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INCEPTIONARY EXPLORATION OF IMINOSTILBENE ; IT'S SALUTARY OUTCOMES.

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ABSTRACT

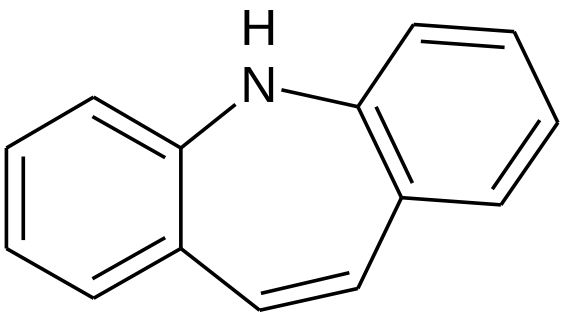
Dibenzazepine have been found wide pharmaceutical applications. It is associated with many pharmacological effects like anti tumor, alpha glucosidase inhibitory activity, sodium channel blocking activity, anti convulsant, anti hypoxic activity, anti anxiety and anti malarial activity. In this review we have discussed about the various pharmacological effects of dibenzazepines.

KEY WORDS

Dibenzazepine, Iminostilbene, Anti tumor, Alpha glucosidase, Sodium channel, Anti convulsant, Anti hypoxic, Anti anxiety, Anti malarial.

INTRODUCTION

Dibenzazepine being a seven membered ring derivative having nitrogen have been eminent in having various promising medicinal effects. It is found to have anti tumor, alpha glucosidase inhibitory activity, sodium channel blocking activity, anti convulsant, anti hypoxic activity, anti anxiety and anti malarial activity . It has a role as a marine xenobiotic metabolite. It is a mancude organic heterotricyclic parent.



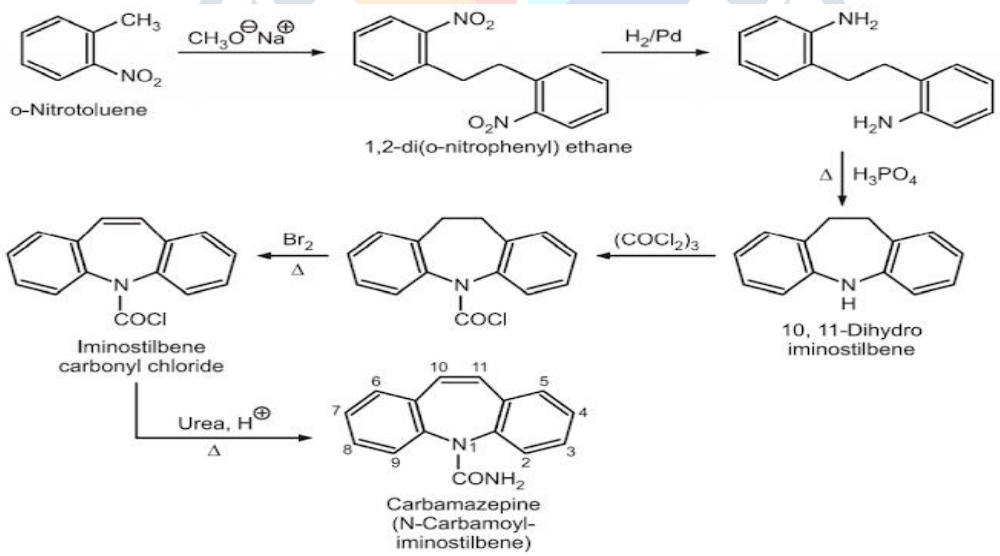
Dibenzazepine or iminostilbene framework consists of two benzene rings fused to azepine group. Dibenzazepine is used as an intermediate in the synthesis of analgesic and antipsychotic drug.

