



DIBENZOTHAZEPINE A BREAK THROUGH HETEROCYCLIC NUCLEUS IN MEDICINAL CHEMISTRY

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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.



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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 dibenzazepine. 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 treatment¹. 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 years⁴ 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 dyskinesia, acute dystopias, pseudo Parkinsonism, tardive dyskinesia (TD) etc. Thus there is a continuous need for newer dopaminergic agents in future for the treatment of neurodegenerative disorders^{7,8}.

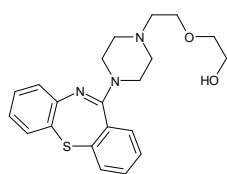


Figure I

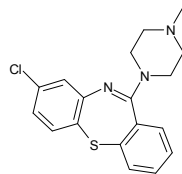


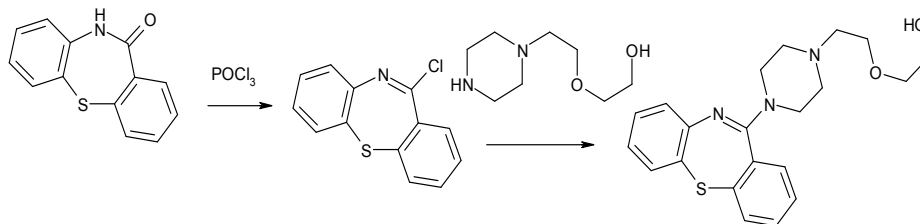
Figure II

SYNTHESIS OF DIBENZOTHIAZEPINES

1. Warawa and Migler (1989) reported the synthesis of 11-(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

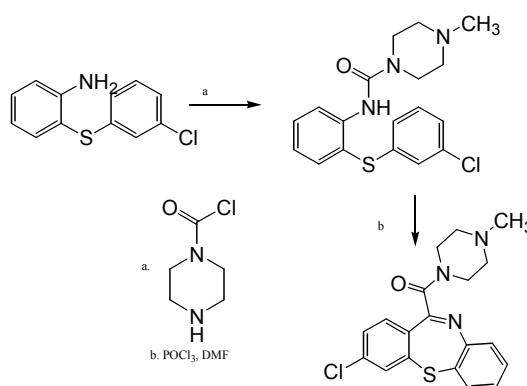
imino chloride (92.6%). Piperazine in toluene and 11-chloro-dibenzo[b,f][1,4]thiazepine were added together and refluxed to give an oil which was treated with a solution of hydrogen chloride in ethanol to get 11-Piperazinyl-dibenzo[b,f][1,4]thiazepine as dihydrochloride salt (88%). This salt, sodium 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 salt⁹ (Figure 1).

Figure 1
Synthesis of Quetiapine



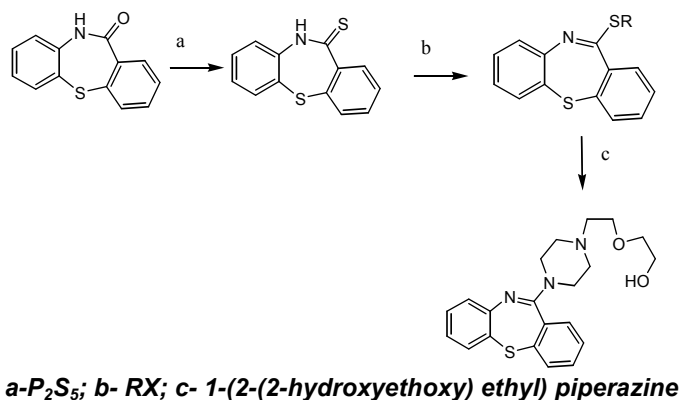
2. Schumtz et al (1965) reported the synthesis of dibenzothiazepine as a result of condensation of 2-amino-3-chlorodiphenyl ether with 4-methyl piperazine-1-carbamoylchloride to afford urea derivative which on cyclization using phosphorous oxychloride gave 3-chloro-11-(N⁴-methyl)piperazinyl dibenzothiazepine⁸ (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 P₂S₅ which on treatment with alkyl halide to get corresponding sulfanyl derivative. This on further reaction with 1-(2-(2-hydroxyethoxy) ethyl) piperazine afforded quetiapine⁸ (Figure 3).

