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Vibrational Spectra of [(3-chloro phenyl) Piprazine 1-yl]-3-[oxy (3-acetamidazole Phenyl) Propane]: A Highly Potent Hypertensive Drug

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Abstract – [(3-chloro phenyl) piprazine 1-yl]-3-[oxy (3-acetamidazole phenyl) propane] is a hypertensive drug. Navane possesses certain chemical and pharmacological similarities to the piperazinephenothiazines and differences from the aliphatic group of phenothiazines. Although widely used in the treatment of schizophrenia for several decades, thiothixene is seldom used today in favor of atypical antipsychotics such as risperidone. A complete assignment of fundamental vibration frequencies has been made, and the spectra have been interpreted in detail. The non-planar frequencies have been calculated with the aid of force constants determined for related molecules. The fundamental vibrational frequencies and intensity of vibrational bands were evaluated using density functional theory (DFT) using standard B3LYP/6-31G methods and basis set combinations.The optimized geometric structure of (9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) has been studied by using Density Functional Theory (DFT). On the basis of ground and excited state geometries, the absorption spectra have been calculated using the DFT method. To understand the Non-Linear Optical properties of (9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene), we computed dipole moment (μ) ,using B3LYP density functional theory method in conjunction with 6-31G basis set.

Keywords: FTIR, DFT, HOMO, LUMO, Vibrational Spectra

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INTRODUCTION

(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) is a typical antipsychotic of the thioxanthene class which is related to chlorprothixene and is used in the treatment of psychoses like schizophrenia and bipolar mania.Chemical Formula of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) isC23H29N3O2S2Tiotixene acts primarily as a highly potent antagonist of the dopamine D2 and D3 receptors (subnanomolar affinity). It is also an antagonist of the histamine H1, α1-adrenergic, and serotonin 5-HT7 receptors (low nanomolar affinity), as well as of various other receptors to a much lesser extent (lower affinity). It does not have any anticholinergicactivity.[3] Antagonism of the D2 receptor is thought to be responsible for the antipsychotic effects of tiotixene. Thiothixene is a thioxanthine used as an antipsychotic agent. Its effects are similar to the phenothiazine antipsychotics. Thiothixene is a thioxanthene derivative and a dopamine antagonist with antipsychotic property. Thiothixene blocks postsynaptic dopamine receptors in the mesolimbic system and medullary chemoreceptor trigger zone, thereby decreasing dopamine activity leading to decreased stimulation of the vomiting center and psychotic effects, such as hallucinations and delusions. In addition, this agent blocks the D2 somatodendritic autoreceptor, thereby increasing dopamine turnover. Thiothixene possesses weak affinity for the histamine H1 and alpha-adrenergic receptors. Dual action hypotheses have suggested that antipsychotic compounds may show a stimulating effect at low doses and an antipsychotic effect at higher doses. The clinical literature of thiothixene in adult schizophrenic patients was reviewed in an attempt to correlate optimal dose with chosen indices of the dual action hypothesis. Activation and side effects of CNS stimulation correlated highly with each other and with dosage; a significant negative regression line on optimal dose was seen. Overall efficacy did not correlate with dosage or with activation-stimulation, but showed the presence of an antipsychotic component at least equal to standard antipsychotics. The method employed seems

suitable to test the hypothesis in other antipsychotic compounds.

Antipsychotics, also known as neuroleptics or major tranquilizers, are a class of medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder. They are increasingly being used in the management of non-psychotic disorders. Antipsychotics are usually effective in relieving symptoms of psychosis in the short term. Psychosis is an abnormal condition of the mind that results in difficulties telling what is real and what is not. Symptoms may include false beliefs and seeing or hearing things that others do not see or hear. Other symptoms may include incoherent speech and behavior that is inappropriate for the situation. There may also be sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities.Antipsychotic drugs such as haloperidol and chlorpromazine tend to block dopamine D2 receptors in the dopaminergic pathways of the brain. This means that dopamine released in these pathways has less effect.