IUPAC name	5H-dibenzo[b,f]azepine
Molecular formula	$C_{14}H_{11}N$
Molecular weight	193.24
Synonyms	5H-dibenzo[b,f]azepine 5H-dibenz[b,f]azepine 2,2'-Iminostilbene

STRUCTURE ACTIVITY RELATIONSHIP

- Presence of chloro-substituents at C-3 is less active than imipramine.
- Presence of dimethyl or keto at C-10 leads to the compounds becoming ineffective.
- Placement of methyl group at 2,8 position or chloro group at 3,7 resulted in compounds becoming ineffective.
- Iminostilbene are equally active.
- Piperazinyl derivatives are ineffective.[22]

SYNTHESIS

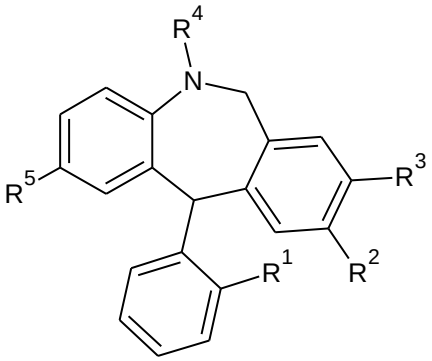


[21]

SALUTARY OUTCOMES

Anti-tumor activity

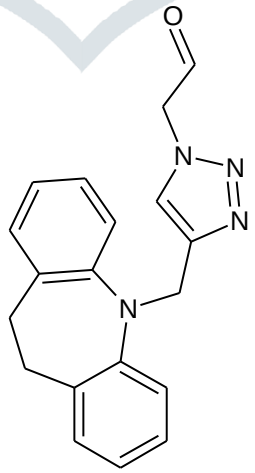
Al-Qawasmeh RA synthesized and tested Compound 1 by performing a sulforhodmine b[SRB] assay for anti proliferative activity using human colon adenocarcinoma cells[HT-29]. The IC_{50} value of compound 1 was 1.2micromol which is tested against a total of 9 tumor cell lines. Compounds 2,3,4,5,6 have submicromolar activity against different cell lines. Compound 2,5 and 6 shows antitumor activity by screening in the NCI60 cell line assay. The result demonstrate promising activity with unique spectrum of activity against the panel of cell lines. The synthetic dibenzazepine compounds [11phenyl[b,e]dibenzazepine] were effective in growth inhibition at submicromolar to micromolar concentration.[1,2,3,4,5]



Compound	R1	R2	R3	R4	R5
1	Cl	H	H	H	H
2	Cl	H	H	4-NO_2Bz	H
3	H	H	H	4-NO_2Bz	H
4	Cl	H	H	4-OMeBz	H
5	Cl	H	OMe	4-NO_2Bz	Cl
6	Cl	OMe	H	4-NO_2Bz	Cl

Alpha glucosidase inhibitor

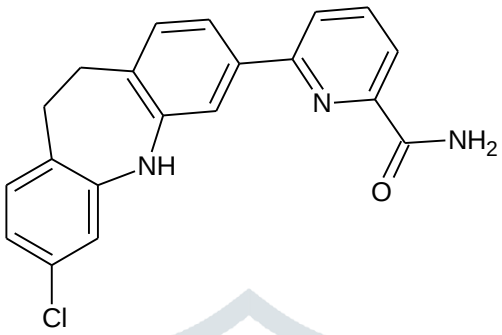
Inhibition of alpha glucosidase enzyme is a valid approach in controlling blood glucose levels. The currently marketed AGIs such as acarbose, voglibose have low efficacy and cause diarrhoea, abdominal discomfort, flatulence etc. Ullah S synthesized Compound 7 and was found to be more potent than the standard acarbose. Unsubstituted congener 7 showed hydrogen bonding interaction with Lys156, Ser157, Asp352, Ser311 and Glu411. Compound with Br at 2″-position showed similar interactions to compound 7.[6,7,8]



