Int J Pharm Bio Sci 2013 Apr; 4(2): (P) 68 - 77

Review Article **Medicinal Chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

DIBENZOTHIAZEPINE A BREAK THROUGH HETEROCYCLIC NUCLEUS IN MEDICINAL CHEMISTRY

SARITA S. PAWAR*

Dept. of Pharmaceutical chemistry, S.R.E.S'S Sanjivani College of pharmaceutical education and research, Kopargaon, Dist-Ahmednagar, M.S., India-423603

ABSTRACT

Dibenzothiazepine, a conjugated heterocyclic ring systems reported for their wide spectrum of pharmacological activity especially for its psychotherapeutic activities. Successful introduction of quetiapine, tianeptine, clotiapine for antipsychotic activity along with its evidence for other biological activity proved potential of dibenzothiazepine moiety. Subsequently dibenzodiazepine were highlighted as important biologically active scaffolds. The discovery of quetiapine fumarate as psychotropic agents attracted much attention worldwide. The current review article focuses on pharmacological and synthetic profile of dibenzothiazepine. This article mainly outlines some structural modifications done on dibenzothiazepine to offer newer derivatives with potential biological activity.

KEY WORDS: **Benzothiazepine, dibenzothiazepine, synthesis, biological activity.**

SARITA S. PAWAR
Dept. of Pharmaceutical chemistry, S.R.E.S'S Sanjivani College of pharmaceutical education and research, Kopargaon, Dist-Ahmednagar, M.S., India-423603

Corresponding author

INTRODUCTION

A heterocyclic compound is a cyclic compound which has atoms of at least two different elements as members of its ring(s). Although heterocyclic compounds may be inorganic, must contain at least one carbon atom, and one or more atoms of elements other than carbon within the ring structure, such as sulfur, oxygen or nitrogen. Since in organic chemistry non-carbons usually are considered to replace carbon atoms, they are called heteroatom, meaning different from carbon and hydrogen. Heterocyclic rings systems that are formally derived by fusion with other rings, either carbocyclic or heterocyclic, have a variety of common and systematic names. For example, with the benzo fused unsaturated nitrogen heterocyclic, pyrrole provides indole or isoindole depending on the orientation. The pyridine analog is quinoline or isoquinoline. For azepine, benzazepine is the preferred name. Similarly, the compounds with two benzene rings fused to the central heterocyclic are carbazole, acridine, and dibenzoazepine. Dibenzothiazepine are chemical compounds which are derivatives of thiazepine with two benzo rings. Dibenzothiazepine are of interest as potential antiviral, in particular, for AIDS prevention and treatment[1]. The scaffold dibenzothiazepine widely used for its diverse biological activities like antipsychotic, antihistaminic, potential high ceiling loop diuretics, antibacterial [2, 3], especially C11-N-substituted analogues were studied and found with significant activity. Dibenzo [b, f] [1, 4] thiazepine is a class of compounds used as antipsychotic drug (11-(4-[2-(2-hydroxyethoxy) ethyl]-1-piperazinyl] dibenzo [b, f] [1, 4] thiazepine (Compound I, trade name Quetiapine), is a typical antipsychotic drug successfully employed for the treatment of schizophrenia and bipolar disorders for many years[4] and recently in the treatment of delirium and agitation[5,6]. Another is clothiapine (Compound II). These compound used as antipsychotic and narcoleptics still had been associated with certain side effects like acute diskinesia, acute dystopias, pseudo Parkinsonism, tardive diskinesia (TD) etc. Thus there is a continuous need for newer dopaminergic agents in future for the treatment of neurodegenerative disorders [7,8].

