Principal Component Analysis Differentiates the Receptor Binding Profiles of Three Antipsychotic Drug Candidates from Current Antipsychotic Drugs

Jos H. M. Lange,* Jan-Hendrik Reinders, Jeroen T. B. M. Tolboom, Jeffrey C. Glennon, Hein K. A. C. Coolen, and Chris G. Kruse

Solvay Pharmaceuticals, Research Laboratories, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

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The receptor binding affinities of the three drug candidates **1** (SLV310), **2** (SLV313), and **3** (SLV314) were positioned against the results from nine (a)typical antipsychotic drugs. The receptor binding data from sixteen monoaminergic receptors served as the input in a principal component analysis (PCA). The PCA outcome revealed a unique binding profile of **1**, **2**, and **3** as compared with the reference compounds **4**−**8** and **10**−**12**. The weight gain inducing antipsychotics **6**−**8** clustered in the PCA by scoring strongly negative for factor 1. The hyperprolactinaemia related antipsychotics **4**, **5**, **10**, and **12** clustered by their negative scores for factor 2.

Introduction

Schizophrenia is a psychotic disorder characterized by the so-called positive and negative symptoms.[1] The disease affects approximately 1% of the world population. Despite intensive investigations, its molecular etiology[2] remains enigmatic. Chlorpromazine (**4**) was the first effective medication for schizophrenia, followed by the discovery of another major typical antipsychotic drug haloperidol (**5**). These dopamine D_2 receptor antagonists[3] are active in the treatment of the positive symptoms (hallucinations, severe excitement, unusual behavior, and delusional thinking) in schizophrenia but fail to treat negative symptoms such as lack of drive, apathy, depressive mood, and social withdrawal. Moreover, these typical antipsychotics cause extrapyramidal side effects (EPS) and increased prolactin levels.

The dopamine hypothesis[4] has dominated schizophrenia research for several decades but more recently it has become clear that the modulation of other neurotransmitters systems, in particular glutamatergic, serotonergic, but also adrenergic and cholinergic receptor pathways[5] plays also an important role in schizophrenia.

Attempts to diminish the side effects of the conventional antipsychotics resulted in the development of the so-called atypical antipsychotics. Initially, this term was merely used for antipsychotics with a reduced risk of causing EPS. Nowadays it is used in a much broader context, thereby including antipsychotics that have a minimized impact on prolactin levels, that act on both positive and negative symptoms, and that affect other neurotransmitter systems.[6] As a consequence, atypical antipsychotics show contrasting actions[7] in animal models of cognition, anxiety, and depression. Important examples of such atypical antipsychotics[8] are **6** (clozapine), **7** (olanzapine), **8** (quetiapine), **9** (aripiprazole), **10** (risperidone), **11** (ziprasidone), and **12** (amisulpride). Many of these atypical antipsychotics act on several neurotransmitters. For example, **6** elicits only modest inhibitory activity on the D_2 receptor but shows in addition affinity for a wide range of other receptors. Compound **12** on the other hand is fairly selective for D_2 and D_3 receptors. The reason that **12** is devoid of EPS is believed to be mainly caused by its preferable interaction[9] with limbic D_2-like receptors. Several of these atypical antipsychotics were reported[10] to cause beneficial clinical effects on mood disorders, mania, and bipolar depression. Although the atypical antipsychotics do not show the side effects like EPS that are related to the conventional typical agents, some of them, in particular, the structurally related **6** and **7**, cause weight gain, diabetes, and dyslipidemia as major side effects. These effects constitute a cardiovascular risk factor.[11] Recently, the efficacy of several atypical antipsychotics in the relief of negative symptoms in schizophrenia has been reviewed.[12] It can be concluded that there is still an unmet medical need for novel atypical antipsychotics that are devoid of metabolic and other side effects (such as agranulocytosis for **6**) and are able to treat the negative symptoms in schizophrenia in a more effective way. This prompted the pursuit of alternative approaches that have resulted[13] in the discovery of three novel drug candidates **1**−**3**. These three compounds have dual modes of action. The compounds **1**[14] and **3**[15] share equipotent D_2 receptor antagonism with selective serotonin reuptake inhibition (SSRI). The drug candidate **2** is a dual D_2 receptor antagonist and a full 5-HT_{1A} agonist.[16,17]

Results and Discussion

Compounds **1**−**3** were designed with the aim to generate new chemical entities having a unique pharmacological (and clinical) profile as compared with the existing typical antipsychotics such as **4** and **5** on the one hand and the newer atypical antipsychotics including **6**−**12** on the other hand (Figure 1).

