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Perspective

Emerging Opportunities for Antipsychotic Drug Discovery in the Postgenomic Era

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1. Introduction

Schizophrenia is a chronic, debilitating mental disorder[1] affecting 1−2% of the global population. It has a median lifetime prevalence of 0.7−0.8%,[2] shows no accepted gender, ethnic, or social boundaries,[3] and is associated with mortality rates 2−3 times higher than those in the general population.[4]

After nearly a century of research, the etiology and pathophysiology of schizophrenia remain largely unresolved. Its existence as a discrete disease state, as contrasted to a spectrum of related psychiatric disorders,[5–8] remains unclear despite a relatively well defined set of symptoms.[9] Current treatment for schizophrenia involves psychotherapy,[10] electroconvulsive therapy, and drug treatment, the latter reflecting almost exclusively the dopamine (DA) hyperfunction hypothesis of disease causality[9,11] Proactive efforts for the early detection of schizophrenia, e.g., the Portland Identification and Early Referral (PIER) Program Prodromal/UHR (ultrahigh risk), involving early drug intervention are also being explored for the potential to reduce the development of psychosis in adolescents.[12,13]

Currently prescribed drugs for the treatment of schizophrenia are the *typical* and *atypical* antipsychotics also known as first generation (FGA[a]) and second (SGA) generation antipsychotics, respectively.[3,11] These drugs have combined sales in excess of $18 billion per year and effectively treat the core "positive" psychotic symptoms of the disorder, e.g., auditory and visual delusions and hallucinations. However even with active drug treatment, approximately 15% of schizophrenics have residual, moderate-to-severe positive symptoms and remain treatment resistant with only 20−30% of schizophrenics under treatment being capable of leading independent lives.[14]

A considerable body of genetic, molecular, and chemical research on the causality, pathophysiology, and treatment of schizophrenia has appeared since the last Perspective on this topic some 7 years ago,[15] much of it controversial with few new insights into disease causality, novel drug treatments, or novel targets that address the limitations in the current generations of antipsychotic medications. Nonetheless, the mapping of the human genome has allowed the identification of a number of potential new drug "targets" through the use of gene association studies in affected schizophrenic populations[16–19] that reinforce (a) the neurodevelopmental nature of the disease, (b) the impact of the environment on disease progress,[17] and (c) the potential role of glutamate in the etiology of schizophrenia.[20] Many of these novel targets appear unique, lacking a clear role in neurotransmission or cellular signal transduction processes.[19] These targets thus remain largely unvalidated from a drug discovery perspective or in the context of an improved/expanded understanding of disease genesis.[19]

Concomitant with these newer findings, increasing concerns have emerged with (i) the life threatening class effects of current antipsychotic agents that include QT prolongation[21] and their potential to cause metabolic syndrome, e.g.,weight gain and diabetes[22,23] and (ii) the highly controversial[24–26] NIMH-sponsored CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and NHS-sponsored CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) clinical trials that have reported no major differences in the clinical effectiveness of FGAs and SGAs.[7,27–29]

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[a] Abbreviations: CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CDS, cognitive deficits of schizophrenia; CUtLASS, Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study; DLB, dementia with Lewy bodies; EAAT, excitatory amino acid transporters; FGAs, first generation antipsychotics; RTK, receptor tyrosine kinase; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MCCB, measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery; SGA, second generation antipsychotics.

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2. Disease State/Diagnosis

While behavioral phenotypes similar to schizophrenia were known before the 18th century,[30] the description of the disorder as schizophrenia (from the Greek "schizo", to tear or split, and from "phren", the intellect or mind) was not coined until 1911 by Bleuler. The current DSM-IV-TR category for schizophrenia, 295.*xx*, "Schizophrenia and Other Psychotic Disorders",[9] has evolved over the past century and can be divided into several major subclasses: paranoid type (295.30), disorganized type (295.10), catatonic type (295.10), undifferentiated type (295.90), residual type (295.6), schizophreniform disorder (295.40), schizoaffective disorder (295.70, including bipolar and depressive types), delusional disorder (297.1), brief psychotic disorder (298.8), and shared psychotic disorder (297.3).

Six diagnostic criteria have been developed for schizophrenia.[9] These include (i) characteristic symptoms of the disorder including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (affective flattening, alogia (poverty or absence of speech), avolition (lack of interest and drive)) (two or more of which must be present for a significant duration over a one month period), (ii) social/occupational dysfunction, (iii) duration of the disturbance for at least 6 months (unless successfully treated after early diagnosis), (iv) schizoaffective and mood disorder exclusion, (v) substance/general medical condition exclusion, and (vi) relationship to a pervasive developmental disorder, e.g., autistic disorder. Schizophrenia is frequently present before actual diagnosis, the various symptoms being expressed in a sufficiently subtle manner that fails to reflect the severity of the clinical disorder or distinguish it from various aspects of the normal developmental process.[8,12]

Schizophrenia can be divided into three main domains: positive and negative symptoms and cognitive dysfunction.[9]

Positive symptoms involve an excess or distortion of normal function. These include bizarre behavior, auditory, and more rarely, visual hallucinations, paranoia, and other delusional states together with disorganized thought.

Negative symptoms involve a decrease or loss of normal function and include affective flattening, anhedonia, social withdrawal, lack of motivation and spontaneity, and alogia and avolition (poverty of thought and speech, respectively).

Cognitive impairment begins before the presentation of any psychotic symptoms and remains severe, with some progression, throughout the course of the disease. While the precise domains of schizophrenia-associated cognitive dysfunction have yet to be elucidated, these are generally widespread and multifaceted involving executive function, attention, processing, vigilance, verbal learning and memory, verbal and spatial working memory, semantic memory and social cognition.[9,31] Cognitive impairment is currently thought to be of equal or greater importance than either the positive or negative symptoms in predicting the functional consequences of schizophrenia, such as work status, quality of life, and social problem solving.[31] This issue has been highlighted by a U.S. federal initiative, Measurement and Treatment Research To Improve Cognition in Schizophrenia (MATRICS),[32] to define the guidelines for the approval of new drugs to treat the cognitive aspects of schizophrenia. A consortium headed by the NIMH, including academic groups and representatives from the FDA and the pharmaceutical industry, is currently validating the MATRICS consensus cognitive battery (MCCB) for evaluating therapeutic effects on cognitive function in schizophrenics.[33] An additional facet of the MATRICS initiative is the matching of domains of clinical efficacy, e.g., working memory, attention/vigilance, speed of processing, social cognition, etc., with appropriately predictive animal models to facilitate the transition of compounds from the research bench to the clinic.

Schizophrenia has a high comorbidity with mood disorders, bipolar disorder, autism, and depression, the last being a key factor in increasing the risk for suicide in schizophrenics compared to the general population, especially in young adult males. While these comorbidities have been considered as an additional phenotypic domain for the disease, it is currently unclear as to whether they share a common etiology with schizophrenia or represent an epiphenomenon associated with either the disease state or its treatment.

Schizophrenia is usually diagnosed early in life with the symptoms following a characteristic developmental pattern.[8] Cognitive symptoms first occur during adolescence, accompanied by changes in social behavior that are reflected in peer group interactions, declining academic performance, and increased irritability. Because many of these symptoms occur, albeit to a lesser degree, in normal adolescents, diagnosis is not commonly made until the emergence of positive symptoms. Positive symptoms usually develop in males in their late teens and early 20s and in females in their mid-20s to early 30s.

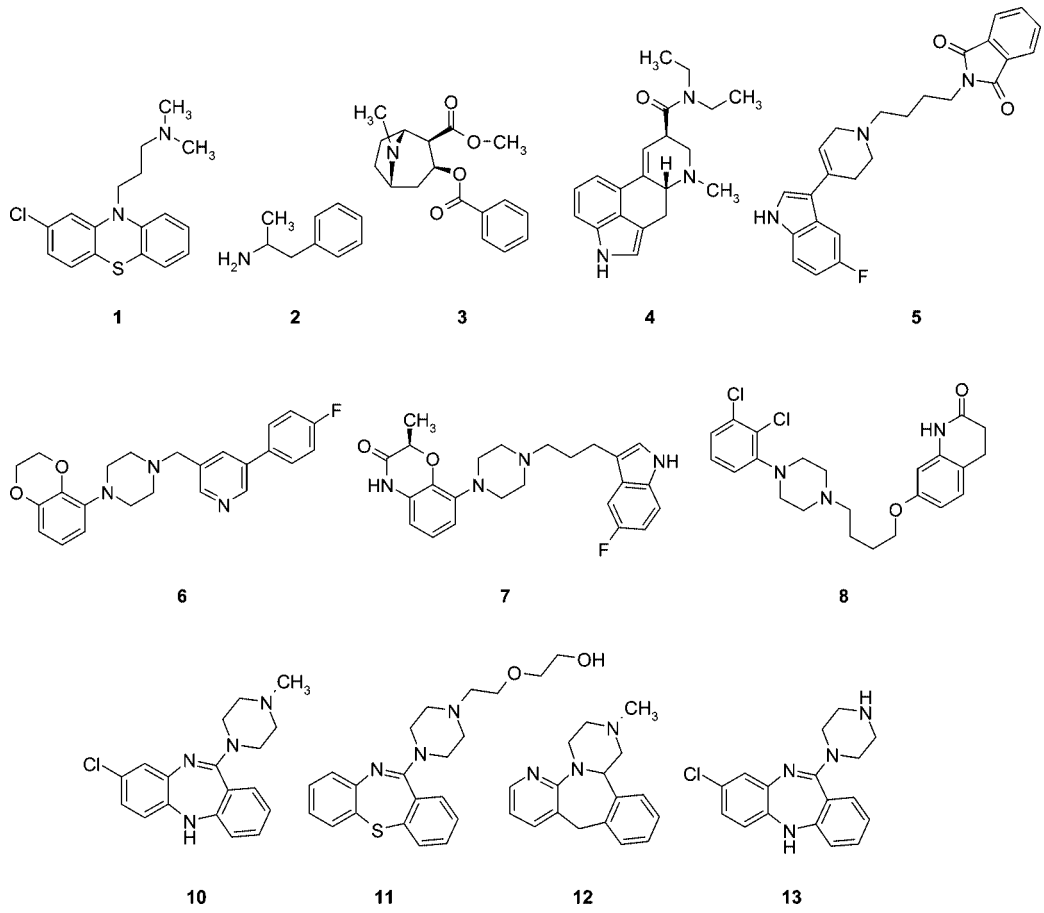
3. Disease Causality

Schizophrenia is currently viewed as a neurodevelopmental[34,35] disease involving both epigenetic and genetic factors.[2,3,17,18,36] Epigenetic risk factors for the disease include[3,18,37] place and time of birth including winter birth and city living,[38] prenatal and obstetric influences,[18] e.g., maternal depression, obstetric complications including maternal nutrition,[39] hypoxia, low birth weight, pre-eclampsia, infection (e.g., influenza,[39] rubella, intrauterine/viral infections related to birth), parasitic infections,[40] autoimmune disorders,[41] miscellaneous factors including low IQ,[34] immigration, low socioeconomic status, cannabis use,[42] as well as a family history of the disorder.[17,18,36,37]

While evidence for a genetic component for schizophrenia was summarized some 60 years ago[43] and multiple family, twin, and adoption studies have reliably demonstrated the inheritability of schizophrenia, there is considerable debate as to the validity of many of these findings[19,36] in light of the current somewhat confusing/misleading outcomes from gene association studies.[44,45] The debate is focused on requirements for precision in the replication of genetic association studies,[46] concerns regarding the inherent usefulness of genome wide scans,[47] newer insights into the complexity of genome function,[48] and concerns regarding the value of the data accumulated to date. As an example, a reassessment[44] of 432 human gene association studies reporting gender-related differences in gene-related effects concluded that "most claims were insufficiently documented or spurious, and claims with documented good internal and external validity were uncommon".

Thus, despite the identification of a large number of candidate genes associated with the diagnosis of schizophrenia,[16–19,36] the number of which has regularly increased without any resolution of previously identified gene-based targets, no single genetic defect has (a) yet been identified that is specifically associated with schizophrenia and (b) been unequivocally found in different populations of schizophrenics.[36] Furthermore, no genetic alterations have been identified that account for more than a small proportion of the risk of inheriting the disease. Schizophrenia is therefore considered genetically heterogeneous with several discrete genes contributing to disease causality—the *schizophrenia spectrum*.[49] Twin studies have, however, further emphasized the major contribution of epigenetic factors to

Chart 1



schizophrenia causality.[17,18,36] A first degree relative of a schizophrenic patient has a 10% increase in the probability of developing schizophrenia, while in the case of an identical twin, this probability is increased to 40−65%.

4. Molecular Lesions in Schizophrenia

Like the majority of CNS disorders,[50] the initial understanding of the molecular targets involved in schizophrenia was based on clinical serendipity. Compound **1** (chlorpromazine, Chart 1), initially developed for use as an analeptic, was found serendipitously to be effective in the treatment of schizophrenics in the 1950s and subsequently found to be a dopamine (DA) receptor antagonsist.[51]

As previously noted, the antipsychotic drugs currently used to treat schizophrenia can be divided into two distinct classes, *typical* or first generation antipsychotics (FGAs) and *atypical* or second generation antipsychotics (SGAs).[3,6,11] The distinction between these two drug classes is based on the time of introduction to the market, FGAs preceding SGAs, and their receptor binding profiles. FGAs block DA D2 receptors,[52,53] while SGAs have antagonist activity at both D2 and $5HT_2$ receptors.[54,55] Of greatest importance, however, is the ability, albeit limited, of SGAs to treat the negative symptoms of schizophrenia that is coupled with a lower risk of developing the tardive dyskinesias associated with FGA use.[3,11]

4.1. The Dopamine (DA) Hyperfunction Hypothesis. The seminal hypothesis regarding the pathophysiology of schizophrenia is that excessive dopaminergic transmission in the forebrain is causal to the disease. This hypothesis[3,6,51,56] was based on the observation that all clinically effective antipsychotics have potent antagonist/inverse agonist activity at DA D2 receptors and that the therapeutic efficacy of these drugs could be correlated with their affinity for striatal D2 receptors.[52,53,55] Similarly, the psychotomimetic properties of the indirect DA agonists **2** (amphetamine) and **3** (cocaine) and alterations in striatal DA release in schizophrenics have provided additional support for the involvement of DA in aspects of the pathophysiology of schizophrenia.