(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) using Gauss view program packages at the Becke3-Lee-Yang-Parr (B3LYP) level with standard 6-31G basis set.DFT computational codes are used in practise to investigate the structural, magnetic and electronic properties of molecules, materials and defects. DFT calculations allow the prediction and calculation of material behaviour on the basis of quantum mechanical considerations, without requiring higher order parameters such as fundamental material properties. DFT computational methods are applied for the study of systems to synthesis and processing parameters. In such systems, experimental studies are often encumbered by inconsistent results and non-equilibrium conditions. Examples of contemporary DFT applications include studying the effects of dopants on phase transformation behaviour in oxides, magnetic behaviour in dilute magnetic semiconductor materials.

METHOD, MATERIAL AND THEORY:

DFT is supported by many quantum chemistry and solid state physics software packages, often along with other methods.Optimized geometrical structure of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene);

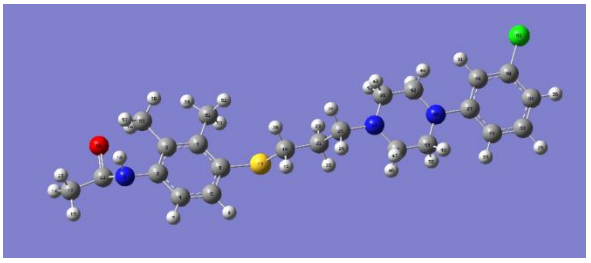

FIG.1

The vibrational frequencies of the solid phase FT-IR and FT-Raman spectra of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) were recorded in the regions 3500-500 and 3500-100 cm(-1), respectively. The optimized geometry, frequency and intensity of the vibrational bands of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) were obtained by the Restricted Hartree-Fock (RHF) density functional theory (DFT) with complete relaxation in the potential energy surface using 6-31G basis set. The harmonic vibrational frequencies for(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) were calculated and the scaled values have been compared with experimental values of FTIR and FT-Raman spectra. The observed and the calculated frequencies are found to be in good agreement. The harmonic vibrational wave numbers and intensities of vibrational bands of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) with its cation and anion were calculated and compared with the neutralThiothixene. The DFT calculated HOMO and LUMO energies shows that charge transfer occurs within the molecule. DFT calculations allow the prediction and calculation of material behavior on the basis of quantum mechanical considerations, without requiring higher order parameters such as fundamental material properties.

IR and Raman Frequencies

Infrared and Raman spectra of different crystalline forms of the same organic compound can be used to identify a pure crystal form and quantify a mixture of two forms. Many organic compounds have one or more crystalline or polymorphic forms. The observed differences in the spectra of different polymorphs include changes in frequencies, relative intensities, band contours and the number of bands.The IR and Raman spectra of (9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) an antipsychotics compound have been computed performing density functional theory calculations at the B3LYP/6-31G(d) level of theory. In Vibrational spectroscopy the infrared and Raman spectra of optimized geometrical structure of pharmaceutical

compound(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) were also evaluate from the calculation of intensities. Then the following figures show the calculated IR and Raman spectra of Optimized geometrical structure(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide(Thiothixene) .These calculations were done by using B3LYP/6-31G methods.

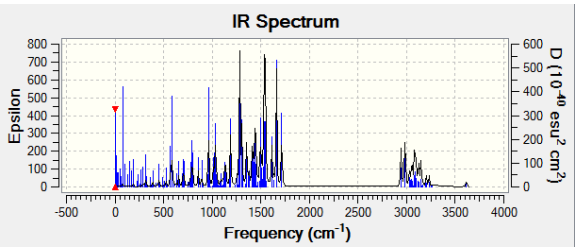

FIG. 2Spectrum of IR

Energy and Dipole Moment

Dipole moment, the measure of the electrical polarity of a system of chargesThe electric dipole moment is a measure of the separation of positive and negative electrical charges within a system, that is, a measure of the system's overall polarity.Bond dipole moment of Optimized geometrical structural compound is the measurement of polarity of a chemical bond and also known as the mathematical product of the separation of the ends of a dipole and the magnitude of the charges. The dipole moment creates by unequal sharing of electron in optimized geometrical molecules by their atoms.

Dipole moment and energy of the medically active compound[(3-chloro phenyl) piprazine 1-yl]-3-[oxy (3-acetamidazole phenyl) propane] is shown in following table:-

Dipole Moment	6.8929 Debye
Total Energy	-1992.04284709a.u.