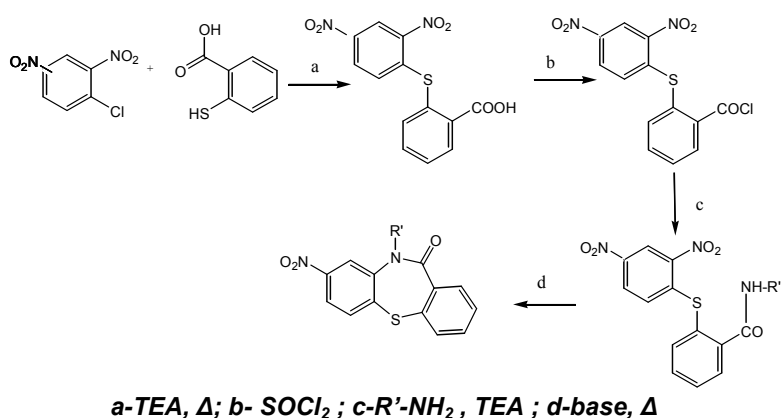
Figure 3



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 agents¹⁰ (Figure 4).

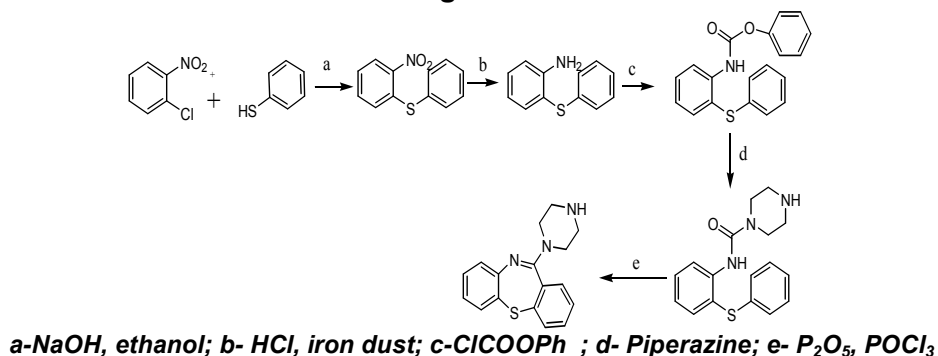
Figure 4



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 oil¹¹ (Figure 5).

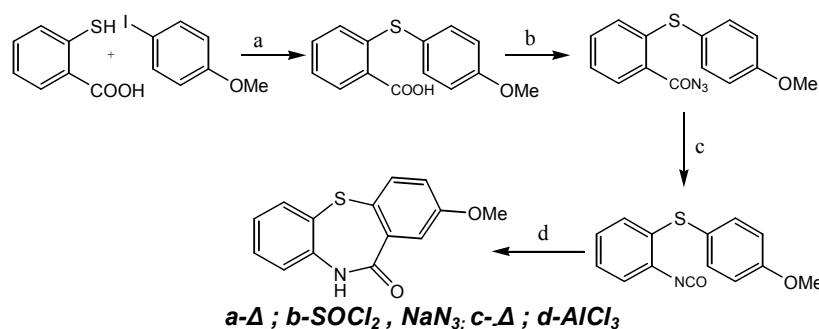
Figure 5



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 POCl₃ and piperazine in presence of N, N-dimethylaniline¹² (Figure 6).

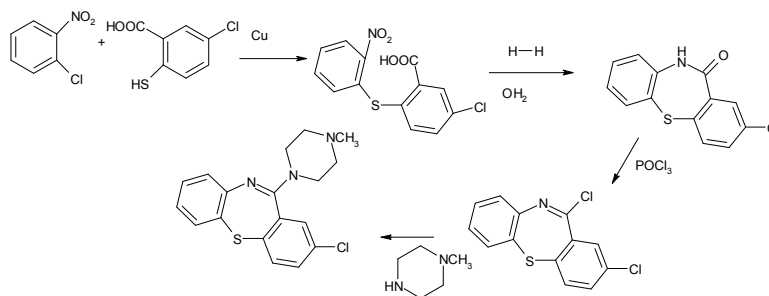
Figure 6



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-11-(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.

