J. Pharm. Res. 2019;18(4):12–16

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

RESEARCH ARTICLE

Z-Isomer Control in the Synthesis of Flupentixol Related Compounds

Vishal Malviya[1], Manjunath Ghate[1]

[1] *Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Bangalore, 560035, Karnataka, India*

ARTICLE INFO

Article history:
Received 18.10.2019
Accepted 22.12.2019
Published 28.12.2019

https://doi.org/10.18579/jopcr/v18.4.vishal

ABSTRACT

Flupentixol, a potent antipsychotic and antidepressant, exists in two geometric isomers, Z and E, with the Z-isomer being the therapeutically active form. The synthesis of flupentixol and related compounds often faces the challenge of controlling the stereochemistry to favor the Z-isomer. The study aimed to identify the optimal conditions for producing the Z-isomer, which is more therapeutically relevant. 2-(trifluoromethyl)-9H-thioxanthen-9-one was prepared from 2-mercaptobenzoic acid and perabromobenzotrifluoride, followed by a Grignard rearrangement to form (9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol. The intermediate was dehydrated with various acids to produce the E and Z isomers of Flupentixol, with the product ratios subsequently analyzed using ^{1}H-NMR spectroscopy. The dehydration reactions yielded different E/Z isomer ratios, yields, and melting points, depending on the acid used. Hydrochloric, oxalic, and methanesulfonic acids favored the formation of the Z-isomer with E/Z ratios of 11:89, 14:86, and 12:88, respectively, while succinic acid achieved the highest yield (84.75%) with a 37:63 E/Z ratio. Maleic acid and ferrous sulfate produced intermediate ratios, and DL- and L(+)-tartaric acids gave similar results with high yields. This study revealed a novel insight into the influence of various acids on the dehydration reactions, highlighting specific acids that significantly favor the formation of the therapeutically active Z-isomer of Flupentixol with optimized yields and ratios.

Keywords: Flupentixol; Zisomer; Eisomer; Antipsychotic drugs; ^{1}HNMR; Racemic resolution

INTRODUCTION

Medicinal chemistry focuses on the discovery, development, and molecular-level analysis of biologically active compounds (pharmacophores) and the study, identification, and synthesis of their metabolic products. Antipsychotic agents are particularly useful as alternatives to electroconvulsive therapy (ECT) for severe depression with psychotic features and are also employed in managing psychotic disorders associated with delirium, dementia, or those induced by other agents like stimulants or L-dopa[1]. Atypical antipsychotics are characterized by their lower risk of extrapyramidal side effects. Examples of these agents include aripiprazole, clozapine, quetiapine, ziprasidone, and low doses of olanzapine and risperidone[2]. Flupentixol, an antipsychotic drug, is a mixture of cis and trans isomers of the compound (3-(2-trifluoromethyl)-8aH-thioxanthen–9(10aH)-ylidene)-N, N-dimethyl propan-1-amine. The trans isomer is more active than the cis isomer. Classified as a thioxanthene derivative, Flupentixol primarily acts by antagonizing D1 and D2 dopamine receptors as well as serotonin receptors. It is used to treat mental illnesses characterized by symptoms such as hallucinations, delusions, and social interaction problems[3]. different research groups have synthesized various thioxanthene derivatives in cis (Z) and trans (E) forms, evaluating them for antipsychotic and antihypertensive activities. It was found that cis(Z)-Chlorprothixene exhibits significant antidopaminergic potency, while trans(E)-Chlorprothixene is virtually inactive. Similarly, Flupentixol exists as cis(Z) and trans(E) isomers, with the Z-isomer being more active than the E-isomer. The ratio of E and Z isomers varies depending on the acid used for the dehydration of the thioxanthene intermediate[4,5]. This study aims to minimize or eliminate the E-isomer in antipsychotic drugs, specifically Flupentixol, and enhance the pharmacological potency of the single, more active Z-isomer.

KRUPANIDHI COLLEGE OF PHARMACY

METHODOLOGY

Chemicals and reagents

The study utilized the following chemicals: acetone, ethyl acetate, phosphoric acid, HCl, methanesulfonic acid, succinic acid, maleic acid, sodium carbonate, ferrous sulfate, oxalic acid, fumaric acid, L(+)-tartaric acid, DL-tartaric acid, 2-mercaptobenzoic acid, perabromobenzotrifluoride, and chloropropyl amine.

Identification and Characterisation

The synthesized compounds were identified and characterized using a range of analytical techniques. These methods included melting point determination, thin layer chromatography, infrared spectroscopy, nuclear magnetic resonance spectroscopy, and mass spectroscopy.