(1 Debye = $3.34*10^{-30}$ cm.)

(1 *a.u.* of *energy* = 1hartree = 4.360×10^{-18} J. = 27.211*eV* = 2625kJ/mol = 627.5kcal/mol.)

MOLECULAR ORBITAL ENERGIES

The most important orbitals in a molecule are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).These orbitals determine the way the molecule interacts with other species. The frontier orbital gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.

HOMO and LUMO are types of molecular orbitals. The acronyms stand for "highest occupied molecular orbital" and "lowest unoccupied molecular orbital", respectively. The energy difference between the HOMO and LUMO is termed the HOMO**–**LUMOgap. HOMO and LUMO are sometimes called frontier orbitalsin frontier molecular orbital theory. The difference in energy between these two frontier orbitals can be used to predict the strength and stability of transition metal complexes, as well as the colors they produce in solution.

Energy levels of the frontier molecular orbital's especially HOMO, LUMO as well as their spatial distributions are important parameters for determining the optoelectronic properties. The density plot of the HOMO and LUMO of(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide (Thiothixene) is calculated at B3LYP/6-31G level of theory and are shown in Figure;

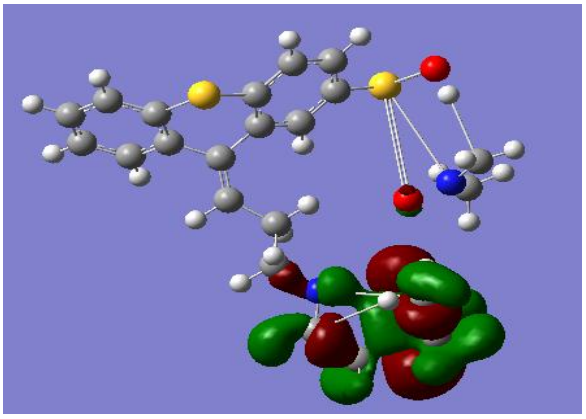

FIG.4HOMO

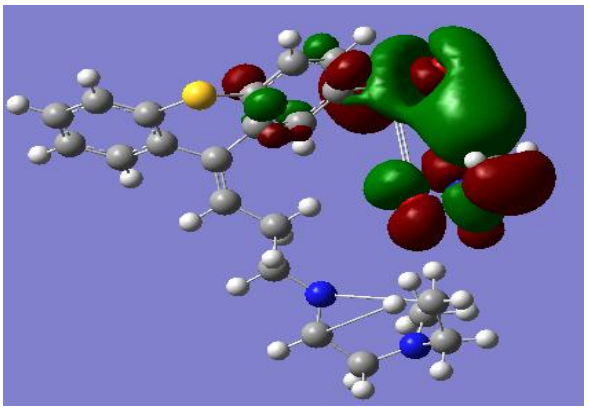

FIG.5LUMO

The energy gap between HOMO and LUMO has been used to prove the bioactivity from intramolecular charge transfer. The energy gap measures the kinetic stability of the molecules. The

HOMO and LUMO energy gap show the charge transfer interaction taking place within the molecule.

The HOMO and LUMO energy calculated by B3LYP /6-31G method as shown below in table:-

HOMO Energy	-0.17636 au
LUMO Energy	-0.06259 au
ENERGY GAP (LUMO-HOMO)	0.10377 au

BOND LENGTH AND BOND ANGLE

In molecular geometry, bond length or bond distance is the average distance between nuclei of two bonded atoms in a molecule. It is a transferable property of a bond between atoms of fixed types, relatively independent of the rest of the molecule. Molecular geometries can be specified in terms of bondlengths, bond angles and torsional angles. The bond length is defined to be the average distance between the nuclei of two atoms bonded together in any given molecule. A bond angleis the angle formed between three atoms across at least two bonds. The such as bond lengths, bond angle are the optimized structural parameters , so these parameters were determined at B3LYP level theory with 6-31G basis set and they are presented in a table, which is given below –