To compare the drug candidates **1**−**3** against marketed antipsychotics, a series of radioligand assays was performed, aimed at 16 monoaminergic receptors. These receptors have been related to schizophrenia treatment, either causing beneficial or side effects. This set consisted of three dopaminergic subtypes D_{2s},[18] D_3,[19] and $D_{4.4}$,[20] seven serotonergic subtypes 5-HT_{1A},[21] 5-HT_{2A},[22] 5-HT_{2b},[22,23] 5-HT_{2c},[22] 5-HT_3,[24] 5-HT_6,[25] 5-HT_7,[26] and 5-HT uptake,[27] muscarinic (M_1[28] and M_4[29]), adrenergic (α_1[29] and α_2[30]), and histaminergic (H_1[31]) sites. In particular, D_{2s}, D_3, $D_{4.4}$, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{uptake} are representative for antipsychotic efficacy, whereas D_{2s}, 5-HT_{2c}, M_1, α_1, and H_1 have been related to the occurrence of side effects. The results from these 16 receptor binding studies for the compounds **1**−**12** are depicted in Table 1.

* To whom correspondence should be addressed. Solvay Pharmaceuticals, Chemical Design & Synthesis Unit, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands. Telephone: +31 (0)294 479731. Fax +31 (0)294 477138. E-mail: jos.lange@solvay.com.

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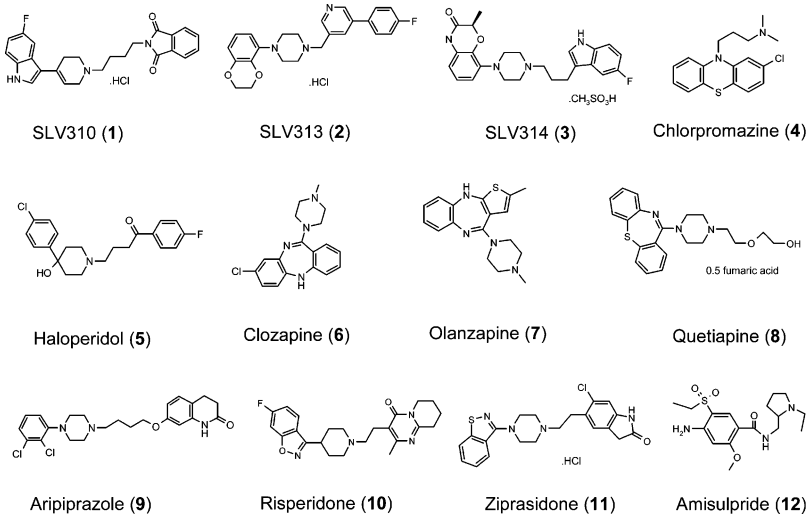

Figure 1. Chemical structures of the drug candidates **1**−**3** and the antipsychotic reference compounds **4**−**12**.

Table 1. Receptor Binding Data of **1**−**12** from 16 Monoaminergic Receptors[a]