The DA hypothesis has accordingly dominated antipsychotic drug discovery efforts for the better part of 60 years[57] but is limited in that it recapitulates, not illogically, the discovery of known antipsychotic agents in a circular manner; e.g., since DA D2 antagonists are effective in treating schizophrenia, schizophrenia is a dysfunction of DA D2 receptor signaling. Moreover, DA hyperfunction does not represent the sole molecular cause of schizophrenia because current antipsychotics, all of which block DA D2 receptors with varying degrees of potency and efficacy, are generally ineffective in treating the negative and/or cognitive symptoms of schizophrenia. Additionally, the clinical efficacy of currently used antipsychotics has a slower time to onset than would be expected from drugs that simply bind to the DA D2 receptor. This suggests that the clinical efficacy of D2 antagonists is not an immediate consequence of acute D2 receptor blockade but may depend on additional effects (e.g., gene expression, neurogenesis) that only occur with chronic treatment.[45,58]

4.2. The Serotonin (5HT) Hypothesis. The serotonin hypothesis of schizophrenia predated the DA hypothesis and was based on similarities between schizophrenic psychosis and LSD-induced hallucinations. The finding that **4** (LSD) antagonized the actions of 5HT on smooth muscle led to the hypothesis[59,60] that schizophrenia resulted from a decrease in central 5HT

function. While many antipsychotics interact with 5HT receptors,[61] this hypothesis was modified when **4** was found to be a 5HT agonist in some tissue systems. Interest in 5HT receptor-mediated signaling dysfunction as causal in schizophrenia waned with the discovery of **1** with DA D2 receptor antagonists becoming the primary target of interest for medicinal chemistry efforts. Research on the role of the 5HT axis in schizophrenia has increased[62] because many of the newer SGAs have been found to have $5HT_{2A}$ antagonist properties[11,54] that can modulate DA neurotransmission.[63] Additionally, most of the effective antipsychotic drugs are $5HT_{2A}$ inverse agonists.[59]

Several studies[54,64,65] have attempted to differentiate the efficacy and safety of novel antipsychotics based on their receptor binding profiles in order to provide a potentially predictive in vitro phenotype for the assessment of newer compounds. These studies have ranged from relatively simple radar plot relationships[64] to more sophisticated principal component analysis.[65] Building on the DA and 5HT receptor interactions of antipsychotics in defining their intrinsic efficacy/side effect profiles,[66] in vitro binding data from the NIMH Psychoactive Drug Screening Program at cloned D1, D2, and 5HT receptors for 22 clinically effective antipsychotics were compared with their efficacy on the positive symptoms of schizophrenia.[54] The authors concluded that clinically effective doses of FGAs were only modestly correlated with D2 receptor binding affinity ($r = 0.54$) with a stronger correlation existing for $5HT_{2C}$ receptor binding ($r = 0.68$). The strongest correlation for FGAs was the $5HT_{2C}$/D2 receptor binding ratio ($r = -0.81$). For SGAs, there was no correlation between clinical efficacy with D2, $5HT_{2A}$, or $5HT_{2C}$ receptor binding, but correlations were observed with the more complex D2 ($5HT_{2A}$/$5HT_{1A}$; $r = 0.80$) and D2 ($5HT_{2C}$/$5HT_{1A}$; $r = 0.78$) binding ratios. These findings further suggested that modulation of $5HT_{2C}$ receptor signaling improved the clinical response to D2 receptor blockade by antipsychotics. For FGAs, increased affinity at D2, $5HT_{2A}$, and $5HT_{2C}$ receptors was associated with enhanced antipsychotic efficacy while increased $5HT_{1A}$ receptor affinity was associated with reduced antipsychotic efficacy.[54] These obtained results, while somewhat complex, did not, as the authors noted, take into account the limitations inherent in in vitro binding studies using cloned receptors. These limitations include (i) the lack of consideration/knowledge of information on the intrinsic efficacy, ADME properties, protein binding, and active metabolite formation of the antipsychotics studied and (ii) the relationship of native receptors in the brain limbic regions in vivo compared to cloned receptors. Given the ongoing debate on the contribution of the degree of receptor occupancy and "on" and "off" rates to the efficacy and side effect liability of antipsychotics, this study is more archival than a useful tool on which to base a drug discovery program.

Use of principal component analysis to analyze the binding profiles of a series of new antipsychotics, **5** (SLV310), **6** (SLV313), and **7** (SLV314) at 15 G-protein-coupled receptors and the serotonin transporter (SERT) in comparison to nine approved antipyschotics identified three domains for activity. The first, accounting for 35% variance, had positive contributions from D2 receptors with negative contributions from muscarinic M_1/M_4, histamine H_1, and $5HT_6$, $5HT_3$, $5HT_{2A}$, and $5HT_{2c}$ receptor interactions. The second, accounting for 15% variance, had positive contributions from $5HT_{1A}$, $5HT_{2B}$, 5HT3, $5HT_6$, and SERT interactions and negative contributions from α_1/α_2 and $5HT_7$ receptor interactions. The third domain, accounting for 13% variance, involved positive contributions from $5HT_7$, $5HT_{1A}$, and $5HT_{2B}$ receptor interactions and negative contributions from D2 and α_1 adrenergic receptors.[65] Compounds **5**−**7** and the SGA **8** (aripiprazole) clustered positively into the first and second domains with the former compounds having binding profiles most similar, of the antipsychotics studied, to that of **8**. Compounds **5** and **7** are D2 antagonists with SERT inhibitory activity, while **6** is a D2 antagonist/$5HT_{1A}$ antagonist. Antipsychotics associated with weight gain scored strongly negative for domain 1, while those associated with hyperprolactinemia clustered with negative scores for domain 2.

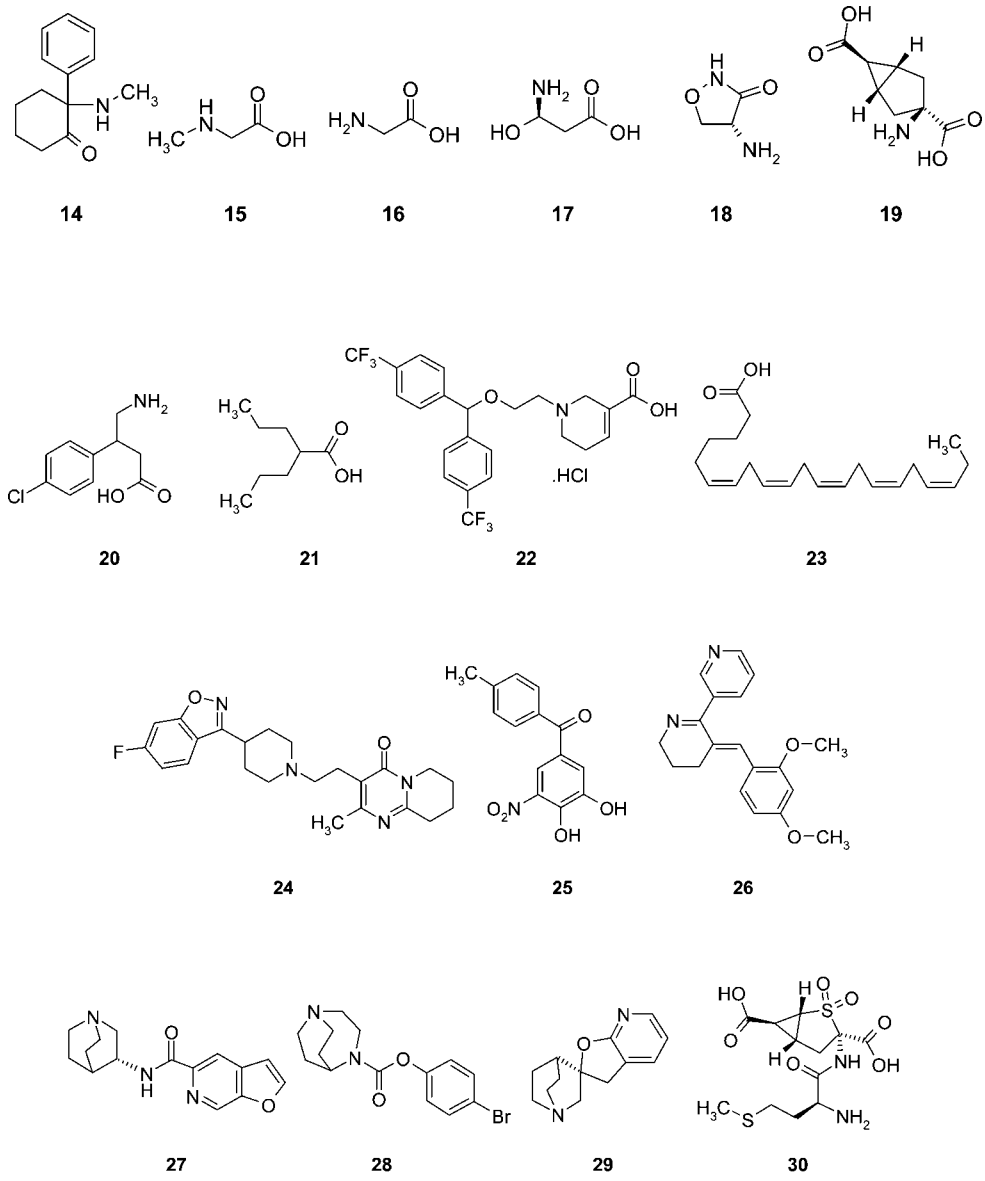
4.3. The Clozapine Hypothesis. The dibenzodiazepine **9** (clozapine) was introduced into human use as an antipsychotic in the 1960s[67] and is considered to be the prototypic SGA.[3,11] It was identified as a D2 receptor antagonist with broad spectrum efficacy in schizophrenia, being effective in the treatment of refractory schizophrenics, with additional efficacy in treating cognitive deficits, having a lower EPS liability[68,69] and a longer average length of therapy prior to discontinuation compared with other antipsychotics. These positive attributes were limited by a high incidence of potentially fatal agranulocytosis that led to **9** being withdrawn in 1975 for unrestricted use. A subsequent large multicenter trial in treatment-resistant schizophrenics showed **9** to be superior to FGAs[70] and led to its reintroduction in 1990 with continuous monitoring for blood dyscrasias in patients with nonresponsive positive symptoms. Compound **9** is the only SGA with unambiguously demonstrated superiority to other compounds in its therapeutic class.[71]

Given the superior therapeutic profile of **9**, a search, now over 30 years old, has been ongoing to identify "clozapine-like" new chemical entities (NCEs) that have the superior antipsychotic efficacy of clozapine with a reduced risk of agranulocyotosis. While many SGAs have been identified,[3,11,54,55] none of them have demonstrated the efficacy profile of **9**.

Considerable effort has also been expended in searching for "the" mechanism of action of **9** in the anticipation that the interaction of this drug with some known/unknown receptor/ion channel will provide a complete insight into its efficacy and side effect profile and perhaps for that of the SGAs as a class. Instead, the receptor binding profile of **9** has expanded with each new receptor that is discovered, only serving to emphasize the polypharmic profile of the drug making it truly deserving of the designation "magic shotgun"[55] and as such difficult to mimic in an SAR-focused medicinal chemistry effort even with the use of "chemometric" computational approaches.[65]

On the basis of the reduction in EPS liability and hyperprolactinemia, it had also been hypothesized that the primary difference between FGAs and SGAs involved the degree to which these drugs occupied DA receptors. In particular, it was suggested that the FGAs occupy the D2 receptor to a greater degree and more persistently at efficacious doses than do SGAs.[72] However, even at very low doses, FGAs induce very different neurochemical outcomes than those seen with SGAs.[73–75] In fact, most SGAs other than **9** and **10** (quetiapine), when used at low doses to treat psychotic symptoms in Parkinson's patients, can elicit EPS and, in rare cases, tardive dyskinesia and neuropleptic malignant syndrome. This suggests that even the SGAs produce too much and too persistent a D2 receptor occupancy that is revealed in DA-compromised Parkinson's patients. Interestingly, the lack of EPS associated with **9** and **10** use may result from their low affinity and rapid dissociation from the D2 DA receptor.[72,76] Since D2 receptor occupancy does not account for the uniqueness of the SGAs, other activities must add to or counteract some of the influences of D2 receptor blockade. Nearly all antipsychotics are potent and efficacious

Chart 2



$5HT_{2A}$ inverse agonists;[59] however, the SGAs are unique in having higher potency as $5HT_{2A}$ inverse agonists than as DA antagonists,[59,66] suggesting that the "atypical" nature of these drugs can be predicted by $5HT_{2A}$ inverse agonism. SGAs can occupy greater than 80% of cortical $5HT_{2A}$ receptors at therapeutic doses, while occupancy of striatal D2 receptors is much less.[77] There are also differences between striatal and extrastriatal D2 receptor occupancy observed between FGAs and SGAs. PET studies[77–79] have suggested that FGAs preferentially interact with striatal D2 receptors while SGAs have a complex pattern of interactions with extrastriatal D2 receptors. Consistent with this, SGAs appear to preferentially increase DA release in rat prefrontal cortex relative to the nucleus accumbens, while FGAs exhibit a reverse pattern of activity.[73]

If the primary difference between FGAs and SGAs involves the ability of the 5-HT_{2A} antagonism to counteract the adverse effects of D2 antagonism, then the combination of a relatively "clean" D2 antagonist and $5HT_{2A}$ antagonist should produce an SGA profile in the clinic. In fact, **11** (mirtazapine), a $5HT_{2A}$ antagonist, given at low doses significantly reduced the acute akathisia produced by high doses of FGAs,[80] suggesting that 5-HT_{2A} antagonism/inverse agonism can alleviate the adverse effects of D2 antagonism.

Most recently, the *N*-desmethyl metabolite **12** (NDMC, ACP-104) of **9**, a potent partial agonist at the muscarinic M_1 receptor that also has $5HT_{2A}$ receptor antagonist activity, has been proposed as the missing link to understanding the unique efficacy of the parent drug.[81,82] In animals, **12** blocked MK-801-induced hyperactivity and enhanced cognition in an eight-arm radial maze[83] supportive of an activity profile as an SGA. However, additional preclinical studies with **12** showed a limited antipsychotic profile except at high doses,[83] leading to the suggestion that this compound would only be useful as an adjunctive therapy with existing antipsychotic agents.

4.4. The Glutamate Hypofunction Hypothesis. Glutamate is the major excitatory neurotransmitter in the CNS. Antagonists of the *N*-methyl-D-aspartate (NMDA) glutamate receptor subtype, the psychotomimetics, **13** (phencyclidine, PCP, Chart 1), and **14** (ketamine, Chart 2), mimic the positive, negative, and cognitive symptoms of schizophrenia.[20,84–86] In both recreational abusers of **13** and controlled human studies of psychosis induced by **13** or **14**, major similarities exist between psychosis induced

by NMDA receptor blockade and schizophrenia. NMDA receptor antagonists exacerbate symptoms in schizophrenics and can trigger the re-emergence of symptoms in stable patients. First generation amino acid based NMDA receptor glycine transporter type 1 (GlyT1) inhibitors, e.g., **15** (sarcosine), and NMDA receptor coagonists, e.g., **16** (glycine), **17** (D-serine), and **18** (D-cycloserine), have produced modest beneficial effects in schizophrenics,[87–89] further implicating NMDA receptor hypofunction in the disorder.[20,86] While these findings suggest that schizophrenia involves a decreased activation of forebrain NMDA receptors, acute NMDA antagonist treatment can increase cortical glutamate levels in freely behaving rats, increasing non-NMDA-mediated glutamatergic transmission and a subsequent increase in DA efflux.[90] The importance of this observed increase is further supported by the finding that activation of group II metabotropic glutamate receptors by agonists such as **19** (LY379268) can decrease presynaptic glutamate release, attenuating both PCP-induced increases in glutamate release and the behavioral effects of this psychostimulant.[91] Together with studies demonstrating a dissociation between cortical DA levels and the behavioral effects of **13**,[92] this finding suggests that NMDA antagonist-induced increases in cortical glutamate are a key event in the psychotomimetic effects of PCP and ketamine. The glutamate/NMDA hypofunction hypothesis of schizophrenia remains consistent with both the DA and 5HT hypotheses representing a unifying link between the two neurochemical systems. The observation that cortical DA efflux increases after NMDA antagonist treatment[90] is also consistent with NMDA hypofunction being causal in inducing a hyperdopaminergic state and may, in part, explain the efficacy of FGAs and SGAs in reversing the psychotomimetic actions of NMDA antagonists in both animal models and the clinic.[20] $5HT_{2A}$ receptor activation increases the frequency of excitatory postsynaptic potentials at thalamocortical synapses in neocortical pyramidal neurons inducing an asynchronous release of glutamate that evokes a slow, late excitatory postsynaptic potential.[93] Both NMDA antagonists and $5HT_{2A}$ agonists could thus share a common path of psychotomimetic action through effects on cortical glutamate release.

