IJPSR (2022), Volume 13, Issue 7 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 May 2021; received in revised form, 31 May 2022; accepted, 02 June 2022; published 01 July 2022

A COMPREHENSIVE REVIEW OF XANTHENE AND THIOXANTHENE

Darakhshan Parveen * and Amrita Parle

Department of Pharmaceutical Chemistry, Delhi Pharmaceutical Sciences and Research University, Mehrauli - Badarpur Rd, Sector 3, Pushp Vihar, New Delhi - 110017, New Delhi, India.

Keywords:

Xanthene, Thioxanthene, Marketed Products, Synthesis, Clinical Trial, Pharmacoeconomics

Correspondence to Author:
Darakhshan Parveen

Research Scholar,
Department of Pharmaceutical Chemistry, Delhi Pharmaceutical Sciences and Research University, Mehrauli - Badarpur Rd, Sector 3, Pushp Vihar, New Delhi - 110017, New Delhi, India.

E-mail: suhana.dk@gmail.com

ABSTRACT: Xanthene (or 9H-xanthene) is a parent active compound in which a pyran ring is combined with a benzene ring on both sides, whereas in thioxanthene, the oxygen of xanthene is replaced by a sulphur atom. Xanthene and thioxanthene are important classes of organic compounds which exhibit diverse pharmacological activities such as anti-spasmodic, anti-parkinsonian, anti-psychotic, anti-rhinitic, anti-inflammatory, anti-asthmatic, anti-ulcer, *etc*. This review covers various methods of synthesis of Xanthene and Thioxanthene. The pharmacoeconomic consideration of various marketed products of Xanthene and Thioxanthene are also discussed. It also covers the ongoing clinical trials of the upcoming Xanthene and Thioxanthene-based products and the newer indication of existing drugs. This review would be of immense use to researchers interested in Xanthene and Thioxanthene-based drugs. This review also helps the physician to preferably prescribe the cheaper brand for the patient's benefit with the help of pharmacoeconomic analysis discussed in the review.

INTRODUCTION: Xanthene (or 9H-xanthene) is a parent active compound in which a pyran ring is combined with a benzene ring on both sides. Substitution at position 9 strongly influences their physical, chemical, and biological properties [1]. Xanthene has a wide range of pharmacological activities such as Antispasmodic [2], Anti-Parkinsonian [3] and Anti-Psychotic [3]. They are also used in the treatment of ulcers [4], rhinitis [5], urinary incontinence [6] and bronchitis [7]. Thioxanthene is a compound in which a thiazine ring is combined with two benzene rings.

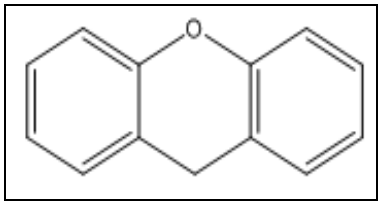
QUICK RESPONSE CODE

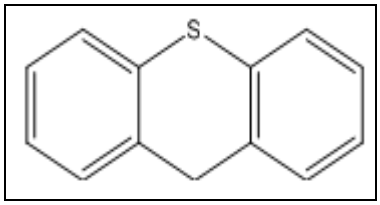
DOI:
10.13040/IJPSR.0975-8232.13(7).2550-61

This article can be accessed online on
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(7).2550-61

Thioxanthene is a chemical compound in which the oxygen atom in xanthene is replaced with a sulphur atom. Thioxanthene-based derivatives are used as typical antipsychotics [8, 9] in treating schizophrenia and other psychoses [3]. It is also used as an antiparkinsonian, antispasmodic and antiemetic drug. They are used to treat bronchitis as well.





Marketed Drugs of Xanthene and Thioxanthene: The xanthene based marketed drugs along with their category, uses, brand names, a manufacturing company, pack size and price are covered in **Table 1**, while the thioxanthene based marketed drugs along with their categories, uses, brand names, a manufacturing company, pack size, and price are covered in **Table 2.**

TABLE 1: USES, BRAND NAME, MANUFACTURING COMPANY, PACK SIZE AND PRICE OF MARKETED DRUGS OF XANTHENE

Marketed Drug and Category	Uses	Brand Name	Company	Pack Size	Price
Propantheline (Marketed in India) (Muscarinic Antagonist[10, 11], Nicotinic Effects {At high doses})	Antispasmodic[2]	Pepler Tablet (Propantheline Bromide 2.5mg + Diazepam 15mg + Dihydroxy Aluminium Amino acetate 100mg)	Sun Pharma	10	Rs5.20[17]
	In Rhinitis [5]	Pro Banthine Capsule/ Tablet 15mg	RPG Life Sciences Ltd.	10	Rs.15.14[17]
	In Urinary Incontinence[6, 12, 13]	Sere Banthine Tablet (Propantheline Bromide 0.2mg + Haloperidol 15mg)	RPG Life Sciences Ltd.	10	Rs22.89[17]
	In the treatment of Ulcer[14,15, 16]	Spastheline Tablet 15mg	Sun Pharma	10	Rs3.98[17]
Phloxine B (Marketed in US) (Coloring Agent)	Colorant in Dental Disclosing Tablets[18]	Red-cote Dental Disclosing Tablets 1.5% w/w	Sunstar Americas	248/pk	USD21.9 (Rs.1628.69)
Oftasceine/ Fluorexon (Marketed in US) (Fluorescent Dye or Luminescent Agent)	Used in ophthalmic solutions as a staining agent when fitting soft and hard lenses[19]	HiGlo STRIPS (0.5mg of fluorexon disodium salt)	Contacare Ophthalmic Private Limited	100/pk	USD18.9 (Rs.1409.01)
Methantheline[20] (Marketed in Germany) (Antispasmodic)	Peptic ulcer disease[21] Urinary problems[22] Irritable bowel syndrome[23] Pancreatitis[24] Gastritis[25] Biliary dyskinesia[26]	VagantinRiemser 50 mg überzogene Tablet	RIEMSER Pharma GmbH	20	€5,00 (Rs.44,285)
Rose Bengal (Marketed in US) (Colouring agent, Diagnostic agent, Ophthalmological)	Diagnostic agent in suspected damage to conjunctival and corneal cells[27]	Rose Bengal Glostrips™ 1.3mg	Amcon Laboratories	100	USD21.9 (Rs.1628.69)
Fluorescein[28] (Marketed in India) (Diagnostic agent)	Dye used in angiography or angioscopy of the iris and retina[29, 30]	Fluresin Inj. 10%	Samarth PharmaPvt. Ltd.	1	Rs.200
		Floure-stain strips (Std.) 4%	Bell PharmaPvt. Ltd.	100	Rs 255.96

Price of Propantheline: Available from: http://www.medlineindia.com. Price of Phloxine B: Available from: Scottsdental.com. Price of Oftasceine/ Fluorexon: Available from: https://worldsportsvision.com/product/higlo-strips/. Price of Methantheline: Available from: https://www.docmorris.de/vagantin-riemser-50-mgueberzogenetablet /10985801?sc= GKV# warenkorb. Price of Rose Bengal: Available from: www.amconlabs.com/product/1257/101/Rose-Bengal-Glostrips-by-Amcon/. Price of Fluorescein: Available from: https://www.medicineindia.org/brands-forgeneric/1822/fluorescein-sodium; https://www.1mg.com/drugs/floure-stain-strip-269741.