Melting point determination

The melting points of the synthesized pure compounds were determined using Thiel's tube method to assess purity, as pure crystalline compounds exhibit sharp melting points. IR spectra were recorded using KBr pellets in the range of 4000–400 cm^{-1} on a Shimadzu 8700 Fourier Transform IR Spectrophotometer. For further analysis, ^1H NMR spectra (400 MHz) were obtained in deuterated chloroform using an Amx-200 NMR spectrometer, with chemical shifts (δ) reported in parts per million, relative to tetramethylsilane (TMS). Mass spectra were recorded at the Indian Institute of Science, Bangalore, using electron spray ionization mass spectrometry, which provided insights into the molecular structure and weight by analyzing ions based on their mass-to-charge ratio.

Synthesis of 2-(trifluoromethyl)-9H-thioxanthen- 9 one

Step 1: Synthesis of 2-{[4-(trifluoromethyl)phenyl] sulfanyl} benzoic acid

The synthesis of 2-{[4-(trifluoromethyl)phenyl]sulfanyl}benzoic acid ($C_{14}H_9F_3O_2S$, 295 g/mol) involved refluxing 2-mercaptobenzoic acid (10 g, 6.49 mmol), perbromobenzotrifluoride (16.06 g, 9.73 mmol), anhydrous K_3PO_4 (20.6 g, 9.73 mmol), and 10% copper iodide in dimethyl sulfoxide (40 mL) at 140°C under vacuum for 12 hours. The reaction mixture was then diluted, acidified to pH 2, and the compound was extracted with dichloromethane. The resulting product, a white solid freely soluble in chloroform, had a practical yield of 19 g (98.44%). IR spectra of the product showed peaks at 3070.6 cm^{-1} (C-H aromatic), 2929.87 cm^{-1} (C-H aliphatic), and 1676.14 cm^{-1} (C=O stretch).

Step 2: Synthesis of 2-(trifluoromethyl)-9H-thioxanthen-9-one

The synthesis of 2-(trifluoromethyl)-9H-thioxanthen-9-one ($C_{14}H_9F_3OS$, 282 g/mol) involved refluxing 2-{[4-(trifluoromethyl) phenyl] sulfanyl} benzoic acid (19 g, 6.44 mmol) with polyphosphoric acid (38 g, 12.8 mmol) in toluene (95 mL) at 108°C under nitrogen for 10 hours. The mixture was diluted, and the product was extracted with dichloromethane. The resulting white solid had a melting point of 346-347°C and a practical yield of 18 g (89.1%). IR spectra showed peaks at 3045.6 cm^{-1} (C-H aromatic), 2924.09 cm^{-1} (C-H aliphatic), and 1647.21 cm^{-1} (C=O stretch). ^1H NMR signals included δ 7.62 (singlet), δ 7.58, δ 7.55, δ 7.51, δ 7.48, and δ 7.47 (aromatic protons).

Synthesis of intermediate (9-(3-dimethyl amino) propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol)

The synthesis of 9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol ($C_{19}H_{22}F_3NOS$, 369 g/mol) involved reacting dried magnesium (12 g, 43.3 mmol) with chloropropylamine (200 mL, 41.3 mmol) in tetrahydrofuran at 80°C for 2 hours under nitrogen. After cooling, 2-(trifluoromethyl)-9H-thioxanthen-9-one (36.1 mmol) was added at 0°C to -5°C, followed by heating to 60-70°C. A freshly prepared NH_4Cl solution was then added, and the mixture was stirred with toluene. The organic layer was separated, distilled, and the product dried, yielding 92% (120 g) of a white solid with a melting point of 102-115°C.

IR spectra showed peaks at 3045.6 cm^{-1} (C-H aromatic), 2924.09 cm^{-1} (C-H aliphatic), and 1647.21 cm^{-1} (C=O stretch). ^1H NMR signals included δ 2.4 (NCH_3), δ 2.06 (NCH_2), δ 1.19 (CH_2), δ 8.22 (Ar-OH), and δ 8.2-7.18 (Ar-H). Mass spectrometry revealed an M^+ ion at m/z 369 and fragment ions at m/z 87, 281, 44, and 184.