4.5. The GABA Hypothesis. GABA, the major inhibitory transmitter in the CNS, has many effects that are opposite those of glutamate, some involving direct GABAergic inhibition of glutamate function. A role of GABA in the etiology of schizophrenia was first proposed in the early 1970s based on the GABAergic regulation of DA neuronal function, specifically in the context of the role of GABA in working memory.[94,95] Furthermore, GABA uptake sites were found to be decreased in the hippocampus, amygdala, and left temporal cortex in schizophrenics with evidence of $GABA_A$ receptor up-regulation[95] and decreases in GABA interneurons.[96] Clinical trials with benzodiazepines,[97] $GABA_A$ agonists, the $GABA_B$ agonist **20** (baclofen), and the anticonvulsant **21** (valproic acid, the last used as a putative GABAergic agent) used alone and in combination with antipsychotics have led to mixed outcomes.[95] However, a prototypic GABA uptake inhibitor, **22** (CI-966) produced psychotic episodes in a small phase I trial[98] producing symptoms similar to that of psychotomimetics. More recently, genetic evidence has implicated alterations in GABAergic function in the etiology of schzophrenia.[99–102]

5. Neurodevelopmental Aspects

Schizophrenia is widely viewed as a neurodevelopmental disorder,[34,35] the occurrence of which is correlated with reductions in the neuropil, the nonmyelinated neuronal processes in the gray matter[103] and white matter.[104] Evidence for a neurodevelopmental contribution has also come from human imaging studies that have documented schizophrenia-associated decreases in cortical volume.[105] By use of diffusion tensor imaging, a disorganization of the white matter was found in the brains of schizophrenics that was associated with myelin abnormalities.[106] This finding led to the concept of a "myelin model" systems biology/connectivity-based approach to the etiology of the disease[107] that is in marked contrast with the more traditional, neurotransmitter-based approaches to schizophrenia therapy and causality.[2,3] Schizophrenia-associated genetic signatures have also been found in multiple myelination-related genes that are associated with oligodendrocytes.[108–110] These are indicative of a potential dysfunction in frontal lobe myelination that can lead to alterations in white-matter tracts,[111] focusing attention on myelination as a possible target for drug discovery.[112,113] The use of **23** (ethyl eicosapentanoic acid, EPA, LAX-101) to alleviate the synaptic membrane phospholipid dysfunction thought to be associated with schzophrenia[114] as add-on therapy in clinical trials has resulted in both positive[115] and negative[116] effects. These have been critiqued on the basis of trial design and dose selection.[117] Treatment of schizophrenics with the SGA **24** (risperidone) has been associated with increases in myelination as assessed by MRI.[118]

6. Genetic Associations with Schizophrenia

Genome scans, linkage disequilibrium and association studies in brain tissues from schizophrenic populations, have resulted in the identification of a number of vulnerability genes associated with schizophrenia.[5,16–20,36,49,69,97–101,107,108,119–121] These associations encompass many neurotransmitter systems in the brain including the enzymes involved in their synthesis and degradation, their receptors and uptake transporters, and a number of novel targets.

There has, however, been considerable debate as to the viability/relevance of many of these genes,[36] the design methodologies used to identify them,[46] and their replication,[122] with frequent "failures to replicate" the initial finding occurring in subsequent studies.[19,36] Additionally, considerable caution is required in ensuring that "schizophrenia-associated" gene associations are not the result of clinical misdiagnosis (one key patient cohort reportedly included brain tissue from a 3-year-old "schizophrenic"), the effects of the drugs used to treat the condition on gene function, or the potential identification of putative targets involved in the side effects of the drug class. Additionally, some of the putative genetic associations with schizophrenia, such as the allelic variations in the enzyme catechol-*O*-methyl transferase (COMT),[123] have been implicated in a broad range of other disease states. These include gender-related pain sensitivity,[124] obsessive-compulsive disorder,[125] myofacial pain syndrome,[126] breast cancer,[127] blood pressure dysfunction,[128] anorexia nervosa,[129] anxiety,[130] panic disorder,[131] depression,[132] and Alzheimer's disease associated psychosis.[133]

Given the expectation that the human genome map would be a facile source for a multitude of new targets for drug discovery[134] representing the lifespring for the future of the pharmaceutical industry, the following sections highlight the progress (or lack thereof) in the identification of new gene-based targets for antipsychotic drug discovery, schizophrenia being perhaps the most actively explored in terms of gene associations in neuropsychiatry research.

6.1. Catechol-*O*-methyl Transferase (COMT).[123] A microdeletion in the COMT gene localized to Chr22q11 produces

velocardiofacial syndrome (22qDS, DiGeorge or Shprintzen syndrome), a genetic subtype of schizophrenia.[135,136] COMT exists in two forms, Met[158] and Val[158], with the former coding for a form of COMT that is thermally unstable and thus has lower activity than the Val[158] form. COMT is an enzyme important in regulating DA but not NE levels in the prefrontal cortex.[137] Val[158] Met heterozygotic mice have higher COMT activity and, correspondingly, lower prefrontal cortex DA levels and show greater tyrosine hydroxylase expression in the midbrain, indicating increased DA synthetic capability.[137] Neuroimaging studies have shown greater midbrain F-DOPA uptake in human Val[158] than Met[158] carriers, consistent with increased DA biosynthesis. Similarly, individuals with 22q11 deletion syndrome have higher urine DA levels and lower plasma levels of the DA metabolite homovanillic acid (HVA) compared to controls supporting a disruption of dopaminergic neurotransmission in this syndrome.[138] DA levels in prefrontal cortex are key to cognitive function and high activity Val[158]COMT is associated with poorer performance and "inefficient" prefrontal cortex function.[137] Despite the large number of studies extending the effects of the Val[158]Met polymorphism to altered P50 sensory gating,[139] the relationship of COMT dysfunction to schizophrenia is controversial. Val[158] is thus considered a "weak risk factor" that may reflect COMT variation providing "a weak general predisposition to neuropsychiatric disease".[140] Similarly, the relationship of allelic forms of COMT to the incidence of schizophrenia in velocardiofacial syndrome has been questioned.[136] Despite this, in normal subjects and in Val[158] carriers, CNS-penetrant COMT inhibitors such as **25** (tolcapone) can improve aspects of working memory and executive function in schizophrenics.[141]

6.2. Neuregulin (NRG1). The *NRG1* (neuregulin 1 growth factor) gene on chr8p13 has been associated with schizophrenia susceptibility.[142] It contains a core EGF domain, and its product can activate the ErbB4 receptor tyrosine kinase (RTK) and the non-RTKs Fyn and PyK2 in hippocampus. These phosphorylate the NR2B subunit of the NMDA receptor, linking NRG1 to the glutamate hypothesis of schizophrenia.[143] *NRG1* is functionally involved in interneuron migration, myelination, receptor recruitment, synaptic plasticity, and signaling between axons and Schwann cells. *NRG1*+/− gene knockout mice show phenotypic symptoms of schizophrenia that can be reversed by **9**[142] as can the NRG1/ErbB4-mediated phosphorylation of NR2B.[143] In a Finnish cohort of schizophrenics, the NRG1 genotype was shown to be overrepresented in nonresponders to FGAs treated with **9**.[144] NRG1 is also involved in interactions between NMDA receptors and PSD-95.[142,145] Blockade of NRG1/ErbB4 signaling in oligodendrocytes results in a defect in myelination that may contribute to the white matter defects associated with schizophrenia.[100] This relationship has been further strengthened by genetic associations between oligodendrocyte lineage transcription factor 2 (*OLIG2*), ErbB4, CNP (2′,3′-cyclic nucleotide 3′-phosphodiesterase), and schizophrenia.[110,135] *OLIG2* encodes a transcription factor that is key to oligodendrocyte development,[146] while CNP, a marker of myelinating oligodendrocytes, is reduced in schizophrenia[147] and has been genetically linked with the disorder.[145] Interaction studies between *OLIG2, CNP, NRG1*, and *ErbB4* showed that brain *OLIG2* expression was highly correlated with that of *CNP* and *ErbB4* but not *NRG1*, supporting a role for this gene in schizophrenia susceptibility via a genetic network linking myelination to glutamate receptor function,[110,142] further reinforcing the neurodevelopmental aspects of the disorder. These findings were further supported by in situ hybridization measurements of a number of gene transcripts involved in myelination, including CNP and ErbB4.[148] Despite the considerable body of evidence implicating NRG1, *OLIG2, ErbB4*, and *CNP* in the pathophysiology of schizophrenia, evidence that has led to new perspectives[113] on the genetic origins of schizophrenia and its neurodevelopmental nature,[120] the role of NRG1 in schizophrenia has been described as "substantial but not incontrovertible".[144] Other studies have also failed to replicate the initial findings regarding the various genes involved in the NRG-1 axis.[149–151]

6.3. Glutamate Receptors. In addition to the NRG1 linkage to NMDA receptor hypofunction, polymorphisms in *GRM3* (metabotropic glutamate receptor-3) on chr7q21.1-q21.2,[152] GRIN1 (NMDA subunit gene) on chr9q34 that encodes for the NMDA receptor subunit NR-1,[153] and GRIN2[154] have been associated with schizophrenia. The C2664T GRIN2 genotype shows an association with **9** treatment.[154] A reduction in GRIN1 expression in mice produces a schizophrenia-like phenotype.[155]

6.4. Dysbindin-1 (DTNBP1, Dystrobrevin Binding Protein 1). Dysbindin-1 at chr6p22.2 is another schizophrenia susceptibility gene identified in several patient cohorts.[156–159] Dysbindin-1 is a part of the dystrophin/dystrobrevin glycoprotein complex, located in synaptic densities, where it may play a role in the reductions in neuropil and neuronal size in the hippocampal formation that are associated with schizophrenia. Dysbindin-1 occurs in high levels in the cells providing the intrinsic glutamatergic input to the hippocampal formation. Cultured neurons with reduced *DTNBP1* expression have reduced glutamate release. Reduced levels of *DTNBP1* mRNA and protein expression have been recorded in brain samples from schizophrenics.[157]

6.5. Regulator of G Protein Signaling 4 (RGS4). RGS4 on chr1q23.3 is another schizophrenia susceptibility locus.[160,161] Patients with alleles containing the rs951436 SNP of *RGS4* show differences in the volume of the dorsolateral prefrontal cortex[162] and also differences in brain activation in a working memory task.[163] The gene product of *RGS4*, one of the family of 23 RGS proteins that control the duration and timing of GPCR-associated intracellular signaling events, down-regulates signaling at DA and 5HT receptors. Its expression can be modulated by stress. A review of replicate studies[161] led to the conclusion that the RGS association with schizophrenia was "enticing but not conclusive". However, subsequent studies[164,165] have provided additional evidence for a role of *RGS4* polymorphisms as a factor in schizophrenia causality and in antipsychotic responsiveness.[165]

6.6. D-Amino Acid Oxidase Activator (DAOA)/G72. DAOA/G72 present on chr13q32-22 is a brain-expressed protein genetically associated with schizophrenia.[166] It binds to the enzyme D-amino acid oxidase (DAAO). DAAO, which occurs in neuronal and glial forms,[167] oxidizes D-serine, a potent activator of the NMDA receptor, leading to an indirect modulation of glutamate receptor function. DAOA/G72 can activate DAAO in vitro.[166] While this effect has not been demonstrated in vivo, DAAO$^{-/-}$ mice have high levels of D-serine and show reduced stereotype and rotational activity in response to NMDA receptor antagonists compared to wild-type mice.[168] Increased transcript levels of DAOA/G72 but not the complementary gene *G30* were identified in the dorsolateral prefrontal cortex of schizophrenics.[169] In addition to the association of DAOA/G72 with schizophrenia,[169–172] there is also evidence of an association with bipolar disorder,[172,173] part of the schizophrenia spectrum,[49] and with analgesia.[174] The several instances of a failure to replicate the schizophrenia association of DAOA/G72[175–177] may

be colored by the associated prevalence of mood disorders with schizophrenia and differences in allelic variants.[178] While the DAOA/G72 gene association with schizophrenia has been described as "among the most compelling in psychiatry",[178] a lack of evidence for a brain-expressed gene for DAOA/G72, the absence of a functional native protein for the gene, and the overlap of the association with bipolar disorder and analgesia[172,173,178,179] have led to this "compelling" gene being described as having a "weak" role in the etiology of schizophrenia.[180]

6.7. Disrupted-in-Schizophrenia 1 (DISC1). DISC1 on chr1q is a component of the microtubule-associated dynein motor complex associated with schizophrenia in Scottish,[181,182] Finnish,[183,184] and Taiwanese[185] patient cohorts. A weaker, gender-linked effect has also been described in a Chinese patient cohort.[186] *DISC1* is involved in maintaining the centrosome complex and microtubular function.[187] Depletion of endogenous DISC1 or mutated DISC1 results in neurite dysfunction in vitro and impairment of cerebral cortex function in vivo, reflected in effects on working memory in mice,[188,189] altered cortical development,[189] and asymmetrical increases in lateral ventricle size in dominant-negative DISC-1 mice.[190] DISC-1 interacts with the UCR2 domain of the phosphodiesterase, PDE4B, suggesting a possible role in cAMP signaling processes involving CREB elements.[191] The association of DISC-1 with schizophrenia has, however, been disputed[192] on the basis of a lack of evidence of linkage to the disease from a cohort of over 1000 sibling pairs.[36]

6.8. GABA. A number of genes involved in GABA neurotransmission have been linked to schizophrenia.[99–102] Genes for the β2 subunit of the $GABA_A$ receptor (GABRB2) on chr5q34 and the $GABA_B$ receptor 1 (GABBR1) on 6p21.3 have been identified as susceptibility loci in schizophrenia.[193,194] Decreases in the mRNA for the 67 kDa isoform of glutamic decarboxylase (GAD, GAD67) were observed in brains from schizophrenics and individuals with related disorders including autism and bipolar disorder.[99] Additional studies in schizophrenics with dysfunction of the dorsolateral prefrontal cortex showed expression deficits in transcripts for GAD, the GABA transporter, and the α1, α4, β3, γ2 and δ subunits of the $GABA_A$ receptor.[98] Network association analysis for hippocampal GAD67 in brains from schizophrenics identified 25 GAD-associated genes. These included those involved in the regulation of kainate receptors, TGF-β, and *wnt* signaling and were consistent with a decreased expression of GAD67 that was epigenetic in origin.[100] Interactions between polymorphisms in the genes for GABRB2, GAD1 (the gene expressing GAD67), and GAD2 have also been associated with schizophrenia.[101]

6.9. α7 Neuronal Nicotinic Receptor (CHRNA7). The association of *CHRNA7* with schizophrenia is of interest in the context of the widely reported phenomenon that schizophrenics self medicate to treat their symptoms by using cigarettes as a nicotine source.[195–197] Schizophrenics show a high degree of comorbid abuse of a variety of substances in addition to nicotine, including alcohol, cannabis, cocaine, and amphetamine, their rate of substance abuse being higher than that seen in the general population. This behavior can exacerbate positive symptoms, increase hospitalization, and increase the frequency of homelessness. This propensity for abuse, regardless of the consequences, suggests that the reward systems of schizophrenics may be dysregulated. Alternatively, high levels of D2 receptor occupancy by SGAs may blunt DA-mediated reward and lead to an enhanced abuse drive. In support of this, a correlation exists between D2 receptor occupancy by antipsychotic drugs and the number of cigarettes smoked by schizophrenics.[198]

Alternative phenotypes of *CHRNA7* on chr15q14 are associated with deficits in the P50 auditory response, a key phenotype in schizophrenia.[199] This finding has been replicated in additional studies[200–202] but not in others.[203] Additional nicotinic receptor genes including CHRNA1, CHRNA2, and CHRNB2 have also been associated with smoking in schizophrenics.[201] On the basis of the strength of the epidemiological and genetic studies, a number of α7 receptor agonists, e.g., **26** (GTS-21/DXMBA), **27** (PHA-5436130), **28** (SSR180711), and **29** (AZD0328), have shown benefit in animal models of sensory gating (prepulse inhibition, PPI) deficit.

6.10. Dopamine Receptors. Despite the unequivocal evidence resulting from the efficacy of known antipsychotics[51–55] that reducing DA neurotransmission is beneficial in treating schizophrenia, there are few robust studies that have implicated DA-related genes in the etiology of the disorder.[204] Polymorphisms of the DA D2 receptor gene DRD2 show limited evidence for an association with schizophrenia.[205] For the DA D3 receptor, a Ser^9Gly polymorphism on *rs6280* showed a modest, "marginal" association with schizophrenia,[206] with other studies being equivocal.[204] Association of the DA D4 receptor with schizophrenia has also been equivocal.[207] The association of the COMT polymorphism $Met^{158}Val$ to schizophrenia[123] and multiple other diseases has already been discussed. Initial studies showing a positive association of the DA transporter (DAT, *SLC6A3*) with schizophrenia[208] were not supported by meta-analysis.[209] Inconsistent associations have also been reported for the DA-interacting proteins NURR (*NR4A21*, orphan nuclear receptor subunit 4), CALCYON (*DRD11P*, D1 receptor interacting protein), DARPP-32 (PPP1R1B, protein phosphatase 1, regulatory (inhibitory) subunit 1B), syntaxin1A (*STX1A*), protein interacting with PRKCA1 (*PICK1*), synaptosomal-associated protein, 25kDa (SNAP 25), and β-adrenoceptor kinase 3(GRK3).[204] In aggregate, most of the studies implicating DA receptors and their associated proteins (COMT, DAT, NURR, etc.) with schizophrenia have been inconclusive.