TABLE 2: USES, BRAND NAME, MANUFACTURING COMPANY, PACK SIZE AND PRICE OF MARKETED DRUGS OF THIOXANTHENE

Marketed Drug and Category	Uses	Brand Name	Company	Pack Size	Price
Pimethixene (Marketed in US) (Anticholinergic)	Treatment of Bronchitis[9]	Muricalm Pimetixeno Oral Solution 1mg/ml	Novartis pharmaceuticals corp	1	USD9,48 (Rs.70341.6)
Metixene (Marketed in Switzerland) (Anticholinergic)	Antiparkinsonian Agent[3, 31] Antispasmodic[32]	SpasmoCanulase Tablet (Methixene hydrochloride 1mg + Dimethylpolysiloxane 40mg + Cellulase 300u + pepsin ph. H. V 100mg + Glutamic acid hydrochloride 50mg + Pancreatinph.H.V. 100mg + Sodium dehydrocholate 10mg)	Novartis pharmaceuticals corp	100	CHF 39.80 (Rs.3,221.58)
Thiothixene (Marketed in US) (Antipsychotic Agent)	Management of Schizophrenia[33]	Thiothixenecapsule 5mg	Mylan Inc.	30	USD29 (Rs.2158.40)
		Thiothixenecapsule 2mg	CVS Pharmacy	18	USD11.33 (Rs.840.686)
		Thiothixenecapsule 2mg	Kroger	18	USD21.92 (Rs.1626.464)
		Thiothixenecapsule 2mg	Harris Teeter	18	USD21.92 (Rs.1626.464)
		Thiothixenecapsule 2mg	Costco Pharmacy	18	USD26.96 (Rs.2000.432)
Zuclopenthixol (Marketed in India) (Antipsychotic Agent)	Management of Schizophrenia[34]	Clopixol Tablet 25mg	Lundbeck India Pvt. Ltd.	10	Rs.150
		Clopixol (200mg) Inj (200mg/1ml)		1	Rs.160
		ClopixolAcuphase Inj. (50mg/1ml)		1	Rs.81.75
		ClopixolAcuphase (2ml) Inj. (50mg/1ml)		1	Rs.110
		Clopixol Depot Inj. (200mg/1ml)		1	Rs.272
Flupentixol[35, 36] (Marketed in India) (Neuroleptic Agent)[37]	Schizophrenia[38, 39] Depression[40] Bipolar disorder[41]	Anxiset Tablet (0.5mg)	Obsurge Biotech Ltd.	10	Rs.34
		Anxiset Tablet (1mg)		10	Rs.48
		Flupen Tablet (0.5mg)	East West Pharma	10	Rs.20.25
		Flupen Tablet (1mg)		10	Rs.39.60
		Flupen Tablet (3mg)		10	Rs.76.50
		Xolybex Tablet (0.5mg)	Vidakem Life Sciences Pvt. Ltd.	10	Rs.40
		Xolybex Tablet (1mg)		10	Rs.55
		Fluwic-ES Tablet (0.5mg/10mg) (Flupentixol 0.5mg + Escitalopram 10mg)	Jaiwik Biotech	10	Rs.85
Chlorprothixene (Marketed in US) (Antipsychotic Agent[42])	Acute mania[43]	Taractan Tablet 100mg	Roche	50	USD50 (Rs.3710)
	Psychotic disorders[44]	Chlorprothixen Pills 50mg	Zentiva KS	50	USD24.85 (Rs.1843.87)
	Anti-emetic[45] Herpes zoster neuralgia[46]	Truxal Tablet 50mg	Lundbeck AS	50	USD26.15 (Rs.1940.33)

Price of Pimethixene: Available from: https://consultaremedios.com.br/muricalm/1mg-ml-caixa-com-1-frasco-gotejador-com-10ml-de-solucao-de-uso-oral/p. Price of Metixene: Available from: https://en.adlershop.ch/p/6739/spasmo-canulase-100-tabletten; https://www.meduweb.com/spasmo-canulase-tablets/. Price of Thiothixene Manufactured by Mylan Inc.: Available from: https://www.empr.com/drug/thiothixene/. Price of Thiothixene manufactured by CVS Pharmacy, Kroger, Harris Teeter, Costco Pharmacy: Available from: https://www.singlecare.com/prescription/thiothixene. Price of Zuclopenthixol: Available from: https://www.medindia.net/drug-price/zuclopenthixol.htm. Price of Flupentixol: Available from: https://www.medindia.net/drug-price/flupentixol.htm. Price of Chlorprothixene Manufactured by Roche: Available from: https://www.ebay.com/itm/124784662630. Price of Chlorprothixene Manufactured by Zentiva KS and Lundbeck AS: Available from: https://pillbuys.com/shop/truxal-chlorprothixen-#/6051-brandmanufacturer-truxal_lundbeck_ as_denmark/2-dosage_form-pills/1604-package_size-50_mg_50_pcs

Pharmacoeconomic Analysis: Pharmacoeconomic considerations of different marketed preparations are described in **Table 1** and **Table 2**.

Our observations indicated that some marketed drugs are manufactured by only one pharmaceutical company while many pharmaceutical companies manufacture some other drugs. We infer that:

1. Propantheline is marketed in India. It is manufactured by Sun Pharma and RPG Life Sciences Ltd.. The marketed preparation of Propantheline, which comes under the brand name of Spastheline Tablet 15mg manufactured by Sun Pharma, is cheaper compared to that of other Pro-Banthine Tablet 15mg manufactured by RPG Life Sciences Ltd.

2. Thiothixene is marketed in the US and not in India.

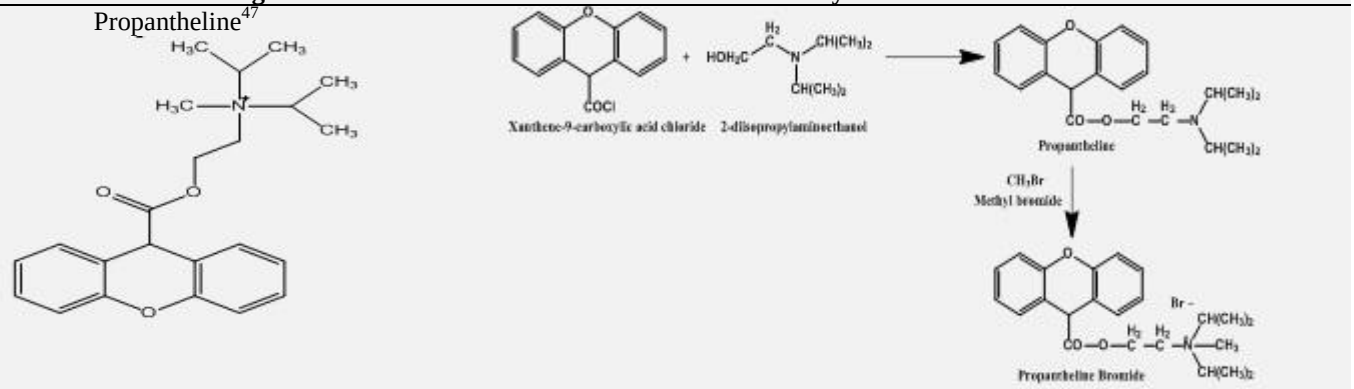
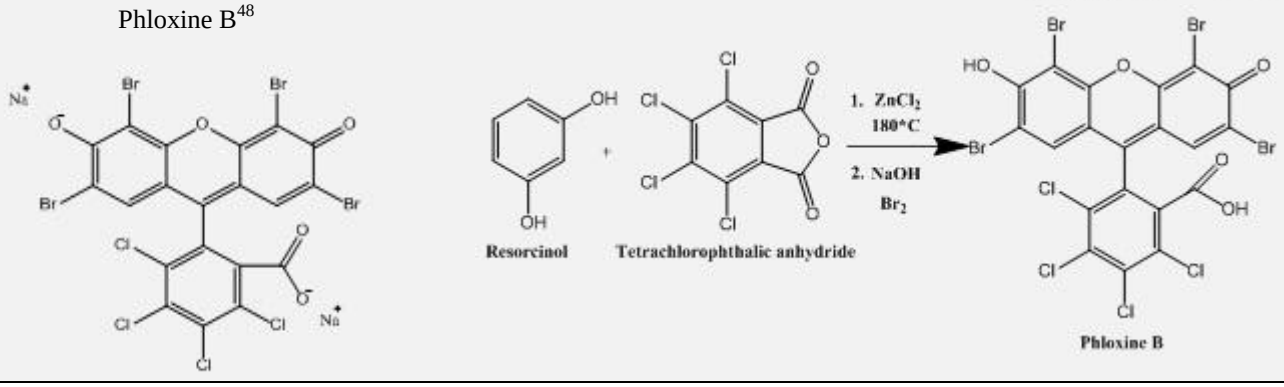
3. Generic marketed preparations of Thiothixene are manufactured by CVS Pharmacy, Kroger, Harris Teeter, Mylan Inc., and Costco Pharmacy, respectively. Thiothixene 2mg manufactured by CVS Pharmacy is cheaper among all, while the one manufactured by Costco Pharmacy is the costliest.