	Assays							
cmpd	D_{2s}	D_3	$D_{4.4}$	5-HT_{1A}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_3
1	8.5 ± 0.3	9.1 ± 0.4	7.1 ± 0.2	8.6 ± 0.3	7.0 ± 0.0	8.8 ± 0.1	7.4 ± 0.1	inactive[b]
2	8.4 ± 0.2	8.4 ± 0.2	8.0 ± 0.2	9.1 ± 0.1	6.6 ± 0.2	7.9 ± 0.1	inactive	inactive
3	9.1 ± 0.2	9.3 ± 0.2	8.8 ± 0.2	8.3 ± 0.2	7.7 ± 0.2	9.0 ± 0.2	6.7 ± 0.0	inactive
4	8.0 ± 0.0	8.8 ± 0.2	7.6 ± 0.1	inactive	8.2 ± 0.2	7.4 ± 0.2[c]	7.4 ± 0.2	inactive
5	8.3 ± 0.2	8.8 ± 0.2	8.2 ± 0.1	inactive	7.0 ± 0.2	inactive	inactive	inactive
6	6.9 ± 0.1	7.0 ± 0.2	7.4 ± 0.1	7.0 ± 0.1	8.3 ± 0.2	8.5 ± 0.1	8.1 ± 0.1	6.4 ± 0.1
7	7.7 ± 0.1	7.7 ± 0.3	7.7 ± 0.3	inactive	8.8 ± 0.1	8.2 ± 0.0	8.3 ± 0.2	6.7 ± 0.1
8	inactive	6.6 ± 0.1	inactive	7.1 ± 0.2	7.2 ± 0.1	6.6 ± 0.1[c]	inactive	inactive
9	8.3 ± 0.2	8.4 ± 0.2	7.0 ± 0.1	8.1 ± 0.1	7.8 ± 0.2	8.9 ± 0.3	7.3 ± 0.2	6.3 ± 0.2
10	8.2 ± 0.1	8.0 ± 0.1	8.0 ± 0.1	6.6 ± 0.1	9.0 ± 0.1	7.7 ± 0.1	7.9 ± 0.1	inactive
11	7.9 ± 0.4	8.2 ± 0.2	7.3 ± 0.2	8.8 ± 0.1	9.2 ± 0.1	8.8 ± 0.1	8.9 ± 0.2	6.4 ± 0.1
12	7.9 ± 0.4	8.4 ± 0.2	inactive[b]	inactive	6.2 ± 0.1	6.5 ± 0.1[c]	inactive	inactive

	Assays							
cmpd	5-HT_6	5-HT_7	5-HT_U	M_1	M_4	α_1	α_2	H_1
1	6.4 ± 0.1	7.0 ± 0.2	9.1 ± 0.1	inactive	inactive	8.5 ± 0.2	6.6 ± 0.1	7.5 ± 0.2
2	inactive	7.2 ± 0.1	inactive	inactive	inactive	6.3 ± 0.2	inactive	inactive
3	inactive	8.1 ± 0.2	9.6 ± 0.1	inactive	inactive	7.8 ± 0.1	inactive	6.9 ± 0.2
4	7.3 ± 0.1	7.5 ± 0.1	7.2 ± 0.1	6.9 ± 0.1	6.8 ± 0.2	8.8 ± 0.0	6.3 ± 0.2	7.3 ± 0.3
5	inactive	6.5 ± 0.1	inactive	inactive	inactive	7.8 ± 0.2	inactive	6.4 ± 0.2
6	8.1 ± 0.1	7.7 ± 0.4	inactive	8.2 ± 0.3	7.9 ± 0.1	8.0 ± 0.2	7.1 ± 0.2	8.1 ± 0.2
7	8.1 ± 0.1	7.1 ± 0.1	inactive	8.0 ± 0.1	7.9 ± 0.2	7.6 ± 0.3	6.5 ± 0.1	8.2 ± 0.2
8	inactive	7.2 ± 0.1	inactive	6.4 ± 0.1	6.9 ± 0.1	7.9 ± 0.1	inactive	7.4 ± 0.1
9	6.7 ± 0.1	7.2 ± 0.2	7.5 ± 0.1	inactive	inactive	7.0 ± 0.2	inactive	7.0 ± 0.1
10	inactive	9.0 ± 0.2	inactive	inactive	inactive	8.8 ± 0.2	8.1 ± 0.	8.1 ± 0.3
11	7.2 ± 0.1	8.3 ± 0.1	7.1 ± 0.2	inactive	inactive	8.1 ± 0.1	6.3 ± 0.1	7.8 ± 0.1
12	inactive	7.6 ± 0.2	inactive	inactive	inactive	inactive	6.9 ± 0.3	inactive

[a] Results are presented as pK_i values (mean ± SD, n = at least 3). [b] *Inactive* denotes the compound to have no significant affinity at concentrations of 1 μM in the assay. [c] 5-HT_{2b} assay with ^{125}I-DOI; the others were with ^{3}H-LSD.