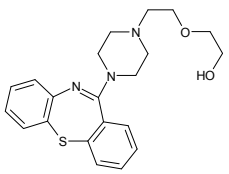


Figure I

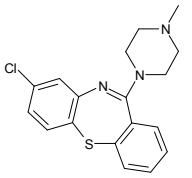
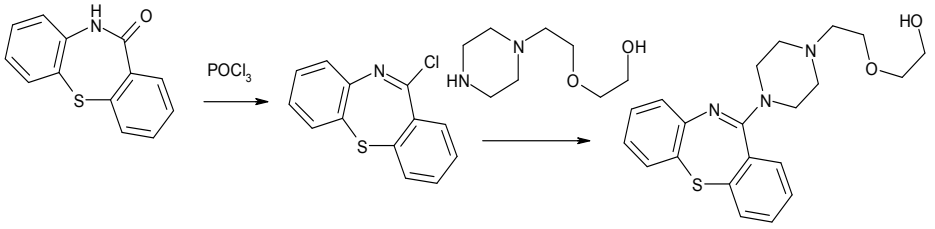


Figure II

SYNTHESIS OF DIBENZOTHIAZEPINES

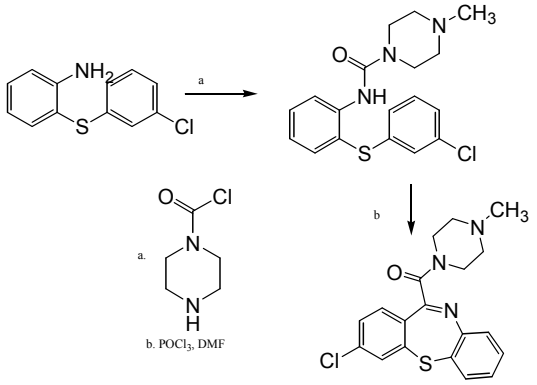
1. Warawa and Migler (1989) reported the synthesis 1 1-[4-[2-(2-Hydroxyethoxy) ethyl]-1 -piperazinyl]-dibenzo [b, f| [1, 4] thiazepine). According to this method, 2-Amino diphenylsulfide and phenyl chloroformate in toluene and alkali were reacted to afford urethane, phenyl 2-(phenylthio-phenylcarbamate (90%) which on heating with polyphosphoric acid and gave dibenzo [b, f] [1, 4] thiazepine-11(10-H) one (87%). Dibenzo [b, f] [1, 4] thiazepine-11(10-H) one and $POCl_3$ were reacted in presence of N, N-dimethyl aniline to give the imino chloride (92.6%). Piperazine in toluene and 11-chloro-dibenzo[b,f][1 ,4]thiazepine were added together and refluxed to give an oil which was treated with a solution of hydrogen chloride in ethanol to get 11-Piperazinyl-dibenzo[b,f][1,4]thiazepine as dihydrochloride salt (88%). This salt, sodium carbonate, sodium iodide and 2-chloroethoxyethanol combined together in n-propanol and N-methyl pyrrolidone to give oil which was isolated as the hemi-fumarate salt[9] (Figure 1).

Figure 1
Synthesis of Quetiapine



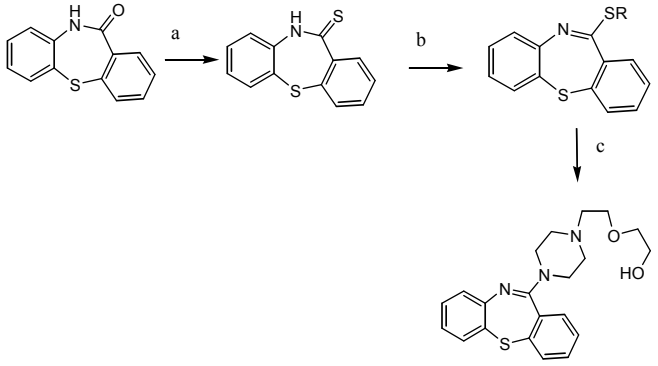
2. Schumtz et al (1965) reported the synthesis of dibenzothiazepine as a result of condensation of 2-amino-3-chlorothiodiphenyl ether with 4-methyl piperazine–1-carbamoylchloride to afford urea derivative which on cyclization using phosphorous oxychloride gave 3-chloro-11-(N^4-methyl)piperazinyl dibenzothiazepine[8] (Figure 2).

