

# Field Alignment Studies on a Series of Piperazine Based CNS Active Agents

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**Abstract** Field alignment studies have been carried out on a series of piperazine based agent with central nervous system activity with respect to a set of standard atypical antipsychotics. This alignment method takes into account the local extrema of electrostatic, vander Waals and hydrophobic potentials of the molecule termed as 'field points' or 'extended pharmacophores' and aligns the molecules based on the relative positioning of these points. The standard drugs taken for the study included the dibenzodiazepine derivative clozapine and some other drugs with extended chain structure ketanserin, ziprasidone and risperidone. The three dimensional similarity of the molecules to the standard drugs based on their field scores and shape scores has been computed. The results obtained were found to agree with the physicochemical similarity of the compounds reported earlier.

**Keywords:** Molecular Fields, Field Similarity, Piperazine, Field Points, 3D Similarity, Shape Similarity

## 1. Introduction

The underlying basis for all the computer aided approaches to molecular design is the interaction of ligand molecules with complimentary sites of a specific target structure. Members of a congeneric series of compounds with a common potential biological target can thus, be assessed and compared with respect to their interaction with the target site based on their mutual similarity. This approach does have its inherent limitations and there are reported studies which suggest that a structural similarity may not always translate into same level of potency/activity [1]. Several two dimensional (based on descriptors, common substructures, etc.) and three dimensional approaches towards quantification of molecular similarity have been worked out in the recent past, which return a mathematical score indicating a level of similarity between the compared molecules [2,3].

Amongst the 3D methods, some are based on descriptors such as geometric atom pairs and their distances, valence and torsion angles, atom triplets, etc. and hence, these are independent of the alignment of molecules. The field-based alignment methods [4,5,6] additionally, take into consideration, the conformational flexibility of the molecules and are based on quantum mechanical calculations. The similarity score is related to the electron density of the molecules which involves calculation of steric fields (van der Waals surface) and electrostatic fields (derived from pre calculated point charges). In these methods, multiple molecules can be aligned to a reference molecule in a predefined conformation and the alignment is based on molecular fields (and not structure) of the molecules. This makes field assessment a valuable tool for library design as well as a means to rationalize prioritization of compounds for synthesis because a ligand-protein interaction also

involves hydrogen bonding and hydrophobic surfaces, etc. which can be explained by electrostatic fields and surface properties of the molecules. This aligning and scoring of molecules is a powerful designing tool as it is based upon the molecular aspects important for biological activity. A useful application of this approach is for rational drug designing in the research areas where the 3D structure of the target site structure is not available or when a single receptor binding profile cannot justify the activity of the compounds due to involvement of multiple target sites. This is particularly relevant for antipsychotics as extremely diverse set of target sites including dopaminergic, serotonergic, glutamatergic, etc. [7,8,9,10,11,12] are known to be involved in determining their atypical profile.

Comparable activities of diverse molecules at the same molecular targets can be explained by considering the molecules' fields rather than their atomic structure, because the field pattern is a far superior description of a molecule's binding properties than its atomic structure. Compounds which are structurally diverse but show comparable activity have similar fields and hence, similar binding properties so that these can bind to the same target site and elicit the same biological effect.

We had recently reported a novel series of piperazine based compounds evaluated for their atypical antipsychotic potential [13] and further assessed for their 2D similarity (physicochemical similarity) with respect to the standard atypical antipsychotic drugs. The present research paper describes the molecular field alignment studies carried out on this set of compounds and assessment of their 3D similarity (based on field similarity and shape similarity) to the standard drugs clozapine, risperidone, ziprasidone and ketanserin.