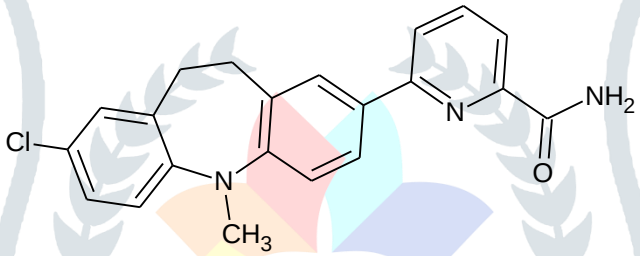
Compound 7

Sodium channel blocker

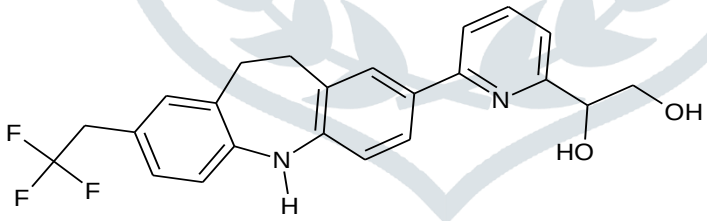
Among nine voltage-gated sodium channel subtypes (Nav1.1– Nav1.9) found in mammals, Nav1.7 has been of important based on human genetic studies. Compound 8,9 and 10 having dibenzaepine nucleus was synthesised. Dib-Hajj SD prepared Compound 8 and was found to be moderately potent in FLIPR (Fluorometric Imaging Plate Reader) assay and prominent in EP (electrophysiology) testing. Compound 9 showed increased FLIPR potency. Compound 10 also had similar FLIPR potency as 9.[9,10,11,12]



Compound 8



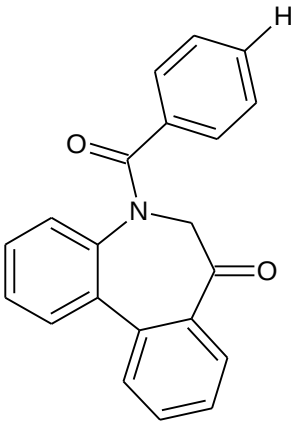
Compound 9



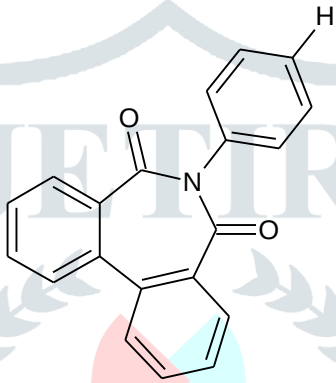
Compound 10

Anti-convulsant and anti-hypoxic activity

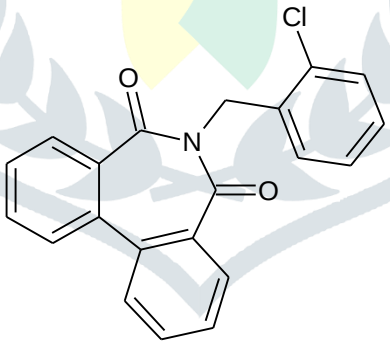
6,7-dihydro-5H-dibenz[c,e]-azepine (I), 6,7-dihydro-5H-dibenz[c,e]azepine-5,7-dione (II), and 6,7-dihydro-5H-dibenz[c,e]azepin-7-one (III) were synthesised according to the study conducted by Gorshkova VK. Experiment is conducted in random-bred mice (18-25 g) on intragastric administration for anticonvulsant activity. Anticonvulsant activity is assessed by maximal electroshock (MES) and Corazol 'titration'. Compound 11 display more marked anti-convulsant action on Corazol convulsions. Almost all the benzene derivatives of dibenzazepinone displayed high antihypoxic activity in the hemic hypoxia model [compounds 12,13,14,15,16,17].[13,14]