Figure 2



3. Also in another method dibenzo[b,f][1,4]thiazepinone was converted into dibenzo[b,f][1,4]thiazepinone-11(10H)-thione with P_2S_5 which on treatment with alkyl halide to get corresponding sulfanyl derivative. This on further reaction with 1-(2-(2-hydroxyethoxy) ethyl) piperazine afforded quetiapine [8] (Figure 3).

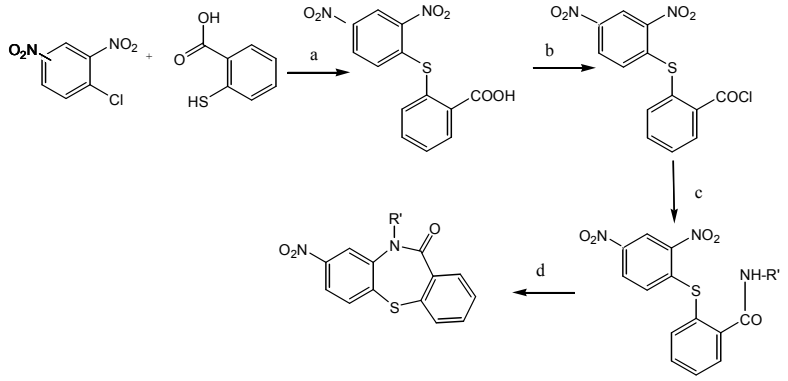
Figure 3



a-P_2S_5; b- RX; c- 1-(2-(2-hydroxyethoxy) ethyl) piperazine

4. A new method has been elaborated which makes it possible to introduce a required substituent at the nitrogen atom even before the ring has formed, using almost any primary amine by intramolecular aromatic substitution of the nitro group (denitrocyclisation). Unlike the known methods, this method Thiosalicylic acid, which readily participates in nucleophilic substitution with various activated aromatic substrates, serves as the main reagent in the synthesis. They used 2, 4-dinitrochlorobenzene to obtain dibenzothiazepine containing a nitro group, which was then converted into an amino group. Intermediate 2-(2, 4-dinitrophenylthio) benzoic acid can be obtained in a high yield by heating equimolar amounts of the specified reagents and triethylamine (hydrogen chloride acceptor). A solution of 2-(2, 4-dinitrophenylthio) benzoyl chloride was obtained. The formation of a thiazepine ring occurs *via* the nucleophilic replacement of the nitro group with the amide nucleophilic centre that is formed on treatment with deprotonating agents[10] (Figure 4).

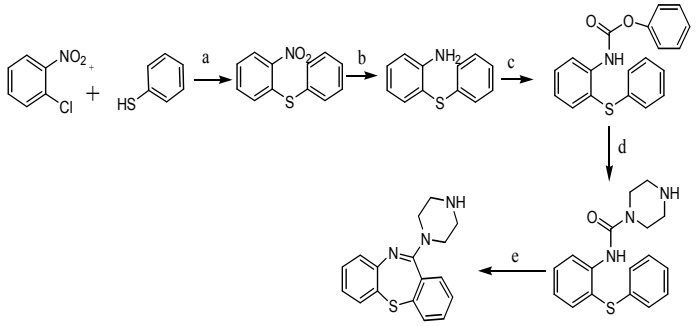
Figure 4



a-TEA, Δ; b- $SOCl_2$; c-R'-NH_2 , TEA ; d-base, Δ

5. According to method described by Kaczmarek et al (2004), o-Chloronitrobenzene, technical ethanol and thiophenol were treated with aqueous NaOH with stirring for 1 hr and then refluxed for 3 hrs. On completion of reaction acidification offered the precipitate of 2-(phenylthio) aniline hydrochloride in yield (89%). Further a solution of phenyl chloroformate in toluene in alkaline medium, piperazine, $POCl_3$ and P_2O_5 were refluxed for 12 hrs to give 11-(1-piperazinyl)dibenzo[b,f][1,4]thiazepine as thick, colorless oil[11] (Figure 5).