## 2. Method

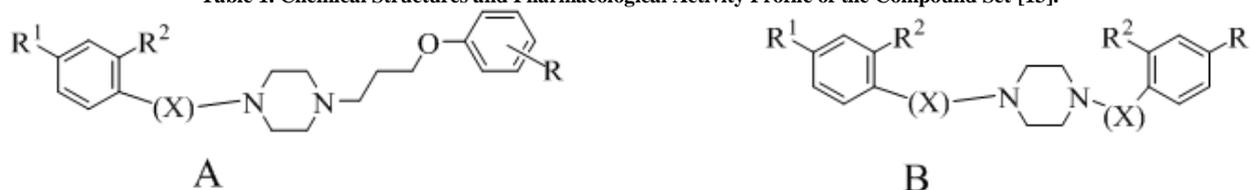
*FieldAlign2.1.1*<sup>TM</sup> (Cresset BioMolecular Discovery Ltd., UK) was used to carry out field based alignment of the compound set with respect to the standard drugs i.e., clozapine, ketanserin, ziprasidone and risperidone. The standard drugs were added as reference molecules for alignment with the test compounds as three dimensional models which were generated using ChemBio3D Ultra 12.0 and energy minimized with MM2 force field to minimum RMS gradient of 0.100. These reference drugs in a defined 3D conformation were then saved in sdf (MDL mol) format and then imported to *FieldAlign2.1.1*<sup>TM</sup>. Further, a 3D reference template was generated for alignment and to assess field similarity taking three reference drug molecules at a time (loaded as single 2D structures) using *FieldTemplator2.1.1* (Cresset BioMolecular Discovery Ltd., UK) The latter searches for common field patterns across the explored conformational space of a set of ligands looking for commonality. The best template (representative of common structural features in the three standard drugs) was selected based on their field similarity, shape similarity and overall similarity scores. Molecules to be aligned were imported as two dimensional structures from ChemBioDraw Ultra 12.0 as sdf (MDL mol) files and various conformations were generated. Coarseness of the sampling of

conformational space was controlled by filtering duplicate conformers at rms 0.5. The maximum number of conformations generated for any molecule was limited to 200 in order to have a balance of the quality of alignments and calculation time. Number of high temperature dynamics for flexible rings was set at 5. Gradient cut-off for the conformer minimization was 0.5. Standard scoring function was used based on 50% field similarity and 50% shape similarity to derive overall similarity score between two conformations.

### 3. Results and Discussion

The chemical structures and pharmacological activity profile of the compound set (1-10) taken for the 3D alignment studies is shown in Table 1. The overall alignment (similarity) scores along with the corresponding field similarity and the shapesimilarity scores of the test molecules were assessed with respect to a selection of standard drugs. The tabulated alignment scores serve as a measure of how similar the molecular fields of the two molecules are in the given alignment. A score higher than 0.5 may be considered satisfactory, though other factors may also need to be considered.

Table 1. Chemical Structures and Pharmacological Activity Profile of the Compound Set [13].



Compound	Structure type	R	R <sup>1</sup>	R <sup>2</sup>	X	Reversal of apomorphine induced mesh climbing <sup>a</sup>	Reversal of apomorphine induced stereotypy <sup>a</sup>	ED <sub>50</sub> (mg/kg) (mesh climbing)	Log ED <sub>50</sub>
1	A	p-COCH <sub>3</sub>	Cl	H	CH <sub>2</sub>	+	+	50.0	1.70
2	A	p-COCH <sub>3</sub>	H	Cl	CH <sub>2</sub>	+	+	23.0	1.36
3	A	o-COCH <sub>3</sub>	Cl	H	CH <sub>2</sub>	+	-	10.0	1.00
4	A	o-COCH <sub>3</sub>	H	Cl	CH <sub>2</sub>	+	-	10.5	1.02
5	A	p-COCH <sub>3</sub>	Cl	H	C=O	-	+	-	-
6	A	p-COCH <sub>3</sub>	H	Cl	C=O	-	+	-	-
7	A	o-COCH <sub>3</sub>	Cl	H	C=O	-	+	-	-
8	A	o-COCH <sub>3</sub>	H	Cl	C=O	-	+	-	-
9	B	-	Cl	H	CH <sub>2</sub>	+	+	10.5	1.02
10	B	-	H	Cl	CH <sub>2</sub>	+	+	7.2	0.86

<sup>a</sup>Statistically significant reduction compared to control at  $p < 0.05$

Table 2. Similarity of Test Compounds with Respect to Risperidone (Ris) and Ketanserin (Ket).