6.11. Miscellaneous Associations. Additional genetic and nongenetic associations with schizophrenia include V-AKT murine thyoma viral oncogene homolog 1(AKT), proline dehydrogenase (*PRODH*), the 5HT transporter, SERT (*SLC6A4*), the $5HT_{2A}$ receptor (*HTR2A*),[18] calcineurin,[210] and reelin.[211] Negative symptoms have been associated with methylenetetrahydrofolate reductase (MTHFR).[212] Other associations include Dickkopf receptor 4(DKK4), a negative regulator of the *Wnt* signaling pathway,[213] the tumor suppressor gene TGFBR2 located at chromosome 3p22,[214] netrins,[215] TRPs (transient receptor potential channels),[216] IL-1β, TGF-B2, HDAC1, DAXX (death associated protein), and cyclin D2 (CCND2).[100] Equivocal data exist for the involvement of the putative σ1 receptor in schizophrenia.[217–219] Negative associations have been reported for carboxy-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON)[220] and the α_{2A} adrenoceptor.[221]

In an approach termed "convergent functional genomics",[222] data from mice separately treated with **9** and **13** were used together with human genetic linkage and post-mortem brain data from schizophrenics to associate genes involved with GABA (*GABAR1*, *GABBR1*, *GAD2*), glutamate (*GRIA2*), and neuropeptide (*TAC1*) signaling, synaptic (*SYN2, KCNJ4*) and myelin/glial (*CNP*, *MAL*, *PLP1*, *MBP*, *MOBP*, *GFAP*) function, and lipid metabolism (*LPL*) to the disorder. Additional associations identified with this "Bayesian" approach included genes involved in neurite outgrowth and circadian rhythm, adding

further to the complexity of the schizophrenia genome (the "schizome"?).

The increasingly large and still evoling number of studies focused on elucidating the genetic basis of schizophrenia, and the multiple genetic foci thus far identified appear to be inversely proportional to the useful knowledge gained in understanding disease causality and treatment and in using viable new targets to drive drug discovery efforts. The genetic and clinical data to date clearly support schizophrenia as having a neurodevelopmental component[34,120] with multiple risk genes of small effect adding to a complex genetic framework that is made additionally complex because of allelic heterogenicity and major epistatic influences.[17,36]

Despite initial promising findings, the lack of reproducibility (the failure to replicate) of many of the schizophrenia gene associations reported has led to ambiguous outcomes. Associations described as having a "compelling rationale" are also described as "weak".[130] The ultimate validation of the several novel gene-associated targets will thus need to be driven by traditional drug discovery efforts using defined molecular targets to develop small molecules that can be used to drive the "proof of concept" in the clinic in the appropriate patient population.

The identification of each new gene putatively associated with schizophrenia, based on the progress to date, appears to lead to at least an additional 5 years of research in order to replicate and extend the original finding. This makes it likely that at least another decade will be required to develop a better understanding of how the various gene associations reported and their expressed proteins (if known) contribute to disease causality, thus providing an appropriate context for a focused drug discovery effort. At what point a gene association for a neuropsychiatric disorder such as schizophrenia can be considered as validated and useful as a novel target is unclear because "there is no obvious criterion for distinguishing signal from noise".[36] The failure of many meta-analyses to identify consistent sites of linkage together with the lack of replication of candidate genes like COMT, RGS4, DISC1, DAOA, neuregulin, COMT, etc. has led to the consideration[36] that "multiple genes of small effect" together with "*the speciation event*" account for the predisposition to schizophrenia. The latter refers to the chromosomal rearrangement occurring in the brain during evolution that separated humans from nonhuman primates. This has been used as the basis for the hypothesis that psychosis is uniquely species-associated and is primarily manifested through epigenetic variation involving DNA methylation or histone phosphorylation, acetylation, and methylation. The last is then superimposable on the DNA transcription process, adding considerable additional complexity to simple alterations in DNA base content.[36] This is in marked contrast to the "common-disease−rare allele" hypothesis[223] and remains the subject of active debate.[36]

Several of the gene associations identified (NRG1, GRM-3, GRIA2, GRIN1, dysbindin-1, DAOA/G72, and GAD67) provide additional support for the glutamate hypothesis of schizophrenia. In addition to the effects of glutamate receptor modulators, the first mGlu2/3 receptor agonist **30** (LY2140023),[224] an orally active prodrug of **31** (LY404039, Chart 3), showed improvements in both positive and negative symptoms at week 4 in a randomized, double-blind, placebo controlled clinical trial. Compound **30** had efficacy equivalent to that of the SGA **32** (olanzapine) but did not differ from placebo in terms of prolactin production, extrapyramidal symptoms, or weight, providing clinical proof of concept that mGlu2/3 receptor agonists may represent a viable alternative approach for the treatment of schizophrenia. While a major advance in the area, issues with proconvulsant activity[225] may still confound the path forward with this compound class in the treatment of schizophrenia.

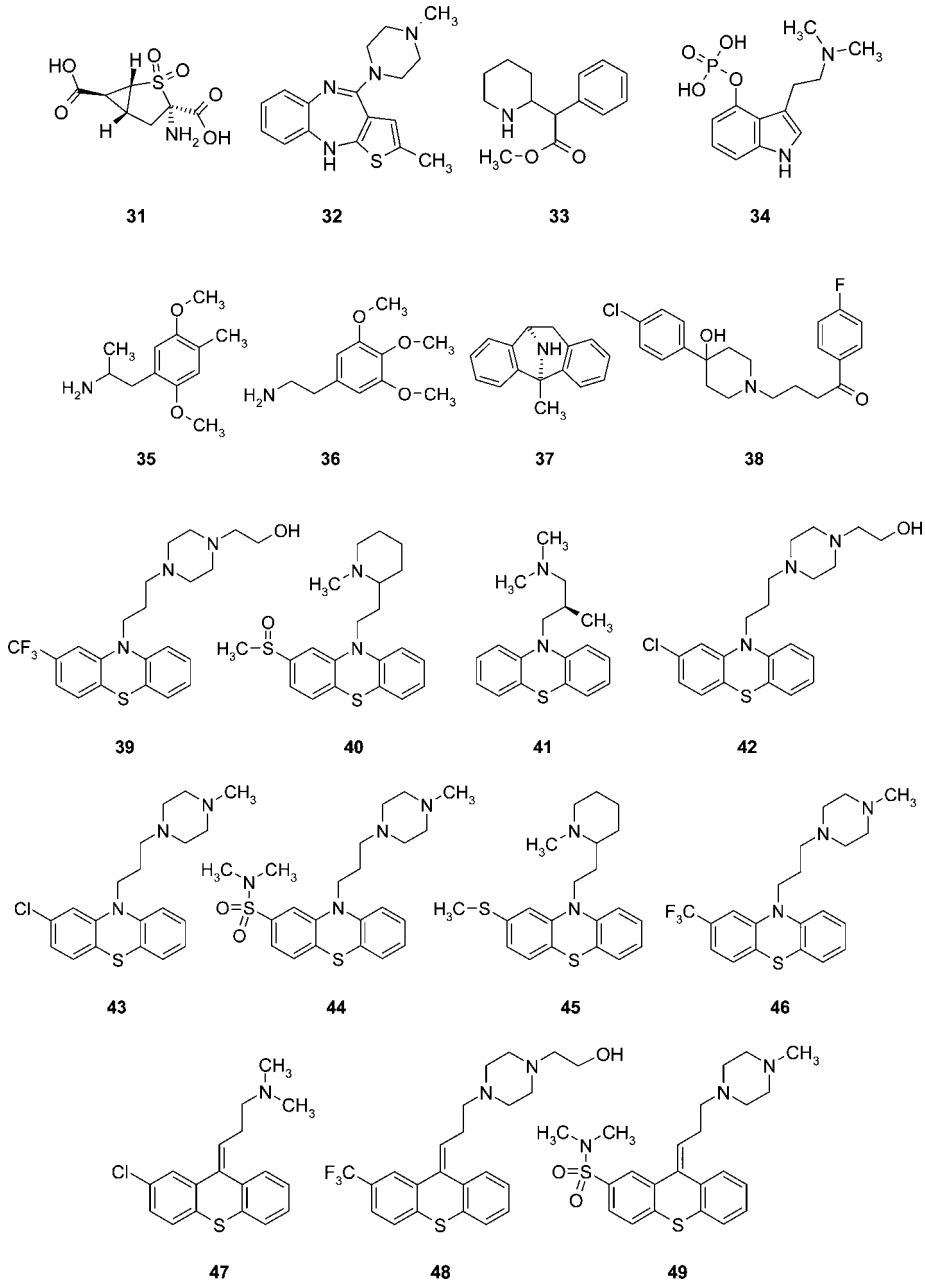
In realistically assessing of the role of the gene-based approach to disease causality and novel drug discovery in schizophrenia, this is weakened by (i) the genetic association of COMT with multiple diseases/disorders in addition to schizophrenia and (ii) the minimal genetic evidence to support the concept that the targets of the currently used antipsychotics, the DA receptor blocking FGAs and SGAs, are involved in the etiology of the disease. Indeed, the use of a gene-based approach to target identification and drug discovery would not have resulted in the discovery of any of the currently used antipsychotics. It is also of interest that the only new drug approved for the treatment of schizophrenia in the past 5 years, **8**, was developed on a purely empirical basis deliberately eschewing a dependence on molecular target or disease-associated genetic approaches. Rather, the intuition of a medicinal chemist and pharmacologist, the latter using animal models, working in proximity led to the identification of this partial DA agonist, the mechanism(s) of which was established after the compound entered the clinic.[226] An additional, and somewhat disturbing, point is the finding that the "magic bullet" of schizophrenia, **9**, is effective in reversing both the phenotypic symptoms of schizophrenia[142] and alterations in ErbB4-mediated phosphorylation of the NMDA receptor subunit NR2B[143] that were observed in NRG−/− mice. This either argues that **9** has additional and as yet unidentified molecular interactions with components of the ErbB4/Fyn/Pyk2 signaling axis[143] or that the signaling dysfunction in this transgenic model can be rectified by modulation of the existing receptor galaxy with which **9** interacts.[55]

7. Animal Models of Schizophrenia

Key in the validation of putative new targets and the identification and iterative development of new drugs for the treatment of schizophrenia are the animal models of efficacy used to advance new chemical entities (NCEs) through the discovery process to the clinic. Given that schizophrenia is a neurodevelopmental disease[35] involving aspects of higher cognitive function that are unique to humans,[36] the modeling of the disorder in less cognitively developed species represents a significant challenge.[227] Currently used animal models have historically been back-validated using clinical benchmarks to provide a basis for arguing for future predictive validity. While this reasoning seems to hold for recent SGAs in that they produce the predicted preclinical effects, the fact that many of these newer compounds are largely subtle variations on the clozapine theme discussed above raises questions regarding the validity of the back-validation approach. The MATRICS initiative[33] emphasizes the critical translational importance of correlating animal models with predictive value for planning human trials to evaluate novel antipsychotic NCEs.

7.1. Behavioral Assays. 7.1.1. Conditioned Avoidance. The ability of an NCE to inhibit the conditioned avoidance response (CAR) to an aversive stimulus is a classical predictor of antipsychotic efficacy. Rats are trained to respond to an audible cue (the conditioned stimulus) in order to avoid a foot shock (the unconditioned stimulus). Both FGAs and SGAs are effective in decreasing the CAR to the conditioned stimulus without altering the escape response elicited by the unconditioned stimulus. Inhibition of CAR is a facile in vivo method of measuring DA receptor blockade, as demonstrated by the findings that the inhibition of the CAR is mediated by a

Chart 3



decreased dopaminergic function in the striatum and nucleus accumbens.[227] Inhibition of the unconditioned response is suggestive of sedation or catalepsy, providing a convenient method to determine a therapeutic index for the adverse effects of an NCE.

7.1.2. Locomotor Activity. The majority of antipsychotic drugs decrease either drug-induced or spontaneous locomotor activity. As in the case of the CAR, decreased locomotor activity can be interpreted as an in vivo readout of DA antagonism. However, the ability of novel, nondopaminergic agents to reduce the hyperlocomotion elicited by **2** or **13**[228] suggests that this particular model involves more complex circuitry and may hold greater clinical relevance.

7.1.3. Latent Inhibition. The ability of a pre-exposed nonreinforced stimulus to inhibit later stimulus-response learning[229] can be disrupted by amphetamine in rodents and humans. This behavior has been suggested as a valid model of the positive symptoms of schizophrenia. However, there is still disagreement on several aspects including the prevalence of disrupted latent inhibition in schizophrenic patients, the ability of SGAs to rescue amphetamine-disrupted latent inhibition, and differences in the protocols used in human and animal studies. While latent inhibition holds considerable interest, results from these studies need to be interpreted with caution until there is better agreement as to the validity and interpretation of results.

7.1.4. Prepulse Inhibition. Many of the symptoms of schizophrenia are hypothesized to be the result of disrupted sensory and cognitive gating. Prepulse inhibition (PPI) describes the ability of a low-intensity stimulus, or prepulse, to diminish the startle response elicited by a higher intensity stimulus. The findings that schizophrenic patients exhibit deficits in sensory and cognitive gating have led to an increased focus on PPI as a preclinical model. One of the interesting aspects of PPI is the possible path forward for performing translational medicine. This is particularly evident in studies of event-related potentials (ERPs) in the electroencephalogram in which the latency and

amplitude of P300 is assessed in response to an unpredictable change in a stimulus series—the "oddball" paradigm. Schizophrenics exhibit a reduction in P_{300} amplitude in response to novelty.[230] The P_{50} ERP in response to pairs of brief auditory stimuli provides a direct clinical analog of the preclinical PPI model because schizophrenic patients do not show a decreased P_{50} response to the second stimulus of a pair.[230] ERP abnormalities have been interpreted as suggestive of a deficit in the gating or processing of sensory information. Consistent with this, schizophrenics show impaired PPI relative to normal control subjects.[231,232] In animals, PPI can be disrupted by various psychotomimetics and restored by antipsychotic drugs[233] and as such is the current gold-standard assay based on the high degree of face and apparent predictive validity.

7.2. Pharmacological Models. Compounds that are psychotomimetic in humans can induce phenotypes in laboratory animals that are presumed to model some of the underlying pathophysiology of schizophrenia. These compounds encompass three of the mechanistic categories already discussed: DA releasing agents, $5HT_2$ agonists, and NMDA receptor antagonists. Compounds **2**, **3**, and **33** (methylphenidate), all of which increase DA release, are psychotomimetic, a property not shared by directly acting DA agonists, suggesting that enhanced dopaminergic transmission produces circuit-level changes in neuronal function. The hallucinogenic effects of **4**, **34** (psilocybin), and the phenethylamines **35** (dimethoxymethylamphetamine) and **36** (mescaline) and the relatively high affinity of these agents for the $5HT_{2A}$ receptor have supported the use of $5HT_{2A}$ agonists as preclinical psychotomimetics. The noncompetitive NMDA receptor antagonists **13**, **14**, and **37** (dizocilpine, MK-801) induce a psychotic state in humans that is very similar to that observed in schizophrenics. The disruption in PPI produced by these three compound classes is responsive to SGAs.[234] As discussed above, DA, 5HT, and NMDA receptor systems are dysregulated in schizophrenia, providing a level of construct validity to these models. However, the pharmacological nature of these models raises an important caveat. Given the incomplete understanding of the pathophysiology of schizophrenia, a purely pharmacological disruption of the model cannot be ruled out even with a truly novel NCE. Care is therefore required in interpreting data from this type of model.