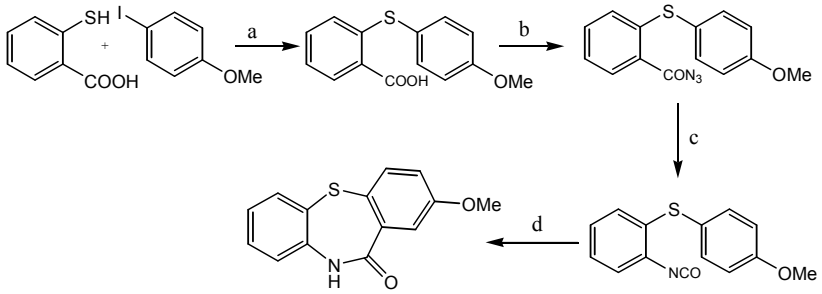
Figure 5



a-NaOH, ethanol; b- HCl, iron dust; c-ClCOOPh ; d- Piperazine; e- P_2O_5, $POCl_3$

6. Yi Liao et al. (1999) described the synthesis of 2-TfO-11-(4-methylpiperazinyl)-dibenzo [*b*,*f*][1,4] thiazepine (Scheme 4). 4-Iodoanisole reacted with 2-carboxythiophenol to form acid intermediate which was converted to its azide derivative. First, the one-pot treatment of azide with aluminum chloride in 1, 3-dichlorobenzene under heating was conducted to generate 2-hydroxylactam directly in only 13-30% yield. Heating of azide derivative alone generated first the isocyanate intermediate, which was further treated with aluminum chloride under heating at 150 °C (oil bath) in 1, 3-dichlorobenzene to give 2-hydroxylactam derivative with improved yield (80%). The ring closure and *O*-demethylation happened simultaneously. The 11-piperazinyl analogue was obtained by treatment with $POCl_3$ and piperazine in presence of N, N-dimethylaniline[12] (Figure 6).