Compd. No.	Similarity		Field Similarity		Field Score		Shape Similarity		Shape Score	
	Ris.	Ket.	Ris.	Ket.	Ris.	Ket.	Ris.	Ket.	Ris.	Ket.
1	0.589	0.661	0.420	0.564	-40.941	-55.892	0.757	0.758	195.486	189.440
2	0.647	0.710	0.527	0.624	-52.182	-63.111	0.766	0.795	197.662	198.740
3	0.686	0.714	0.560	0.651	-57.846	-62.548	0.812	0.778	209.543	194.446
4	0.663	0.719	0.579	0.641	-55.182	-64.617	0.747	0.796	192.895	199.238
5	0.610	0.691	0.486	0.565	-47.740	-57.132	0.734	0.817	190.748	205.588
6	0.631	0.652	0.512	0.541	-51.708	-57.877	0.751	0.763	195.140	192.260
7	0.680	0.753	0.567	0.651	-58.327	-65.677	0.792	0.855	205.850	215.339

8	0.651	0.694	0.508	0.593	-53.732	-61.263	0.794	0.795	206.606	200.066
9	0.638	0.672	0.524	0.570	-45.758	-50.915	0.753	0.773	181.062	179.644
10	0.610	0.627	0.487	0.557	-42.793	-48.960	0.733	0.697	176.383	161.899

**Table 3. Similarity of Test Compounds with Respect to Ziprasidone (Zip) and Clozapine (Clz).**

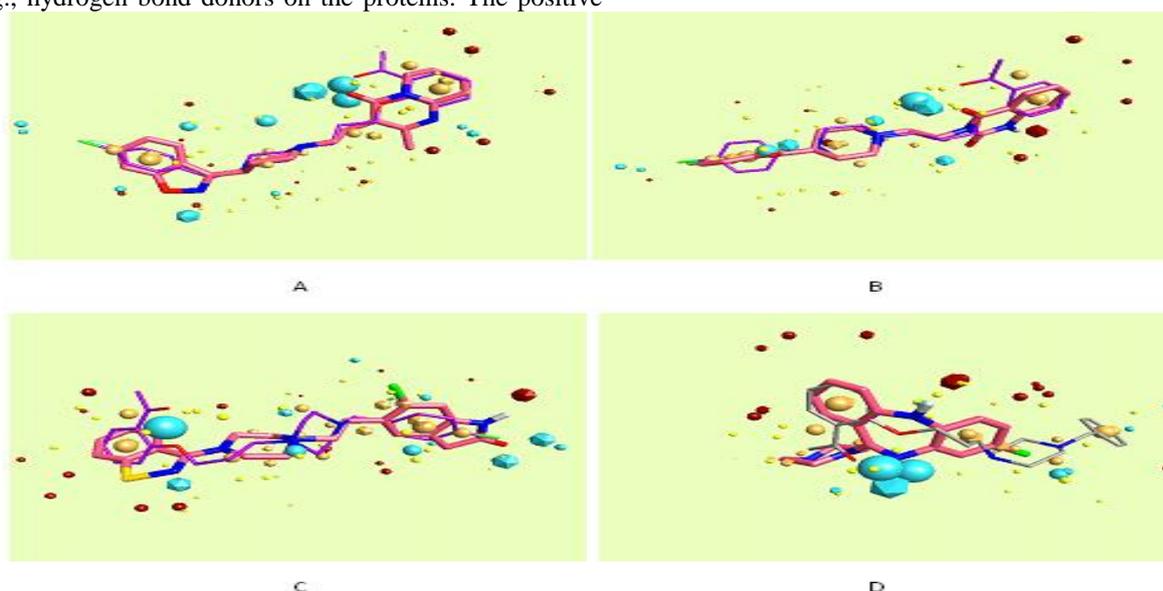
Compd. No.	Similarity		Field Similarity		Field Score		Shape Similarity		Shape Score	
	Zip.	Clz.	Zip.	Clz.	Zip.	Clz.	Zip.	Clz.	Zip.	Clz.
1	0.627	0.663	0.532	0.614	-54.593	-57.475	0.721	0.712	185.344	165.198
2	0.658	0.586	0.543	0.565	-57.542	-54.702	0.773	0.608	198.641	140.963
3	0.646	0.590	0.590	0.594	-59.986	-55.653	0.702	0.778	209.543	136.087
4	0.658	0.592	0.502	0.583	-55.182	-53.115	0.815	0.601	209.275	139.540
5	0.622	0.565	0.492	0.532	-52.192	-51.264	0.753	0.598	194.688	139.856
6	0.682	0.538	0.567	0.520	-62.382	-49.934	0.797	0.557	206.211	130.353
7	0.621	0.546	0.502	0.514	-52.913	-49.789	0.741	0.579	191.677	135.501
8	0.662	0.557	0.515	0.545	-54.500	-52.046	0.808	0.569	209.261	133.236
9	0.659	0.622	0.565	0.616	-52.347	-50.586	0.753	0.627	180.504	134.632
10	0.708	0.649	0.611	0.635	-55.774	-53.381	0.805	0.662	193.009	142.191

