

Synthesis and Biological Evaluation of Novel Triazoles from Chalcones And 1h-1,2,4-Triazol-3-Amine

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ABSTRACT

Triazoles are an important class of nitrogen-containing five-membered heterocyclic compounds consisting of two carbon atoms and three nitrogen atoms in the ring structure. Depending on the arrangement of nitrogen atoms, triazoles are classified into two major isomeric forms: 1,2,3-triazoles and 1,2,4-triazoles. These heterocyclic systems possess aromatic stability, high dipole moments, and strong hydrogen-bonding capabilities, which contribute to their wide range of chemical and biological properties. Because of these unique characteristics, triazole derivatives have attracted considerable interest in medicinal chemistry, pharmaceutical sciences, agriculture, and material science. Heterocyclic chemistry plays crucial role in novel drug design and in the field of pharmaceutical chemistry. In the presence work, synthesis of novel chalcones were carried out from (S)-1-(3-bromo-4-fluorophenyl) ethanamine, 2,4,6-trichloro-1,3,5-triazene and various aromatic aldehydes. After this, Condensation of prepared chalcones with 1H-1,2,4-triazol-3-amine to produced novel triazoles A1-A15. All synthesized compounds were characterized using ¹HNMR, ¹³CNMR, IR, and MASS spectrometry and tested for antimicrobial activity against gram +ve and gram -ve bacteria.

Keywords: Triazole, Chalcones, 1,3,5-Triazine, Spectroscopy, Antimicrobial Activity and Optical Activity.

INTRODUCTION

Triazoles are an important class of nitrogen-containing five-membered heterocyclic compounds characterized by the presence of three nitrogen atoms within the ring system. Based on the arrangement of nitrogen atoms, triazoles are classified into two principal isomeric forms, namely 1,2,3-triazoles and 1,2,4-triazoles. These heterocyclic systems possess remarkable chemical stability, aromatic character, and diverse physicochemical properties, which make them highly valuable in medicinal, pharmaceutical, agricultural, and material sciences. Due to their ability to participate in hydrogen bonding and dipole–dipole interactions, triazole derivatives exhibit strong affinity toward various biological targets, resulting in a broad range of pharmacological activities [1, 2].

Over the past few decades, triazole chemistry has gained significant attention because of the wide therapeutic potential of triazole-containing compounds. Numerous triazole derivatives have been reported to exhibit antimicrobial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antitubercular, antioxidant, and anticancer activities [3-5]. The development of efficient synthetic methodologies has further accelerated research on triazole derivatives. Among these, the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, commonly referred to as “click chemistry,” represents one of the most significant advances in heterocyclic synthesis. Introduced by Sharpless and co-workers, click chemistry provides a simple, regioselective, and high-yielding route for the synthesis of 1,2,3-triazoles under mild reaction conditions [6-7]. Because of its operational simplicity and broad functional group tolerance, this methodology has become a powerful tool in medicinal chemistry, combinatorial synthesis, and drug discovery. Several clinically

important drugs such as fluconazole, itraconazole, and voriconazole contain the triazole nucleus and are widely used as antifungal agents. These compounds act by inhibiting cytochrome P450-dependent enzymes involved in ergosterol biosynthesis, thereby disrupting fungal cell membrane formation. The extensive biological profile of triazoles has encouraged medicinal chemists to design and synthesize novel derivatives with enhanced efficacy and reduced toxicity [8-10].

