Synthesis & Pharmaceutical Characterization of 1,5-Benzothiazepine Derivatives

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***Abstract*—The 1,5-benzothiazepine core serves as a notable privileged framework in medicinal chemistry, defined by a seven-membered heterocyclic ring that features sulfur and nitrogen atoms combined with a benzene ring. This review offers a comprehensive examination of the synthetic environments related to 1,5-benzothiazepine derivatives, compiling information from an extensive body of pharmaceutical research. The conversation focuses on the condensation of 2-aminothiophenols with α,β-unsaturated carbonyl compounds (chalcones), contrasting traditional thermal reflux techniques with contemporary green chemistry approaches like microwave-assisted organic synthesis (MAOS), ultrasound-facilitated reactions, and the use of ionic liquids. This manuscript focuses on the thorough assessment of various catalytic systems, such as Lewis acids, metal nanocatalysts, and solid heterogeneous supports, emphasizing reaction kinetics and diastereoselectivity. In addition, the review outlines the pharmacological importance of these derivatives, especially their function as L-type calcium channel blockers (e.g., diltiazem, clentiazem) and CNS-active compounds (e.g., quetiapine, thiazesim). Insights from structural-activity relationship (SAR) are utilized to clarify how modifications at C-2, C-3, and C-5 affect therapeutic results. Main findings emphasize the transition to solvent-free and catalyst-free approaches to improve atom economy and minimize ecological impact. Future projections indicate the incorporation of in silico pharmacokinetic modeling and nano-formulation techniques to enhance the bioavailability of drug candidates based on 1,5-benzothiazepine.**

***Index Terms*—1,5-Benzothiazepine; Diltiazem; Heterocyclic Synthesis; Eco-friendly Chemistry; Calcium Channel Inhibitors; Thia-Michael Reaction; Chalcone Formation; Pharmacophore Design; Quetiapine; Stereochemical Configuration**

I. INTRODUCTION

Heterocyclic frame architectures have been key components of medicinal chemistry, aiding in the design of pharmacophores that demonstrate strong binding to various biological targets. While there are several different heterocyclic systems, the benzothiazepine system is now classified as a "privileged" structure, meaning that it is a class of chemical structures that can yield useful ligands for multiple types of receptors, simply by making small modifications in structure. More specifically, 1,5-benzothiazepine is described as a bicyclic heteroaromatic compound consisting of a benzene ring fused to a seven-membered ring (heterocycle) which contains a sulfur atom and a nitrogen atom at position 1 and position 5, respectively.

Although the unsubstituted 1,5-benzothiazepine has historically been difficult to isolate, its substituted derivatives now account for many of the most studied and successful agents currently in use in the treatment of cardiovascular disease. The scientific relevance of 1,5-benzothiazepine derivatives is especially evident in their use as cardiovascular modulators, exemplified by dilitiazem (a potent coronary vasodilator and calcium channel blocker that transformed the treatment of angina pectoris, supraventricular arrhythmias and hypertension). From a structural standpoint, they are often considered bioisosteric to the benzodiazepine family, with the notable exception being the effect of replacing the nitrogen atom at the 1-position with a sulfur atom, which dramatically modifies the lipophilicity, electronic.

Contemporary synthetic approaches have transitioned to creating new, gentle, and highly effective methods, departing from harmful reagents in favor of green chemistry concepts. In today's pharmaceutical environment, the significance of 1,5-benzothiazepine goes beyond just cardiovascular uses. Derivatives exhibit a wide range of biological effects, such as antimicrobial, antifungal, anti-HIV, anticonvulsant, and anticancer activities. For example, quetiapine, a derivative of dibenzothiazepine, is fundamental in treating schizophrenia and bipolar disorder, functioning as an antagonist at the receptors. Additionally, exploring 1,5-benzothiazepines as blockers of enzymes like alpha-glucosidase and acetylcholinesterase has created new possibilities for tackling type 2 diabetes and Alzheimer's disease, respectively.

II. PRINCIPLE

The production of 1,5-benzothiazepine relies on a single-step reaction involving 2-aminothiophenol and chalcones through a thia-Michael addition succeeded by intramolecular cyclization. In this process, the sulfur atom adds to the chalcone's double bond through a conjugate addition, followed by the amino group's attack on the carbonyl carbon to form the seven-membered ring. The procedure ends with a dehydration phase (removal of water) to create the stable 2,3-dihydro-1,5-benzothiazepine core

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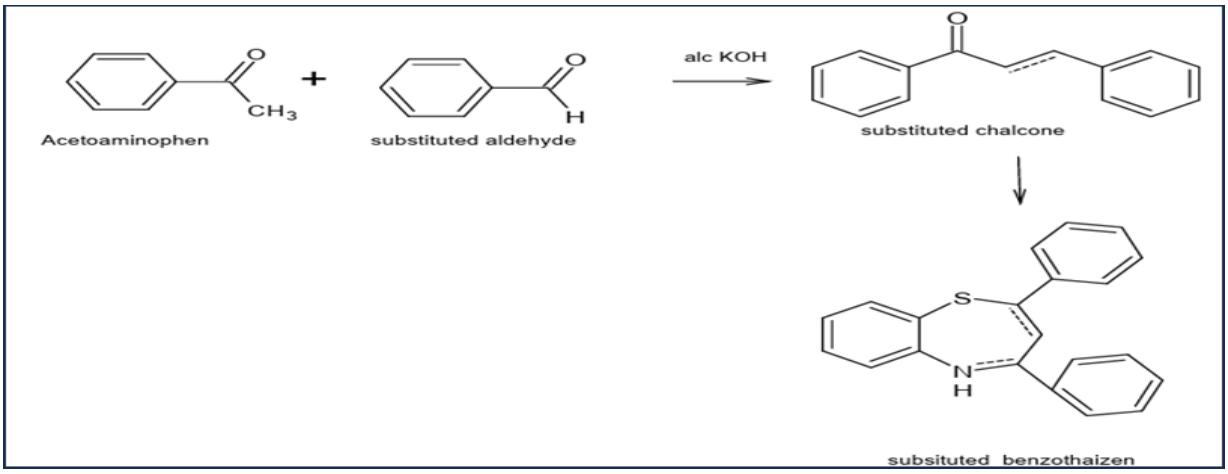

