) also shows antagonistic effects at cerebral D_1 and D_2 DA receptors, displacing the binding of striatal [^{3}H]SCH 23390 (D_1) with IC_{50} of 400 nM and of [^{3}H]raclopride (D_2) at 500 nM; at a high dose of 40 mg/kg (intraperitoneally [ip]), it had no effect on striatal [^{3}H]raclopride binding in rat forebrain (striatum) but decreased [^{3}H]SCH 23390 binding by 25%.[25] Orally administered **20** has a plasma elimination half-life of only a few minutes and is rapidly glucuronidated in the liver.[26,27] Another natural product, glaucine (**21**), which has no free hydroxyl group, had 10-fold lower affinity at these DA receptor sites, but in vivo at 40 mg/kg (ip), it displaced both radioligands by about 50%.[25] Behaviors (climbing, sniffing, grooming) elicited in mice by apomorphine (0.75 mg/kg, subcutaneously [sc]) were not modified by **20** at doses of 40 mg/kg (ip) but were almost completely abolished by **21** at the same dose. These compounds both inhibited apomorphine (0.1 mg/kg sc) induced rat yawning and penile erection in the rat by more than 50% at 40 mg/kg (ip).[25] However, at the same dose, neither compound affected metabolism of DA in mouse and rat forebrain tissue. These observations suggest that **20** does not display effective central DA antagonist activities despite its in vitro affinity at D_1 and D_2 receptors and that **21**, though less potent in vitro, has some antidopaminergic properties in vivo.

Pukateine (**23**, Figure 4) is a natural monohydroxyaporphine derivative present in the bark of the pukatea tree (Laurelia novae-zelandiae).[28] Its dopaminergic and antioxidant properties

[a] Abbreviations: DAT, dopamine transporter; 8-OH-DPAT, (±)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene; SERT, serotonin transporter; 5-HT, 5-hydroxytryptamine.

Table 1. Binding Affinity (nM) of Natural and Synthetic Aporphines[a]

compd	ref	K_i or IC_{50}	D_1	D_2	DAT	5-HT_{1A}	SERT	compd	ref	K_i or IC_{50}	D_1	D_2	DAT	5-HT_{1A}	SERT
1	53	K_i	210	13				**61**	66, 67	K_i	49	740			
2	54	K_i	730	10				**62**	66, 67	K_i	2.0	68			
R-**3**	54	K_i	700 (1100)	29 (13)		(40)		**63**	68	K_i	520	2400			
S-**3**	53	K_i	1413	105				**64**	68	K_i	2110	4500			
4	51	IC_{50}	740	14000				**65**	68	K_i	15	610			
5	19	IC_{50}	68000	19000	800			**66**	68	K_i	6.0	830			
6	19	IC_{50}	4800	27000	1400			**70**	71	K_i		83		41	7.0
7	19	IC_{50}	36000	15000	8100			*R*-**71**	71	K_i		24		31	14
8	19	IC_{50}	9800	30000	2500			*S*-**71**	71	K_i		210		1210	100
9	19	IC_{50}	17200	2800	40000			*R*-**73**	71	K_i		180		310	28
10	19	IC_{50}	>100000	>100000	32000			*S*-**72**	71	K_i		26		62	4.3
11	19	IC_{50}	2500	6800	16500			*R*-**73**	71	K_i		19		5.1	3.3
12	19	IC_{50}	63000	500	>100000			*S*-**73**	71	K_i		39		31	6.0
13	19	IC_{50}	12500	80000	24600			*R*-**74**	71	K_i		7.0		17	1.1
14	19	IC_{50}	75000	59000	31000			*S*-**74**	71	K_i		71		17	1.1
15	19	IC_{50}	800	300	41000			*R*-**75**	71	K_i		3600		200	540
16	19	IC_{50}	100	200	57000			*S*-**75**	71	K_i		8000		720	1320
17	19	IC_{50}	50000	2000	86000			*R*-**76**	71	K_i		260		140	13
18	19	IC_{50}	1000	1500	>100000			*S*-**76**	71	K_i		2250		360	18
19	19	IC_{50}	60	30	>100000			**77**	72	K_i		540		1150	280
20	67	IC_{50} (K_i)	400 (290)	500 (370)				**78**	72	K_i		270		2000	1500
21	68	K_i	2900	2800				**79**	72	K_i		55		180	55
22	68	K_i	240	760				**80**	72	K_i		6100		370	340
23	47	IC_{50}	400	600	46000			**81**	73	K_i	3000	270			
29	47, 43	IC_{50} (K_i)	3300 (1800)	10.2 (0.17)				**82**	73	K_i	3500	6500			
30	47, 43	IC_{50} (K_i)	1720 (920)	0.07 (0.053)				**83**	73	K_i	>10000	>10000			
31	47	IC_{50}	1300	0.071				**84**	73	K_i	4800	720			
32	47	IC_{50}	970	0.89				**85**	73	K_i	6800	>10000			
33	47	IC_{50}	>10000	5.5				**86**	73	K_i	>10000	>10000			
34	48	K_i		3.7				**87**	74	K_i	6400	8900			
35	49	K_i	170	3.8				**88**	74	K_i	>20000	15000			
37	51	IC_{50}	170	660				**89**	74	K_i	30000	40000			
38	51	IC_{50}	110	58				**90**	74	K_i	3700	20000			
42	54	K_i	800	39				**91**	74	K_i	8600	8200			
43	54	K_i	>10000	72				**92**	74	K_i	6600	9700			
44	54	K_i	>20000	34				**93**	74	K_i	11600	14000			
45		K_i	>10000	180				**94**	74	K_i	6300	19000			
46	61	K_i	380	1070		0.45		**95**	74	K_i	6100	15000			
53	62	K_i	2000	250		12		**96**	74	K_i	8300	16000			
54	62	K_i	>20000	>10000		3.2		**97**	74	K_i	22300	6700			
55	63	K_i	1100	1000		5.7		**98**	74	K_i	10800	8000			
56	63	K_i	270	79		4.5		**99**	74	K_i	7200	>20000			
57	64	K_i		2500		800000	21	**100**	74	K_i	>60000	4900			
58	64	K_i		500		140	3.8	**101**	74	K_i	>70000	14000			
59	64	K_i		>100000		300000	4.3	**102**	74	K_i	4300	13000			
60	64	K_i		>100000		49000	23								