4. Flupentixol is marketed in India. It is manufactured by East West Pharma, Obsurge Biotech Ltd., Vidakem Life Sciences Ltd. and Jaiwik Biotech respectively. Flupen 0.5mg manufactured by East West Pharma is cheaper than Anxiset 0.5mg and Xolybex 0.5mg manufactured by Obsurge Biotech Ltd. and Vidakem Life Sciences Ltd.. Similarly, Flupen 1mg manufactured by East West Pharma is cheaper than Anxiset 1mg and Xolybex 1mg manufactured by Obsurge Biotech Ltd. and Vidakem Life Sciences Ltd., respectively.

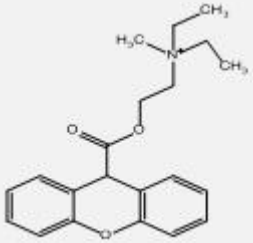
5. Chlorprothixeneis marketed in the US and not in India. Roche manufactures it, Zentiva KS and Lundbeck AS. Chlorprothixen 50mg manufactured by Zentiva KS is cheaper than Truxal 50mg manufactured by Lundbeck AS. The physician should preferably prescribe the cheaper brand for the patient's benefit.

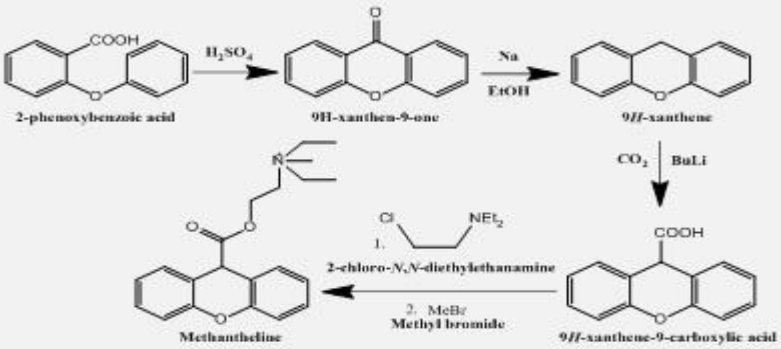
Synthetic Pathways: Several marketed preparations of xanthene and thioxanthene derivatives are available. The synthesis of various marketed xanthene-based drugs is elaborated in **Table 3,** while **Table 4** elaborates on the synthesis of various marketed thioxanthene-based drugs.

TABLE 3: SYNTHESIS OF MARKETED DRUGS OF XANTHENE

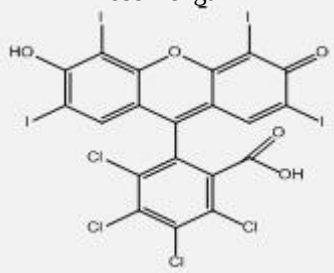
Marketed Drug	Synthesis
Propantheline[47]	
Phloxine B[48]	

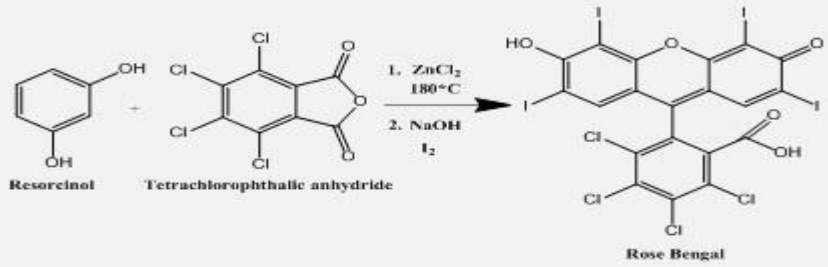
Methantheline[47]



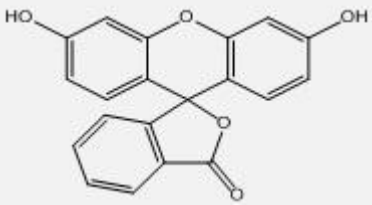


Rose Bengal[49]





Fluorescein[50]