Principal component analysis[32] (PCA[a]) constitutes an essential tool in chemometrics, which has widely been applied in drug discovery.[33] PCA generates new variables from combinations of old variables and rotates data to discover more useful views of its structure. It provides a reduction of data multidimensionality (the pharmacological activities of the input molecules) and detects trends, groupings, and outliers. It was decided to apply a PCA on the receptor binding data (the pK_i values, as depicted in Table 1) of the aforementioned compound set to assess the position of **1**−**3** against the nine reference antipsychotics **4**−**12**. The PCA condensed the information from the 16 receptor binding assays into three main principal factors with a minimal loss of information. Factor 1 (accounting for 35% variance) had a main positive contribution of the dopamine D_2-like receptors, while muscarinic M_1/M_4, histamine H_1, and serotonin 5-HT_6, 5-HT_3, 5-HT_{2A}, and 5-HT_{2C} scored on the negative side of this axis. Factor 2 (accounting for 13% variance) had significant positive contributions of serotonin 5-HT_{1A}, 5-HT_{2B}, 5-HT_3, 5-HT_6, and 5-HT_{uptake}, whereas adrenergic α_1/α_2 and serotonin 5-HT_7 receptors had a negative contribution. Factor 3 (accounting for 13% variance) was mainly composed of serotonin 5-HT_7, 5-HT_{1A}, and 5-HT_{2B} on the positive and dopamine D_2-like and α_1 receptors on the negative end of this axis (Figure 2).

Graphical plots are provided to facilitate the interpretation of the PCA outcome. Herein, similar compounds appear in clustered groupings of points, whereas those with deviating properties differ considerably from the other by dispersed points. The drug candidates **1**−**3** as well as the reference **9** scored

[a] Abbreviations: PCA, principal component analysis; EPS, extrapyramidal side effects; 5-HT, 5-hydroxytryptamine.

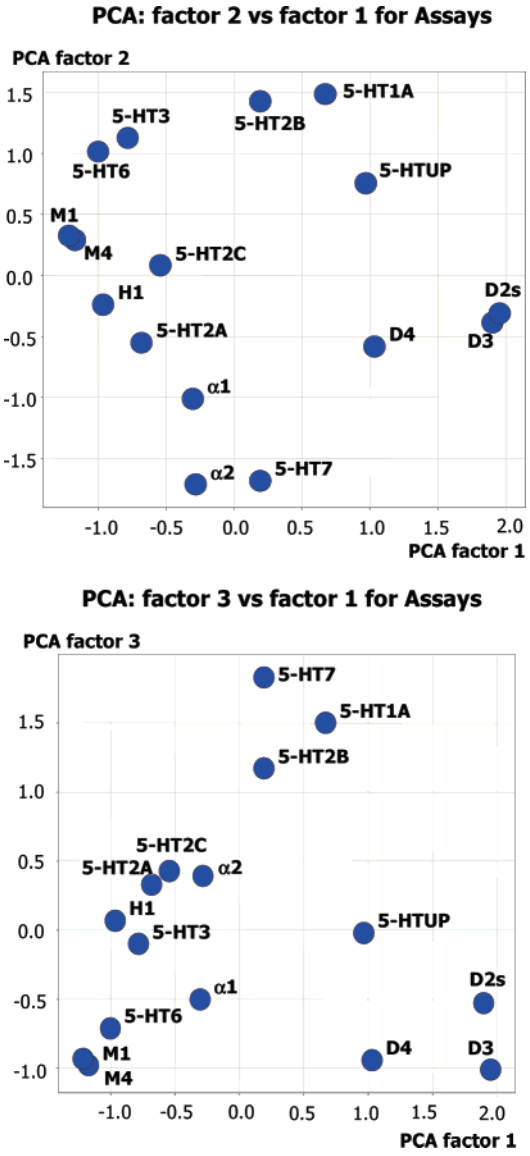

Figure 2. Individual contributions of the receptor binding assays to the three PCA factors.