General procedure for preparation of (E) & (Z) (3-(2-trifluoromethyl)-8aH-thioxanthen–9(10aH)-ylidene)-N, N-dimethyl propan-1-amine

The synthesis of the (E) and (Z) isomers of (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N, N-dimethylpropan-1-amine involved refluxing 9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol (5 g, 1.37 mmol) with an acid (2.05 mmol) in benzene (150 mL) at 80°C for 22-24 hours. After cooling, the mixture was diluted with water, basified to pH 9 using sodium carbonate, and extracted with toluene. The toluene extract was then distilled, acidified to pH 2 with IPA HCl, and redistilled with toluene. The dried residue yielded 21-84% of the product.

DHY-01 : Dehydration by using HCl

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine, had a molecular formula of $C_{19}H_{20}F_3NS$ and a molecular weight of 351 g/mol. It was a white solid with a melting point of 205-207°C and was freely soluble in water. The practical yield was 1 gram (21.04%). IR spectra revealed key absorption peaks at 3012.8 cm^{-1} (C-H aromatic), 295.8 cm^{-1} (C-H aliphatic), 1606.7 cm^{-1} (C=C stretch), and 1116.7 cm^{-1} (C-N stretch). NMR spectra showed shifts at 2.4 ppm (NCH_3), 2.06 ppm (NCH_2), 2.01 ppm (CH_2), 1.19 ppm (CH_2), 8.22 ppm (Ar-OH), and 8.2-7.18 ppm (Ar-H).

DHY-02: Dehydration by using Oxalic acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 206-208°C and was freely soluble in water. The practical yield was 1 gram (21.04%).

IR spectra showed peaks at 3010.8 cm^{-1} (C-H aromatic), 2960.7 cm^{-1} (C-H aliphatic), 1604.7 cm^{-1} (C=C stretch), and 1114.8 cm^{-1} (C-N stretch). NMR spectra displayed shifts at 6.78-7.41 ppm (multiplet, Ar-H, 7H), 4.65-5.56 ppm (triplet, C=CH, 1H), 2.89 ppm (singlet, 2 × CH_3, 6H), and 2.68-2.14 ppm (triplet, CH_2, 4H).

DHY-03: Dehydration by using Maleic acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 200-203°C and was freely soluble in water. The practical yield was 3 grams (63.15%).

IR spectra showed absorption bands at 3012.8 cm^{-1} (C-H aromatic), 2958.8 cm^{-1} (C-H aliphatic), 1606.6 cm^{-1} (C=C stretch), and 1116.7 cm^{-1} (C-N stretch). NMR spectra displayed peaks at 6.77-7.39 ppm (multiplet, Ar-H, 7H), 4.59-5.95 ppm (triplet, C=CH, 1H), 2.88-2.65 ppm (singlet, 2 × CH_3, 6H), and 2.62-2.12 ppm (triplet, CH_2, 4H).

DHY-04: Dehydration by using Succinic acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 190-195°C and was freely soluble in water. The practical yield was 4 grams (84.75%). IR spectra showed absorption bands at 3055.67 cm^{-1} (C-H aromatic), 2960.73 cm^{-1} (C-H aliphatic), 1606.7 cm^{-1} (C=C stretch), and 1118.71 cm^{-1} (C-N stretch). NMR spectra revealed peaks at 6.83-7.43 ppm (multiplet, Ar-H, 7H), 4.5-5.63 ppm (triplet, C=CH, 1H), 2.93-2.89 ppm (singlet, 2 × CH_3, 6H), and 2.7-2.15 ppm (triplet, CH_2, 4H).

DHY-05: Dehydration by using Methenus sulphonic acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 208-210°C and was freely soluble in water. The practical yield was 2 grams (42.1%). IR spectra showed absorption bands at 3012.8 cm^{-1} (C-H aromatic), 2958.8 cm^{-1} (C-H aliphatic), 1606.6 cm^{-1} (C=C stretch), and 1116.7 cm^{-1} (C-N stretch). NMR spectra exhibited peaks at 6.74-7.39 ppm (multiplet, Ar-H, 7H), 4.72-5.53 ppm (triplet, C=CH, 1H), 2.87 ppm (singlet, 2 × CH_3, 6H), and 2.65-2.13 ppm (triplet, CH_2, 4H).

DHY-06: Dehydration by using Ferrous sulphate

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 194-196°C and was freely soluble in water. The practical yield was 3 grams (63.15%). IR spectra showed absorption bands at 3059.1 cm^{-1} (C-H aromatic), 2960.7 cm^{-1} (C-H aliphatic), 1612.4 cm^{-1} (C=C stretch), and 1120.6 cm^{-1} (C-N stretch). NMR spectra displayed peaks at 6.83-7.43 ppm (multiplet, Ar-H, 7H), 4.65-5.63 ppm (triplet, C=CH, 1H), 2.92-2.89 ppm (singlet, 2 × CH_3, 6H), and 2.7-2.43 ppm (triplet, CH_2, 4H).