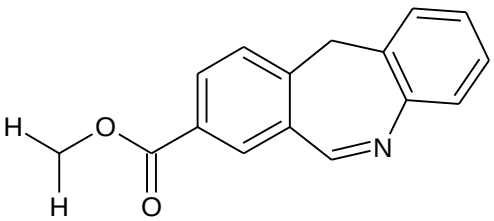
compound 11



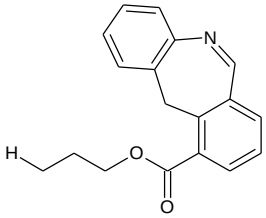
Compound 12



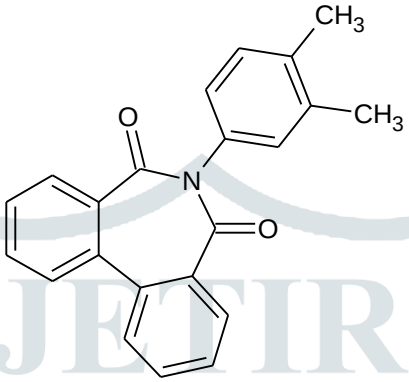
Compound 13



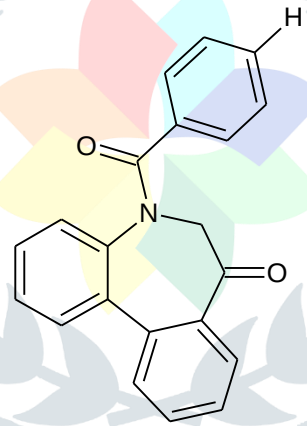
Compound 14



Compound 15



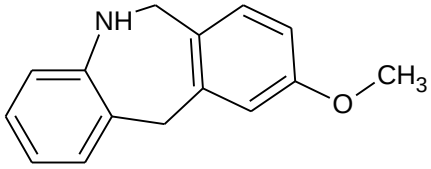
Compound 16



Compound17

Anti-anxiety activity

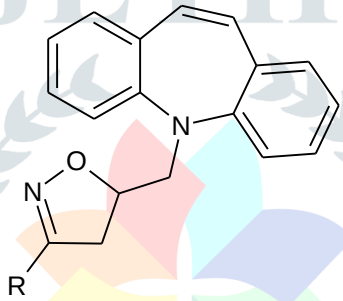
Anxiety ailment are a type of psychiatric condition concerning extreme behavioural response to strain. Benzodiazepine nucleus has been shown to present in diazepam, imipramine, and lorazepam, which are mood disorder drugs. Reamtong and colleagues synthesised a series of dibenzazepine compounds and evaluated for their cytotoxicity against normal kidney cell lines. Garg N synthesised 14 compounds and they were well characterised using NMR and MS. Among the tested compounds, compound 18 showed the lowest cytotoxicity which are comparable to the potent standard drug diazepam. From the result of the cytotoxicity study, dibenzazepine compounds were selected for anti anxiety activity against stressed rats. From the result it is clear that compound 18 showed better anxiolytic activity than diazepam.[15,16,17,18,19]



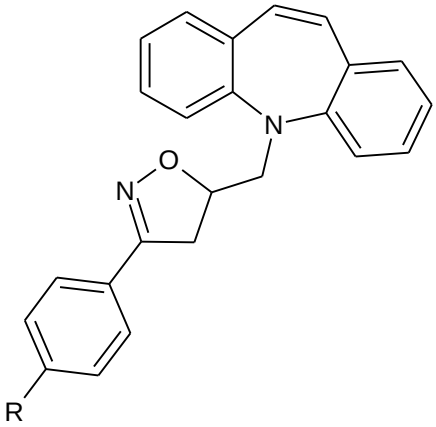
Compound 18

Anti-malarial activity

Malaria is considered as a complex and deadly parasitic infectious disease. Chloroquine and other quinine derivatives have been used to treat malaria since years. According to the study conducted by Kumar KS, firstly, a sequence of 3,5-disubstituted isoxazolines bearing aryl, heteroaryl and alicyclic group at C-3 position of isoxazoline ring and containing dibenzazepine moiety at C-5 position were prepared. Dibenzazepine derivatives synthesised here were found to exhibit promising biological and pharmacological properties with short side effects. The synthesised compounds were examined for antimalarial activity against chloroquine sensitive P. falciparum 3D7 strain. All the synthesised compounds showed excellent anti malarial activity with IC50 values of 0.2 -7.7 micromol. [20]