ATOMS	BOND LENGTH
C12-C11	1.51816
C11-O16	1.24664
C11-N9	1.38346
N9-C3	1.43225
C4-C5	1.39067
C2-C1	1.42128
C55-C2	1.51032
H54-C51	1.09511
C6-S17	1.85980
C18-C21	1.52881
H26-C24	1.09845
N32-C39	1.46842
C42-H44	1.10386
N38-C48	1.47603
C27-C28	1.41448
Cl59-C30	1.83525
C34-C32	1.40253
C29-H33	1.08324

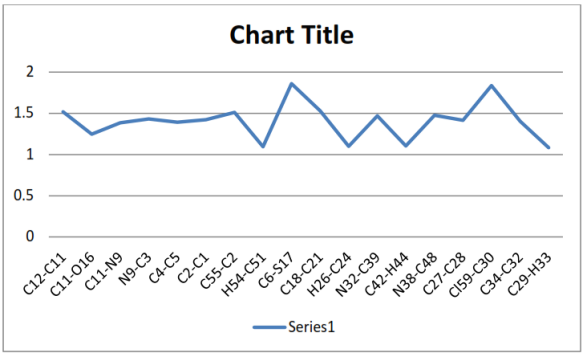

Fig.6 Graph of Bond Length

ATOMS	BOND ANGLE
H13-C12-H14	107.697
O16-C11-N9	123.027
C3-C4-H7	119.556
H58-C55-C2	111.611
C4-C5-H8	120.453
C2-C1-C6	119.179
S17-C18-H19	107.241
C21-C24-H26	109.164
H40-C39-N37	108.632
C42-N38-C48	113.035
H47-C45-N37	108.630
N38-C27-C29	120.829
Cl59-C30-C28	117.785
H36-C34-C32	121.700
C29-C32-C34	121.394

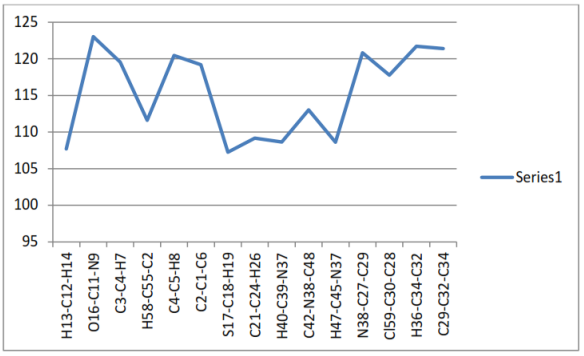

Fig. 7Graph of Bond Angle

CONCLUSION:

Thus, the Simulation report of[(3-chloro phenyl) piprazine 1-yl]-3-[oxy (3-acetamidazole phenyl) propaneis on progress. It will be reported very soon.

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REFERENCES:

1. XF, Deng C (2012). Chang AY, ed. "Alterations to melanocortinergic, GABAergic and cannabinoid neurotransmission associated with olanzapine-induced weight gain". PLOS One. 7 (3): e33548. DOI:10.1371/journal.pone.0033548. PMC 3306411 . PMID 22438946.

2. "American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults". Journal of the American Geriatrics Society. 60 (4): pp. 616–31. April 2012. doi:10.1111/j.1532-5415.2012.03923.x. PMC 3571677 . PMID 22376048.

3. Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, Fusar-Poli P (November 2012). "Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication". Neuroscience and Biobehavioral Reviews. 36 (10): pp. 2325–33. doi:10.1016/j.neubiorev.2012.07.012. PMID 22910680.

4. Chattopadhyay A, ed. (2007). Serotonin receptors in neurobiology. Boca Raton: CRC Press. ISBN 0-8493-3977-4. Archived from the original on 31 December 2015..

5. Gross G, Geyer MA (2012). Current Antipsychotics. Springer. pp. 88–89. doi:10.1007/978-3-642-25761-2. ISBN 978-3-642-25761-2. Archived from the original on 2013-10-13.

6. Sanchez M (May 2012). Farmacología y endocrinologíadelcomportamiento. Editorial UOC. pp. 148–149. ISBN 978-84-9788-424-2. Archived from the original on 25 November 2017.

7. "Archived copy". Archived from the original on 11 October 2016. Retrieved 27 September 2017.

8. "Archived copy". Archived from the original on 18 August 2017. Retrieved 7 May 2017.