In addition to pharmaceutical applications, triazole derivatives have found considerable importance in agriculture and industrial chemistry. Many triazole-based compounds are used as fungicides, herbicides, corrosion inhibitors, dyes, and plant growth regulators. Furthermore, the strong coordinating ability and electronic characteristics of the triazole ring make these compounds useful in material science, supramolecular chemistry, and coordination chemistry [2]. The incorporation of triazole moieties into polymers and nanostructured materials has also expanded their applications in catalysis, sensing technologies, and advanced functional materials. Because of their synthetic versatility and broad spectrum of biological activities, triazoles continue to attract substantial interest among researchers worldwide. Ongoing studies are focused on the synthesis of novel triazole derivatives with improved pharmacological properties and better therapeutic profiles. Therefore, triazole chemistry remains a highly active and promising area of heterocyclic and medicinal chemistry research. In the present study, synthesis of chalcones was carried out by one pot condensation of (S)-1-(3-bromo-4-fluorophenyl) ethanamine, 2,4,6-trichloro-1,3,5-triazene and various aromatic aldehydes. Prepared chalcones were refluxed with 1H-1,2,4-triazol-3-amine under ethanol as the solvent to produce Triazoles A1-A15. All synthesized compounds were characterized using various spectrometry and screened for their biological activity.

MATERIALS AND METHODS

Reagents and Chemicals

The materials included 2,4,6-trichloro-1,3,5-triazene, (S)-1-(3-bromo-4-fluorophenyl)ethanamine, Pyridine., KOH, 1H-1,2,4-triazol-3-amine, Ethanol and various aldehydes. All chemicals utilized were of laboratory reagent grade and were used as received without additional purification.

Experimental

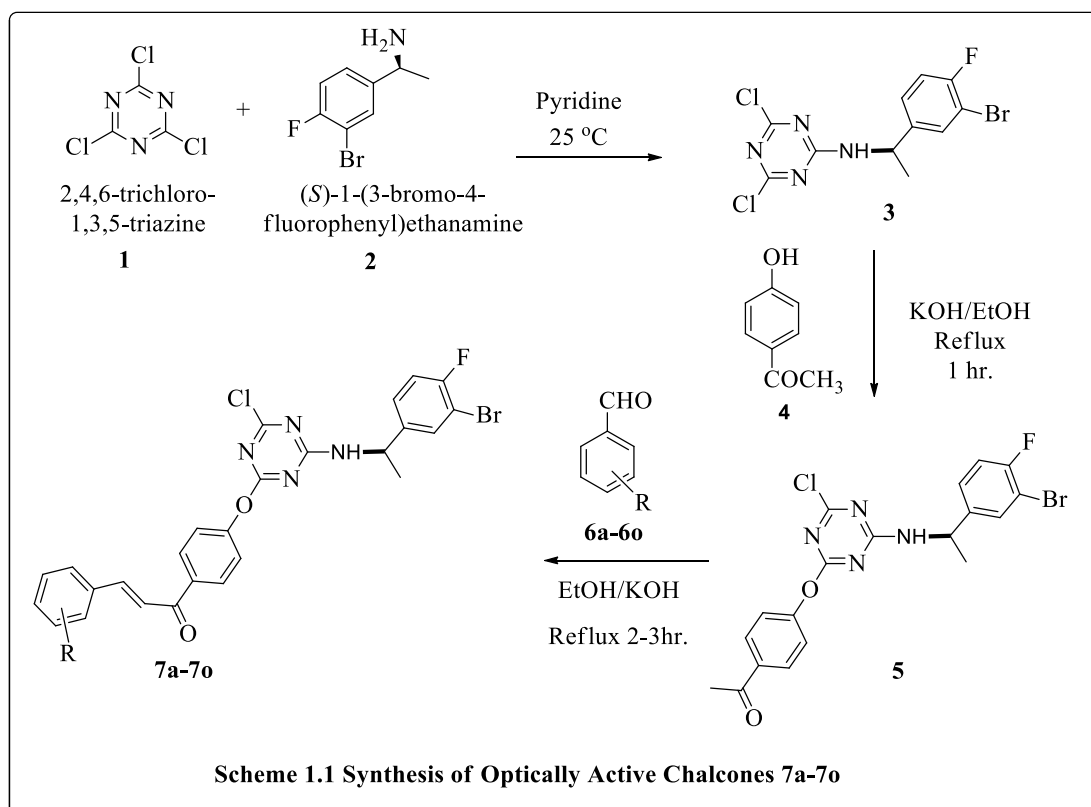
Melting points were measured using the open capillary method and are reported without correction. The ^1H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 400 spectrometer, operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR, with solutions in DMSO- d_6 . Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent. FT-IR spectra were recorded on a Shimadzu FT-IR 8400 spectrometer using KBr discs, with results expressed in wavenumbers (cm^{-1}). Mass spectra (ESI-MS) were acquired on a Shimadzu LCMS-2010 spectrometer. Carbon, hydrogen, and nitrogen contents were analyzed using a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. Thin-layer chromatography (TLC) was employed to monitor all reactions.