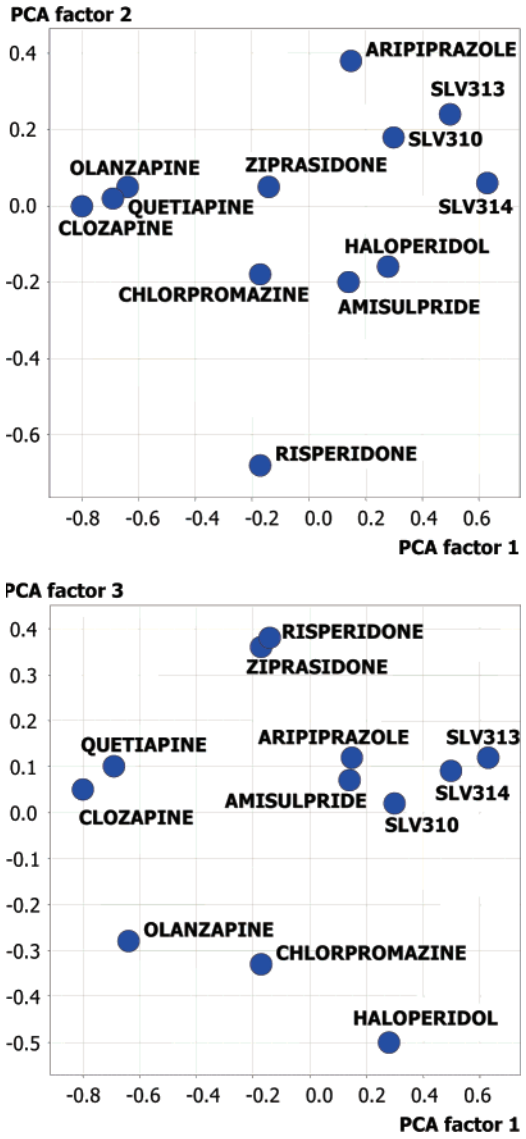

Figure 3. Scores of PCA factors for **1**−**3** and the antipsychotic reference compounds **4**−**12**.

positively on both factors 1 and 2, which separates them from **4**−**8** and **10**−**12**, respectively (Figure 3, top picture). Interestingly, **1**−**3** elicited a rather low score on factor 3, whereas both typical neuroleptics **4** and **5** elicited a negative score. Several of the atypicals **6**, **8**, **9**, and **12** scored also low on factor 3, but intriguingly, **10** and **11** both scored positively. A graphical 3D plot of the PCA-based clustering results of **1**−**12** reveals the binding profile of Solvay's antipsychotic candidates **1**−**3** as compared with the references **4**−**12** (Figure 4).

It is of interest to view how the similarities and differences in binding profile from the PCA translate into similarities and differences in vivo. This could be informative in terms of the biological activities giving rise to these effects based on the loadings (Figure 2). Obviously, the specific pharmacodynamic[34] (including functional activities, and more subtle parameters like differences in striatal D_1/D_2 receptor occupancies, and dissociation rates from the D_2 receptor), and pharmacokinetic properties of the compounds **1**−**12** will have their additional impact on the in vivo and clinical results discussed below.

This analysis will focus on the outcome of the PCA in relation to common side effects of antipsychotic drugs, in particular, weight gain and metabolic disorders, EPS and hyperprolactinaemia.

As noted already before, the atypical antipsychotics **6**, **7**, and (to some lesser extend) **8** were reported[11] to induce weight gain and metabolic side effects, whereas **9**, **10**, **11**, and the typical antipsychotic **5** are much less orexigenic. Such orexigenic effects of antipsychotics have mainly been attributed to interactions with H_1, 5-HT_{2C}, and muscarinic receptors. In particular, the activation of hypothalamic AMP kinase linked to histamine H_1 receptor blockade has recently been shown[35] to contribute to the orexigenic action of **6** and **7**. H_1 was found to be negatively correlated to factor 1 in the PCA and showed not much impact on the other two factors (Figure 2). Also, the muscarinic and 5-HT_{2C} receptor contributions are negatively linked to factor 1. The structurally related fused tricyclics **6**−**8**, which have several receptor affinities in common, cluster in the left part (due to a negative contribution of factor 1) in Figure 4, wherein the PCA factors are plotted. The drug candidates **1**−**3** are located in the right part of Figure 4, accompanied by weak orexigenic antipsychotics, like **5**, **9**, and **12**.