**Table 4. Similarity of Test Compounds with Respect to Chlorpromazine (CPZ) and Template (Temp).**

Compd. No.	Similarity		Field Similarity		Field Score		Shape Similarity		Shape Score	
	CPZ	Temp	CPZ	Temp	CPZ	Temp	CPZ	Temp	CPZ	Temp
1	0.567	0.590	0.567	0.447	-54.095	-46.150	0.568	0.732	137.423	187.175
2	0.567	0.612	0.475	0.489	-43.837	-51.255	0.659	0.735	159.369	187.684
3	0.582	0.613	0.539	0.509	-51.647	-50.700	0.625	0.717	151.041	183.110
4	0.565	0.640	0.517	0.546	-45.878	-55.824	0.614	0.735	148.522	187.634
5	0.533	0.606	0.510	0.466	-48.321	-50.810	0.556	0.746	135.419	192.033
6	0.546	0.595	0.499	0.510	-49.493	-53.054	0.592	0.680	144.374	174.732
7	0.579	0.636	0.543	0.537	-53.123	-57.331	0.614	0.736	149.671	189.230
8	0.582	0.591	0.551	0.475	-55.053	-50.756	0.794	0.706	149.601	181.497
9	0.584	0.616	0.554	0.426	-45.202	-38.279	0.614	0.806	137.620	191.472
10	0.641	0.631	0.577	0.507	-47.121	-46.355	0.704	0.755	158.135	179.545

The graphic display shown in Figure 1 shows the best alignment (highest alignment score) of the compound 3 with standard drugs along with the various field points. The negative field points (blue) indicate that these are likely to interact with positively charged receptor areas, e.g., hydrogen bond donors on the proteins. The positive

field points (red) are likely to interact with negatives, e.g., hydrogen bond acceptors. The van der Waals surface points (yellow) indicate areas for van der Waals interactions. The hydrophobic field points (brown) indicate regions of high hydrophobicity/polarizability.



**Figure 1.** Alignment of compound 3 (thin sticks) with risperidone (A), ketanserin (B), ziprasidone (C) and clozapine (D). Reference compounds (standard drugs) are shown as capped sticks (pink). Tetrahedra and dodecahedra depict field points for 3 and reference compounds respectively. Blue, maroon, yellow and brown colors depict negative field, positive field, surface field and hydrophobic field points.

Compounds 3 and 4 are the lead compounds which had demonstrated a good activity and potential atypical antipsychotic profile in our earlier studies [13]. In

comparison, compounds 1 and 2 had shown a somewhat reduced potency. The best alignment obtained with risperidone shows the field superposition of negative field

points corresponding to the ether oxygen in compounds **3** and **4** and carbonyl oxygen in the drug as a major contributor to field similarity. Interestingly, this was not seen in case of less active compounds **1** and **2** although, hydrophobic field points showed good overlap. Further, a near perfect overlap of the chloro group and piperazine ring in **3** and **4** with fluoro group and the piperidine ring in the drug was observed coupled with superposition of several hydrophobic field points. The acetyl group does not however, assume correspondence with any of the two heterocyclic nitrogens in risperidone. However, good intersection of field points of the acetyl group with those of quinazolinone oxygens in ketanserin is seen in addition to the superposition of negative field points of ether moiety, piperazine nitrogens and the corresponding halogen atoms in compounds **3** and **4** with similar moieties in ketanserin which accounts for their higher similarity to ketanserin than to risperidone.