[a] Potency (K_i or IC_{50} in nM) estimates are for radioligand competition assays with rat forebrain tissue for dopamine (DA) D_1 ([^{3}H]SCH 23390) and D_2 receptors ([^{3}H]raclopride) and transporter (DAT, [^{3}H]DA) and for serotonin (5-HT) 1A receptor ([^{3}H]8-OH-DPAT) and transporter (SERT, [^{3}H]5-HT). Data for compounds **1**−**102** with references to sources are provided above and include previously unpublished data from Neumeyer, Baldessarini, and Zhang (2005).

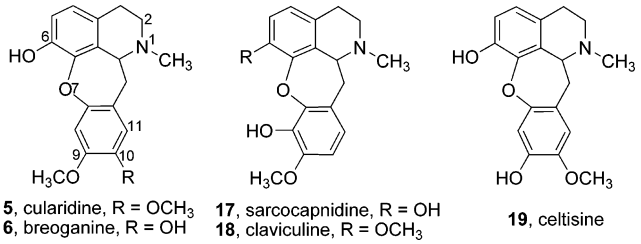

Figure 3. Cularine derivatives (**15**−**19**).

were analyzed recently in rats.[29] This agent dose-dependently inhibited lipid peroxidation in rat cerebral tissues (IC_{50} = 15 μM).[29] At D_1 ([^{3}H]SCH 23390) and D_2 ([^{3}H]raclopride) binding sites, **23** showed IC_{50} values of 400 and 600 nM, respectively, with much weaker antagonism of [^{3}H]DA transport (IC_{50} = 46 000 nM; Table 1). In rats given the DA neurotoxin 6-OH-DA unilaterally, **23** at a dose of 8 but not 4 mg/kg elicited a significant contralateral circling associated with DA agonist action. When perfused through a microdialysis probe placed in rat striatum, **23** (at 340 μM) increased extracelluar DA levels,

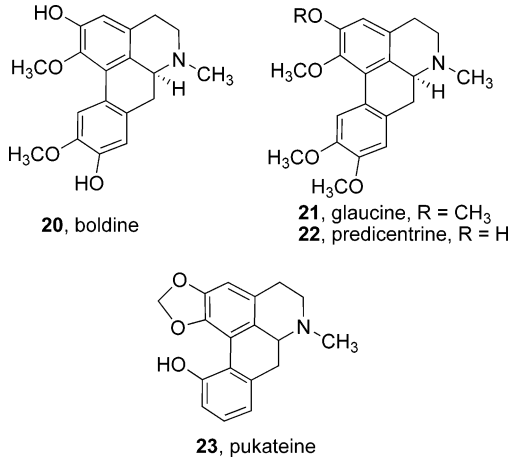

Figure 4. Boldine and its derivatives.

though it had no effect on monoamine oxidase at concentrations up to 100 μM in vitro.[29] These findings indicate that **23** has

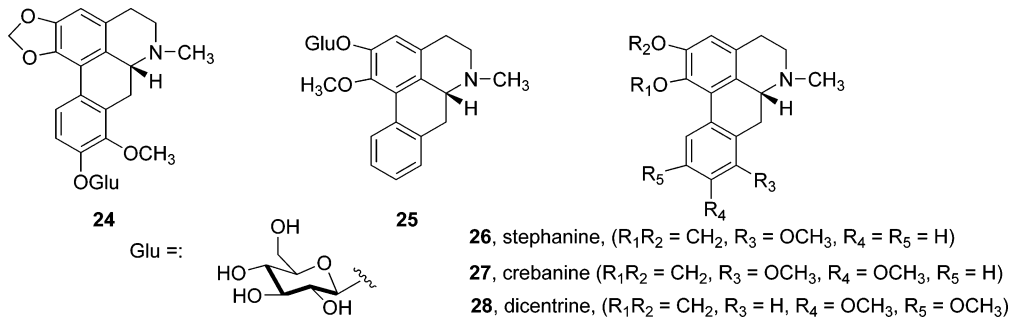

Figure 5. Aporphine glycosides (**24**−**28**).

unique pharmacodynamics, including unexplained increases in extracellular cerebral DA, agonist-like interaction with DA receptors, and antioxidant activity, suggesting potential therapeutic utility in Parkinson's disease.

Aporphine glycosides **24** (stesakine-9-*O*-β-D-glucopyranoside) and **25** (*N*-methylasimilobine-2-*O*-β-D-glucopyranoside) were isolated from the seeds of *Stephania cepharantha* cultivated in Japan,[30] together with other aporphine analogues, such as stephanine (**26**), crebanine (**27**), and dicentrine (**28**, Figure 5).[31,32] These compounds can be viewed as potential metabolic intermediates or prodrugs of corresponding phenols, but their lack of a DA-like pharmacophoric fragment in their structures suggests that their still untested dopaminergic properties may be limited.

3. Synthetic Aporphine Analogues

Naturally occurring aporphine alkaloids provide a fruitful source for identifying compounds acting on cerebral DA systems. However, the available structural variations are relatively limited and their pharmacological activities often are weak or nonselective. Accordingly, collaborative efforts of chemists and pharmacologists during the past two decades have identified a growing number of novel, synthetic aporphinoid compounds with enhanced dopaminergic activities.