Compound	R
Compound 19	p-(NO_2)Ph
Compound 22	p-(F)Ph
Compound 21	p-(Cl)Ph
Compound 22	p-(Br)Ph
Compound 23	p,o-di-(Me)2Ph
Compound 24	p-(OMe)Ph
Compound 25	p-(OH)Ph
Compound 26	p-(OCOPh)Ph
Compound 27	p-(CF_3)Ph
Compound 28	p-(3-pyridyl)Ph
Compound 29	4-piperidyl



Compound	R
Compound 30	p-(Cl)Ph
Compound 31	p-(OH)Ph
Compound 32	p-(OH)Ph
Compound 33	p-(CH_2OH)Ph
Compound 34	p-(CHO)Ph
Compound 35	p-(OMe)Ph
Compound 36	p-(OCF_3)Ph
Compound 37	p-(CN)Ph
Compound 38	p-(CH_2NHPh)Ph
Compound 39	2-thiophene
Compound 40	4-pyridyl
Compound 41	5-(6-Chloro-1,3dihydro-indol-2-one)

FUTURE PERSPECTIVES

From this review, we noted that dibenzazepine derivatives showed anti tumor, alpha glucosidase inhibition, sodium channel blocking, anti convulsant, anti hypoxic, anti anxiety and anti malarial activities. This can be taken as a good scope for future study. Hence, the discovery of the dibenzazepine derivatives with these activities have been proven to be more effective and selective, and are much freer of unwanted side effects.

REFERENCE

1. Al-Qawasmeh RA, Lee Y, Cao MY, Gu X, Viau S, Lightfoot J, Wright JA, Young AH. 11-Phenyl-[b, e]-dibenzazepine compounds: novel antitumor agents. Bioorganic & Medicinal Chemistry Letters. 2009 Jan 1;19(1):104-7.