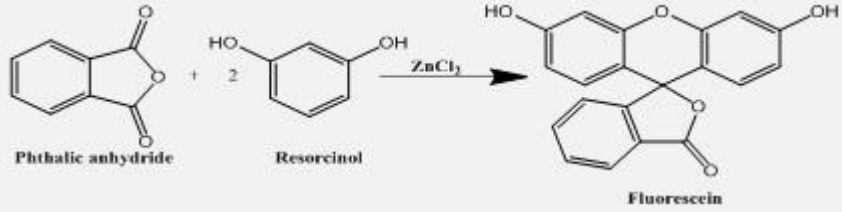
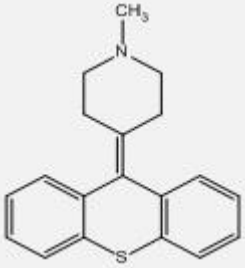
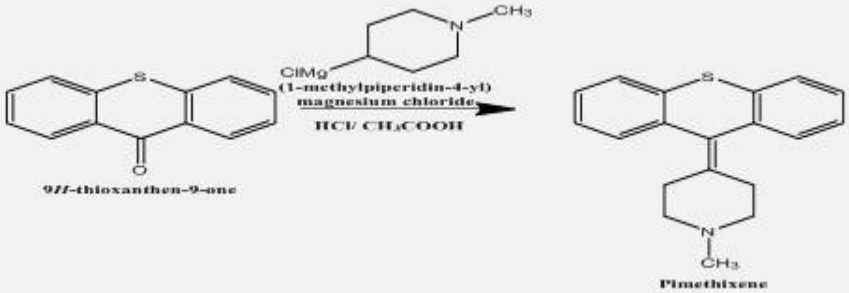
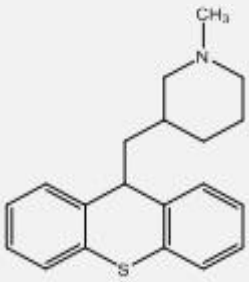
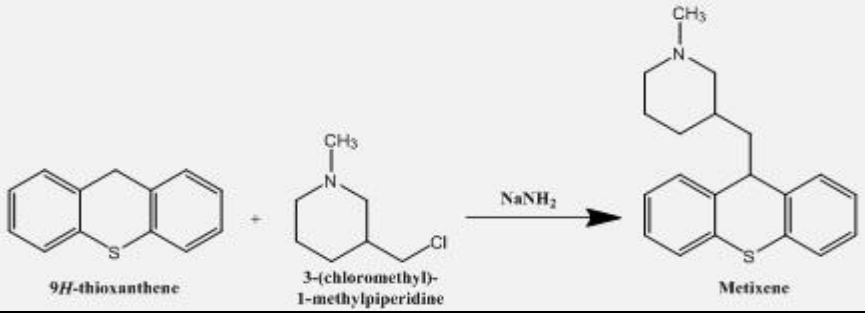
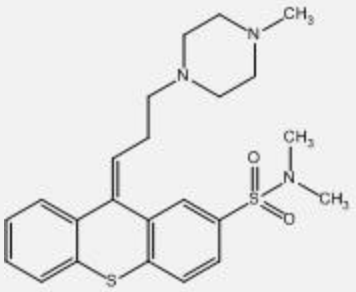
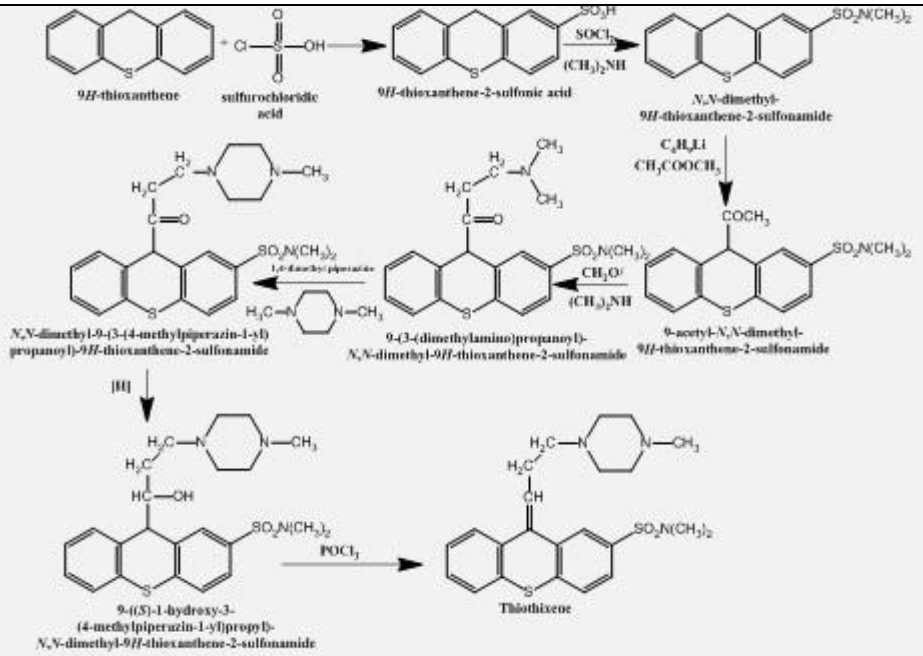


TABLE 4: SYNTHESIS OF MARKETED DRUGS OF THIOXANTHENE

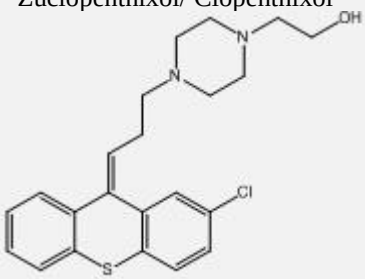
Marketed Drug	Synthesis
Pimethixene[7] 	
Metixene[51] 	

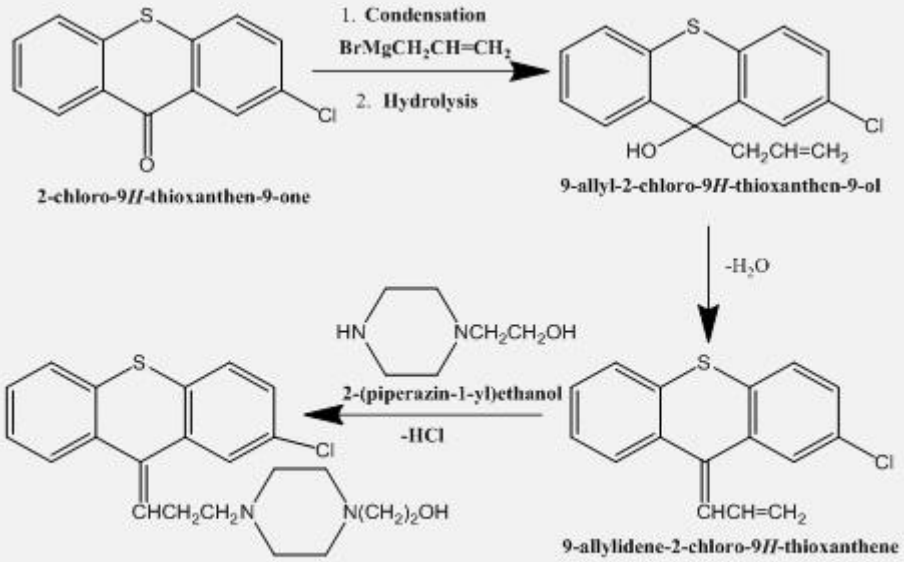
Thiothixene[47]



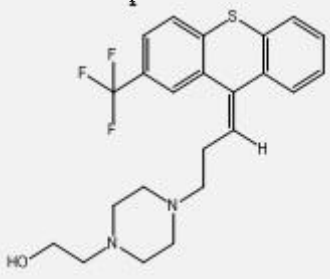


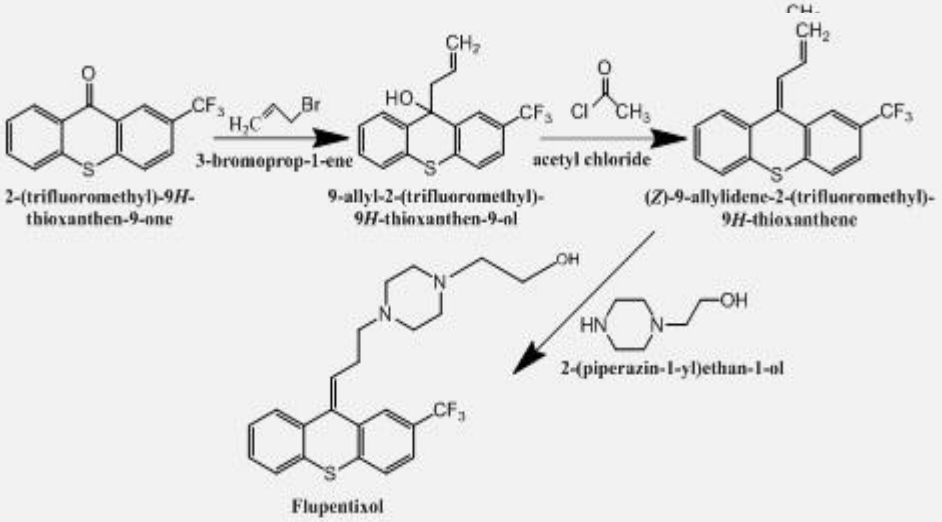
. Zuclopenthixol/ Clopenthixol[52]