3.1. Apomorphine Analogues. 3.1.1. Pharmacological Investigations of Isomers of Apomorphine (1) and Its Synthetic Analogues (2 and 3). A critical factor for the dopaminergic properties of *R*-(−)-apomorphine (**1**) and its analogues (e.g., **2** and **3**) is the absolute configuration of C-6a. The *R*-(−)-enantiomers typically are more potent DA agonists, and *S*-(+)-antipodes usually have DA antagonist effects in various assays.[3,4] Notably, *R*-(−)-apomorphine (**1**) has been characterized extensively in vitro and in vivo as a DA agonist, but *S*-(+)-apomorphine has shown weak agonist, partial-agonist, or antagonist effects at D_1 and D_2 receptors and at both pre- and postsynaptic DA receptor functions. Behavioral studies[33] based on antagonizing the effects of DA injected into limbic vs extrapyramidal sites in rat forebrain had found that systemically injected *S*-**2** had potent anti-DA effects, with high selectivity for limbic over extrapyramidal target sites, suggesting potential leads to novel atypical antipsychotic agents.[34] Moreover, the 10,11-methylenedioxy congener of *S*-**2** had shown behavioral inhibitory effects after oral administration.[35]

In 1990 Waszczak and co-workers[36] made extracellular single-unit recordings in male rats to determine responses of DA neurons in midbrain substantia nigra to intravenous administration of the enantiomers of apomorphine (**1**), *N*-*n*-propylnorapomorphine (**2**), and 11-hydroxy-*N*-*n*-propylnoraporphine (**3**). All three *R*-(−)-aporphines were potent agonists and fully inhibited firing of DA neurons at potencies (ID_{50}, nmol/kg) ranking **2** (2.0) > **3** (4.7) > **1** (18.0), indicating 9-fold increase in potency by replacing the *N*-methyl of **1** with an *n*-propyl in **2**, in otherwise identical catecholaporphines. In contrast, *S*-(+)*N*-*n*-propylnorapomorphine exhibited weak DA agonist-like inhibition of DA neurons (ID_{50} = 1.6 μmol/kg), with even weaker effects of *S*-(+)-APO (ID_{50} = 8.4 μmol/kg), and *S*-(+)11-OH-*N*-*n*-propylnoraporphine was devoid of effects on the electrophysiological activity of DA neurons.[36]

Baldessarini and co-workers evaluated D_2-like presynaptic autoreceptor-mediated modulations of DA synthesis[37] and metabolism[38] in rat brain regions of these *R*- and *S*-aporphines (**1**−**3**). Both *R* and *S* enantiomers of *N*-*n*-propylnorapomorphine inhibited tyrosine hydroxylase activity in vitro at IC_{50} = 300 and 1000 nM, respectively, indicating an *R*/*S* potency ratio of 3.3. These effects were fully blocked by the nonselective DA receptor antagonist fluphenazine, as well as by the D_2-selective antagonist spiperone but not by the D_1 antagonist SCH 23390. These results indicate inhibition of DA synthesis by a D_2-type autoreceptor-mediated effect, with moderate enantiomeric selectivity of this *N*-*n*-propylcatecholnoraporphine.[37] The corresponding monohydroxy analogues, *R*-(−)- and *S*-(+)-11-hydroxy-*N*-*n*-propylnoraporphine (*R*- and *S*-**3**), were about 100 times less potent (IC_{50} = 42 and 87 μM, respectively) than the respective *R*-enantiomers in inhibiting the tyrosine hydroxylase activity in normal tissue, but after depletion of endogenous DA by acute in vivo pretreatment with reserpine (which did not alter the tissue density of D_1 or D_2 binding sites), *R*-**3** showed potent DA synthesis-inhibiting activity (IC_{25} = 7 nM). Fluphenazine and spiperone fully antagonized this effect, and SCH 23390 was ineffective. The limited stereoselectivity of the inhibitory effects of *R*- and *S*-**2** on DA synthesis suggests that its actions may include a "catechol effect" to inhibit tyrosine hydroxylase directly.[38] In addition, *R*-(−)-**2** and *R*-(−)-**3** had high affinity at D_2 receptor sites in rat brain and exhibited behavioral effects of typical DA agonists.[38]

These results, overall, suggest that *N*-*n*-propylnorapomorphine (*R* > *S*-**2**), containing a catechol moiety, acted as a full agonist to inhibit striatal DA synthesis probably through a D_2-type presynaptic autoreceptor with moderate stereoselectivity and that its monohydroxy analogue (*R*-**3**) was a D_2-autoreceptor partial-agonist with some *R* > *S* stereoselectivity, with activity at D_2-like autoreceptors as well as postsynaptic D_2 receptors.[37,38] It may be a useful probe for the further characterization of DA receptors and autoreceptors.

DA agonists (*R*-**1**, *R*-**2**, *R*-**3**) stimulated locomotion and stereotyped behaviors in the rat, and repeated pretreatment of rats with the typical neuroleptic fluphenazine induced supersensitivity with respect to *R*-**1**-induced stereotyped behavioral responses, whereas responses to the *S*-enantiomers of **1**−**3** were little altered by the supersensitizing pretreatment.[39] These findings added to the impression that *S*-(+)-aporphines or other D_2 partial-agonists might be potential atypical antipsychotic agents with low risk of inducing acute adverse extrapyramidal neurological effects or long-term adaptive changes in DA

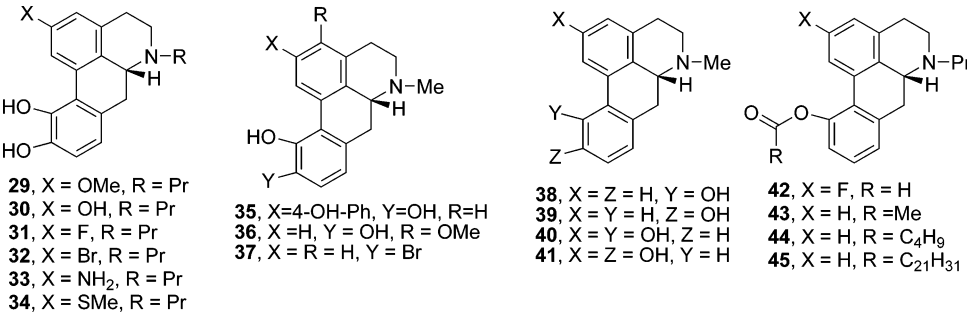

Figure 6. Apomorphine derivatives.