9. Csernansky JG (6 December 2012). Antipsychotics. Springer Science & Business Media. pp. 360–. ISBN 978-3-642-61007-3.

10. William Andrew Publishing (22 October 2013). Pharmaceutical Manufacturing Encyclopedia. Elsevier. pp. 1077–. ISBN 978-0-8155-1856-3.

11. William Andrew Publishing (22 October 2013). Pharmaceutical Manufacturing Encyclopedia. Elsevier. pp. 1102–. ISBN 978-0-8155-1856-3.

12. Protiva, M. (2010). "ChemInform Abstract: Fifty Years in Chemical Drug Research". ChemInform. 23 (9): no–no. DOI:10.1002/chin.199209338. ISSN 0931-7597.

13. Melich H (April 1971). "[Clotepin]". CasopisLekaruCeskych (in Czech). 110 (17): pp. 404–5. PMID 5576292.

14. Isbister GK, Balit CR, Macleod D, Duffull SB (August 2010). "Amisulpride overdose is frequently associated with QT prolongation and torsades de pointes". Journal of Clinical Psychopharmacology. 30 (4): 391–5. doi:10.1097/JCP.0b013e3181e5c14c. PMID 20531221.

15. Deeks ED, Keating GM (January 2010). "Blonanserin: a review of its use in the management of schizophrenia". CNS Drugs. 24 (1): pp. 65–84. DOI:10.2165/11202620-000000000-00000. PMID 20030420.

16. José Miguel Vela; Helmut Buschmann; JörgHolenz; Antonio Párraga; Antoni Torrens (2007). Antidepressants, Antipsychotics, Anxiolytics: From Chemistry and Pharmacology to Clinical Application. Weinheim: Wiley-VCH. p. 520. ISBN 3-527-31058-4.

17. Roth, BL; Driscol, J. "PDSP Ki Database" (HTML). Psychoactive Drug Screening Program (PDSP). University of North Carolina at Chapel Hill and the United States National Institute of Mental Health. Retrieved 14 August 2017.

18. Silvestre JS, Prous J (2005). "Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes". Methods Find ExpClinPharmacol. 27 (5): pp. 289–304. doi:10.1358/mf.2005.27.5.908643. PMID 16082416.

19. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL (2003). "H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs". Neuropsychopharmacology. 28 (3): pp.

519–26. doi:10.1038/sj.npp.1300027. PMID 12629531.

20. Burstein ES, Ma J, Wong S, Gao Y, Pham E, Knapp AE, Nash NR, Olsson R, Davis RE, Hacksell U, Weiner DM, Brann MR (2005). "Intrinsic efficacy of antipsychotics at human D2, D3, and D4 dopamine receptors: identification of the clozapine metabolite N-desmethylclozapine as a D2/D3 partial agonist". J. Pharmacol. Exp. Ther. 315 (3): pp. 1278–87. DOI:10.1124/jpet.105.092155. PMID 16135699.

21. William Andrew Publishing (22 October 2013). Pharmaceutical Manufacturing Encyclopedia. Elsevier. pp. 3214–. ISBN 978-0-8155-1856-3.

22. Edward Shorter (2009). Before Prozac: The Troubled History of Mood Disorders in Psychiatry. Oxford University Press, USA. pp. 51–. ISBN 978-0-19-536874-1

23. Tenjin T, Miyamoto S, Ninomiya Y, Kitajima R, Ogino S, Miyake N, Yamaguchi N (2013). "Profile of blonanserin for the treatment of schizophrenia". Neuropsychiatric Disease and Treatment. 9: pp. 587–94. doi:10.2147/NDT.S34433. PMC 3677929 . PMID 23766647.

24. "Clozapine". Martindale: The Complete Drug Reference. Royal Pharmaceutical Society of Great Britain. 30 January 2013. Retrieved 2 November 2013.

25. Matar HE, Almerie MQ, Sampson S (July 2013). Matar HE, ed. "Fluphenazine (oral) versus placebo for schizophrenia" (PDF). The Cochrane Database of Systematic Reviews. 7 (7): CD006352. doi:10.1002/14651858.CD006352.pub2. PMC 3997140. PMID 23861067. Archived from the original on 7 December 2013.