7.3. Lesion Models. Increases in ventricle size, decreases in cortical and hippocampal volume, and a selective decrease in subpopulations of GABAergic interneurons in brains from schizophrenics all indicate that neuronal loss is a key part of the pathophysiology of the disease. In the absence of robust indications of gross neurodevelopmental abnormalities, attention has focused on pathological changes that may occur during the pre- or perinatal period. Several rodent models have been developed including the modeling of perinatal hypoxia and anoxia to mimic obstetric complications[235] and the modeling of aspiration, electrolytic, or excitotoxic lesioning of the prefrontal cortex or hippocampus.[236]

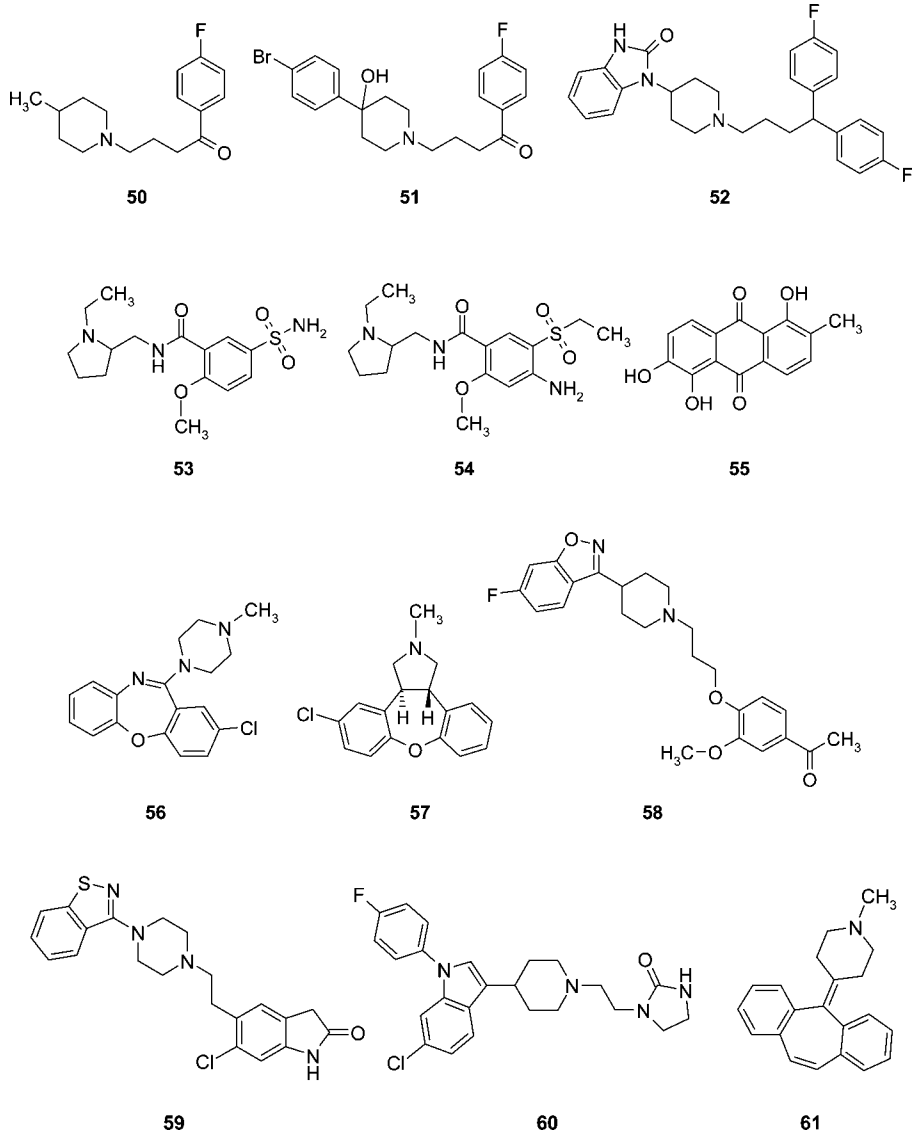
Symptom onset is delayed in a number of neonatal lesion models, a finding that has been suggested to mirror the clinical presentation of symptoms in schizophrenic humans. For example, the increased sensitivity to amphetamine, a reduced sensitivity to **38** (haloperidol), disrupted latent inhibition, and deficits in PPI observed after postnatal excitotoxic lesion of the ventral hippocampus do not become apparent until postnatal day 53.[237,238] While these models have several attractive features, the extent and nature of the lesions are distinct from those observed in brains from schizophrenics.

7.4. Genetic Models. Several transgenic mouse models have been developed that involve the selective knockout or knockdown of neurotransmitter receptors thought to be relevant to schizophrenia, e.g., D1-D5 and NMDA.[239,240] Knockdown of the obligatory NR1 subunit of the NMDA receptor to approximately 5% of normal expression levels resulted in mice that exhibited increased spontaneous hyperlocomotion and social deficits that respond to an antipsychotic drug.[155] Other genetically modified mouse models for schizophrenia include knockout of D-amino acid oxidase,[168,241] neuregulin 1,[242] and DISC-1.[190,243] The number of largely inconclusive human genetic studies[36] indicates schizophrenia as being a nonhomogeneous multifactorial disorder. Thus, the generation of a "schizophrenic mouse" model appears unlikely because any selective alteration of implicated genes will likely result in an incomplete model of the disorder requiring caution in their use.[244] An interesting genetic knockout is the Df1/+ mouse generated by engineering a chromosomal deletion spanning the same region as the human 22q11 deletion responsible for velocardiofacial syndrome[245] resulting in a mouse that exhibits a number of pathologies consistent with the human deletion including deficits in PPI and learning and memory.

7.5. Spontaneous Models. Animal models of schizophrenia that do not rely on genetic or pharmacological manipulation involve rodents that appear to have a naturally occurring behavioral deficit relevant to the disorder. These include the PPI deficits evident in the spontaneously hypertensive rat,[246] the Brattleboro rat,[247,248] and the DBA/2 mouse.[249] Of these, the DBA/2 mouse has been the most extensively characterized and has become a valuable tool for drug discovery research. However, care must be exercised with this type of model because subtle differences in variables such as the source and choice of vehicle can dramatically affect the experimental outcome.[250]

7.6. Models of Cognitive and Negative Symptom Domains. Most of the models discussed above focus on the positive symptoms of schizophrenia. This has been useful in developing clozapine-like molecules but does not address the debilitating negative or cognitive symptoms of the disease. Enhanced cognitive function can be assessed through a variety of classical behavioral pharmacology tests including the Morris water maze, passive avoidance, and operant tasks, e.g., delayed alternation.[251–253] While these assays measure cognitive enhancement in normal, aged, or pharmacologically impaired animals, it is not yet known if these models are predictive for efficacy against the cognitive symptoms of schizophrenia. Available antipsychotics produce only modest improvement in the negative symptoms of schizophrenia.[254] With the realization that the negative symptoms of schizophrenia constitute a distinct therapeutic domain and with the understanding that the negative symptoms are a significant contributor to poor quality of life,[31] there has been increased interest in the development of preclinical models of this symptom domain. These models are primarily focused on anhedonia and social withdrawal. Anhedonia can be measured in both rats and nonhuman primates by a variety of methods including sucrose preference and intracranial self stimulation. While there is conflicting data on the ability of amphetamine to induce anhedonia,[255,256] **13** can decrease voluntary sucrose consumption in rats,[257] an effect reversed by subcronic treatment with **9** but not by acute **9** or **38**.[258] Social withdrawal can be assessed in both rodents and nonhuman primates and can be induced by both **2** and **13**.[259–262] While these models are of considerable interest, it is not possible to estimate their predictive validity without the availability of clinically efficacious com-

Chart 4



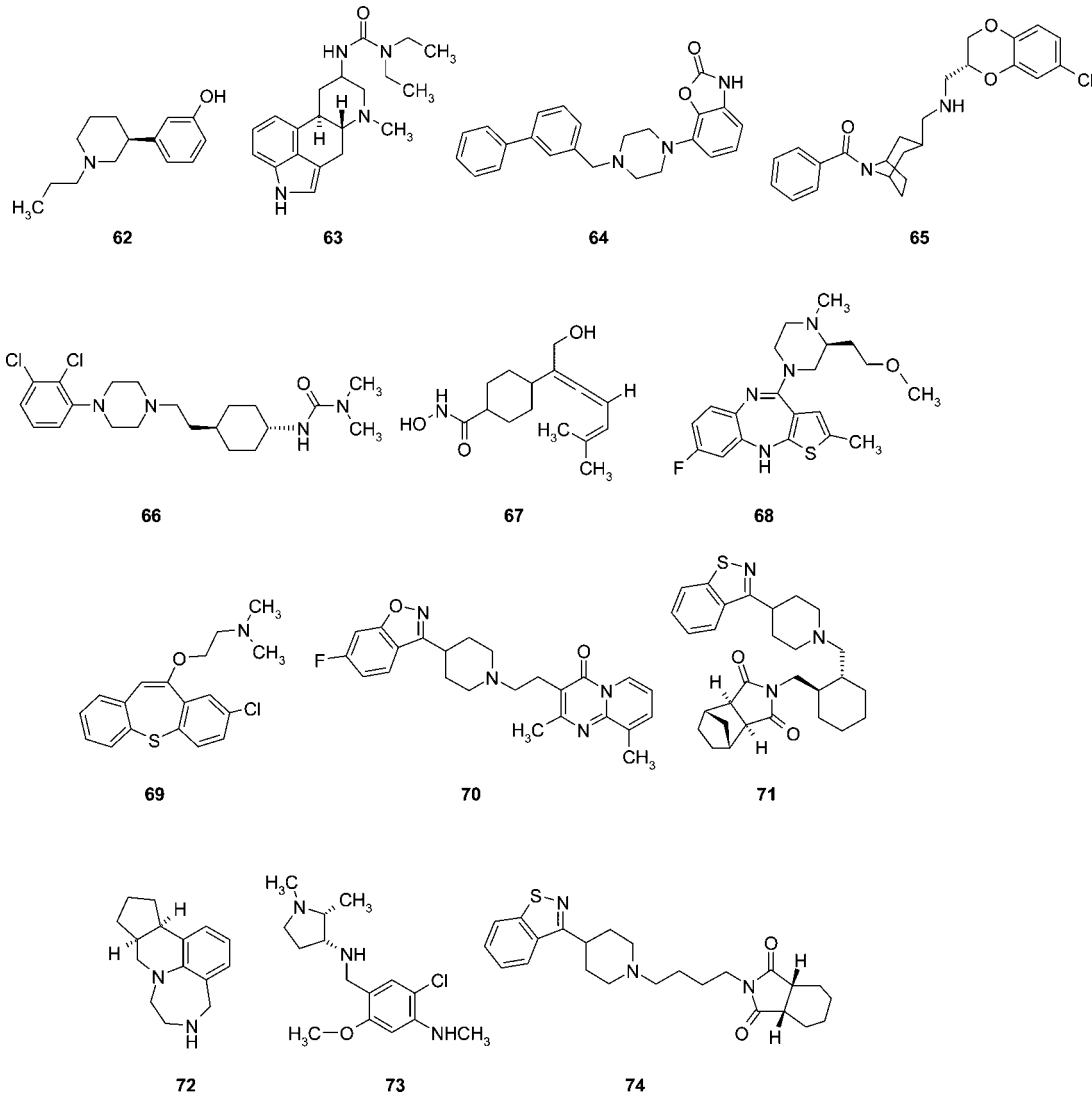
parators, the "derived knowledge" that results from the development of effective therapeutics.[244]

8. Current Treatment Options

8.1. First Generation "Typical" Antipsychotic Drugs (FGAs). The discovery of the DA receptor antagonist properties of **1**[51] led to the discovery of numerous drugs with a similar mechanism of action, e.g., D2 receptor antagonism. These included the phenothiazines (e.g., **39** (fluphenazine), **40** (mesoridazine), **41** (methotrimeprazine), **42** (perphenazine), **43** (prochlorperazine), **44** (thioproperazine), **45** (thioridazine), and **46** (trifluoperazine)), the thioxanthenes (e.g., **47** (chlorprothixene), **48** (flupenthixol), and **49** (thiothixene)), the butyrophenones (e.g., phenylbutylpiperadines that include **38**, **50** (melperone), **51** (bromperidol), and **52** (pimozide)), the substituted benzamides (e.g., **53** (sulpiride) and **54** (amisulpride)), the dihydroindolone (**55** (molindone)), and the dibenzoxazepine (**56** (loxapine)) (Chart 4). Treatment with FGAs, including **38**, was associated with the development of extrapyramidal side effects (EPS) (e.g., dystonias, akathisias)[3] and tardive dyskinesia in about 20% of patients, the latter characterized by abnormal involuntary movements of the tongue, facial muscles, or limb muscles. Additional adverse effects with FGAs were increased prolactin secretion (leading to gynecomastia, galactorrhea, menstrual irregularities, sexual dysfunction, sedation), hypotension, weight gain, Parkinsonism, and the sometimes fatal neuroleptic malignant syndrome. While all FGAs effectively control the positive symptoms of schizophrenia, they do not treat, and in some cases may worsen, the negative and cognitive dysfunction aspects of the disease. Because of their limited efficacy, narrow therapeutic window, and the development of more effective and tolerable agents, FGAs generally do not represent the preferred treatment option for schizophrenia.

8.2. Second Generation "Atypical" Antipsychotic Drugs (SGAs). On the basis of the improved efficacy and therapeutic index of clozapine, the prototypic SGA, a number of analogues of **9**, e.g., **32**, **56**, and **57** (asenapine), the benzisoxidils **24**, **58** (iloperidone), and **59** (ziprasidone), and the phenylindole **60** (sertindole) were identified. While the SGAs have clearly exhibited a unique therapeutic profile that prompted their discovery and introduction to the clinic, 60 years of research in academia and industry have failed to identify a convincing mechanistic theory to explain this "atypicality", a topic that has been discussed in detail above. Compound **58**, which has been in clinical trials for over a decade, has been reported to have

Chart 5

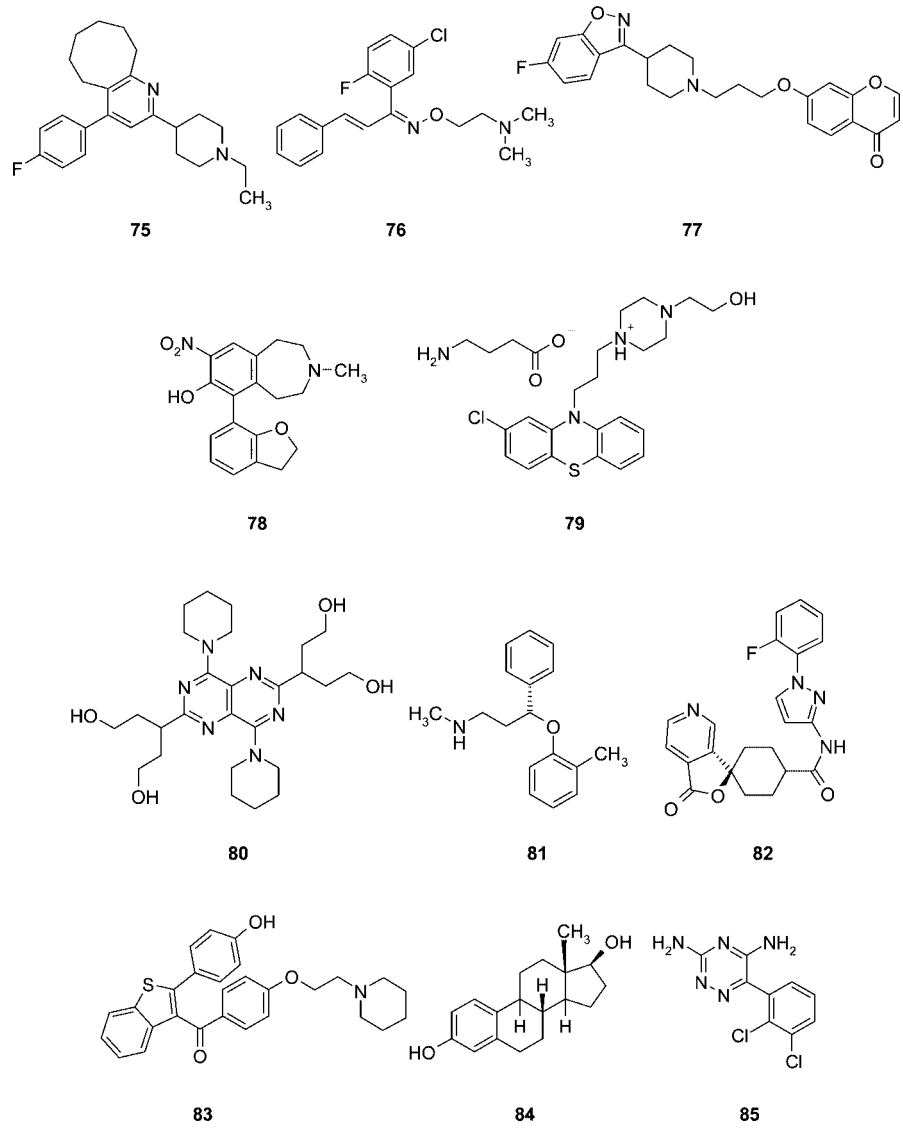


less propensity to produce metabolic syndrome but still produces QT prolongation.[263]

The outcomes of CATIE and CUtLASS trials[24–29] provide a dilemma for those involved in the drug discovery process to identify new antipsychotics. These trials have indicated that the older and less expensive FGAs can offer equivalent or better efficacy than the SGAs, a conclusion that has been considered as flawed on the basis of issues with study design and data interpretation.[24–26] Furthermore, considerable preclinical data exist that differentiate FGAs from SGAs and many clinical studies conducted prior to the CATIE and CUtLASS trials similarly differentiate individual SGAs from FGAs.[3,6,11] An interesting outcome from this debate has been data[263] suggesting that the prototypic heterocycle **61** (cyproheptadine) resembles **9** in animal models.