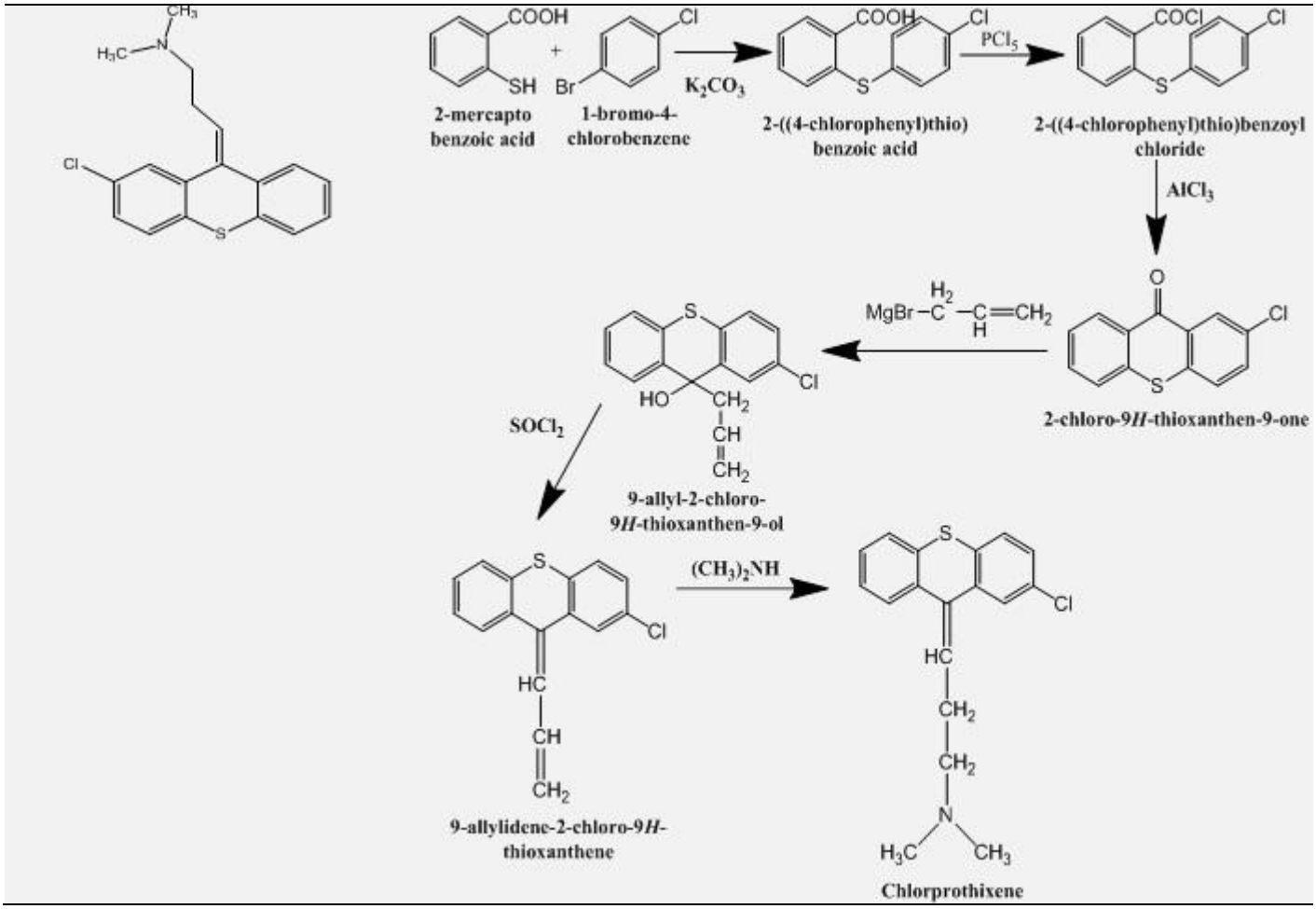


Flupentixol[53]



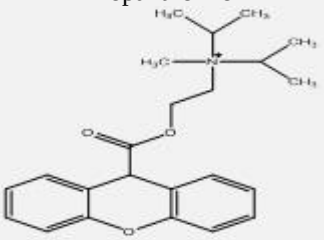
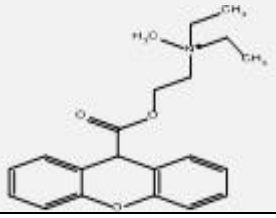


Chlorprothixene[47]



Ongoing Clinical Trials: Xanthene and thioxanthene derivatives are still being explored for various new indications. Propantheline, Methantheline, Rose Bengal, and Fluorescein are the existing marketed drugs, but they are explored for newer indications, whereas newer drugs such as Fluorescein lisicol and EC-17 are explored for various diseases. Xanthene-based drugs and their ongoing clinical trials are mentioned in **Table 5,** while thioxanthene-based drugs and their ongoing clinical trials are mentioned in **Table 6**. Zuclopenthixol and Flupentixol are the existing thioxanthene-based marketed drugs, but they are explored for newer indications.

TABLE 5: XANTHENE IN CLINICAL TRIALS

Drug	Newer Indication	Phase
Propantheline 	Urinary tract lithiasis (excl renal)[54]	4
	Overactive Bladder Associated with HTLV-1[55]	1
Methantheline 	Neurogenic Bladder Dysfunction[56]	1