Method of Synthesis

Synthesis of Chalcones

A solution of (S)-1-(3-bromo-4-fluorophenyl)ethanamine (0.01 mol) and 2,4,6-trichloro-1,3,5-triazene (0.01 mol) was prepared in a 250 mL round-bottom flask. To this reaction mixture, 2–3 drops of pyridine were added, and the contents were stirred at room temperature for 30 minutes. Subsequently, p-hydroxyacetophenone (0.01 mol) was introduced, followed by the addition of 10 mL ethanol and 5 mL of 2% KOH solution. The resulting mixture was refluxed for 1 hour to obtain intermediate compound 5. Thereafter, compound 5 was reacted with benzaldehyde 6a (0.01 mol) in the presence of 10 mL of 2% KOH using 30 mL ethanol as the reaction solvent. The reaction mixture was refluxed for 2.5 hours. The progress of the reaction was periodically monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled in an ice bath and poured into cold water. The precipitated solid product was

collected by filtration, washed, dried, and recrystallized from ethanol to afford the desired chalcone **7a** (Scheme 1.1).



Synthesis of Triazoles A1-A15:

Take Novel optically active Chalcone **7a** (0.01 mol) in 250 ml RBF, add 0.01 mol 1H-1,2,4-triazol-3-amine, 10 ml ethanol and 5ml 2% KOH. Reflux the entire mixture for 1hr to produced Triazole. Completion of process was monitored by TLC method. Optically active Triazole obtained called **A1**. (Scheme 1.2).

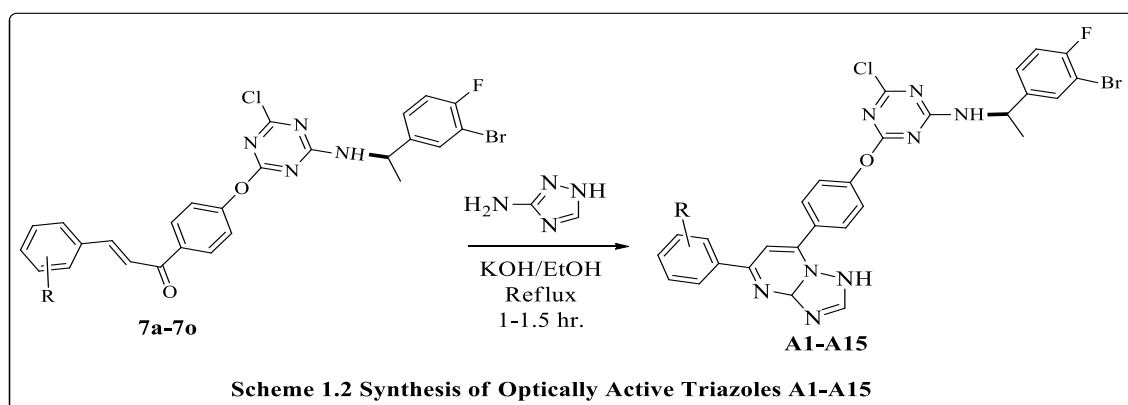


Table 1.1 Characteristic data showing synthesis of Triazoles A1-A15

Compounds Code	R	Reaction Time ^a (hr)	% Yiled ^b	M. P. of Compounds
A1	-H	1	80	238
A2	2-OH	1.5	75	252
A3	3-OH	1.5	76	256