The best alignment of **3** and **4** with ziprasidone shows superposition of negative field points corresponding to ether oxygen in **3** and **4** with benzothiazole system in the drug. Further, hydrophobic field superposition seems to account significantly for the overall 3D similarity in this case. All the compounds **1-10**, especially, the active analogs have shown somewhat different overlay models and the only common feature was the superposition of piperazine rings. Although, a strong negative field point overlap is shown with ring nitrogens of clozapine, however, a good similarity score is not obtained due to absence of significant van der Waals and hydrophobic point overlap. Further, the alignment with the three compound template generated from risperidone, ketanserin and ziprasidone does not improve the similarity scores as evident from the graphic display in [Figure 1](#).

The overall similarity scores of the compounds were found to be higher for *ortho*-acetyl substituted compounds (compared to their corresponding *para* analogs) with respect to risperidone, ketanserin and ziprasidone. The difference was not found to be significant with respect to clozapine, chlorpromazine and the three-compound template. The similarity scores for the compounds were found to be the highest with respect to ketanserin followed by ziprasidone and risperidone. Interestingly, these results are in agreement with our previously reported physicochemical similarity values. In line with the results from our previous computational studies, wherein, the physicochemical similarity was lowest with respect to the more compact dibenzodiazepine derivative clozapine (nearly 35%), the 3D similarity values were also found to be the lowest with respect to clozapine as well as the conventional neuroleptic chlorpromazine. However, a very significant difference is noted for the compounds **1** and **2** which were reported to be having lowest physicochemical similarity scores ranging from 16-45% with respect to risperidone, ziprasidone and ketanserin [13], but their field alignment scores are comparable to active compounds of the series. This can possibly explain their observed good *in vivo* activity in the apomorphine induced mesh climbing assay.

An analysis of the breakup of the overall alignment scores shows that the contribution of the shape similarity was found to be significantly greater than the corresponding field similarity values in all the cases. As evident from the tables, the shape similarity is more than 0.7 for all the drug examples (except clozapine and

chlorpromazine) whereas, their field similarity scores range from 0.54 to 0.58.

This study particularly highlights the importance of negative field points likely to contribute towards interactions with the corresponding receptor sites by acting as hydrogen bond acceptors. Virtually all the test compounds and the standard drugs have significantly prominent negative field regions which are also seen to superimpose in the overlay studies. Hydrophobicity (polarizability) is seen to be another striking feature in the pharmacological activity of the compound series as seen from the overlap of the rather prominent hydrophobic field points of the compounds with drug examples. Overlap of smaller areas (albeit in greater number) of van der Waals surface points (yellow) suggest the shape contribution towards overall similarity and these relatively weak intensity interactions can contribute eminently towards the drug target bonding. The positive field points (red) are seen to contribute minimally towards overall similarity with respect to all the drugs except clozapine where a fairly significant overlap is seen. Hence, overall inclusion of hydrogen bond acceptor regions in the chemical structure of the prospective drug candidates is more likely to generate active molecules compared to hydrogen bond donor moieties.

## 4. Conclusions

The selected set of quinolyl oxypropyl piperazine derivatives analyzed for their three dimensional similarity to a selection of atypical antipsychotic drugs have demonstrated a higher similarity with respect to the extended chain structures such as risperidone, ziprasidone and ketanserin and lesser similarity to the prototypic agent clozapine. Further, specific patterns were observed for the change in similarity scores with change in chemical structure. An introspection of the field alignments obtained for the molecules (especially, the lead compound from our studies **3**) with respect to standard drugs suggests a good correspondence of quinoline nitrogen, piperazine system, etheroxygen and chlorine atom with the corresponding groupings in the standard drug molecules. This highlights the importance of these structural features as a part of the pharmacophoric system of this class of compounds and emphasizes the requirement of negative field points and hydrophobic regions for good pharmacological activity. Further development of this compound series can be carried out by appropriate modifications whilst retaining these salient features. Hence, the information generated from the molecular field analysis of this compound series can be used as a valuable tool for designing novel analogues by interpretation of their pharmacological activity in terms of their field pattern.

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