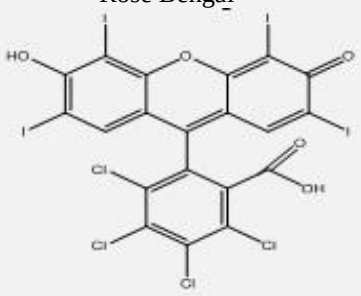
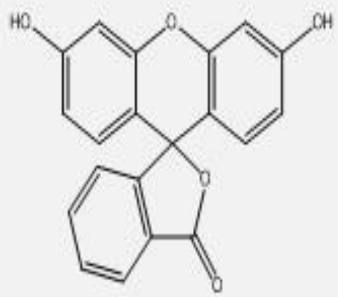
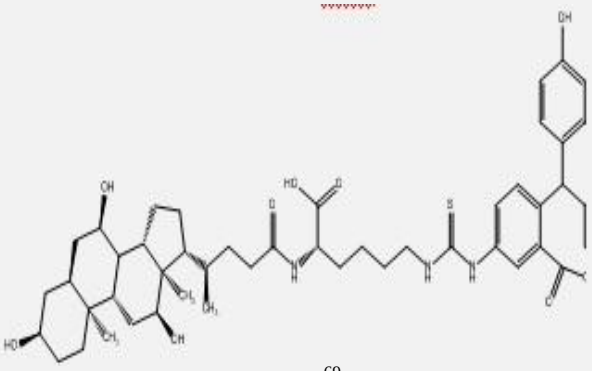
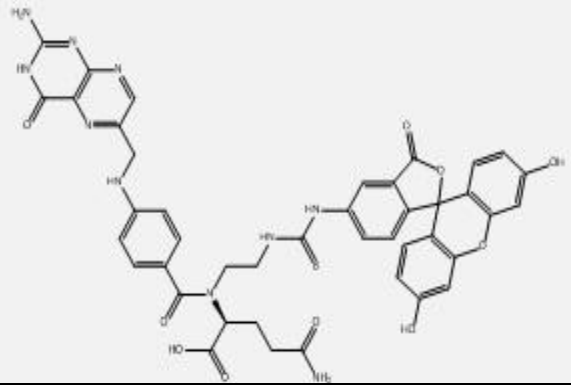
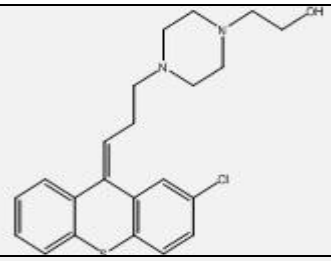
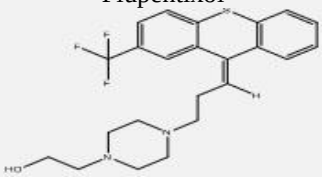
Rose Bengal 	Candida albicans infection / Smoking, Cigarette[57]	3
	Neuroendocrine Tumors Metastatic to the Liver[58]	1
	Cancer Metastatic to the Liver / Hepatocellular Carcinoma / Metastatic Breast Cancer / Metastatic Colon Cancer / Metastatic Colorectal Cancer (MCRC) / Metastatic Lung Cancer / Metastatic Melanoma / Metastatic Ocular Melanoma / Metastatic Uveal Melanoma / Pancreatic Cancer Metastatic[59]	1
Fluorescein 	Retinopathy/ Retinal Vein Occlusion/ Diabetic Retinopathy/ Macular Degeneration[60]	1 (Early)
	Cerebrovascular Diseases / Neoplasms, Intracranial[61]	4
	Hyperemia[62, 63]	3
	Glioblastoma, Adult[64]	3
	Brain Cancer[65]	2
	Pancreatic Acinar Cell Carcinoma /Pancreatic Ductal Adenocarcinoma / Recurrent Pancreatic Carcinoma / Stage IV Pancreatic Cancer	2
Fluorescein lisicol 	Cirrhosis of Liver[66]	3
	Hepatitis, Viral, Human[67]	2
	Non-Alcoholic Fatty Liver Disease (NAFLD)/Nonalcoholic Steatohepatitis[68]	2
EC-17[69] 	Resectable Breast Cancer[70]	1
	Malignancies[71]	1

TABLE 6: THIOXANTHENE IN CLINICAL TRIALS

Drug	Newer Indication	Phase
Zuclopenthixol	Schizoaffective Disorders / Schizophrenia / Schizophrenia and Disorders with Psychotic Features[72]	4
	Bipolar Disorder (BD)[73]	4
	Anxiety Disorders / Dementia / Depression / Psychosomatic Disorders /	3

	Schizophrenia[74] Psychosis Nos/Other[75]	3
Flupentixol 	Emotional Disorder/ Neurologic Disorder[76]	4
	Schizophrenia/ Psychosis/ Metabolic Syndrome/ Antipsychotic Agents/ Central Nervous System Diseases[77]	4
	Tinnitus	4
	Globus[78]	3
	Anxiety Disorders / Dementia / Depression / Psychosomatic Disorders / Schizophrenia[79]	3
	Psychosis Nos/Other[80]	3
	Cocaine-Related Disorders[81]	2
	Substance-Related Disorders[82]	2
	Bioequivalence Study in Healthy Subjects[83]	1

CONCLUSION: Xanthene and Thioxanthene are versatile but complicated structural moieties from which many drugs are synthesized. These drugs treat spasms, Parkinson's disease, psychosis, rhinitis, urinary incontinence, emesis, ulcer, and bronchitis. Even today, the interest in the xanthene and thioxanthene-based drugs is alive, which can be understood from the ongoing clinical trial for newer indications of existing drugs and newer drugs. This review would be of immense use to the researchers interested in xanthene and thioxanthene-based drugs as it covers not only marketed preparations of xanthene and thioxanthene but also the Pharmacoeconomic analysis synthesis as well as ongoing clinical trials.

ACKNOWLEDGEMENT: The authors are thankful to the Vice-Chancellor of Delhi Pharmaceutical Sciences and Research University (DPSRU) and the Director of Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR) for their motivational support and guidance.

CONFLICT OF INTEREST: Declared none

REFERENCES:

1. Maia M, Resende DISP, Durães F, Pinto MMM and Sousa E: Xanthenes in Medicinal Chemistry – Synthetic strategies and biological activities. Eur J Med Chem 2021; 210: 113085.
2. Kern F, Almy TP and Stolk NJ: Effects of certain antispasmodic drugs on the intact human colon, with special reference to banthine (β-diethylaminoethyl xanthene-9-carboxylate methobromide). Am J Med 1951; 11(1): 67–74.
3. O'Connor KDJ and Mastaglia FL: Drug-Induced Disorders of the Nervous System. Amin Neurol Gen Med Fifth Ed 2014; 685–711.
4. Roberts DM: Treatment of peptic ulcer by high dosage of propantheline bromide. The American journal of gastroenterology 1967; 47(2): 12(1)4-33.
5. Hendeles L, Weinberger M and Wong L: Medical management of noninfectious rhinitis. Am J Hosp Pharm 1980; 37(11): 1496–504.
6. Owens RG and Karram MM: Comparative tolerability of drug therapies used to treat incontinence and enuresis. Drug Saf 1998; 19(2): 123–39.
7. Höfgen N, Beckh S, Szelenyi I and Bölcskei PL: Antiallergic Agents, Ullmann's Encyclopedia of Industrial Chemistry Wiley 2006: 618.
8. Karimi G and Vahabzadeh M: Thioxanthenes: Encyclopedia of Toxicology. Third Edition Elsevier 2014; 553–557.
9. Balasa R: Iatrogenic Lesions in Neurology: Textbook of Iatrogenic Pathology. Bentham Science Publ 2017; 210-26
10. Barry J, McKay G and Fisher M: Propantheline. Pract Diabetes 2017; 34(3): 104–105.
11. Kobayashi S, Ikeda K, Suzuki M, Yamada T, Miyata K: Effects of YM905, a Novel Muscarinic M3-Receptor Antagonist, on Experimental Models of Bowel Dysfunction *In-vivo*. Jpn J Pharma 2001; 86(3): 281–88.
12. Hay-Smith J, Herbison P, Ellis G and Moore K: Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2002; (3):CD003781.
13. Nabi G, Cody JD, Ellis G, Herbison P and Hay-Smith J: Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2006; (4): CD003781.
14. Gustavsson S, Adami HO, Björklund O, Enander LK, Lundqvist G, Löof L and Nordahl A: Fasting blood levels of gastrin, somatostatin, and pancreatic polypeptide in