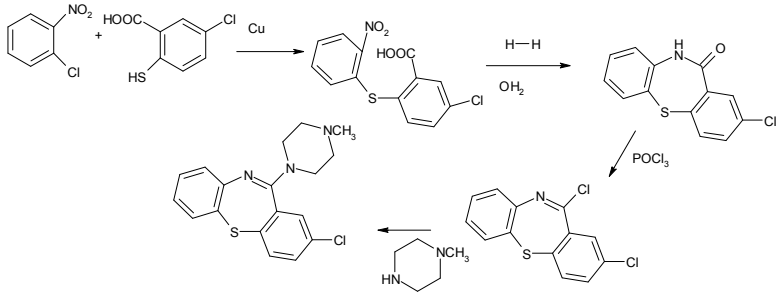
Figure 6



a-Δ ; b-SOCl₂ , NaN₃; c-Δ ; d-AlCl₃

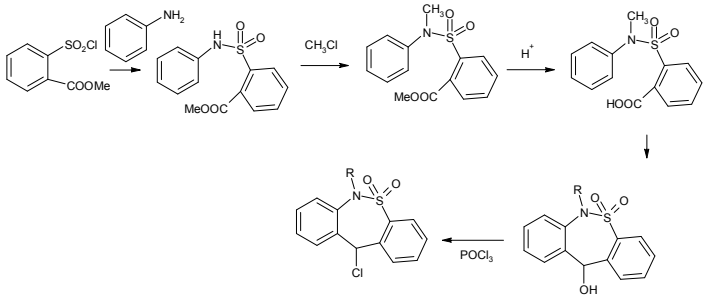
7. Synthesis of clotiapine (2-chloro-11-(4-methyl-1-piperazinyl)dibenzo-[*b*,*f*][1,4]-thiazepine) (Figure 7)-However, the methods of their synthesis are usually limited to the reaction of *ortho*-aminothiophenols with the derivatives of *ortho*-halobenzoic acids, which does not offer a wide variety of these compounds. The new compound HF-2159 (2-chloro-ll-(4'-methyl)piperazino-dibenzo-[b,f] [1,4]-thiazepine) studied in this paper in comparison with chlorpromazine shows the following properties: Inhibition of motor drive, as manifested in the locomotor activity of mice and in the 'open field' test with rats. Its effectiveness here is respectively six and sixteen times greater than that of chlorpromazine. In both species of animals HF-2159 is only half as toxic as chlorpromazine. Cataleptic action, which in rats is more than five times as strong as that of chlorpromazine. Inhibition of apomorphine—induced gnawing in rats, an effect roughly thirty times as intense as that of chlorpromazine. Temperature-lowering action in rats and rabbits, in the same range as that exerted by chlorpromazine. Inhibition of the electrographic arousal reaction elicited by stimulation of the mesencephalic reticular formation, of intensity not otherwise encountered in neuroleptics drugs with strong cataleptic activity. Further, HF-2159 relaxes decerebration rigidity in cats, and is active in the usual analgesia tests. HF-2159 has only slight and transitory effects on circulation, and no notable action on the autonomic nervous system (pupillary size, salivation, heart rate, bowel function). On the basis of the present pharmacological results, the compound may be expected to exert a neuroleptics effect in clinical use.

Figure 7



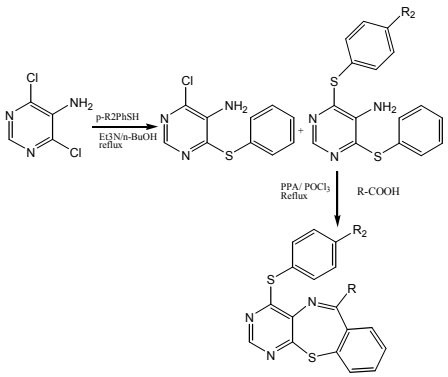
8. Synthesis of substituted dioxodibenzothiazepines as farnesyltransferase inhibitors (Figure 8)
   A new series of FTase inhibitors containing a tricyclic moiety—dioxodibenzothiazepine or dibenzocycloheptane—has been designed and synthesized. Among them, dioxodibenzothiazepine displayed significant inhibitory FTase activity (IC50 = 17.3 nM) and antiproliferative properties[1].
9. Alexander et al (2005) reported synthesis of quetiapine in which the 10H-dibenzo[b,f][1,4] thiazepine-11-one was reacted with a 1-(2-(2-hydroxyethoxy)ethyl)piperazine derivative in the presence of titanium alkoxide of general formula Ti $(OR)_4$ where R is a straight or branched alkyl group (1-8 carbon atoms) to obtain quetiapine[13].

Figure 8



10. Wagmode et al. (2011) reported a green procedure for the synthesis of dibenzothiazepine using water as solvent in the presence of an inorganic base where metal halides and phase transfer catalysts increases the rate of reaction[3].
11. Renzhong Fu et al (2005) reported the synthesis of novel tricyclic pyrimido[4,5-*b*][1,4]benzothiazepines via bischler-napieralski-type reactions. The 6-aryl sulfide group of the resulting pyrimido [4,5-b][1,4]benzothiazepines could be selectively oxidized to its corresponding sulfoxide, which underwent facile substitution reactions when treated with nucleophiles such as an amine. This synthetic strategy provides an efficient way to access a library of novel heterocyclic compounds that are of interest in drug discovery[14] (Figure 9).