8.3. Dopamine Receptor Modulators/Dopamine Partial Agonists. The introduction of **8** in 2002[226] was heralded as the first breakthrough in antipsychotic treatment since the discovery of **9**. As noted above, **8** was discovered through the same serendipitous process that led to the identification of **1** and **9**, observation of the effects of NCEs by experienced pharmacologists using carefully designed in vivo pharmacological studies. Compound **8** is structurally unique with a mechanism of action that appears to reflect its partial agonist properties at DA D2 receptors.[264] This latter functional profile depends on a number of factors including receptor reserve and endogenous agonist tone.[265] A partial agonist will thus function as a full agonist in a tissue with high receptor reserve. In contrast, in a tissue with low receptor reserve in the absence of endogenous agonist, a partial agonist will function as a partial agonist. However, if the tissue has low receptor reserve with significant endogenous DA tone, a partial agonist will function as an antagonist by occupying receptors that would have otherwise been occupied by the endogenous agonist. Differences in receptor reserve occur in the various DA D2 receptor systems in the brain; presynaptic D2 autoreceptors have a high receptor reserve, while postsynaptic D2 receptors have very low receptor reserve.[266] A partial agonist can thus act as an antagonist at postsynaptic DA receptors in the mesolimbic system where overactivity is thought to elicit positive symptoms and as a presynaptic agonist at DA autoreceptors eliciting a decrease in postsynaptic DA tone. Theoretically, a partial agonist can dynamically modulate DA neurotransmission as a direct function of dopaminergic tone. The first partial DA agonist to be tested clinically was the *S*-(−)-isomer of **62** (*S*-(−)-3-PPP, preclamol; Chart 5).[267] In the clinic, **62** produced initial improvements in schizophrenics relative to placebo during the first week of therapy; however, efficacy decreased with continued treatment. Other partial DA agonists, including **63**(terguride),[268] have antipsychotic efficacy, albeit in limited clinical trials. As expected with a partial agonist,[269] **8** appears to stabilize dopaminergic neurotransmission by acting as an antagonist at

Chart 6



functionally hyperdopaminergic D2 receptors and as a D2 agonist in hypodopaminergic states. The additional interactions of **8** at $5HT_{1A}$, $5HT_{2A}$, D_4, $5HT_{2c}$, $5HT_7$, α1-adrenergic, and histamine H_1 receptors[270] may also contribute to the efficacy of this novel SGA. In vivo studies indicate, however, that **8** has low levels of $5HT_{1A}$ and $5HT_{2A}$ receptor occupancy when administered at clinically relevant doses, suggesting that its efficacy is DA rather than 5HT mediated.[271] Compound **8** effectively treats the symptoms of acutely exacerbated schizophrenics, improving both positive and negative symptoms without eliciting EPS, hyperprolactinemia, weight gain, or QTc interval prolongation.[272]

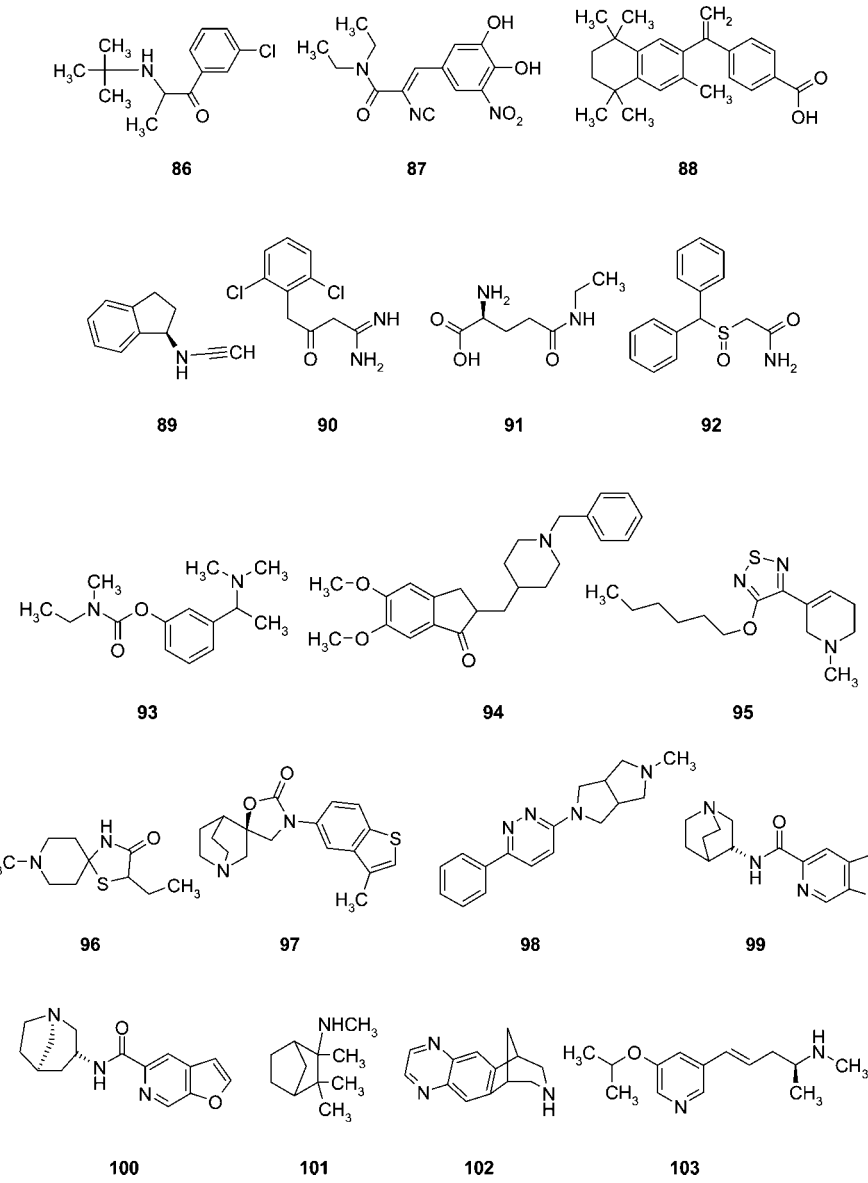
Compounds **6**[273] and **64** (bifeprunox, DU-127090)[274–276] are other compounds with partial D2/$5HT_{1A}$ agonist−antagonist activity that have minimal interactions at $5HT_{2A}$, $5HT_{2c}$, α1-adrenergic, and histamine H_1 receptors.[65,273,275] These NCEs, like **8**, may represent a new generation of potential antipsychotics that will allow the further evaluation of the hypothesis that $5HT_{2A}$ antagonism is critical for SGA efficacy.[59,271,275,277,278] Early clinical reports with **64** indicated that this NCE could stabilize schizophrenic symptoms without prolonging QTc or altering metabolic parameters (lipid profile, glucose dysregulation) and with EPS symptoms similar to placebo.[274] Compound **64** was, however, not approved by the FDA in August 2007 because of a lack of demonstrated efficacy. Compounds **65** (SSR-181507),[279] **66** (RGH-188), and **67** (F-15603)[275] are other D2 receptor partial agonists. It remains to be demonstrated in a large clinical study that partial DA receptor agonism alone is sufficient to reliably elicit antipsychotic efficacy because it is unclear as to what degree of partial D2 agonism is required for efficacy.[275]

9. Unmet Medical Needs

Nearly all SGAs have significant side effects with a limited therapeutic index that can limit efficacy and compliance.[3] Compounds **24** and **32** have a lower risk of inducing EPS when compared to FGAs, but this risk is still present. As a class, the SGAs are sedating and increase the risk of metabolic syndrome (obesity, high diabetes, stroke) and neuroleptic malignant syndrome, a rare but potentially fatal reaction characterized by fever, altered mental status, muscular rigidity, and autonomic dysfunction. Many of these effects appear to be linked to an extension of the D2 receptor antagonist pharmacology, while metabolic syndrome is associated with histamine H_1 receptor activity.[280]

9.1. QTc Liability. As a class, antipsychotics are associated with the potential for prolongation of the cardiac QTc interval, torsade de pointes, and sudden cardiac death.[21] The last occurs nearly twice as often in antipsychotic treated patients as in the

Chart 7



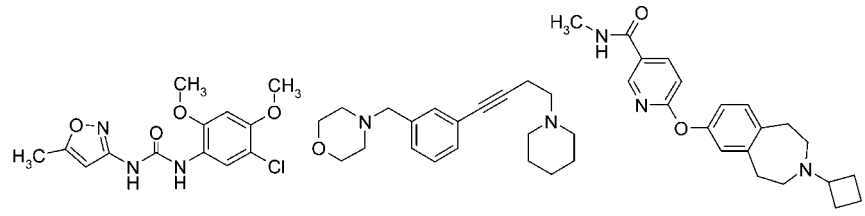
general population with 10–15 such events in 10 000 person-years of observation.[281] Compounds **38**, **45**, **52**, **59**, and **60** are associated with torsade and sudden death. In a population-based case-control study of 554 cases of sudden cardiac death, currently used antipsychotics were associated with a 3-fold increase in risk of sudden cardiac death.[282]

9.2. Metabolic Syndrome. SGA use is associated with marked weight gain progressing, in some instances, to diabetes,[22] the prevalence of which is 2-fold greater among schizophrenics than in the general population.[283] Metabolic syndrome includes abdominal obesity, dyslipidemia, hypertension, and insulin resistance and has an increased prevalence in schizophrenics. Mechanistically, metabolic syndrome is thought to be associated with histamine H_1 receptor activity.[280] While the role of the histamine H_1 receptor activity as the molecular mediator of antipsychotic-induced weight gain has been questioned,[284] H_1 receptor activation has been linked to modulation of hypothalamic AMP kinase.[285] NCEs with antipsychotic potential and decreased H_1 receptor activity, e.g., **68** (FMPD), are under investigation.[286] The CATIE study[287] reported that **32**, of four atypical antipsychotics studied, had the greatest incidence of weight gain (0.9 kg/month) with greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides, effects consistent with the development of metabolic syndrome.

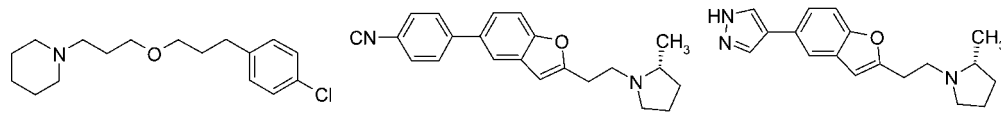
9.3. Efficacy. While current antipsychotics are, to a major extent, effective at treating the positive symptoms of schizophrenia, the negative and cognitive symptoms along with comorbid mood disorders are not improved and remain a major outstanding challenge to finding new drugs.

The FDA's clinicaltrials.gov Web site[288] lists 345 clinical trials ongoing in schizophrenia with a number of novel SGAs being evaluated as monotherapy or adjunct therapy. Those not covered in the new research areas section below include several new SGAs, **7**, **17**, **18**, **21**, **23**, **57**, **58**, **69** (zotepine), **70** (ocaperidone), **71** (lurasidone), **72** (vabicaserin, SCA-136), **73** (nemonapride), **74** (perospirone), **75** (blonaserin), **76** (eplivanserin), **77** (abaperidone), **78** (ADX-10061), **79** (BL-1020, the 4-aminobutyrate salt of **42**), the adenosine uptake inhibitor **80** (dipyridamole), the monoamine uptake inhibitor **81** (atomoxetine), **82** (MK-0557), an NPY5 receptor antagonist AL-108 (activity-dependent neuroprotective protein), the selective estrogen receptor modulator (SERM) **83** (raloxifene), and **84** (estradiol) for use in female schizophrenics, **85** (lamotrigine),

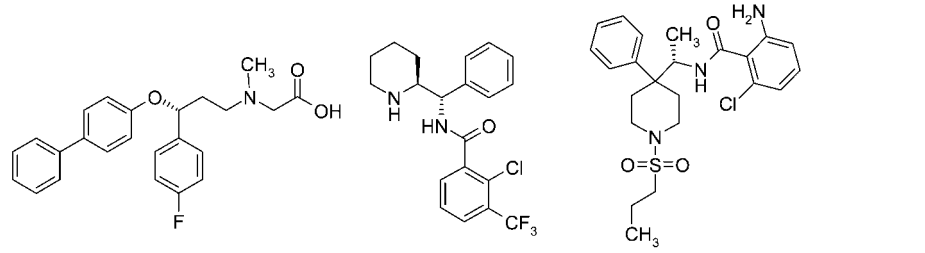
Chart 8



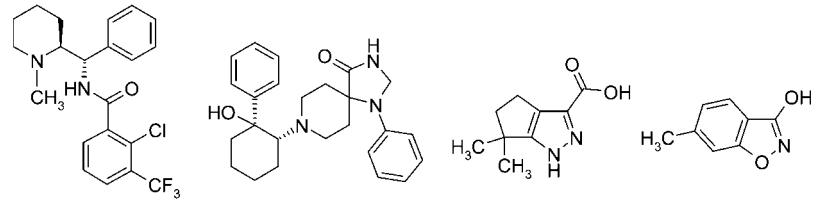
104 **105** **106**



107 **108** **109**



110 **111** **112**



113 **114** **115** **116**

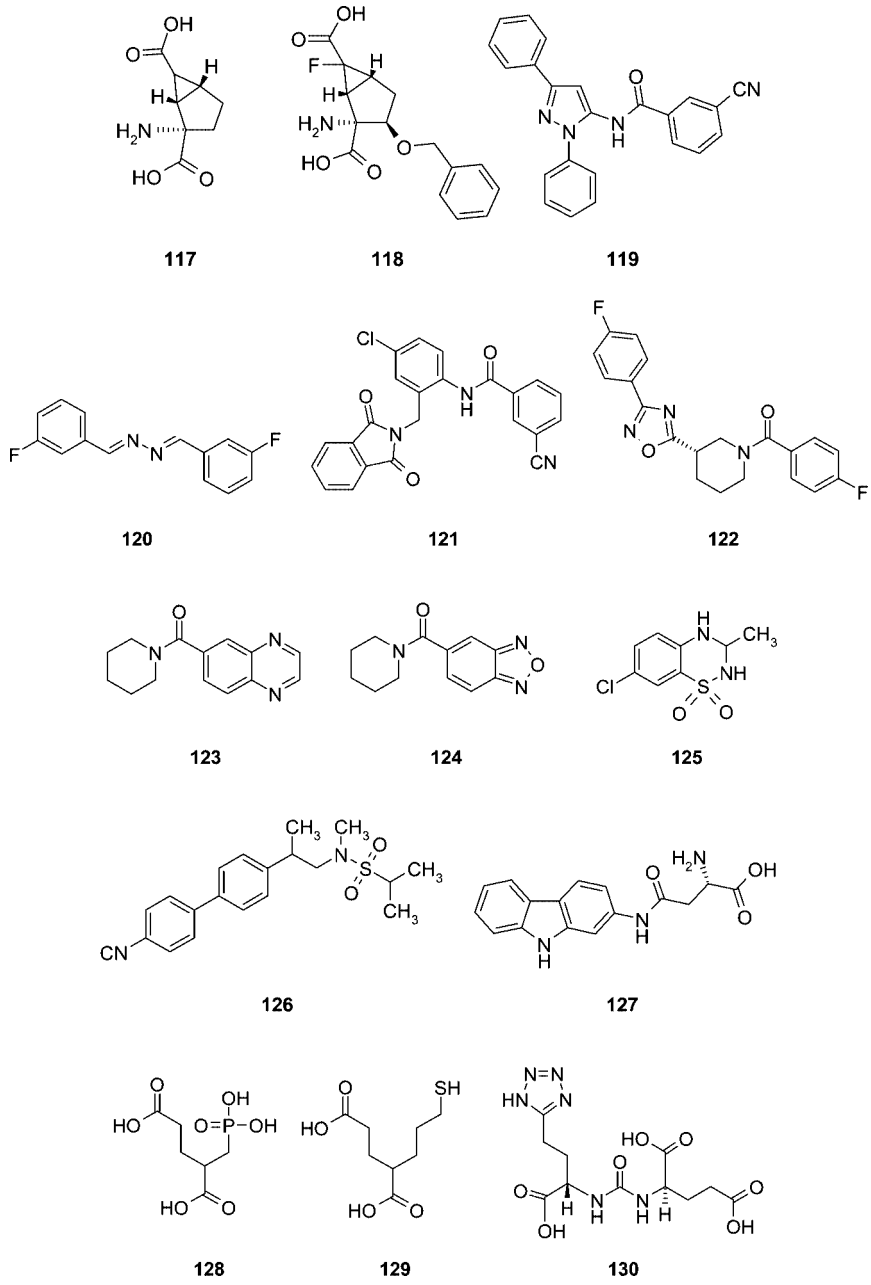
86 (buproprion), the COMT inhibitors **25** and **87** (entacapone), the retinoid **88** (bexarotene), the MAO-B inhibitor **89** (rasagiline), **90** (guanfacine), **91**(L-theanine), RG1068, a form of recombinant human secretin, the wake promoting agent **92** (modafinil), and its *R*-enantiomer and a series of compounds with unknown structure and unspecified mechanisms of action that include ABT-925, MK-249, LX6171, and PF02545920. Additionally, transcranial magnetic and direct current stimulation and shiatsu, the latter a form of psychotherapy,[10] are also being evaluated for efficacy in schizophrenia as a further indication of the unmet medical need in this area.