III. MATERIAL

Ingredient	Role in Synthesis/Formulation	Scientific Rationale
2-Aminothiophenol	Primary Bicyclic Precursor	Provides the essential sulfur and nitrogen heteroatoms for the 1,5-heterocyclic system.
Substituted Chalcones	Michael Acceptor	Serves as the α,β-unsaturated carbonyl framework for thia-Michael addition.
Glacial Acetic Acid	Catalytic Promoter	Acts as a mild acid to activate the carbonyl group for nucleophilic attack and facilitates ring closure.
PEG-400	Green Solvent / Medium	Provides an environmentally benign reaction medium that enhances yields and allows for catalyst recyclability.
Silica Sulfuric Acid	Solid Support Catalyst	Increases surface area for reaction, lowering activation energy under microwave conditions.
CuO Nanocatalyst	Heterogeneous Catalyst	Offers high surface-to-volume ratio for improved catalytic activity and shorter reaction times.
HPMC K4M	Controlled Release Polymer	Used in matrix tablets to modulate the dissolution rate of the API via swelling and erosion.
Ethanol (Absolute)	Recrystallization Solvent	Facilitates purification of the final crystalline product through differential solubility.

IV. EQUIMENT

1. Microwave Synthesis System (e.g., BPL 2300 ET): Employed for accelerated heterocyclization at 800W power outputs.
2. Double Beam UV-VIS Spectrophotometer: Essential for determining lambda_{max} (200–400 nm range).
3. FT-IR Spectrophotometer (KBr Pellet Method): Utilized to identify C=N stretching (1585–1602 cm^{-1}) and the absence of SH bands (2570 cm^{-1}).
4. NMR Spectrometer (300/600 MHz): Crucial for structural elucidation identifying diastereomeric protons at C-2 and C-3.Rotary Tablet Compression Machine: Employed for preparation of solid dosage forms.

V. METHODOLOGY

1. Substituted chalcones are first prepared by using the Claisen–Schmidt condensation reaction.
2. Equal quantities (0.01 mol each) of 2-aminothiophenol and the chalcone are then combined.
3. A suitable catalyst, such as silica sulfuric acid or glacial acetic acid, is added along with a solvent like DMF or PEG-400.
4. The mixture is then subjected to microwave heating (800 W for 1–3 minutes) or ultrasonic treatment (30–60 minutes) to promote the reaction.
5. The reaction progress is checked using TLC with a benzene:ethanol:ammonia (7:2:1) solvent system.
6. Once the reaction is complete, it is stopped by adding the mixture to ice-cold distilled water.
7. The resulting solid is collected by filtration and washed to remove any impurities.
8. The crude product is purified by recrystallization using hot absolute ethanol.
9. The final purified product obtained is a 1,5-benzothiazepine derivative.

VI. PHARMACOLOGICAL TARGET PROFILE

Derivative	Main Use	Biological Target	Mechanism of Action
Diltiazem	Angina / Hypertension	L-type Ca^{2+} Channels	Reduces the entry of calcium ions into heart muscle cells, helping to relax them.
Quetiapine	Schizophrenia	D_2 / 5-HT_2 Receptors	Works by blocking dopamine and serotonin receptors to control psychiatric symptoms.
Thiazesim	Depression	CNS (Amygdala region)	Acts on the amygdala in the brain to produce antidepressant effects.

CGP37157	Neuroprotection	Mitochondrial Na^+/Ca^{2+} Exchanger	Prevents ion exchange in mitochondria, thereby protecting cells from oxidative damage.

VII. STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

1. C-2 Position: Substitution with a 4-methoxyphenyl group (diltiazem class) enhances vasodilatory activity. Halogenated phenyl rings at C-2 increase cytotoxic activity against Hep G-2 liver cancer lines.
2. C-4 Position: Carbonyl or aryl substituents determine the pharmacodynamic profile. Electron-withdrawing groups (EWGs) like chloro or nitro on the C-4 aryl ring improve antimicrobial and anticonvulsant properties.
3. N-5 Position: A basic side chain, such as 2-(dimethylamino)ethyl, is essential for calcium channel binding.

VIII. CONCLUSION

The 1,5-benzothiazepine framework continues to be a fundamental element in drug discovery. This review emphasizes that although traditional methods set the standard, green approaches particularly microwave and ultrasound-assisted syntheses provide enhanced efficiency and environmental friendly. The variety of chemicals provided by substitution enables a shift between cardiovascular modulation and CNS impacts. Future studies need to connect lab-scale green synthesis with the production of enantiopure derivatives at an industrial level.

IX. RESULT

The systematic review finds that microwave-assisted methods decrease reaction times from 12 hours to less than 3 minutes, achieving yields above 85%. The pharmacological importance is primarily influenced by antagonism of L-type calcium channels and modulation of CNS receptors. SAR research indicates that the cis-configuration and N-5 basic chains are essential for cardiovascular efficacy, whereas halogenated substitutions at C-2 boost anticancer effectiveness.

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