A4	4-OH	1.5	72	260
A5	2-Cl	1	84	240
A6	3-Cl	1	85	245
A7	4-Cl	1	83	248
A8	2-Br	1	84	260
A9	3-Br	1	81	265
A10	4-Br	1	84	258
A11	2-NO ₂	1	85	235
A12	3-NO ₂	1	86	239
A13	4-NO ₂	1	84	232
A14	2-OCH ₃	1.5	72	227
A15	4-OCH ₃	1.5	70	233

^aReaction is monitored by TLC, ^bIsolated yield

RESULT AND DISCUSSION

From the **Table 1.1** A series of substituted compounds (A1–A15) were successfully synthesized and evaluated for reaction time, percentage yield, and melting point. The parent compound A1 (R = –H) was obtained in 1 h with an 80% yield and a melting point of 238 °C, providing a useful baseline for comparison of substituent effects. The reaction time data indicate a clear influence of substituent type on reaction kinetics. Compounds bearing hydroxyl (–OH) and methoxy (–OCH₃) groups (A2–A4 and A14–A15) required longer reaction times (1.5 h), whereas halogen (–Cl, –Br) and nitro (–NO₂) substituted derivatives (A5–A13) completed within 1 h. This trend suggests that electron-donating groups, such as –OH and –OCH₃, decrease the electrophilic character of the reacting center, thereby slowing the reaction. In contrast, electron-withdrawing substituents facilitate faster reaction rates by stabilizing intermediates or enhancing electrophilicity. Positional effects were also evident. Para-substituted compounds often exhibited higher melting points (e.g., A4 and A10), likely due to improved molecular symmetry and efficient crystal packing. However, positional variation had minimal influence on reaction time and yield, suggesting that steric hindrance does not significantly affect the reaction under the given conditions.

In summary, the results demonstrate that electron-withdrawing groups enhance reaction efficiency and yield, while electron-donating substituents tend to prolong reaction time and slightly reduce yields. Melting point variations are primarily governed by intermolecular interactions, hydrogen bonding, and molecular symmetry, highlighting the combined influence of electronic and structural factors on the physicochemical properties of the synthesized compounds.

Characterization

Compound A1 were taken as the model compounds for the characterization using ¹H NMR, ¹³C NMR, IR, MASS spectroscopy. Results obtained are shown below.

Triazole A1 Spectroscopic Analysis	
Mol. Formula:	C ₂₈ H ₂₁ BrClFN ₈ O
¹ H NMR (400 MHz, CDCl ₃) δ ppm: 1.3 (–CH ₃ , d), 3.8 (NH, s), 4.2 (–CH proton attached to –NH, multiplet), 4.6 (1H, CH, s), 5.1 (1H, –CH of imidazole ring, s), 5.6 (–CH proton of pyrimidine ring, s), 6.5–7.9 (12H, Ar-	

H, complex), 9.8 (NH, s).

^{13}C NMR (100 MHz, CDCl_3) δ ppm : 23.1 ($-\text{CH}_3$), 55.2 (NH-CH), 101.2 (CH= of Pyrimidine ring), 109.1, 127.2, 134.5, 136.3, 140.1, 143.1, 145.5, 146.3, 146.7, 147.3, 148.4, 148.5, 148.7, 148.9, 151.2 (Aromatic Carbon), 161.2, 162.3, 180.4 (Carbon of s-triazine).