2. Al-Qawasmeh RA, Lee Y, Cao MY, Gu X, Vassilakos A, Wright JA, Young A. Triaryl methane derivatives as antiproliferative agents. Bioorganic & medicinal chemistry letters. 2004 Jan 1;14(2):347-50.
3. Cao MY, Lee Y, Feng NP, Al-Qawasmeh RA, Viau S, Gu XP, Lau L, Jin H, Wang M, Vassilakos A, Wright JA. NC381, a novel anticancer agent, arrests the cell cycle in G0-G1 and inhibits lung tumor cell growth in vitro and in vivo. Journal of Pharmacology and Experimental Therapeutics. 2004 Feb 1;308(2):538-46.
4. Belal A. Design, Synthesis and Anticancer Activity Evaluation of Some Novel Pyrrolo [1, 2-a] azepine Derivatives. Archiv der Pharmazie. 2014 Jul;347(7):515-22.
5. Frimayanti N, Yaeghoobi M, Ikhtiarudin I, Putri DR, Namavar H, Bitaraf FS. Insight on the in silico study and biological activity assay of chalcone-based 1, 5-benzothiazepines as potential inhibitor for breast cancer MCF7. CMUJ. Nat. Sci. 2021;20(1):e2021019.
6. Ullah S, Khan MA, Zafar H, Younus M, Choudhary MI, Basha FZ. Dibenzazepine-linked isoxazoles: New and potent class of α-glucosidase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2021 May 15;40:127979.
7. Reuser AJ, Wisselaar HA. An evaluation of the potential side-effects of α-glucosidase inhibitors used for the management of diabetes mellitus. European journal of clinical investigation. 1994 Aug;24(S3):19-24.
8. Ali F, Khan KM, Salar U, et al. Hydrazinyl arylthiazole based pyridine scaffolds: Synthesis, structural characterization, in vitro α-glucosidase inhibitory activity, and in silico studies. Eur J Med Chem. 2017;138:255–272.
9. Lynch SM, Tafesse L, Carlin K, Ghatak P, Kyle DJ. Dibenzazepines and dibenzoxazepines as sodium channel blockers. Bioorganic & Medicinal Chemistry Letters. 2015 Jan 1;25(1):43-7.
10. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annual review of neuroscience. 2010 Jul 21;33:325-47.
11. Black JA, Frézel N, Dib-Hajj SD, Waxman SG. Expression of Nav1. 7 in DRG neurons extends from peripheral terminals in the skin to central preterminal branches and terminals in the dorsal horn. Molecular pain. 2012 Nov 7;8:1744-8069.
12. Eijkelkamp N, Linley JE, Baker MD, Minett MS, Cregg R, Werdehausen R, Rugiero F, Wood JN. Neurological perspectives on voltage-gated sodium channels. Brain. 2012 Sep 1;135(9):2585-612.
13. Gorshkova VK, Saratikov AS, Tignibidina LG. Investigation of the anticonvulsant and antihypoxic activity of new dibenzazepine derivatives. Pharmaceutical Chemistry Journal. 1994 Mar;28:158-62.
14. Marchi N, Guiso G, Rizzi M, Pirker S, Novak K, Czech T, Baumgartner C, Janigro D, Caccia S, Vezzani A. A pilot study on brain-to-plasma partition of 10, 11-dyhydro-10-hydroxy-5H-dibenzo (b, f) azepine-5-carboxamide and MDR1 brain expression in epilepsy patients not responding to oxcarbazepine. Epilepsia. 2005 Oct;46(10):1613-9.
15. Garg N, Jain P, Neyol S, Kishore D, Sahu A, Jain D. Synthesis and Medicinal Importance of Dibenzazepine Derived Compounds: A Review. Contemporary Advances in Science & Technology-V: Pharmaceutical Chemistry and Technology. 2022 Sep 21:1.
16. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology. 2016 Jan;41(1):297-319.
17. Rickels K, DeMartinis N, García-España F, Greenblatt DJ, Mandos LA, Rynn M. Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. American Journal of Psychiatry. 2000 Dec 1;157(12):1973-9.
18. Rickels K, Chung HR, Csanalosi IB, Hurowitz AM, London J, Wiseman K, Kaplan M, Amsterdam JD. Alprazolam, diazepam, imipramine, and placebo in outpatients with major depression. Archives of general psychiatry. 1987 Oct 1;44(10):862-6.
19. Reamtong O, Lapmanee S, Tummatorn J, Palavong N, Thongsornkleeb C, Ruchirawat S. Synthesis of benzoazepine derivatives via azide rearrangement and evaluation of their antianxiety activities. ACS Medicinal Chemistry Letters. 2021 Aug 25;12(9):1449-58.

20. Kumar KS, Lingaraju GS, Bommegowda YK, Vinayaka AC, Bhat P, Kumara CS, Rangappa KS, Gowda DC, Sadashiva MP. Synthesis, antimalarial activity, and target binding of dibenzazepine-tethered isoxazolines. RSC advances. 2015;5(110):90408-21.
21. Ravinder B, Reddy SR, Sridhar M, Mohan MM, Srinivas K, Reddy AP, Bandichhor R. An efficient synthesis for eslicarbazepine acetate, oxcarbazepine, and carbamazepine. Tetrahedron Letters. 2013 May 29;54(22):2841-4.
22. Singh B, Maheshwari A, Dak G, Sharma K, Talesara GL. Studies of antimicrobial activities of some 4-thiazolidinone fused pyrimidines,[1, 5]-benzodiazepines and their oxygen substituted hydroxylamine derivatives. Indian journal of pharmaceutical sciences. 2010 Sep;72(5):607.