EPS is thought to result from inhibition of the dopaminergic motor control pathways in the nigro-striatal area of the brain, producing symptoms such as akathisia, parkinsonism, dystonia, and dyskinesia. In addition, EPS may increase[36] the likelihood of subsequent tardive dyskinesia, neuroleptic dysphoria, negative

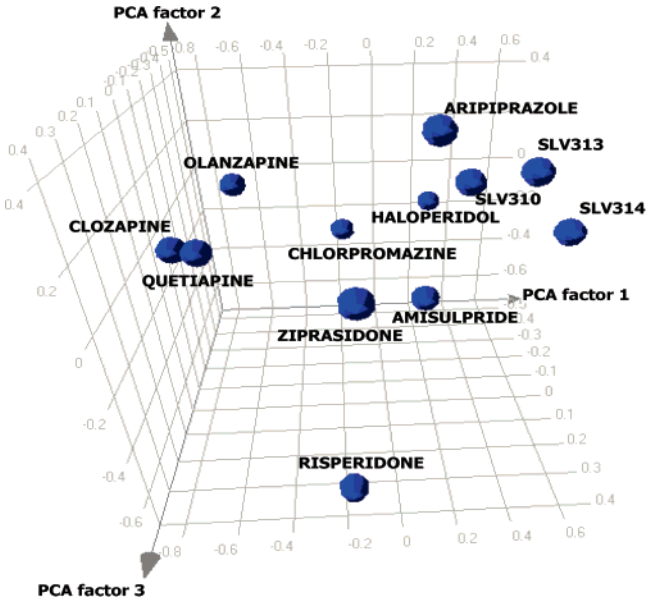

Figure 4. 3D plot displaying the results of a PCA-based clustering for compounds **1**−**12**, using a set of 16 different receptor binding results.

symptoms, and cognitive impairment. The typical antipsychotics **4**−**5** produce EPS already at their therapeutic dose. The atypicals **6** and **8**−**9** were reported to be devoid of EPS,[37] whereas **7** and **11**−**12** elicit less EPS than **4**−**5** albeit they still show evidence[38] of a dose-related increase in EPS. The sensitivity of EPS liability to **10** was the primary reason to lower its initially recommended target dose.[37] The three compounds **6** and **8**−**9**, which are devoid of EPS, do not cluster in the ^{3}D plot (Figure 4). However, all these three compounds scored moderately positive for PCA factor 3. Interestingly, the three drug candidates **1**−**3** also exhibit a low positive value for factor 3 (Figure 3, bottom picture).

Although hyperprolactinaemia has attracted less attention than EPS, it constitutes a serious adverse effect that may result in sexual dysfunction and infertility.[39] Hyperprolactinaemia is common for typical antipsychotics such as **4** and **5**, but also for the atypicals **10** and **12**. Contrarily, the atypical antipsychotics **6**−**9** and **11** were reported[40] to rarely elicit a raise in prolactin serum levels. It is interesting to note that these compounds **4**, **5**, **10**, and **12** cluster by a negative contribution of factor 2 (Figure 3, top picture), whereas all the other compounds are neutral or have a positive contribution of factor 2. The 5-HT$_7$ and the adrenergic α_1/α_2 receptors are strongly negatively linked to factor 1. In addition, the contributions of D_{2-4} and 5-HT$_{2A}$ are linked to a lesser extend. It should be realized that prolactin secretion from the pituitary is regulated in a complex way via several peptide and steroid hormones and receptors, including dopamine D_2, serotonin receptors, GABA, and acetylcholine.[40] Although 5-HT$_{2A}$ receptor stimulation can cause the release of prolactin, 5-HT$_{2A}$ receptor antagonism seems irrelevant in counteracting D_2 antagonist-induced prolactin elevation. This is in line with the potent 5-HT$_{2A}$ receptor antagonistic actions of **10**. For compound **12** its limited brain penetrability may account for its relatively high level of induction of prolactin release[39] because the pituitary gland lies outside the blood−brain barrier.