IR (cm^{-1} , KBr): 3410 (N-H stretch.), 3320 (N-H stretch.), 3100-3010 (aromatic C-H stretch.), 3000-2900 (Aliphatic C-H stretch.), 1650-1540 (C=C, stretch.), 1535 (C=N stretch.), 1310 (C-N stretch.), 1210 (C-O, stretch.), 820 (Mono sub. Phenyl ring)

MASS ($\text{M}+1$): 618.2

Elemental Analysis: Calculated (%) : C, 54.25, H, 3.41, N,18.08

Found (%) : C, 54.30, H, 3.45, N,18.12

Antimicrobial Activity

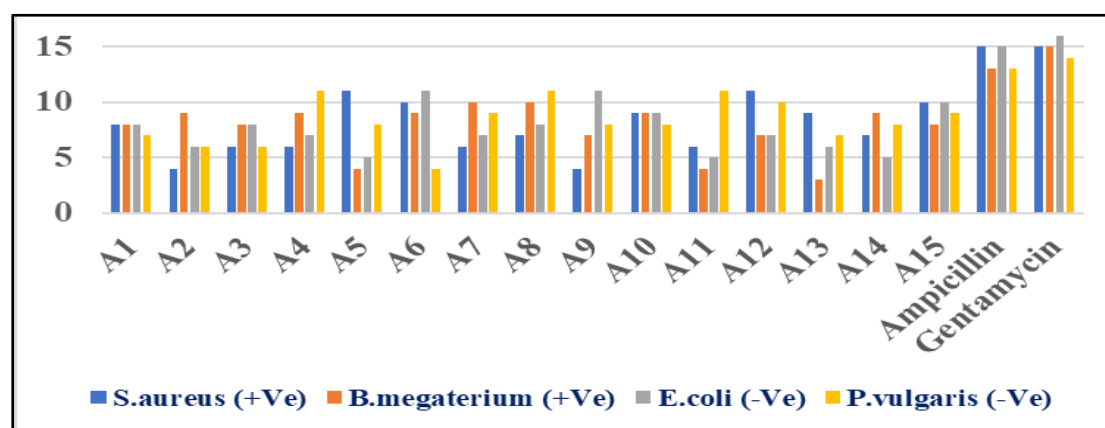


Table 1.2 Antimicrobial activity data of Triazoles A1-A15

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E.coli (-Ve)	P.vulgaris (-Ve)
A1	8	8	8	7
A2	4	9	6	6
A3	6	8	8	6
A4	6	9	7	11
A5	11	4	5	8
A6	10	9	11	4
A7	6	10	7	9
A8	7	10	8	11
A9	4	7	11	8
A10	9	9	9	8
A11	6	4	5	11
A12	11	7	7	10
A13	9	3	6	7
A14	7	9	5	8

A15	10	8	10	9
Ampicillin	15	13	15	13
Gentamycin	15	15	16	14

From Table 1.2, The antibacterial activity of Triazole derivatives appears to be strongly influenced by the nature and position of substituents on the heterocyclic ring:

- Broad-spectrum activity observed in A6, A8, A12, and A15 suggests that these compounds may contain substituents that enhance lipophilicity, facilitating better penetration through bacterial cell membranes.
- Compounds such as A6 and A9, which show high activity against *E. coli*, indicate that certain structural features favor interaction with Gram-negative bacterial targets, possibly overcoming the outer membrane barrier.
- Enhanced activity of A4, A8, and A11 against *P. vulgaris* suggests selective binding affinity or improved permeability specific to this strain.
- Lower activity in compounds like A2, A5, A11, and A13 against certain strains may be attributed to electron-withdrawing or sterically hindered substituents, which could reduce interaction with bacterial enzymes or receptors.
- Compounds showing consistent activity across multiple strains likely maintain an optimal balance between electronic effects and steric factors, which is crucial for antimicrobial efficacy.

CONCLUSION

In summary, the highly functionalized Triazoles A1-A15 were successfully synthesized from various chalcones and 1H-1,2,4-triazol-3-amine. It was noted that compounds with electron-withdrawing groups were produced in shorter reaction times compared to those containing electron-donating groups. Each synthesized compound was thoroughly characterized using various spectroscopic techniques.

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