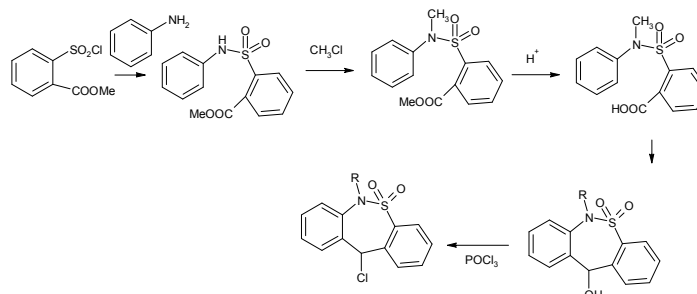
Figure 7



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 ($IC_{50} = 17.3 \text{ nM}$) and antiproliferative properties¹.

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 quetiapine¹³.

Figure 8

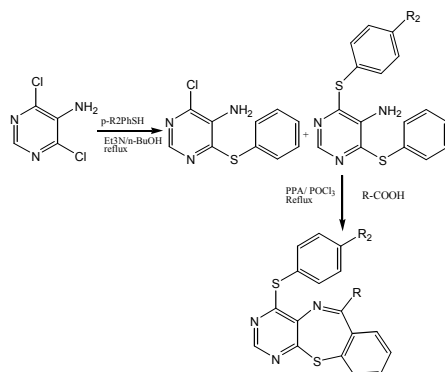


10. Wagmode et al. (2011) reported a green procedure for the synthesis of dibenzothiazepine using water as solvent in the presence of an inorganic base where metal halides and phase transfer catalysts increases the rate of reaction³.

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 discovery¹⁴ (Figure 9).

Figure 9

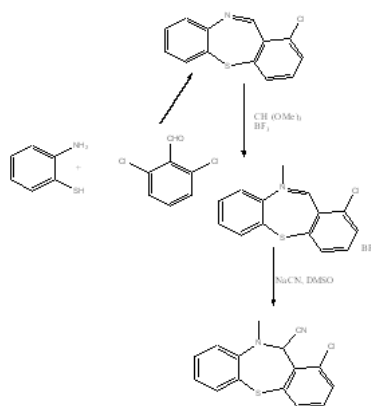


12. Jens- Uwe Bliesener (1978) reported A preparative simple method has been found for the synthesis of novel 2,3-dihydrodibenzo-[b,f]imidazo[1,2-d][1,4]thiazepines and 3,4-dihydro-2H-dibenzo[b,f]pyrimido[1,2-d][1,4]-thiazepines. Base-catalyzed reaction of the bifunctional 2-(1,3-diaza-2-cycloalken-2-yl)-thiophenols with variously activated o-halonitrobenzenes leads via a Smiles rearrangement to the products¹⁵.

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-methylimidazole. The product was transformed into the 10-methyl derivative 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-10,11 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-10-one- 5,s-dioxide in satisfactory yields¹⁶ (Figure 10).

Figure 10

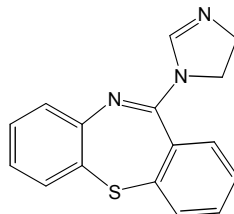


PHARMACOLOGICAL ACTIVITY

1. Antimicrobial activity²

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-imidazolylidibenzo[b,f][1,4]thiazepine



2. Anticancer activity¹

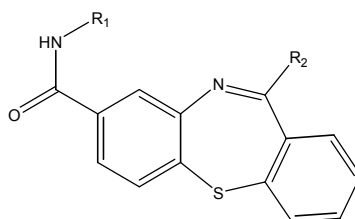
A new series of FTase inhibitors containing a tricyclic moiety dioxodibenzothiazepine or dibenzocycloheptane—has been designed and synthesized. Among them, dioxodibenzothiazepine displayed significant inhibitory FTase activity (IC₅₀ = 17.3 nM) and antiproliferative properties.

3. Cannabinoid receptor agonists¹⁷

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 antagonists¹⁸

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 prepared¹⁹, some of which were reported to exhibit activity against the HIV virus^{20, 21} or useful agents for the prevention and treatment of AIDS²² while others act as leukotriene antagonists²³.

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, antiarteriosclerotic, 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 LD₅₀ 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.

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