10. New and Emerging Research Areas

10.1. Muscarinic Cholinergic Agonists. The cholinergic deficits that occur in patients with dementia with Lewy bodies (DLB)[289] lead to visual hallucinations, delusions, apathy, agitation, dementia, and mild-Parkinsonism, all aspects of the schizophrenia phenotype.[9] Treatment of DLB patients with cholinesterase inhibitors such as **93** (rivastigmine) and **94** (donepezil) can diminish these symptoms, thus leading to antipsychotic-like activity.[290,291] However, the peripheral cholinergic side effects of these drugs preclude their broader use outside of DLB and Alzheimer's disease (AD). Compound **95** (xanomeline) and other selective muscarinic agonists (e.g., **96**, NGX267) have an antipsychotic-like profile in animal models of psychosis similar to that seen with D2 antagonists with the exception that muscarinic agonists do not elicit catalepsy.[292] A small study suggested that **95** had antipsychotic-like activity in AD patients.[293] Compound **12**, the demethylated metabolite of **9**, occurs in serum at concentrations comparable to those of the parent.[294] Like other SGAs, **12** has weak partial agonist activity at DA D2 receptors and is a potent inverse agonist at $5HT_{2A}$ receptors.[82] It also has partial agonist/allosteric activity at muscarinic M_1 and M_5 receptors and is a competitive antagonist of M_3 muscarinic receptors. Compound **12** can potentiate NMDA receptor currents in CA1 pyramidal cells via activation of muscarinic receptors[81] and is active in animal models predictive of antipsychotic activity. This supports the hypothesis that the muscarinic agonist properties of **12** may contribute to the unique therapeutic properties of **9**. The **12/9** plasma ratio is apparently a better predictor of the clinical response to **9** than **9** levels particularly for negative symptoms and cognitive enhancement.[295]

10.2. Neuronal Nicotinic Receptor Agonists and Positive Modulators. Smoking, a form of nicotine self-administration, is high in schizophrenics, at a rate at least 3 times higher

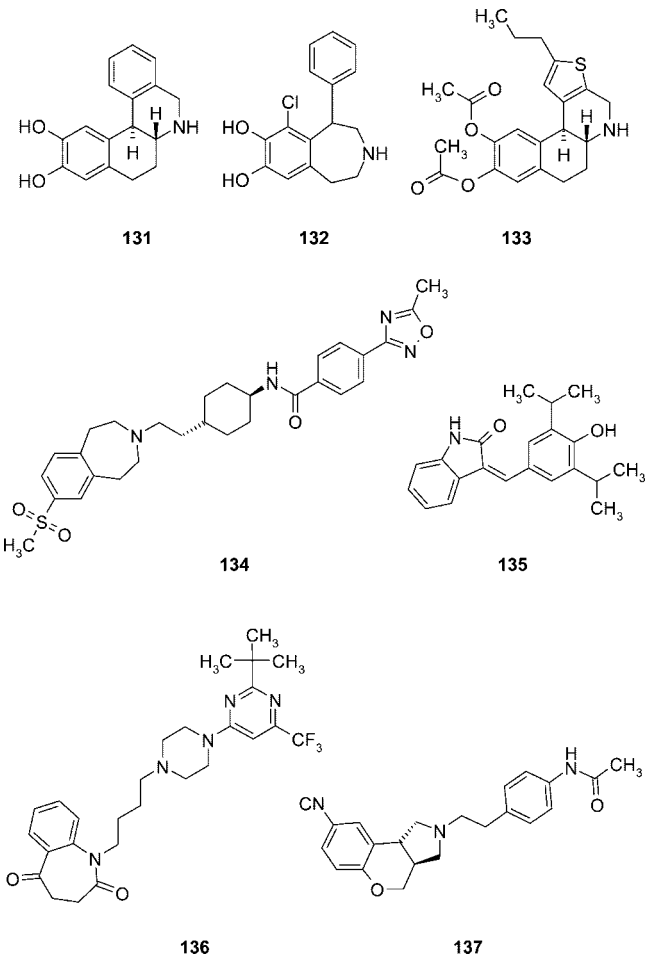
Chart 9



than that in the general population.[195–197] Nicotine can produce modest transient improvements in cognitive and sensory deficits in these patients, while **9**, but not **38**, can improve sensory gating deficits in mice via a nicotinic α7 receptor mechanism.[296] A number of selective α7 nicotinic receptor agonists including **26**, **28**, **29**, **97** (W-56203), ABT-107, TC-2216, PH399733, and SEN12333/WAY-317538 are being assessed for the treatment of cognition deficits in schizophrenia (CDS).[297] Compound **28** can improve PCP-induced cognitive deficits in mice[298] and is currently in phase II clinical trials. The α7 nicotinic agonist, **98** (A-582941), which on its own has no effect on PPI responses, can enhance the efficacy of **24** and **38** when the latter two are given at suboptimal doses. This suggests that α7 agonists might be useful in combination with FGAs and SGAs to reduce their clinical dose and, as a consequence, to reduce their side effects. The selective α7 nicotinic agonists **99** (PHA-543613) and **100** (PHA-709829) showed efficacy in animal cognition models and in phase I trials. Their clinical development was discontinued because of a low (5%) incidence of cardiac arrythmias (non-sustainable ventricular tachycardia). It is unclear whether these were target or compound related. The nicotinic receptor antagonist **101** (mecamylamine) and the α4β2 agonist **102** (varenicline) are also being evaluated clinically for their positive effects on cognitive performance. In addition to being a partial agonist acting at α4β2 nicotinic receptors, **103** (TC-1734/AZD3480, ispronicline) is also a full agonist at α7 receptors.[299] Compound **103** improved episodic memory, power of attention, and speed of response and is currently in CDS (cognitive domain of schizophrenia) trials to study the cognitive domain of schizophrenia.[300] Allosteric modulators of nicotinic receptor function such as **104** (PNU-120596, Chart 8) may also have potential in the treatment of the cognitive domains of schizophrenia.[301]

10.3. Histamine H_3 Receptor Antagonists. Examination of the therapeutic utility of histamine for the treament of schizophrenia dates back to the 1930s[302] with inconclusive results.

Chart 10



With the discovery of the histamine H_3 receptor[303,304] and the development of selective druglike antagonists for this GPCR,[305,306] it has been well established in animal models that NCEs like **105** (JNJ-10181457),[307] **106** (GSK189254),[308] and **107** (BF2.649)[309] and analogues of **108**[310] like **109** (A-688057)[311] may have potential in the treatment of the cognitive dysfunction associated with schizophrenia.[309] There has been no proof of concept in clinical trials for this approach to date.

10.4. Glutamatergic Agents. The glutamate hypofunction hypothesis of schizophrenia has been discussed in the context of both clinical and genetic data. In rodents, NMDA antagonists increase locomotor activity and enhance amphetamine-induced DA release. However, $5HT_{2A}$ antagonists are more effective than D2 antagonists in blocking increases in locomotor activity, consistent with the concept that SGAs that are both $5HT_{2A}$ and D2 receptor antagonists, e.g., **9** and **24**, and are more effective in treating the disorder and that dysregulation of the DA function associated with schizophrenia is secondary to NMDA hypofunction. The balance between D2 antagonism and NMDA receptor modulation may thus be pivotal for the improvement of both positive and negative symptoms in schizophrenia. While NCEs that directly activate NMDA receptors may be useful in treating schizophrenics, these are usually proconvulsant and neurotoxic, leading to a strategy of indirect activation of glutamate receptors. Compound **16** is the prototypic obligatory positive allosteric modulator of the NDMA receptor that, like **17** and **18** and the glycine transporter (GlyT) inhibitor **15**, can treat the negative symptoms and cognitive impairment of schizophrenia when used adjunctively with existing antipsychotics.[312] Newer GlyT inhibitors include **110** (ALX-5407/JNJ-17305660),[313] **111** (SSR504734),[314] **112**,[315] **113** (PF-3311945), and **114**. Of these NMDA receptor modulators, **17** is currently the most promising on the basis of druglike characteristics and clinical outcomes. In combination with **24** and **32**, **17** improves both positive and negative symptoms in treatment-resistant patients.[87] However, the efficacy of **17** appears to be modest and is not useful in patients receiving **9**.[316,317] Despite the lack of agreement regarding the strength of the genetic association of DAOA/G72 with schizophrenia,[180] inhibitors of DAAO, **115** and **116**, have been reported.[318,319]

10.4.1. Metabotropic Glutamate Receptors. Metabotropic glutamate receptors comprise eight receptor subtypes grouped into three families, group I (mGluR1, mGluR5), group II (mGluR2, mGluR3), and group III (mGluR4, mGluR6−8), that are also viable targets for the treatment of schizophrenia.[320] Groups II and III receptors are located presynaptically and modulate glutamate release. Group II agonists, e.g., **31**, **117** (LY354740), and **118** (MGS 0039) (Chart 9), can block **2**- and **13**-induced behavioral activation in rats,[321,322] and both orthosteric and allosteric modulators have antipsychotic-like activity in animal models.[321,323] Allosteric modulators may not induce rapid tachyphylaxis[321,324] and may thus have utility as a novel approach as a maintenance therapy for the treatment of schizophrenia.

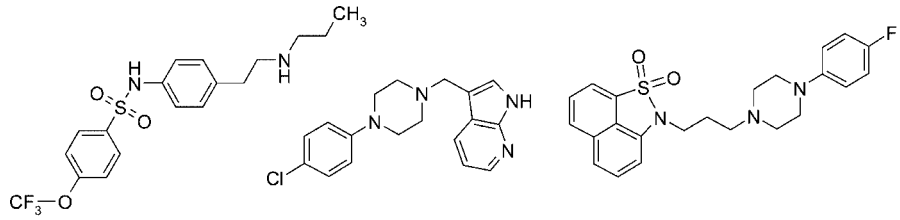
As already noted, the orally active mGlu2/3 receptor agonist **30**[224] improved both positive and negative symptoms at week 4 in a randomized, double-blind, placebo controlled clinical trial with efficacy equivalent to that of the SGA **32** without increasing prolactin production, extrapyramidal symptoms, or weight. The group I mGluR, mGluR5, is also a potential novel target for schizophrenia. Pharmacological blockade[325,326] and genetic ablation of mGluR5[325,327] decreased PPI in rodents with **119** (CDPPB), a selective positive allosteric modulator of the mGluR5 receptor reversing the psychotomimetic effects of amphetamine in rats.[328] Additional mGluR5 potentiators include **120** (DFB), **121** (CPPHA), and **122** (ADX47273).

10.4.2. Ampakines, e.g., 123 (CX516), Allosterically Enhance AMPA Receptor Activity.[329] In combination with **9**, **123** improved some symptoms associated with schizophrenia but was ineffective as monotherapy in improving positive symptoms or cognition in schizophrenics. It has, however, not faired well in clinical trials because of animal toxicity issues. Another ampakine, **124** (ORG 24448/CX-691), is under evaluation as adjunctive therapy as part of the NIMH MATRICS effort to facilitate the development of medications to enhance cognition in patients with schizophrenia.[288] Compounds **125** (IDRA-21) and **126** (LY404187) are other AMPA allosteric modulators currently in clinical trials.

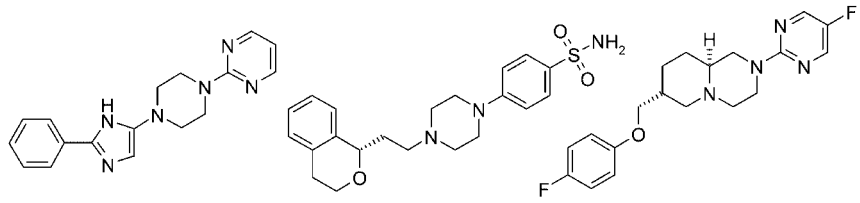
10.4.3. Glutamate Transport Inhibitors. Blockade of excitatory amino acid transporters (EAATs), specifically the EAAT3 neuronal subtype, may also have potential in physiologically manipulating endogenous glutamate tone.[330] This represents a relatively unexploited area in drug discovery. However, EAAT3 expression is altered in schizophrenia[331] and epilepsy[332] and a prototypic EAAT3 inhibitor, **127** (NBI-59159), can dose-dependently attenuate amphetamine-stimulated motor activity.[330]

10.4.4. *N*-Acetyl-L-aspartyl-L-glutamate (NAAG). NAGG is a peptide with putative neurotransmitter function[333] that acts as an endogenous agonist at group II mGluR receptors.[334] It is catabolized to *N*-acetylaspartate and glutamate by the NAAG peptidases, glutamate carboxypeptidase II and III, present on the cell surface of astrocytes. Therefore, NAAG peptidase inhibitors, by increasing NAAG levels, could provide antipsy-