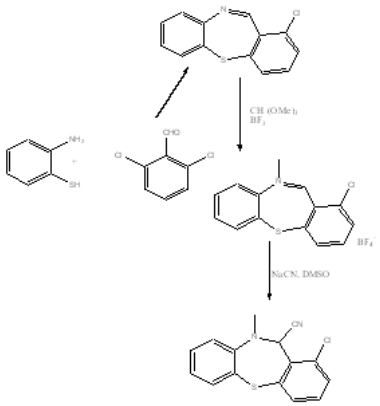
Figure 9



12. Jens- Uwe Bliesener (1978) reported A preparative simple method has been found for the synthesis of novel 2,3-dihydrodibenzo- [b,f]imidazo[l,2-d][1,4]thiazepines and 3,4-dihydro-2H-dibenzo[b,f]pyrimido[1,2-d][1,4]-thiazepines. Base-catalyzed reaction of the bifunctional 2-(1,3-diaza-2-cycloalken-2-yl)-thiophenols with variously activated o-halonitrobenzenes leads via a Smiles rearrangement to the products[15].

13. Okafor, Charles (1978) reported Chlorodibenzo [b, f] [1,4] thiazepine was prepared in 50% yield by condensing 2-aminothiophenol with 2,6dichlorobenzaldehyde in fused 2-methyl-imidazole. The product was transformed into the 10-methylderivative and isolated as the tetrafluoroborate salt by the action of trimethyl orthoformate in the presence of boron trifluoride at room temperature. When treated with sodium cyanide in dimethyl sulfoxide at room temperature it was converted to 11-cyano-10-methyl-10,ll dihydrodibenzo [b,f [1,4]-thiazepine in 70% yield. Ring-closure dehydration of the amides 1–piperazinecarboxylic acid o-phenylthioanilide using phosphorus oxychloride, good yields of 11–piperazinyldibenzo[b,f][1,4]thiazepines were obtained. Cyclization of 4{2-pyridylmethyl)-l –piperazinecarboxylic acid o-phenylsulfonyl anilide in the presence of ortho phosphoric acid and phosphorus oxychloride led to the corresponding S dioxide. Beckmann rearrangement of 1 O-(hydroxyimino) thioxanthene S dioxide led to dibenzo [b,f] [1,4]thiazepin-l0-one- 5,s-dioxide in satisfactory yields[16] (Figure 10).

Figure 10

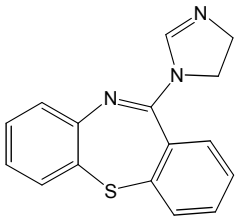


PHARMACOLOGICAL ACTIVITY

1. Antimicrobial activity[2]

Waghmode et al reported the synthesis and antibacterial activity of some new dibenzothiazepine carrying imidazole and triazole and their substituted moieties at C-11 position and screened them for antibacterial activity against gram negative and gram positive bacteria. The compound containing imidazole at C-11 (Figure 11) was found to be most active against all the bacterial strains.

Figure 11
11-imidazolyldibenzo[b,f][1,4]thiazepine



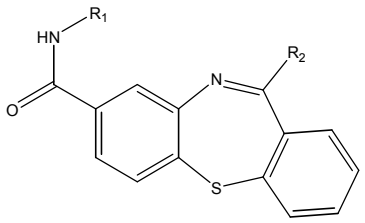
2. Anticancer activity[1]

A new series of FTase inhibitors containing a tricyclic moiety dioxodibenzothiazepine or dibenzocycloheptane—has been designed and synthesized. Among them, dioxodibenzothiazepine displayed significant inhibitory FTase activity (IC50 = 17.3 nM) and antiproliferative properties.

3. Cannabinoid receptor agonists[17]

Hanna Pettersson et al. reported a novel class of CB1 inverse agonists. To efficiently establish structure-activity relationships (SARs), new synthetic methodologies amenable for parallel synthesis were developed. The compounds were evaluated in a mammalian cell-based functional assay and in radioligand binding assays expressing recombinant human cannabinoid receptors (CB1 and CB2). In general, all of the compounds exhibited high binding selectivity at CB1 vs. CB2 and the general SAR revealed a lead compound 11-(4-chlorophenyl)dibenzo[*b,f*][1,4]thiazepine-8-carboxylic acid butyl amide which showed excellent in vivo activity in pharmacodynamic models related to CB1 receptor activity. The low solubility that hampered the development of this was solved leading to a potential preclinical candidate 11-(3-chloro-4-fluorophenyl)- dibenzo[*b,f*][1,4]thiazepine-8-carboxylic acid butyl amide (Figure 12).