26. Chakrabarti A, Bagnall A, Chue P, Fenton M, Palaniswamy V, Wong W, Xia J (October 2007). Chakrabarti A, ed. "Loxapine for schizophrenia" (PDF). The Cochrane Database of Systematic Reviews (4): on 7 December 2013.

27. Harvey PD, Ogasa M, Cucchiaro J, Loebel A, Keefe RS (April 2011). "Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone". Schizophrenia Research. 127 (1–3): pp. 188–94. doi:10.1016/j.schres.2011.01.004. PMID 21277745.

28. Röhricht F, Gadhia S, Alam R, Willis M (2012). "Auditing clinical outcomes after introducing off-license prescribing of atypical antipsychotic melperone for patients with treatment refractory schizophrenia". The Scientific World Journal. 2012: 512047. doi:10.1100/2012/512047. PMC 3330679 . PMID 22566771.

29. Molindone Hydrochloride (2013). Martindale: The Complete Drug Reference. The Royal Pharmaceutical Society of Great Britain. 30 January 2013. Retrieved 5 November 2013.

30. Leucht S, Helfer B, Hartung B (January 2014). "Perazine for schizophrenia". The Cochrane Database of Systematic Reviews(1): CD002832. DOI:10.1002/14651858.CD002832.pub3. PMID 24425538.

31. Onrust SV, McClellan K (April 2001). "Perospirone" (PDF). CNS Drugs. 15 (4): pp. 329–37; discussion 338. DOI: 10.2165/00023210-200115040-00006. PMID 11463136. Archived from the original (PDF) on 4 November 2013.

32. Wu S, Xing Q, Gao R, Li X, Gu N, Feng G, He L (2005). Response to chlorpromazine treatment may be associated with polymorphisms of the DRD2 gene in Chinese schizophrenic patients. NeurosciLett, Mar 7;376(1): pp. 1-4. Epub 2004 Dec 2.

33. Wu SN, Gao R, Xing QH, Li HF, Shen YF, Gu NF, Feng GY, He L: Association of DRD2 polymorphisms and chlorpromazine-induced extrapyramidal syndrome in Chinese schizophrenic patients. ActaPharmacol Sin. 2006 Aug;27(8): pp. 966-70.

34. Chen X, Ji ZL, Chen YZ: TTD: Therapeutic Target Database. Nucleic Acids Res. 2002 Jan 1;30(1): pp. 412-5.

35. Seeman P. (2010). Dopamine D2 receptors as treatment targets in schizophrenia. ClinSchizophr Relat Psychoses, Apr;4(1): pp. 56-73. DOI: 10.3371/CSRP.4.1.5.

36. Brayfield A., ed. (23 September 2011). Perospirone. Martindale: The Complete Drug Reference. London, UK: Pharmaceutical Press. Retrieved 3 November 2013.

37. Hartung B., Sampson S., Leucht S. (March 2015). "Perphenazine for schizophrenia". The Cochrane Database of Systematic

Reviews(3): CD003443. doi:10.1002/14651858.CD003443.pub3. PMID 25749632.

38. Mothi M, Sampson S (November 2013). "Pimozide for schizophrenia or related psychoses". The Cochrane Database of Systematic Reviews (11): CD001949. doi:10.1002/14651858.CD001949.pub3. PMID 24194433.

39. Wang J, Sampson S (April 2014). "Sulpiride versus placebo for schizophrenia". The Cochrane Database of Systematic Reviews(4): CD007811. doi:10.1002/14651858.CD007811.pub2. PMID 24729184.

40. Fenton M, Rathbone J, Reilly J, Sultana A (July 2007). Reilly J, ed. "Thioridazine for schizophrenia" (PDF). The Cochrane Database of Systematic Reviews (3): CD001944. doi:10.1002/14651858.CD001944.pub2. PMID 17636691. Archived from the original on 3 September 2015.

41. Marques LO, Lima MS, Soares BG (2004). Marques Ld, ed. "Trifluoperazine for schizophrenia" (PDF). The Cochrane Database of Systematic Reviews (1): CD003545. doi:10.1002/14651858.CD003545.pub2. PMID 14974020. Archived from the original on 7 December 2013.

42. "Zotepine". Martindale (2013). The Complete Drug Reference. Royal Pharmaceutical Society of Great Britain. 16 August 2013. Retrieved 2 November 2013.

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