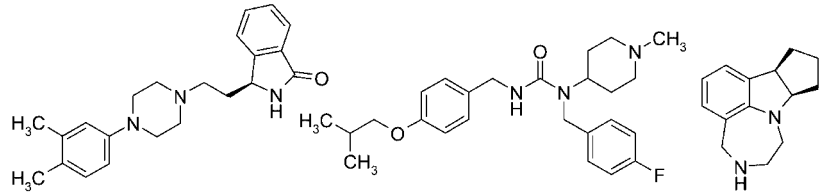
Chart 11



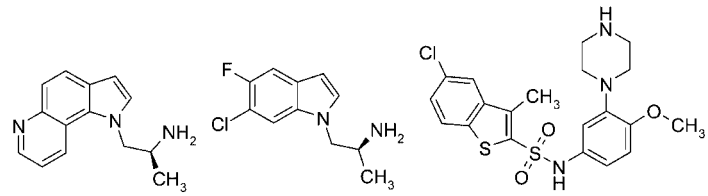
138 **139** **140**



141 **142** **143**



144 **145** **146**



147 **148** **149**

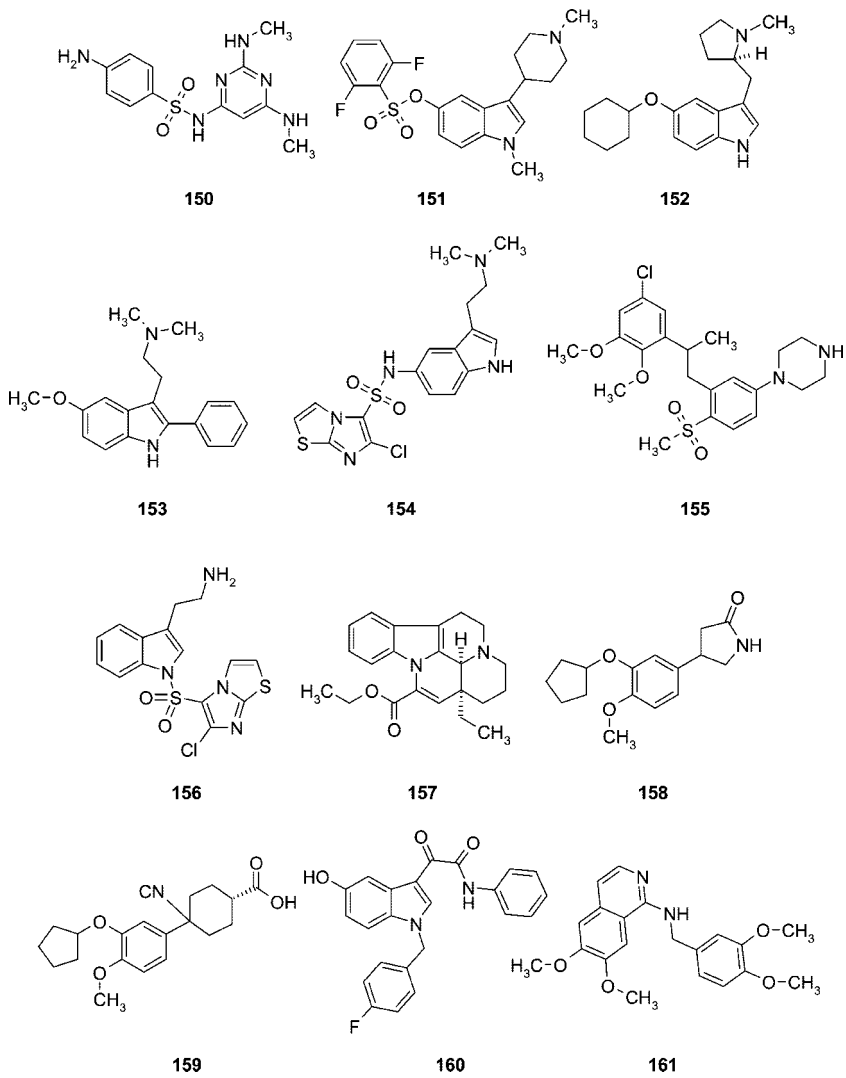
chotic efficacy via activation of group II mGluRs. Compounds **128** (2-PMPA), **129** (GPI5693), and **130** (ZJ38) represent first generation NAAG peptidase inhibitors.[335]

10.5. DA Receptor Modulators. DA D1 receptor agonists such as **131** (dihydrexidine) and **132** (SKF-81297) have procognitive effects in animal models (Chart 10).[336] The D1/D5 agonist **133** (adrogolide, ABT-431, DAS-431) had cognition enhancing activity in a rat model of antipsychotic-induced working memory deficit[337] that was not replicated in more traditional animal models of cognitive performance, e.g., Morris water maze (M. W. Decker, unpublished data). D1/D5 agonists also have limited potential as drugs because of the inherent tolerance of their mechanism. Nonetheless, there still appears to be to continuing interest in D1/D5 agonists for the treatment of cognitive deficits.[338] There is also an ongoing effort to identify improved D2 receptor antagonists with the current focus being on selective D3 receptor antagonists. These are anticipated to have reduced EPS liability compared to D2 receptor antagonists.[57] Recent examples include the tetrahydrobenzazepine, **134** (SB-414796), the arylalkylpiperazine **135** (ST-280), the benzazepinone, **136** (A-706149), **137** (S-33138),[339] and **138** (PNU-177864) (Charts 10 and 11).

Past interest in selective D4 receptor antagonists as antipsychotics was driven by the higher affinity of clozapine for the dopamine D4 receptor relative to the D2 receptor.[340] D4 receptors appear to be involved in working memory[341] and can prevent stress-induced cognitive deficits in monkeys.[342] A number of selective D4 antagonists have been identified including **139** (L-745,870), **140** (fananserin, RP62203), **141** (NGD 94-1), **142** (PNU-101,387), **143** (CP-293019), and **144** (PD-172938). In both preclinical[343] and clinical studies,[344] **139** failed to show an antipsychotic profile, a result that may reflect partial D4 agonist activity similar to that reported for **141**.[345]

10.6. 5HT Receptor Ligands. Research has also continued on the 5HT receptor axis of schizophrenia. Newer targets/ligands include the 5-HT_{2A} receptor inverse agonist **145** (ACP-103)[346] and the $5HT_{2C}$ receptor agonists **146** (WAY-163909), **147** (VER-2692), and **148** (Ro 60-0175). Activation of the $5HT_{2C}$ receptor reduces mesolimbic DA neurotransmission.[347] Interest in $5HT_6$ receptor antagonists, like that for D4 receptor antagonists, was driven by the high-affinity binding of **9** to this receptor[348] and also the ability of **9** to down-regulate the $5HT_6$ receptor.[349] This has resulted in considerable patent activity in the area of $5HT_6$ antagonists.[350] While these antagonists have been implicated in enhancing cognition with potential utility in Alzheimer's disease and schizophrenia,[349] NCEs including **149** (SB-271046) and **150** (Ro 04-6790, Chart 12) have been reported to have cognition enhancing activity, an effect sensitive to NMDA receptor antagonists.[351] The utility of $5HT_6$ antagonists as cognition enhancers has, however, been questioned.[352,353]

Chart 12



Newer compounds active at this 5HT receptor include **151** (SGS-518), **152** (ALX-0440), **153** (BGC-20-761), **154** (E-6801), **155** (PRX-07034), and **156** (WAY181187).

10.7. PDE Inhibitors. Members of the PDE (phosphodiesterase) family of enzymes including PDE1B, PDE4, and PDE10A have been targeted as new approaches for the treatment of CNS disorders including cognitive dysfunction.[354–356] The PDEs, comprising a superfamily of some 11 enzymes,[354] are responsible for the breakdown of the intracellular messenger cAMP. PDE inhibitors were first shown to have therapeutic potential with the serendipitous development of the erectile dysfunction drug sildenafil.[357]

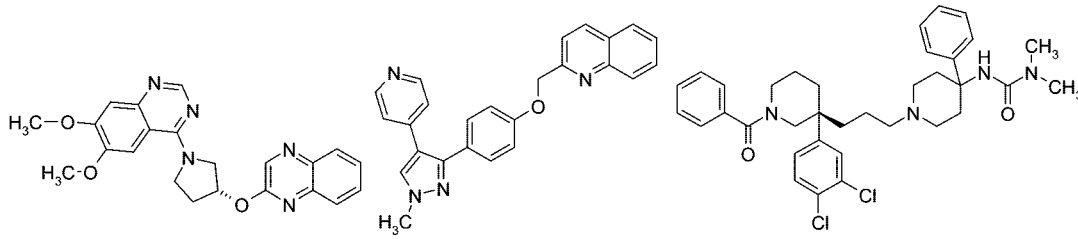
Mice with disrupted PDE1B function are hyperactive and show altered responses to **2** and **38**.[358] Compound **157** (vinpocetine) represents the first generation of PDE1B inhibitors. The PDE4 inhibitor **158** (rolipram) has antidepressant-like[359] and cognition-enhancing properties[360] and may thus have potential in the treatment of schizophrenia.[361] PDE4B, a member of the PDE4 family, has been linked with DISC1 in the genetic aspects of schizophrenia.[191] Prototypic PDE4 inhibitors had pronounced emetic activity that has been reduced in second generation compounds such as **159** (cilomilast) and **160** (AWD 12-281).[362]

PDE10A is highly expressed in the striatum and has been implicated in psychotic disorders like schizophrenia.[354,363] Animals treated with the prototypic PDE10A inhibitor **161** (papaverine)[354] and *PDE10A*$^{-/-}$ mice[364] exhibited reduced conditioned avoidance behavior (CAR), reductions in spontaneous locomotor activity, and deficits in locomotor or visual acuity tests.[365] While there is considerable medicinal chemistry activity in this area as evidenced by patent applications, only **161**, **162** (PQ-10), and **163** (MP-10) have been identified as selective PDE10A inhibitors (Chart 13).[354,366]

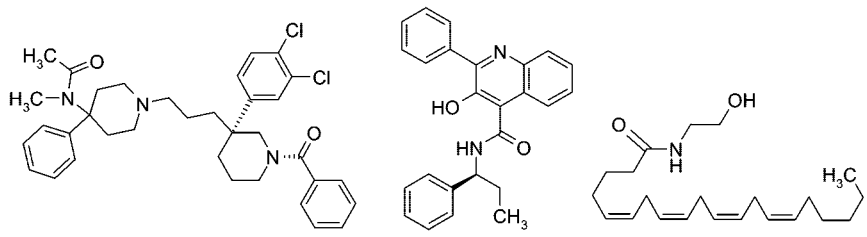
10.8. Neurokinin$_3$ (NK$_3$) Receptor Antagonists. NK$_3$ receptors are present on DA neurons in the A9 and A10 groups and modulate DA release and cholinergic tone.[367] In animal models, the NK$_3$ receptor antagonist **164** (SSR146977) prevented NK$_3$ agonist-induced release of ACh, 5HT, and DA. In the clinic, **165** (osanetant) showed similar efficacy compared to haloperidol on positive symptoms in schizophrenia with reduced EPS and weight gain liabilities but failed to show dose-dependent related efficacy. Compound **166** (talnetant) is currently in phase II trials in schizophrenics.[367]

10.9. Cannabinoids. An emerging literature has suggested that endocannabinoids including **167** (anandamide) may be involved in aspects of the pathophysiology of schizophrenia[368] with conflicting reports[369,370] of changes in cannabinoid (CB) receptors in schizophrenics. Individuals with Δ-9-tetrahydrocannibinol intoxication have a perceptual dysfunction similar to that seen in schizophrenics.[42,371] Compound **168** (rimonabant/SR141716), a selective CB$_1$ receptor antagonist, can reduce

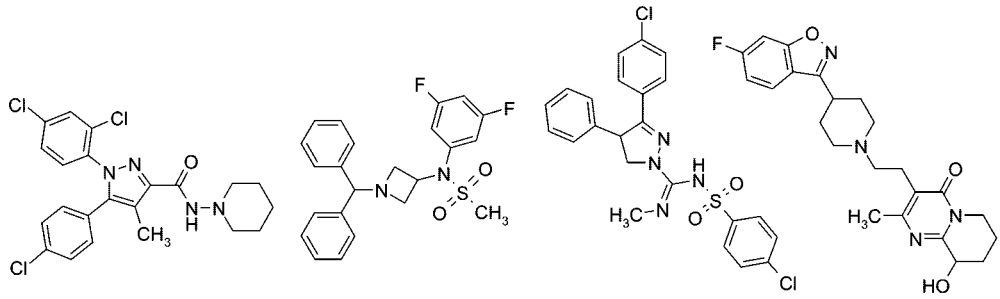
Chart 13



162 **163** **164**



165 **166** **167**



168 **169** **170** **171**

stimulant-induced hyperactivity.[372] CB ligands including **168**, **169** (AVE-1625), and **170** (SLV-319) are under investigation for the treatment of schizophrenia.[288]

11. Future Directions

Improved treatments for schizophrenia are, not surprisingly, most likely to come from a better understanding of disease origin, pathophysiology, and newer, disease-related, drug tractable targets. Existing antipsychotic drugs, both FGAs and SGAs, and the many compounds currently in clinical development represent modest clinical and chemical improvements on earlier drugs (variations on a theme (**32** versus **9**), metabolites of existing drugs (**171** (9-hydroxyrisperidone/paliperidone) versus **24**; **12** versus **9**)) or attempts to mimic a limited set of molecular attributes (**8** (partial dopamine agonism) and **57** (5-HT_{2A}/D2 antagonism). In this context, the controversial CATIE/CUtLASS clinical studies[24–29] have confounded the basic premise that has driven DA receptor-based antipsychotic drug discovery research for the past 30 years, namely, that SGAs have an improved efficacy and safety profile compared to FGAs. The objective resolution of the CATIE controversy and the integration of the CATIE/CUtLASS trials with the many previous clinical trials that have shown superiority for individual SGAs over FGAs will be crucial in helping to define continuing medicinal chemistry efforts around the traditional DA/5HT approaches to antipsychotic drug research. Given the CATIE/CUtLASS studies, it is likely that the regulatory hurdles to the approval of yet another SGA acting primarily through a "conventional" $5HT_2$/D2 receptor antagonist mechanism will probably be insurmountable. Nonetheless, the NDA for **58** was recently accepted by the FDA.[373] It remains to be seen whether the CATIE/CUtLASS studies represent the death knell for the advancement of "classical" SGAs like **58**.

The decades-old interest in the superior efficacy of the prototypic SGA **9** represents a major theme in drug discovery efforts. Efforts continue to find "a" mechanism of action for **9** beyond its current multitude of receptor interactions (GPCRs and LGICs (ligand gated ion channels)) that could more clearly define unique clinical profile of the compound. The search for selective "magic bullets" to treat schizophrenia has been debated in the context of "magic shotguns"[55] or "selectively" nonselective agents,[374] neither concepts of which make the task of the medicinal chemist any less empirical. The anticipation that the deconvolution and prioritization of the many genetic associations with schizophrenia may lead to tractable new targets has, as has been discussed in detail above, been less than productive. Indeed, to the casual reader, the efforts focused on the many novel targets identified is, in many ways, reminiscent of Horrobin's contrary but insightful view[375] of the "Castalian" nature of modern biomedical research: intellectually compelling, eminently fundable, self-contained, and ultimately tangential to any real life situation.

Continuing evidence supports a major neurodevelopmental aspect of the genesis of schizophrenia that may argue that unless

drug treatment is initiated before, or concomitant with, birth (assuming a reliable diagnostic test[376]), then it will inevitably be palliative, its effect being superimposed on aberrant neuronal circuitry, the genesis of which is probably long gone by the time of adolesence.

It has also been proposed[377] that disrupted cortical circuitry resulting from neuronal apoptosis represents a key event in the pathophysiology of schizophrenia. Changes in key enzymes involved in the apoptotic cascade, e.g., Bax/Bcl2, have been observed in brains from schizophrenics[378] and have been viewed in terms of proapoptotic stress in schizophrenia. Stress-related dysfunction of neuronal plasticity mechanism and neurogenesis in psychiatric disorders has evolved in the context of a consideration of a "failure to recover".[379] Neurogenesis is a key event in the delayed onset of antidepressants[380] and may also be involved in the delayed onset of action of antipsychotics.[381]

Whether the contributions from the various genomic studies and an improved understanding of the neurocircuitry and plasticity of the brain will provide new insights into the molecular targeting for the next generation of antipsychotic drugs remains to be seen. In the meantime, there is considerable work to be done to advance the various molecular targets related to the glutamate hypofunction hypothesis (e.g., mGluRs, GlyT, $EAAT_3$, AMPA) and newer targets with a compelling rationale ($5HT_6$, PDE10A, $\alpha 7$ nicotinic agonists/partial agonists/modulators) to the level of optimized druglike leads using the proven approach of iterative medicinal chemistry in conjunction with in vivo and in vitro functional pharmacological assays.

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Biographies

Michael J. Marino received his Ph.D. in Neuroscience in 1995 from the University of Pittsburgh. After working as a postdoctoral fellow with Jeff Conn at Emory University studying the role of metabotropic glutamate receptors in regulating the circuitry of the basal ganglia, he joined Merck Research Laboratories in West Point, PA, in 2001 where he worked on projects in schizophrenia, Parkinson's disease, and related movement disorders. He joined Cephalon, Inc. in 2005 where he is Associate Director of CNS Biology.

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Michael Williams received his Ph.D. in Neurochemistry from the Institute of Psychiatry, University of London, in 1974 and his D.Sc. in Pharmacology also from the University of London in 1987. He has worked in the U.S. based pharmaceutical industry for 30 years at Merck, Sharp and Dohme Research Laboratories, Nova Pharmaceutical, CIBA-Geigy, and Abbott Laboratories. Following retirement in 2000, he worked as a consultant/manager with various biotechnology/pharmaceutical/venture capital companies in the U.S. and Europe including Genset and Molecumetics. He joined Cephalon, Inc. in 2003 where he is Vice President, Worldwide Discovery Research.

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