receptor sensitivity associated with typical neuroleptic agents that might be associated with tardive dyskinesias.[35,39]

Baldessarini and his colleagues also screened the *R*-(−)-**1**−**3** and their *S*-(+) enantiomers for affinity of over 40 representative sites in rat brain tissue that included amine, purine, amino acid and peptide receptors, transporters, ion channels, and effector components.[40] Only DA receptors and α-adrenoceptors showed appreciable affinity. The aporphines showed *R* > *S* isomeric selectivity as well as D_2 > D_1 selectivity at DA receptors. Whereas the *R*-(−) isomers were preferred at α_2-adrenoceptors, *S*-(+)-aporphines were α_1-selective, with similar affinity at α_1-adrenoceptors and DA D_2 receptors. Interactions of *S*-(+)-aporphines at α_1-adrenoceptors as well as DA D_2 receptors may contribute to their unusual behavioral properties suggestive of activities as atypical antipsychotics. In addition, the *S*-aporphines (*S*-**1**, *S*-**2**, *S*-**3**), with parallels to the D_4/D_2 selectivity of the atypical antipsychotic drug clozapine, bound to the D_4 DA receptor with selectivity up to 20 times greater than to D_2 sites.[41] In tests for effects on circulating prolactin, unlike the typical D_2 antagonist-neuroleptic haloperidol, which elevated circulating prolactin concentrations, *S*-**2** and **3** had little or no effect, even at high doses, whereas the potent D_2 agonist *R*-enantiomers lowered prolactin levels. These observations further support the hypothesis that such enantiomers may represent leads to novel atypical antipsychotic agents.[32,24,42]

3.1.2. Substituted Aporphinoids. The majority of recently developed synthetic aporphinoids are derivatives of apomorphine or naturally occurring alkaloids such as boldine, bulbocapine, glaucine, and others with variant substituents on the tetracyclic aporphine skeleton, developed largely with the objective of further elucidating the SAR of such compounds and identifying those with improved dopaminergic activity and selectivity.

The first total synthesis of *R,S*-(±)-apomorphine (racemic **1**) in 1970 by Neumeyer and his colleagues[8] led to the synthesis of a variety of hydroxy and methoxy substituted aporphines previously not available from naturally occurring aporphinoids. Starting from thebaine, morphine, bulbocapnine, or naturally occurring aporphines, a number of dihydroxynoncatecholic, masked catecholic, mono- and trihydroxyaporphines, with or without C2 substituents, and *N*-alkyl substituents have been synthesized and evaluated pharmacologically.[3,4]

Compounds **29**−**34** (Figure 6) contain an electropositive or electronegative C2 substituent, mostly display high D_2 binding affinity and good D_2/D_1 receptor selectivity.[43−47] D_2 binding potency (IC_{50}, nM) decreased in the following order: 2-F (**31**, 0.07) > 2-OH (**30**, 0.32) > 2-Br (**32**, 0.89) > 2-MeO (**29**, 1.02) > 2-MeS (**34**, 3.7) > 2-NH_2 (**33**, 5.5 nM).[43] The differences between 2-F− (**31**[47]) and 2-NH_2− (**33**[47]) or 2-MeS (**34**[48]) substituted aporphines suggest that a lipophilic cleft might exist on the D_2 receptor that can interact with 2-substituents on the A ring of aporphines.[4] This postulated lipophilic site would repel relatively hydrophilic groups, such as NH_2 and MeS, so as to limit binding at the functional sites involved in the ligand−receptor interactions. Apparently a steric factor also is involved in the hydrophobic interactions between the 2-substituent and the hypothesized D_2 receptor lipophilic cavity and may contribute to the relatively low D_2 receptor affinity of compounds **33** and **34** relative to that of the 2-fluoro-analogue **31**. Sondergaard et al.[49] recently reported that a larger substituent (hydroxyphenyl) **35** can be tolerated at the C2 position.

A meta OH-substituent on phenyl ring A (which includes the C2 position) appears to be critical for D_2 receptor affinity and may involve hydrogen bonding between the hydroxyl group and the D_2 peptide surface. Compound **36** (Figure 6), with a substituent at position C3, also has been reported, but its dopaminergic activity has not.[50] The D_1 antagonist activity of a series of substituted aporphines also has been reported.[51] Compared to *S*-bulbocapnine (**4**), *R*-11-hydroxyaporphines are potent D_1 antagonists, and C8 and C10 monosubstituted phenolic *R*-aporphines were approximately equipotent.[51] Compound **37**, with a 10-Br group replacing the 10-OH of apomorphine (**1**), was particularly selective for the D_1 receptor and 4.3-fold more potent than *S*-bulbocapnine (**4**, Table 1).

There has also been interest in developing aporphines with increased oral bioavailability and longer duration of action than **1** or **2**. The in vivo elimination of apomorphine (**1**) is complex because of its interactions with proteins and other tissue components affecting its disposition, in addition to its rapid first-pass hepatic clearance by oxidative and congugation mechanisms.[52] The metabolic stability of apomorphine can be enhanced by eliminating its 10,11-hydroxyl groups or masking them to provide prodrugs. Neumeyer and co-workers developed a series of monhydroxy aporphines and their esters (**38**−**45**).[53,54] In this series, 11-hydroxy-*N*-*n*-propylnoraporphine (**3**) showed D_2 receptor affinity (K_i = 29 nM) and D_2/D_1 selectivity (24-fold) that compared well with its catecholic congeners **1** and **2**. Introduction of a 2-F group (compound **42**) did not change D_2 receptor affinity substantially, suggesting again that the receptor binding site corresponding to the C2 position is relatively tolerant to groups at C2.[55] *R*-11-OH-*N*-*n*-propylnoraporphine (**3**) exhibited a longer duration of locomotor arousal in the rat than **1** or **2**.[55] Of note, the acetic (**43**) and valeric (**44**) esters of **3** retained affinity at the D_2 receptor (K_i of 72 and 34 nM) with very low D_1 receptor affinity (Table 1), despite partial occlusion of its presumably critical 11-OH binding site at D_2 receptors. At moderate doses, these esters had superior oral bioavailability and longer behavioral actions in the rat.[54]