DHY-07: Dehydration by using Dl-Tartaric acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 188-192°C and was freely soluble in water. The synthesis yielded 4 grams (84.75%). IR spectra showed absorption bands at 3012.8 cm^{-1} (C-H aromatic), 2960.7 cm^{-1} (C-H aliphatic), 1604.7 cm^{-1} (C=C stretch), and 1118.7 cm^{-1} (C-N stretch). NMR spectra displayed peaks at 6.91-7.46 ppm (multiplet, Ar-H, 7H), 4.58-5.67 ppm (triplet, C=CH, 1H), 2.97-2.93 ppm (singlet, 2 × CH_3, 6H), and 2.78-2.55 ppm (triplet, CH_2, 4H).

DHY-08 : Dehydration by using L+ tartaric acid

The compound, (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol), was a white solid with a melting point of 191-195°C and was freely soluble in water. The practical yield from the synthesis was 4 grams, corresponding to an 84.75% yield. IR spectra showed key absorption bands at 3012.8 cm^{-1} (C-H aromatic), 2958.8 cm^{-1} (C-H aliphatic), 1606.6 cm^{-1} (C=C stretch), and 1116.7 cm^{-1} (C-N stretch). NMR spectra displayed peaks at 6.76-7.4 ppm (multiplet, Ar-H, 7H), 4.64-5.58 ppm (triplet, C=CH, 1H), 2.91-2.84 ppm (singlet, 2 × CH_3, 6H), and 2.64-2.14 ppm (triplet, CH_2, 4H).

DHY-09: Dehydration by using Phosphoric acid

The compound (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol) was a white solid with a melting point of 196-198°C and was soluble in water. It was synthesized with a 63.15% yield. IR spectra showed peaks at 3010.8 cm^{-1} (aromatic C-H), 2958.8 cm^{-1} (aliphatic C-H), 1604.7 cm^{-1} (C=C), and 1116.7 cm^{-1} (C-N). NMR spectra displayed signals at 6.81-7.41 ppm (Ar-H, 7H), 4.64-5.60 ppm (C=CH, 1H), 2.92-2.88 ppm (2 × CH_3, 6H), and 2.72-2.13 ppm (CH_2, 4H).

Table 1: Composition of Flupentixol Isomers as determined by ^{1}H-NMR Spectroscopy following Dehydration Reactions

Sr. No	Compounds	Acid	E isomer	Z isomer	Total	Yield in g & %	^{1} HNMR	Melting point (°C)
1		HCl	0.119	0.926	1.045	1 gm (21.04)	11:89	205-207
2		Oxalic acid	0.156	0.944	1.1	1 gm (21.04)	14:86	206-208
3		Maleic acid	0.354	0.998	1.352	3 gm (63.15)	26:74	200-203
4		Succinic acid	0.548	0.943	1.491	4 gm (84.75)	37:63	190-195
5	Alcohol	CH_3SO_3H	0.0184	0.1385	0.1569	2 gm (42.1)	12:88	208-210
6	(Intermediate)	Ferrous sulfate	0.0647	0.0826	0.1473	3 gm (63.15)	44:56	194-196
7		DL Tartaric acid	0.0641	0.1185	0.1826	4 gm (84.75)	35:65	188-192
8		L(+)Tartaric acid	0.0551	0.0988	0.1539	4 gm (84.75)	36:64	191-195
9		Phosphoric acid	0.0334	0.1269	0.1603	3 gm (63.15)	21:79	196-198
10		Fumaric acid	0.0663	0.989	0.1652	2 gm (42.1)	40:60	197-203

DHY-10: Dehydration by using Fumaric acid

The compound (3-(2-trifluoromethyl)-8aH-thioxanthen-9(10aH)-ylidene)-N,N-dimethylpropan-1-amine ($C_{19}H_{20}F_3NS$, 351 g/mol) was a white solid with a melting point of 197-203°C and was soluble in water. The synthesis yielded 2 grams, or 42.1%. IR spectra showed absorption bands at 3010.8 cm^{-1} (aromatic C-H), 2960.7 cm^{-1} (aliphatic C-H), 1604.7 cm^{-1} (C=C), and 1118.7 cm^{-1} (C-N). NMR spectra exhibited peaks at 6.75-7.39 ppm (Ar-H, 7H), 4.58-5.57 ppm (C=CH, 1H), 2.86-2.82 ppm (2 × CH_3, 6H), and 2.57-1.96 ppm (CH_2, 4H).