peptic ulcer disease. Scand J Gastroenterol 1982; 17(1): 81–5.
15. Okabe S, Tabata K and Kawakami M: Effects of prolonged treatment of pirenzepine 2HCl on gastric secretion and plasma gastrin levels in rats. Arzneimittel-Forschung 1982; 32(6):664-8.
16. Richardson CT, Barnett CC, Walsh JH and Feldman M: Comparison of two antimuscarinic drugs, pirenzepine and propantheline, on gastric acid secretion, serum gastrin concentration, salivary flow and heart rate in patients with duodenal ulcer disease. Aliment Pharmacol Ther 1987; 1(4): 281–91.
17. Leys D: Value of Propantheline Bromide in Treatment of Enuresis. BMJ 1956; 1(4966): 549–550.
18. Oliveira LM, Pazinatto J and Zanatta FB: Are oral hygiene instructions with aid of plaque-disclosing methods effective in improving self-performed dental plaque control? A systematic review of randomized controlled trials. Int J Dent Hyg 2021; 19(3): 239–54.
19. Norn MS: Lissamine green: Vital staining of cornea and conjunctiva. Actaophthalmologica 1973; 51(4): 483-91.
20. Müller C, Lötsch J, Giessmann T, Franke G, Walter R, Zschiesche M and Siegmund W: Relative bioavailability and pharmacodynamic effects of methantheline compared with atropine in healthy subjects. European Journal of Clinical Pharmacology 2012; 68(11): 1473-81.
21. Liebowitz D, Raisin A, Berry C and Roth HP: Treatment of Intractable Peptic Ulcer with Methantheline (Banthine®) Bromide. Journal of the American Medical Association 1952; 150(7): 672-7.
22. Lapides J, Dodson AI: Observations on Effect of Methantheline (banthine®) bromide in urological disturbances. AMA Archives of Surgery 1953; 66(1): 1-9.
23. Cummins AJ: Use and Abuse of Anticholinergic Drugs in the Management of Gastrointestinal Disease. Annals of Internal Medicine 1957; 46(2): 352-9.
24. Shingleton WW and Anlyan WG: Methantheline (banthine®) Bromide in Acute Pancreatitis. Journal of the American Medical Association 1951; 147(17): 1655.
25. Wharton GK: Effective medical management of peptic ulcer and gastritis. The American Journal of Digestive Diseases 1955; 22(9): 262.
26. Rosenberg N: The Role of the Sphincter of Oddi in the Etiology of Peptic Ulcer: I. Evidence from a Review of the Literature. AMA archives of surgery 1955; 71(2): 239-45.
27. Saini M, Nath M and Vanathi M: Ocular diagnostic agents. Pharmacology of Ocular Therapeutics. Springer International Publishing 2016; 359–373.
28. Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W and Zang E: Fluorescein angiography complication survey. Ophthalmology 1986; 93(5): 611-7.
29. Spaide RF, Klancnik JM and Cooney MJ: Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA ophthalmology 2015; 133(1): 45-50.
30. Doughty MJ, Jalota V, Bennett E, Naase T and Oblak E: Use of a high molecular weight fluorescein (fluorexon) ophthalmic strip in assessments of tear film break-up time in contact lens wearers and non-contact lens wearers. Ophthalmic and Physiological Optics 2005; 25(2): 119-27.
31. Clarke S, Hay GA and Vas CJ: Therapeutic action of methixene hydro-chloride on parkinsonian tremor and a description of a new tremor-recording transducer. British J of Pharmacology and Chemotherapy 1966; 26(2): 345-50.
32. Lauener H and Pogge RG: Antispasmodic effects of 9-[(N-methyl-3-piperidyl) methyl] thioxanthene hydrochloride. Journal of Pharmaceutical Sciences 1964; 53(5): 568-70.
33. Dufresne RL, Kass DJ and Becker RE: Bupropion and thiothixene versus placebo and thiothixene in the treatment of depression in schizophrenia. Drug Development Research 1988; 12(3-4): 259-66.
34. Kumar A and Strech D: Zuclopenthixoldihydrochloride for schizophrenia. Schizophrenia Bulletin 2009; 35(5): 855.
35. Wu L, Xu C, Wu G, Zhou H, Lv D and Zhai Y: Bioequivalence study of a fixed-dose combination tablet containing melitracen 10 mg and flupentixol 0.5 mg in healthy chinese volunteers under fasted and fed conditions. Drug Des Devel Ther 2019; 13: 3331–42.
36. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, Enkusson D, Leval A, Sermon J, Tanskanen A and Taipale H: Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry 2017; 74(7): 686-93.
37. Tse L, M Barr A, Scarapicchia V and Vila-Rodriguez F: Neuroleptic malignant syndrome: a review from a clinically oriented perspective. Current Neuropharmacology 2015; 13(3): 395-406.
38. Ruhrmann S, Kissling W, Lesch OM, Schmauss M, Seemann U and Philipp M: Efficacy of flupentixol and risperidone in chronic schizophrenia with predominantly negative symptoms. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2007; 31(5): 1012-22.
39. Bailey L and Taylor D: Estimating the optimal dose of flupentixoldecanoate in the maintenance treatment of schizophrenia—a systematic review of the literature. Psychopharmacology 2019; 236(11): 3081-92.
40. Balasubramani K, Sivarajasekar N, Muthusaravanan S, Ram K, Naushad M, Ahamad T and Sharma G: Efficient removal of antidepressant Flupentixol using graphene oxide/cellulose nanogel composite: Particle swarm algorithm based artificial neural network modelling and optimization. J of Molecular Liquids 2020; 319: 114371.
41. Wu CS, Hsieh MH, Tang CH and Chang CJ: Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder. J of Affecti Disorders 2016; 197: 189-95.
42. Gardos G and Cole JO: A forgotten antipsychotic. Psychiatric Services 1990; 41(11): 1261.
43. Pinero LE, García C, Lhiaubet-Vallet V, Oyola R and Miranda MA: Photophysics and Photochemistry of z-Chlorprothixene in Acetonitrile. Photochemistry and Photobiology 2009; 85(4): 895-900.
44. Barsa JA and Saunders JC: Chlorprothixene in the treatment of psychotic patients. American Journal of Psychiatry 1962; 119(5): 468-9.
45. Wampler G: The pharmacology and clinical effectiveness of phenothiazines and related drugs for managing chemotherapy-induced emesis. Drugs 1983; 25(1): 35-51.
46. Kramer PW: The management of postherpetic neuralgia with chlorprothixene. Surgical Neurology 1981; 15(2): 102-4.
47. Vardanyan R and Hruby V: Antipsychotics (Neuroleptics), Synthesis of essential drugs, Elsevier, Edition 1, 2006: 83-101.
48. Wight P: Xanthene dyes, Kirk-OthmerEncyclopedia of Chemical Technology, Wiley, Edition 5, 2000: 6-19.
49. Neckers DC: Rose bengal. Journal of Photochemistry and Photobiology A: Chemistry 1989; 47(1): 1-29.
50. Thielbeer F: Fluorescein. Synlett 2012; 23(11): 1703-4.