In an effort to further investigate the role of the 10- and 11-hydroxy substituents pattern in catecholaporphines (such as **1** and **2**) to their affinity and activity as D_2 DA receptor ligands, Cannon and his colleagues developed a series of compounds lacking one of the hydroxyl groups (**46**−**52**, Figure 7). 10-Methyl substitution in compound **3** (compound **46**) proved to be detrimental to DA receptor activity, despite the presence of

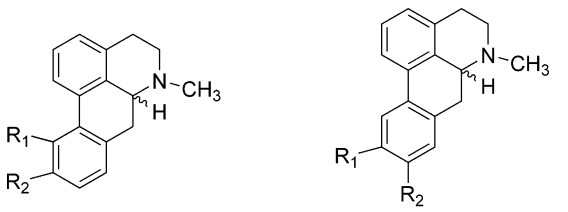

Figure 7. Mono- or nonhydroxylaporphines.

a critical free 11-OH moiety.[56,57] Thus, neither *R*- or *S*-11-hydroxy-10-methylaporphine (**46**) showed significant affinity or activity at DA receptors. Interestingly, however, *R*-**46** was a potent 5-HT_{1A} agonist, and *S*-46 was an antagonist.[57] Mixing the enantiomers nullified these effects, and racemic *R*,*S*-**46** also lacked pharmacological activity at the 5-HT_{1A} receptor. The *R*- and *S*-enantiomers of compound **47**, which does not contain the 11-hydroxy group, and compound **48**, which lacks both the 11-hydroxy and 10-methyl groups of **46**, showed no significant dopaminergic or serotonergic activities.[58]

These findings led to the proposal that ortho dihydroxy substitution enhances affinity to DA receptors, whereas contiguous monohydroxy and methyl substitution on the aporphine D ring enhances interactions with 5-HT receptors. Further, the C10 and C11 locations of ortho dihydroxy groups are necessary for DA receptor activity, since other locations for hydroxy substitution, such as carbons 9 and 10 in isoapomorphine, yield pharmacologically inactive aporphines.[3,4] To examine the sensitivity of the location of ortho hydroxy/methyl substitution in **46**, the *R*- and *S*-enantiomers of 9-methyl-10-hydroxyaporphine (**49**) and 9-hydroxy-10-methylaporphine (**51**) also were synthesized and evaluated. Both positional isomers in both enantiomeric forms proved to be inactive at the 5-HT_{1A} receptor.[59,60] The corresponding 9,10-dimethoxy ethers (**50**, **52**) also demonstrated low affinity and agonist activity at the 5-HT_{1A} receptor, and their enantiomers differed little in potency in vivo behavioral testing.[59,60] These findings support the conclusion that agonism and antagonism at DA or 5-HT receptors displayed respectively by *R*- or *S*-enantiomers of aporphines require a unique and specific substitution pattern on the aporphine skeleton; 10,11-dihydroxy substitution is preferred by D_2 DA receptors, whereas 11-hydroxy-10-methyl substitution is preferred by 5-HT_{1A} receptors.

In further studies aimed at understanding the critical determinants of the aporphine C10 and C11 substituents for dopaminergic and serotonergic activities, Johansson and co-workers resynthesized *R*-11-hydroxy- (**38**) and *R*-11-hydroxy-10-methyl- (**46**) aporphines from morphine using a short and efficient process and further evaluated their neuropharmacological properties.[61] Similar to previous findings,[57] **46** was found to be a potent, selective, and efficacious 5-HT_{1A} full agonist and inhibited forskolin-stimulated adenylyl cyclase activity similarly to 5-HT; this effect was fully antagonized by the nonselective 5-HT_{1A} (and β-adrenoceptor) receptor antagonist (−)-pindolol. Compound **38**, on the other hand, acted as a partial-agonist, inhibiting forskolin-stimulated cyclase to about 60% of the maximal effect produced by 5-HT. This compound also displayed D_1 and D_2 receptor activities that were lacking in **46**. Molecular modeling of ligand−receptor interactions using homology-based receptor models indicated that the C10-methyl component of **46** was not accommodated by a binding site model of the D_2 receptor but was accommodated by a lipophilic pocket in the 5-HT_{1A} receptor.[61]

An additional series of compounds derived from *R*-11-hydroxy-10-methylaporphine (**46**) and C11-substituted *R*-aporphines (**57**−**60**, Figure 8), containing various substituents in the C10 or C11 position or the nitrogen, were synthesized using efficient Stille or Suzuki cross-coupling reactions.[62−64] All of these compounds displayed low (nM) affinities at D_1 and D_2 DA receptors. Changes in the steric bulk or electronic properties of the C10 substituent compared to a C10 methyl group, as well as substitution of the *N*-methyl group for a hydrogen or an even larger *N*-alkyl group, markedly decreased 5-HT_{1A} receptor affinity. Only the *N*-*n*-propylaporphine **53** showed even moderate D_2 receptor affinity (Table 1).[62]

In the series of C11-substituted *R*-aporphines and C11-oxygenated *R*-noraporphines, several compounds retained high affinity at the 5-HT_{1A} receptor in spite of major differences in steric bulk and electronic properties of the various C11 substituents.[63] Interestingly, the *N*-methylaporphine (**38**) and *N*-*n*-propylaporphine (**3**) showed good affinity at both D_2 and 5-HT_{1A} receptors, but the noraporphine **55** lacked D_2 affinity (Table 1). Modeling of ligand−receptor binding site interactions again suggested the presence of a "methyl pocket" (at aporphine position C10) at the 5-HT_{1A} receptor binding site and a "propyl pocket" (at the N atom) for the D_2 receptor. It is intriguing and unexpected that the 11-ethylaporphine **56** displayed high affinity for the 5-HT_{1A} receptor (K_i = 4.5 nM), as well as quite high affinity at the D_2 receptor (K_i = 79 nM; Table 1).[63]