Figure 12



4. Calcium antagonists[18]

Li R et al reported A number of dibenzothiazepinones and dibenzoxazepinones have been designed, synthesized and evaluated as calcium antagonists. Vasorelaxation properties among these compounds appear to be relatively insensitive to the flexure angle and to chain

length. Vasorelaxation is profoundly influenced by the nature of the basic terminal moiety.

5. Several dibenzo [*b,f*][1,4]thiazepin-11(10*H*)-ones were also prepared [19], some of which were reported to exhibit activity against the HIV virus[20, 21] or useful agents for the prevention and treatment of AIDS[22] while others act as leukotriene antagonists[23].

6. Okafor, Charles et al (1978) reported the biological properties of these compounds were extensively investigated in birds and mammals. Strong antihistaminic, antidepressant, antiasthma, antiallergic, antiphlogestic, analgesic, cholesterol depressant, anti-inflammatory, antiartesclerotic, sedative and neuroleptics, neurotropic, antiemetic, anxiolytic, tranquillizer, psychotropic, bactericidal and fungicidal activities were exhibited by these derivatives. In the 10-aminoalkylcarboxylate derivatives which showed CNS activities, the LD_5o in mice on i.p. or oral application is 75-500 mg/kg or 300-2000 mg/kg respectively.

CONCLUSION

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by dibenzothiazepine derivatives. The biological profiles of these new generations of dibenzothiazepine would represent a fruitful matrix for further development of better medicinal agents. An attempt is made to focus on some synthetic methods of dibenzothiazepine including denitrocyclisation, oxidative cyclization methods of synthesis. It can act as an important tool for medicinal chemists to develop newer compounds possessing dibenzothiazepine moiety that could be better agents in terms of efficacy and safety.

REFERENCES

1. Gilleron P, Wlodarczyk N, Houssin R, Farce A, Laconde G, Franc J¸ Goossens O, Lemoine A, Pommery N, He´nichart JP and Millet R, Design, synthesis and biological evaluation of substituted dioxodibenzothiazepines and dibenzocycloheptanes as farnesyltransferase inhibitors *Bioorganic & Medicinal Chemistry Letters,* 17: 5465–5471, (2007).
2. Mahale GD, Kumar A, Singh D, Ramaswamy AV and Waghmode SB, Synthesis and antibacterial activities of new dibenzothiazepine derivatives, *Indian Journal of chemistry*, 50B: 1196-1201, (2011).
3. Mahale GD, Kumar A, Singh D, Ramaswamy AV and Waghmode SB, A green process for preparation of (11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo[b, f]-1,4-thiazepine,*J. Serb. Chem. Soc.*, 73 (4): 385- 391, (2008).
4. Horrom BW, Minard FN, Zaugg HE Dibenzo[b,e][1,4]diazepines,U.S.patent *US 4097597*, 1978.
5. Torres R, Mittal D, Kennedy R , Use of quetiapine in delirium: case reports. *Psychosomatics,* 42(4): 347-349, (2001).
6. Chaudhary K, Rana AC, Bala R, Seth N*,* Review: Depression as a common disorder in teenagers and its treatment. *Int J Pharm Bio Sci*, *2(2): 269-279, (2012).*
7. Stille G, Ackermann H, Eichenberger E, Lauener H, The pharmacological properties of a potent neurotropic compound from the dibenzothiazepine group *International Journal of Neuropharmacology*, 4(6): 375-391, (1965).
8. Schmutz J, Künzle F, Hunziker F, Gauch R, Über in 11-Stellung amino-substituierte Dibenzo[b,f]-1, 4-thiazepine und -oxazepine. Mitteilung über siebengliedrige Heterocyclen *Helv. Chim. Acta* 50: 245-253, (1967).