51. Abdel-Moety EM, Khattab NA and Mian MS: Methixene Hydrochloride. Analytical Profiles of Drug Substances and Excipients 1993 Vol. 22. Academic Press 1993; 317-358.
52. Alagarsamy V: Tranquillizers, Textbook of Medicinal Chemistry Vol I. Elsevier 2013; 178-203.
53. Huang Q, Ye XJ, Liu WJ, Hai L and Wu Y: Improved synthesis of 2-trifluoromethyl-9-thioxanthone. West China Journal of Pharmaceutical Sciences 2009; 01.
54. Zhang MY, Ding ST, Lue YH, Zhang H and Xia QH: Comparison of tamsulosin with extracorporeal shock wave lithotripsy in treating distal ureteral stones. Chinese Medical Journal 2009; 122(07): 798-801.
55. Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V and Artibani W: A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. European Urology 2008; 54(4): 740-64.
56. Müller C, Lötsch J, Giessmann T, Franke G, Walter R, Zschiesche M and Siegmund W: Relative bioavailability and pharmacodynamic effects of methantheline compared with atropine in healthy subjects. European Journal of Clinical Pharmacology 2012; 68(11): 1473-81.
57. Labban N, Al Taweel SM, ALRabiah MA, Alfouzan AF, Alshiddi IF and Assery MK: Efficacy of Rose Bengal and Curcumin mediated photodynamic therapy for the treatment of denture stomatitis in patients with habitual cigarette smoking: A randomized controlled clinical trial. Photodiagnosis and Photodynamic Therapy 2021; 35: 102380.
58. McGregor M, Price TJ, Cehic G, Kirkwood ID, Sebben R, Reid JJ, Neuhaus S, Wachter EA and Maddern G: Cohort 1 results of a phase I study of autolytic immunotherapy of metastatic neuroendocrine neoplasms using intralesional rose bengal disodium 2020: e16694-e16694.
59. Goldfarb P, Low R, Lyon J, Agarwala S, Rosemurgy A and Wachter E: P-116 Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver. Annals of Oncology 2015; 26: 33.
60. Yazdi MK, Zarrintaj P, Hosseiniamoli H, Mashhadzadeh AH, Saeb MR, Ramsey JD, Ganjali MR and Mozafari M: Zeolites for theranostic applications. Journal of Materials Chemistry B 2020; 8(28): 5992-6012.
61. Schebesch KM, Proescholdt M, Höhne J, Hohenberger C, Hansen E, Riemenschneider MJ, Ullrich W, Doenitz C, Schlaier J, Lange M and Brawanski A: Sodium fluorescein–guided resection under the YELLOW 560 nm surgical microscope filter in malignant brain tumor surgery a feasibility study. Actaneurochirurgi 2013; 155(4): 693-9.
62. Toris CB, Camras CB and Yablonski ME: Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. American Journal of Ophthalmology 1999; 128(1): 8-14.
63. Larsson LI: Aqueous humor flow in normal human eyes treated with brimonidine and timolol, alone and in combination. Archives of Ophthalm 2001; 119(4): 492-5.
64. Mansouri A, Beyn ME, Pancholi A, Chow CT, Wang R, Boutet A, Elias GJ, Germann J, Loh A, Voisin MR and Lozano AM: Evolution of the neurosurgeon's role in clinical trials for glioblastoma: a systematic overview of the clinicaltrials. Gov Database. Neurosurgery 2021; 89(2): 196-203.
65. Rey-Dios R, Hattab EM and Cohen-Gadol AA: Use of intraoperative fluorescein sodium fluorescence to improve the accuracy of tissue diagnosis during stereotactic needle biopsy of high-grade gliomas. Actaneurochirurgica 2014; 156(6): 1071-5.
66. Peng Y, Qi X and Guo X: Child–Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine 2016; 95(8).
67. Boyanova Y, Antonov K, Aleksiev A, Kosseva O, Jelev D, Mateva L, Krastev Z and de Mey C: P662 Fluorescein lisicol (NRL972) as an in vivo marker of liver dysfunction. Journal of Hepatology 2014; 1(60): 289.
68. Cobbina E and Akhlaghi F: Non-alcoholic fatty liver disease (NAFLD)–pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug Metabolism Reviews 2017; 49(2): 197-211.
69. Mahalingam SM, Kularatne SA, Myers CH, Gagare P, Norshi M, Liu X, Singhal S, Low PS: Evaluation of novel tumor-targeted near-infrared probe for fluorescence-guided surgery of cancer. J of Med Chem 2018; 61(21): 9637-46.
70. de Jong JM, Hoogendam JP, Braat AJ, Zweemer RP and Gerestein CG: The feasibility of folate receptor alpha-and HER2-targeted intraoperative fluorescence-guided cytoreductive surgery in women with epithelial ovarian cancer: A systematic review. Gynecologic Oncology 2021; 162(2): 517-25.
71. Keating JJ, Okusanya OT, De Jesus E, Judy R, Jiang J, Deshpande C, Nie S, Low P and Singhal S: Intraoperative molecular imaging of lung adenocarcinoma can identify residual tumor cells at the surgical margins. Molecular Imaging and Biology 2016; 18(2): 209-18.
72. Rubio G, Martínez I, Recio A, Ponce G, López-Muñoz F, Alamo C, Jiménez-Arriero MÁ and Palomo T: Risperidone versus zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity: a long-term randomized, controlled, crossover study. The European Journal of Psychiatry 2006; 20(3): 133-46.
73. Gouliaev G, Licht RW, Vestergaard P, Merinder L and Lund H, Bjerre L: Treatment of manic episodes: Zuclopenthixol and Clonazepam versus Lithiim and Clonazepam. Acta Psychiatri Scand 1996; 93(2): 119-24.
74. Degner D, Bleich S, Kropp S, Landen H and Ruther E: Tolerability and efficacy of zuclopenthixol in the treatment of gerontopsychiatric patients-A prospective study. Psychopharmakotherapie 2001; 8(4): 152-7.
75. Simonsen E, Friis S, Opjordsmoen S, Mortensen EL, Haahr U, Melle I, Joa I, Johannessen JO, Larsen TK, Røssberg JI and Rund BR: Early identification of non-remission in first-episode psychosis in a two-year outcome study. Acta Psychiatrica Scandinavica 2010; 122(5): 375-83.
76. Yu YY, Fang DC, Fan LL, Chang H, Wu ZL, Cao Y and Lan CH: Efficacy and safety of esomeprazole with flupentixol/melitracen in treating gastroesophageal reflux disease patients with emotional disorders. Journal of Gastroenterology and Hepatology 2014; 29(6): 1200-6.
77. Shafti SS: Adjunctive depot antipsychotic in treatment-resistant schizophrenia. Current Psychopharmacology 2016; 5(1): 20-7.
78. Lan QL, Lin XX, Wang Y, Xu BB, Shu KY and Zhang XJ: The Relationship Between Upper Esophageal Sphincter Pressure and Psychological Status in Patients with Globus Sensation. International Journal of General Medicine 2021; 14: 8805.
79. Kinzler E: Therapie von Angst und Depression mitniedrigdosierten Neuroleptika in der Gerontopsychiatrie. In Thioxanthene Springer Berlin Heidelberg 1990; 234-241.
80. Burgerhout K: Postpartum Psychosis: Treatment, followup and immunological parameters 2016: 41-125.

81. Bennett ME, Bradshaw KR and Catalano LT: Treatment of substance use disorders in schizophrenia. The American journal of drug and alcohol abuse 2017; 43(4): 377-90.
82. Scheffler F, Kilian S, Chiliza B, Asmal L, Phahladira L, du Plessis S, Kidd M, Murray RM, Di Forti M, Seedat S and Emsley R: Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders. Schizophrenia Research 2018; 199: 90-5.
83. Correll CU, Kim E, Sliwa JK, Hamm W, Gopal S, Mathews M, Venkatasubramanian R and Saklad SR: Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. CNS drugs 2021; 35(1): 39-59.

How to cite this article:
Parveen D and Parle A: A comprehensive review on xanthene and thioxanthene. Int J Pharm Sci & Res 2022; 13(7): 2550-61. doi: 10.13040/IJPSR.0975-8232.13(7).2550-61.