Compounds **57**−**60** (Figure 8) contains a 2′,6′-substituted phenyl group and have two atropisomers (6a*R*,a*R*)-**57** and -**59** and (6a*R*,a*S*)-**58** and -**60**.[64] These stable atropisomeric biaryl *R*-aporphines interacted stereoselectively with 5-HT_{1A}, 5-HT_7, and D_2 receptors, with low D_2 receptor affinity and some preference for the 5-HT_7 receptor subtype.[64]

3.2. Boldine and Predicentrine Analogues. The aporphine alkaloids boldine (**20**), glaucine (**21**), and predicentrine (**22**) have moderate and nearly equipotent affinity at both D_1 and D_2 receptors and exhibit "neuroleptic-like" behavioral actions in rodents, suggesting that they may act as DA antagonists.[65,66] Substitution at the C1 and C2 positions in such compounds may contribute to their antagonist activity since C9 and C10 substitutions do not increase interactions with DA receptors.[3,4] Cassels and colleagues reported a series of analogous aporphines with a halogen atom at C3 that showed substantial affinity at the D_1 receptor.[67−70] Compared to boldine (**20**), the 2,9-dimethoxyaporphine glaucine (**21**) displayed very low affinity as well as little selectivity at D_1 and D_2 DA receptors. The 9-methoxy-2-hydroxyaporphine congener, predicentrine (**22**), showed moderate D_1 and D_2 affinity with 3-fold D_1/D_2 selectivity. These observations indicated that hydrogen-bonding at C2 and C10 positions contribute heavily to D_1 and D_2 DA receptor affinity and that the free hydroxyl group at C2 is particularly beneficial for binding to the D_1 receptor. Interestingly, halogenation of **20** and **22** at C3 produced compounds with further enhanced affinity and selectivity for the D_1 receptor, with the highest D_1 affinity (K_i = 2 nM) shown by 3-iodoboldine (**62**), which exceeded that of boldine (**20**) itself by 150-fold. The D_2 receptor affinity of **62** (K_i = 68 nM) also was greater than that of boldine **20** (K_i = 370 nM), and D_1/D_2 selectivity of **62** was 34-fold.[67,68] Similarly, C3 iodination of predicentrine (**22**) yielded compound **66** with high D_1 potency (K_i = 2 nM) that was 40 times greater than that of predicentrine, with lower D_2 affinity and substantial D_1/D_2 selectivity (139-fold).[68] The corresponding 3-bromo analogues **61** and **65** also were more

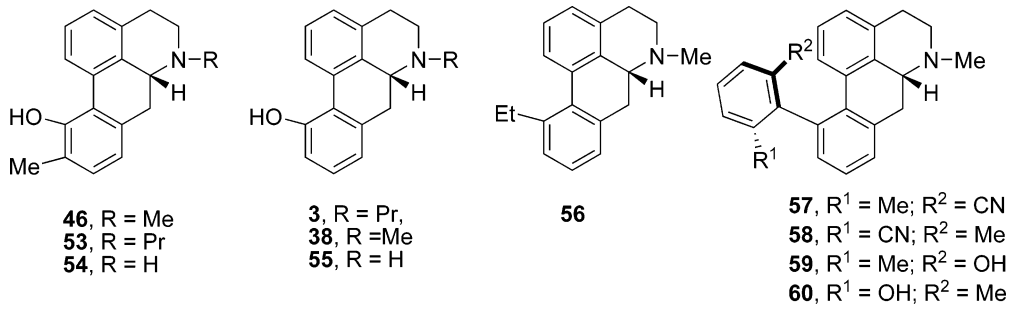

Figure 8. C11-substituted aporphines.

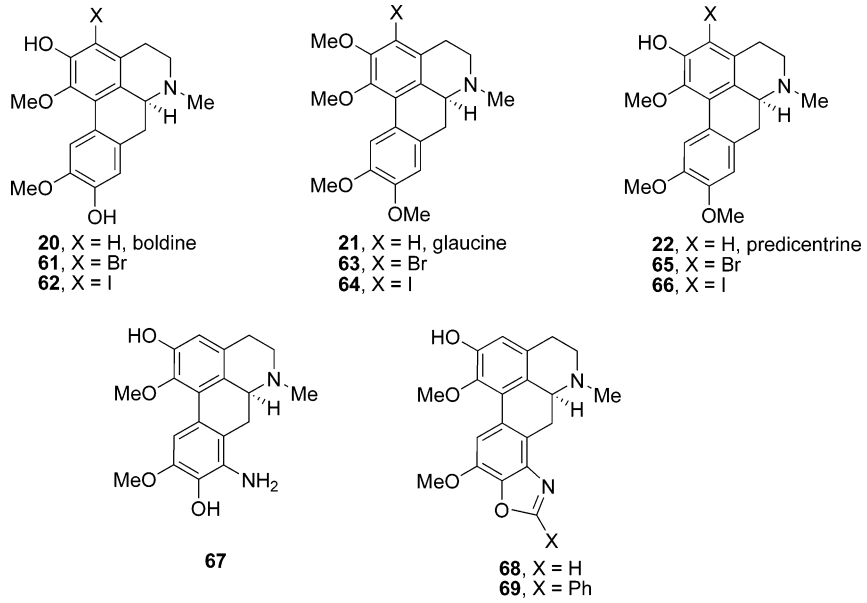

Figure 9. Boldine and its synthetic analogues.