It should be noted that the PCA is based on receptor binding affinity values. Differences in the degree of receptor activation/inactivation are not accounted for in the PCA. Differences in functional activities that are notably present for D_2 and 5-HT$_{1A}$ will impact the differentiation between the antipsychotics to a certain degree. For example, the recently launched drug aripiprazole was found most similar to the profile of **1**−**3**, but **9** is unique in the sense that it behaves as a partial D_2 agonist whereas **1**−**3** (and the other refererences **4**−**8** and **10**−**12**) are all D_2 receptor antagonists. Partial D_2 agonism is believed to influence dopaminergic neurotransmission in schizophrenia in the mesocortical and mesolimbic pathways, but objectively, there were no differences found[41] with the experimental D_2 partial agonist SDZ HDC 912 regarding efficacy or tolerability with haloperidol, although subjectively, patients had better experiences. There has been a great deal of speculation regarding the role of serotonin modulation in regard to antipsychotic effects, especially in relation with the stimulation of dopamine activity in mesocortical pathways. Compound **2** is a full 5-HT$_{1A}$ agonist, whereas **9** elicits partial 5-HT$_{1A}$ agonism.[42] In vivo, this subtle difference in 5-HT$_{1A}$ activation gave rise to differences in observed behavioral effects in animal models. For example, oral administration of **2** gave rise to 5-HT$_{1A}$ stimulation associated effects such as lower lip retraction, whereas **9** failed to elicit significant 5-HT$_{1A}$ stimulation related behavior and both **6** and the 5-HT$_{1A}$ agonist **11** showed[17] only limited ability to increase lower lip retraction in rats. It can be concluded that although **9** was found most similar to the profile of **1**−**3** in the PCA, it has a different functional profile on both D_2 and 5-HT$_{1A}$ receptor modulation that may lead[43] to a different clinical profile.

Conclusion

The PCA of the three clinical candidates **1**−**3** and a set of nine antipsychotic reference compounds **4**−**12** for a set of 16 receptors relevant for antipsychotic activity and observed side effects, provided clustered groups of compounds.

The weight gain inducing antipsychotics **6**−**8** clustered in the PCA by scoring strongly negative for factor 1. The hyperprolactinaemia related antipsychotics **4**, **5**, **10**, and **12** clustered by scoring negatively for factor 2. The PCA outcome reveals a unique binding profile of the three drug candidates **1**−**3** as compared with the reference compounds **4**−**8** and **10**−**12**. Aripiprazole was found most similar to the profile of **1**−**3** in the PCA.

Experimental Section

Chemistry. The drug candidates **1**−**3** were synthesized according to the published procedures.[14−16] Compounds **4**−**12** are commercially available: **4** (Alltech Associates Inc., Deerfield); **5** (Sigma, St. Louis); **6** (Biomol International, Plymouth meeting); **7**, **9**, **10**, and **12** (Toronto Research Chemicals, North York, Canada); **8** (SST Corporation, Clifton); **11** (ACC Corporation, San Diego).

Receptor Binding Methods. The receptor binding assays were performed at CEREP (Celle l'Evescault, France) using the conditions outlined in the Supporting Information. Following incubation, the receptor preparations were rapidly filtered under vacuum through glass fiber filters; the filters were washed extensively with an ice-cold buffer using a harvester. Bound radioactivity was measured by scintillation counting using a liquid scintillation cocktail. Compounds were tested in duplicate at a log 3 concentration range around a predetermined IC_{50}. IC_{50} values were determined by nonlinear regression analysis using Hill equation curve fitting. The inhibition constants (K_i) were calculated from the Cheng−Prushoff equation.[44] Results are expressed as means ± SD of at least three separate experiments. Compounds with no significant affinity at concentrations of 1 μM and higher were concluded to be "inactive".

PCA and Statistical Methods. For the PCA, the pK_i values of the compounds **1**−**12** in the sixteen receptor binding assays were considered. A two-step statistical procedure was applied herein. First, the censored (pK_i < 6) observations were replaced by their predicted mean and standard deviation, derived from the assumption that the pK_i values of the compounds have a normal distribution.

This normal distribution was estimated by maximum likelihood for censored data.[45] Conditional on the estimated mean (μ) and standard deviation (σ), each $pK_i < 6$ value corresponds to a truncated normal distribution for which the predicted mean μ_i and standard deviation σ_i were calculated.[46] The censored observations were downweighted to weight $1 - \sigma_i^2/\sigma^2 < 1$. For example, for the censored result of **5** in 5-HT_{1A}, the value 5.0 with weight factor 0.76 was calculated. Second, the factor analysis was performed by stepwise expansion of a mixed-model (PROC MIXED[47]) with compound as fixed effect and with a factor-analytic covariance structure across receptors. Three factors were retained. The compound effect served as an implicit fourth factor corresponding to the compound average over the receptors.

Acknowledgment. The compound **2** is codeveloped with Wyeth Pharmaceuticals, a division of Wyeth.

Supporting Information Available: Conditions of receptor binding assays and contributions from the 16 pharmacological assays to the three factors from the stepwise PCA. This material is available free of charge via the Internet at http://pubs.acs.org.

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