RESULTS

The 2-{[4-(trifluoromethyl)phenyl]sulfanyl}benzoic acid was prepared by the reaction between 2-mercaptobenzoic acid and perabromo benzotrifluoride, yielding a product with a 98% yield. In the next step, this compound reacted with polyphosphoric acid under nitrogen to form 2-(trifluoromethyl)-9H-thioxanthen-9-one, with a yield of 89.1%. The purity of the product was confirmed by melting point, IR, and ^{1}H-NMR. 9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol was prepared via the Grignard reaction by reacting 2-(trifluoromethyl)-9H-thioxanthen-9-one with chloropropylamine, resulting in a yield of 92.36%. The purity of this product was ascertained by melting point, IR, ^{1}H-NMR, and mass spectrometry.

The dehydration reaction to form (3-(2-trifluoromethyl)-8aH-thioxanthen–9(10aH)-ylidene)-N,N-dimethylpropan-1-amine [Flupentixol] involved the dehydration of (9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol using various acids. The dehydration of (9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol to form Flupentixol was achieved using various acids, each resulting in different yields. Hydrochloric acid and oxalic acid both yielded Flupentixol with a 21.04% yield. Maleic acid, ferrous sulfate, and phosphoric acid each resulted in a yield of 63.15%. Succinic acid, tartaric acid DL, and tartaric acid L(+) all produced Flupentixol with an 84.75% yield. Methenus sulfonic acid yielded Flupentixol at 42.1%, while fumaric acid resulted in a 56% yield (Table 1). The purity of each final product was confirmed through analysis of their melting points, IR spectra, and ^{1}H-NMR spectra.

DISCUSSION

In this study, we synthesized different isomer derivatives of Flupentixol, a tricyclic antipsychotic that exists as a mixture of E and Z isomers, with the Z-isomer being the active form. We synthesized Flupentixol and separated the E and Z isomers using ^{1}H-NMR to determine the percentage of the Z-isomer. The synthesis began with 2-(trifluoromethyl)-9H-thioxanthen-9-one, prepared from mercaptobenzoic acid, which was then used in a Grignard reaction to form 9-(3-dimethylamino)propyl)-2-(trifluoromethyl)-9,10aH-dihydro-8aH-thioxanthen-9-ol. This intermediate was converted into the E and Z isomers of (3-(2-trifluoromethyl)-8aH-thioxanthen–9(10aH)-ylidene)-N,N-dimethylpropan-1-amine by stirring at 80°C in toluene with various acids for 22-24 hours. The conversion was confirmed by IR spectra showing the C=CH peak at 1604 cm^{-1} and ^{1}H-NMR revealing the formation of the E and Z isomers at δ values of 4.5 to 5.9. The best results were obtained with hydrochloric acid, yielding Flupentixol with an 89% Z-isomer content. Other acids, such as methenus sulfonic acid, oxalic acid, and phosphoric acid, also yielded the Z-isomer in an acceptable range of 88-79%.

CONCLUSION

This study synthesized the E and Z isomers of Flupentixol, resolving the racemic mixture to obtain a pure form or reduce the E-isomer percentage, achieving Z-isomer yields of 56% to 89% using various acids and ^{1}H-NMR separation.

REFERENCES

1. Adams CE, Fenton MKP, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *British Journal of Psychiatry*. 2001;179(4):290–299. Available from: https://dx.doi.org/10.1192/bjp.179.4.290.
2. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: review and analysis of 115 cases. *Biological Psychiatry*. 1987;22(8):1004–1020. Available from: https://dx.doi.org/10.1016/0006-3223(87)90010-2.
3. Raymond B, Neumeyer J. Antipsychotics and Anxiolytic agents. *Foyes Principles of Medicinal Chemistry Philadelphia: Lippincott*. 2002;p. 408–433. Available from: https://books.google.co.in/books/about/Foye_s_Principles_of_Medicinal_Chemistry.html?id=qLJ6Bs1Qml4C.
4. Kaiser C, Setler PE. Antipsychotic: Burger's medicinal chemistry and drug discovery. *John Wiley and Sons New York*. 2007;6:485–510.
5. Marone S, Rozas I, Weaver DF. Theoretical structural analyses of tricyclic neuroactive drugs: quantum pharmacologic descriptors for clustering anticonvulsant, antidepressant, and antipsychotic activities. *Journal of Molecular Structure: THEOCHEM*. 1999;467(1):25–30. Available from: https://dx.doi.org/10.1016/s0166-1280(98)00468-0.