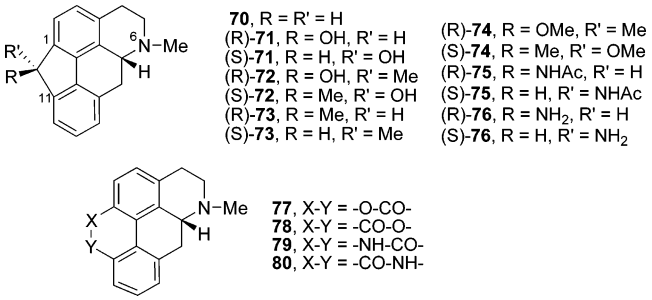

Figure 10. C1,C11-bridged aporphines.

potent and selective than their parent compounds at the D_1 receptor but about half as potent as the 3-iodo congeners **62** and **66**. Such results were not observed with glaucine analogues, although 3-bromoglaucine (**63**) showed moderate D_1 affinity and selectivity (Table 1).

Other aporphines derived from boldine (**20**) also have been reported, including 8-aminoboldine (**67**)[65] and oxazoloboldines **68** and **69** (Figure 9), but they had low affinity at DA receptors and greater affinity at α-adrenoceptors.[70]

3.3. Bridged Aporphines. 3.3.1. C1,C11-Bridged Aporphines. Johansson and colleagues established an approach to the design and synthesis of a novel series of aporphines (**70**−**76**, Figure 10) with a methylene bridge at C1−C11.[71] Two epimers (*R* and *S*) were obtained and structurally characterized by a combination of X-ray crystallography, NMR spectroscopy, and chemical correlations. The interesting and diverse pharmacological profiles of these derivatives were indicated by binding studies at 5-HT_{1A} and 5-HT_7 receptors as well as at D_2 receptors. Generally, these compounds have shown good affinity at 5-HT receptors but more variable interactions at DA receptors. In most cases the *R*-epimers had higher 5-HT receptor affinities than the *S*-epimers except for 12-hydroxymethyl-substituted **72** whose *S*-epimer was 5- to 7-fold more potent at 5-HT and D_2 receptors than the *R*-epimer. The highest affinity for all three receptor types was found with compound *R*-**74** (K_i of 1.1, 17.1, and 7.1 nM at 5-HT_7, 5-HT_{1A}, and D_2 receptors). *S*-**74** showed similar affinities compared with the *R*-epimer at 5-HT_7 and 5-HT_{1A} receptors but was 10-fold less potent at the D_2 receptor. These incompletely characterized compounds represent an approach to the development of novel aporphines that interact with both 5-HT and DA receptors. In addition, a series of aporphines (**77**−**80**, Figure 10) with a two-atom bridge (ester, imine, or amide) between C1 and C11 also have been developed.[72] These compounds had lower 5-HT and DA receptor affinity than their one-atom bridged analogues. A variant affinity was observed between the regiomer pairs **77** and **78**, and **79** and **80**. The most pronounced regioselectivity (112-fold) at the D_2 receptor was observed with the lactams **79** and **80**; otherwise, regioselectivity at 5-HT1A, 5-HT7, and D2 receptors was only moderate (of 2- to 6-fold). The lactam **79** showed the highest D_2 and 5-HT_7 affinity (both with K_i = 55 nM).

3.3.2. C12,C13-Bridged Aporphines. Claudi and colleagues recently reported a series of novel aporphines with a methylene or oxygen link between two phenyl groups.[73,74] In a series of benzoxepino[2,3,4-*ij*]isoquinolines (**81**−**86** (Figure 11), a 2- or 9-hydroxy group was introduced to retain a *m*-hydroxyphenethylamine component in these molecules that is widely considered the key element to provide for binding to DA

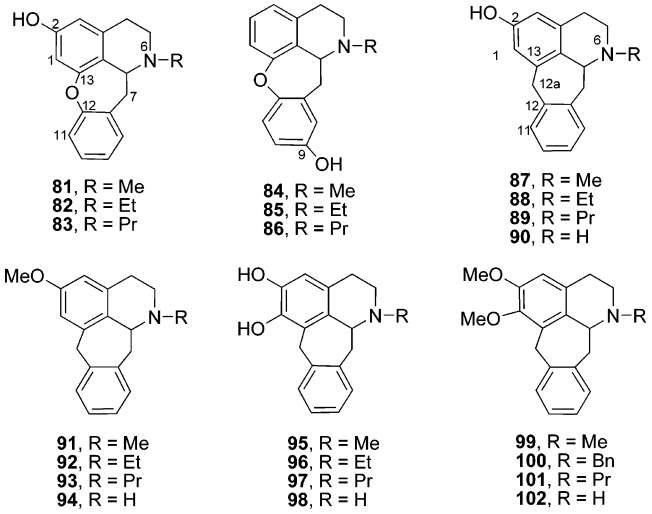

Figure 11. C12,C13-bridged aporphines.

receptors. All of these compounds showed low affinity at D_1 and D_2 receptors (nanomolar K_i values). These findings indicating the importance of a *m*-hydroxyphenethylamine pharmacophoric moiety for DA receptor affinity agree with observations made with the naturally occurring aporphinoids **15**−**19**. Only the *N*-methyl-5-hydroxy (**81**) and *N*-methyl-10-hydroxy (**84**) derivatives showed even moderate D_2 receptor affinity (K_i of 270 and 720 nM; Table 1), resembling DA itself.[73,74] These compounds did not interact with recombinant human D_4 receptors, and only **81** showed even low affinity for recombinant rat D_3 receptors. Analysis of the influence of Na^+ on [^{3}H]-spiperone binding to D_2-like sites indicated that **81** displayed a potential D_2-agonist profile, whereas **84** probably has D_2-antagonist activity. The D_2-agonist activity of **81** was shown by its ability to decrease prolactin release from primary cultures of rat anterior pituitary cells.[73]