9. Warawa EJ, Migler BM, Novel dibenzothiazepine antipsychotic, US patent 4789288, 1989.
10. Smirnov AV, Kalandadze LS, Sakharov VN and Dorogov MV, Denitrocyclisation in the synthesis of dibenzothiazepinones *Mendeleev Commun.* 262-264 (2006).
11. Kaczmarek L, Rosłonek KB, Stolarczyk E, Szelejewski W, Process for the preparation of 11-(1-piperazinyl)dibenzo[b, f][1 ,4]thiazepine, an intermediate in the synthesis of the antipsychotic drug quetiapine, PCT/EP2004/051520 (2004).
12. Liao Y , Bastiaan JV, Rodenhuis N, Timmerman W, Wikström H, Meier E, Bartoszyk GD, Böttcher H, Seyfried CA, Sundell S New (Sulfonyloxy)piperazinyldibenzazepines as Potential Atypical Antipsychotics: Chemistry and Pharmacological Evaluation. J MED CHEM. 42 (12): 2235-2244, (1999).
13. Comely, Alexander, Christian, European Patent, *WO 2005/012274* (10.02.2005 Gazette 2005/06).
14. Fu R, Xu X, Dang Q and Bai X, Synthesis of Novel Tricyclic Pyrimido[4,5-*b*][1,4] benzothiazepines via Bischler-Napieralski-Type Reactions *J Org Chem*., 70(26) : 10810-10816, (2005).
15. Bliesener JU, Einfache Synthese anellierter Dibenzo[b,f][l,4]thiazepine Liebigs *Ann. Chem*., 259-266, 1978.
16. Charles O, 'studies in the heterocyclic series. xiv. the chemistry and biological activity of new aza- and thia-phenothiazines, and related dibenzothiazepines *Phosphorus, Sulfur, and Silicon and the Related Elements*, 4(1): 79-99, (1978).
17. Pettersson H, Bu¨low A, Ek F, Jensen J, Ottesen LK, Fejzic A, Ma JN, Del AL, Currier EA, Gardell LR, Tabatabaei A, Craig D, McFarland K, Ott TR,Piu F, Burstein ES, and Olsson R, Synthesis and Evaluation of Dibenzothiazepines: A Novel Class of Selective Cannabinoid-1 Receptor Inverse Agonists *J. Med. Chem. 52: 1975-1982, (*2009).
18. Li R, Farmer PS, Wang J, Boyd RJ,
19. Cameron TS, Quilliam MA, Walter JA,
24. Molecular geometries of dibenzothiazepinone and dibenzoxazepinone calcium antagonists,*Drug Design and Discovery.* 12(4): 337-358, (1995).

19 Kwak B, Chung K, Koh K, Hwang H, Method of preparing 10*H*dibenzo[b,f]]1,4]thiazepin-11-one *PCT Int. Appl. WO 047722*, 2004.

20 Nicol RH, Slater MJ, Hodgson ST, Preparation of dibenzothiazepinethiones as antiviral agents *PCT Int. Appl. WO 19607*, 1992;

21 Hargrave KD, Schmidt G, Engel W, Schromm K, Preparation of dibenz[*b*,*f*][1,4]oxazepin (and thiazepin)-11(10*H*)-ones and-thiones for prevention and treatment of AIDS *Can. Pat. Appl. 2024040,* 1991.

22 Belanger PC, Rokach J, Scheigetz J, Preparation of 10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepines as leukotriene antagonists *U.S. Pat. 4728735*, 1988.

23 Katano K, Satoh T, Soneda T, Kamitoh N, Fujishima K, Hachisu M, 5-(4-piperidinyl)dibenzothiazepine derivatives and 5-(4-piperidinyl)dibenzoxazepines derivatives, and antiarrhythmic agents *US patent 6063779*, 2000.