Compounds **87**−**102** (Figure 11) represents another series of compounds with a methylene unit between the two phenyl groups (at C12, C13).[74] In the series of benzoxepino[2,3,4-*i*,*f*]-isoquinolines **81**−**86** (Figure 11), a 2-hydroxy or 9-hydroxy group was introduced to retain a *m*-hydroxyphenylethylamine fragment in these molecules, which was proposed to be the key element for DA receptor binding. All of these compounds showed significantly lower D_1 and D_2 affinities than the traditional aporphines. The 2-hydroxy and 1,2-dihydroxy analogues (**87**, **95**) showed D_2 agonist activity indicated by their inhibitory effects on prolactin release from primary cultures of rat anterior pituitary cells. Molecular modeling studies indicated that the geometric parameters of the presumptive dopaminergic pharmacophore embedded in these compounds (especially distances from meta and para hydroxyl oxygen atoms to the nitrogen and the height of nitrogen from the hydroxylated phenyl-ring plane) are less favorable than those observed in other known D_1 and D_2 selective aporphine ligands, and these molecular characteristics may explain the relatively low DA receptor affinities of these novel compounds.[74]

4. Aporphinoids as DA D_2 PET and SPECT Imaging Agents

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are major brain imaging techniques that enable the investigation of human neurochemistry and neuropharmacology in vivo. The techniques can be used to measure receptor parameters (B_{max}, K_d, binding potential, and volume of distribution), to monitor receptor occupancy by drugs, and hence to guide dosing.[75] In the past two decades, PET and SPECT techniques have been used widely for imaging neurotransmitter systems (receptor and transporter proteins) in the living human brain to identify neurochemical dysfunctions in major neuropsychiatric disorders by administration of suitable radioligands to patient-subjects. Such nuclear medicine methods have advanced understanding of such neuropsychiatric disorders as Parkinson's disease,[76,77] Alzheimer's disease,[78,79] schizophrenia,[80−84] attention deficit hyperactivity disorder (ADHD),[85−87] and other prevalent neuropsychiatric conditions.[88]

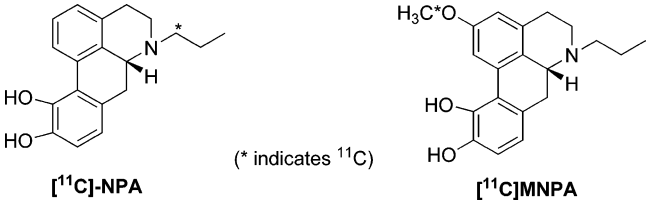

Figure 12. D_2 agonist radiotracers [^{11}C]NPA and [^{11}C]MNPA.

It is hoped that development of D_2 receptor agonist radiotracers will be useful for endogenous competition experiments, better characterize alterations in DA transmission in particular disorders whose pathophysiology or treatment has implicated cerebral DA systems, and address fundamental aspects of D_2 receptor functioning in the human brain. Early experiments using ^{11}C and ^{18}F to radiolabel apomorphine analogues met with little success, and none has shown suitable properties for in vivo imaging.[89,90] Recently, however, the aporphines *R*-[^{11}C]*N*-*n*-propylnorapomorphine[91−95] and *R*-2-[^{11}C]methoxy-*N*-propylnorapomorphine[96,97] have been used successfully to image DA D_2 receptors in vivo in nonhuman primate forebrain using PET imaging. Further development of radiolabled aporphinoids as D_2 agonists promises to be a fertile area in the search for novel and selective brain-imaging agents for the diagnosis of a variety of CNS disorders.

5. Conclusions

R-Apomorphine (**1**) and *S*-bulbocapnine (**4**) are highly characterized structural skeletons, respectively, with DA D_2 receptor agonist and antagonist properties. Hundreds of their derivatives and analogues (including proaporphines, aporphines, secoaporphines, oxoaporphines, dehydroaporphines, 7-hydroxyaporphines, aporphine dimers, aristolactams, and others have been isolated from plants or synthesized, but most lack evidence of major dopaminergic activities. This review concentrated on SARs of compounds with activities at the DA receptor, DA transporter, or DA biosynthesis, with selected comparisons to interactions with some 5-HT receptors. Except for earlier findings that the C6a-*R* configuration, *m*-hydroxyphenethylamine component, and an *N*-*n*-propyl substituent are critical structural elements for DA properties of aporphinoids, the biphenyl unit and the 11-hydroxy substitutions also play critical roles. In addition, one or more accessory binding sites on DA receptors corresponding to position C2 or C3 of aporphines are suggested by some of the findings reviewed. Thus, C2- or C3-substituted 11-hydroxyaporphine or 10,11-dihydroxyaporphine derivatives remain among the most potent aporphinoids, especially at the D_2 DA receptor. Of note, C1,C11-bridged aporphines have shown D_2 affinities comparable to those of more traditional catecholaporphines such as *R*-apomorphine (**1**) and *R*-*N*-*n*-propyl-norapomorphine (**2**), and they represent a novel atypical structural model for development of dopaminergic agents as potential treatments of Parkinson's disease and psychotic disorders.

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Yi Zhang received the B.S. degree in Chemistry from East China University of Science and Technology in 2006, and now is a graduate student at Shanghai Institute of Materia Medica under the supervision of Professor Ao Zhang. Yi Zhang's research interests include the preparation of new dopaminergic ligands and their structure−activity relationship studies.

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John L. Neumeyer received a B.S. degree in Pharmacy from Columbia University in 1952 and a Ph.D. in Medicinal Chemistry from the University of Wisconsin, Madison, WI, in 1961. He began his career as a Research Scientist at Ethicon, Inc., a division of Johnson and Johnson, FMC Corp., and Arthur D. Little, Inc. before joining the faculty at Northeastern University in 1969 as Professor of Medicinal Chemistry and Chemistry. He was appointed Matthews Distinguished Professor in 1980. He was the Cofounder, Chairman, and Scientific Director of Research Biochemicals International (RBI) from 1980 to 1997. At present, he continues his research activities at Harvard Medical School and the Alcohol and Drug Abuse Research Center at McLean Hospital where he is a Lecturer in Psychiatry (Neuroscience) and the Director of the Medicinal Chemistry Program.

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