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التحضير الأخضر والمحسن زمنيا لهجائن جديدة من التترازول –البنزوثايوزول المحتوية على روابط الآزو–ماليميد: نهج مستدام

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المستخلص:

تم في هذه الدراسة تطوير منهج تخليقي عالي الكفاءة لتحضير جيل جديد من هجائن التترازول–بنزوثايازول متعددة الوظائف، والتي تحتوي على روابط آزو–ماليميد. ومن أبرز مساهمات هذا العمل هو التقليل الكبير في زمن التفاعل؛ إذ اكتمل تفاعل الإضافة الحلقية [٣+٢] الحرج خلال أقل من ٦–١٠ ساعات، وهو زمن أسرع بكثير مقارنة بالطرائق التقليدية. واستنادًا إلى مبادئ الكيمياء الخضراء، تم اختيار الإيثانول المطلق كمذيب مستدام وصديق للبيئة. وعلى الرغم من أن حمض الخليك الجليدي كان ضروريًا لإتمام غلق الحلقة النهائية، فإن استخدامه اقتصر بصورة أساسية على تقليل الأثر البيئي. تم تأكيد التراكيب الكيميائية للهجائن باستخدام تقنيات التحليل الطيفي، بما في ذلك مطيافية الأشعة تحت الحمراء بتحويل فورييه(FT–IR) ، والرنين المغناطيسي النووي للبروتون(^{1}H–NMR) ، والرنين المغناطيسي النووي للكربون–١٣(^{13}C–NMR) ، والتي وفّرت دليلًا قاطعًا على نجاح عملية التهجين. ومن الناحية البيولوجية، أظهرت اختبارات الفعالية المضادة للبكتيريا ضد البكتيريا موجبة الغرام مثل *Staphylococcus aureus* و*Staphylococcus epidermidis*، والبكتيريا سالبة الغرام مثل *Escherichia coli*و

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Klebsiella pneumoniae، أن هذه الهجائن تمتلك تأثيرًا مضادًا قويًا للبكتيريا. وتشير النتائج إلى أن الهياكل المطورة واعدة، وصديقة للبيئة، وملائمة للاستخدام في الكيمياء الدوائية الحديثة.

الكلمات المفتاحية: التخليق الأخضر، التفاعل المحسن زمنيًا، هجائن التترازول–بنزوثايازول، روابط الآزو–ماليميد، مذيب قائم على الإيثانول، التوصيف الطيفي، الفعالية المضادة للبكتيريا.

Time-Optimized and Green Synthesis of New Tetrazole-Benzothiazole Hybrids Incorporating Azo-Maleimide Linkages: A Sustainable Approach

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Abstract:
This study identifies a high-efficiency synthetic approach to a new generation of multifunctional tetrazole-benzothiazole hybrids containing azo-maleimide linkages. One of the significant contributions of this work is that the reaction time has been greatly reduced; the critical [3+2] cycloaddition is completed in fewer than 6-10 hours, which is much faster than conventional methods. Based on green chemistry principles, absolute ethanol was chosen as a sustainable, environmentally friendly solvent. Although glacial acetic acid was necessary to close the final ring, its use was limited to reducing the environmental footprint. Chemical forms of the hybrids were confirmed using spectroscopic methods, including Fourier-transform infrared spectroscopy (FT-IR), Proton nuclear magnetic resonance (^{1}H-NMR), and Carbon-13 nuclear magnetic resonance (^{13}C-NMR), which provide conclusive evidence of successful hybridization. Gram-positive (S. aureus, S. epidermidis) and Gram-negative (E. coli, K. pneumoniae) screening showed that these hybrids have strong antibacterial activity. These

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findings make the developed scaffolds promising, environmentally friendly, and well suited for use in modern medicinal chemistry.

Keywords: Green Synthesis, Time-Optimized reaction, Tetrazole-Benzothiazole hybrids, Azo-Maleimide linkages, Ethanol-Based solvent, Spectroscopic characterization, Antibacterial activity.

1. Introduction

Nitrogen-containing heterocyclic compounds are a fundamental pillar of medicinal chemistry and are characterized by their structural plasticity and pharmacological breadth (Patowary et al., 2021). Tetrazoles with four nitrogen atoms have received considerable attention as vital bioisosteres of the carboxylic acid group (Jawad et al., 2023). This isosteric substitution is an effective drug-design strategy because it enhances lipophilicity, metabolic stability, and bioavailability while reducing potential side effects (Radwan et al., 2020). Tetrazole derivatives have therefore exhibited a wide range of therapeutic effects, including antibacterial, antifungal, anticancer, anti-inflammatory, and anti-viral effects (Ceramella et al., 2022; Sharma et al., 2025). These strong heterocycles are typically synthesized from Schiff bases and the azomethine bond (–C=N–) (Khdir et al., 2024). Originally synthesized in 1864 by Hugo Schiff, these bases can be utilized both in organic synthesis and as versatile pharmacophores (Subasi, 2022; Swami et al., 2021). Their structural flexibility enables efficient interaction with biological receptors, making them ideal building blocks for complex heterocyclic structures (Mashhoori & Sandaroos, 2022). The Schiff bases were azo-hybridized to produce azo-Schiff bases, which are more electronically delocalized, more stable, chromophoric, and have numerous applications in industrial chemistry and the biological sciences (Biswas et al., 2024; Cherfi et al., 2024). Moreover, the strategic introduction of maleimide and benzothiazole functionalities into these hybrid systems offers a ray of hope to counter the ineffectiveness of traditional antibiotics (El-Sewedy et al., 2023; Maged & Naeemah, 2024). The high affinity of the benzothiazole ring for many biological targets and the structural rigidity of maleimides create a complex molecular microenvironment that can interfere with bacterial resistance mechanisms (Ramezani et al., 2025). These multi-

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target systems are needed in the modern world to address the growing challenge of multi-drug-resistant (MDR) pathogens and provide a strong foundation for discovering next-generation antimicrobial agents (Abdulhadi et al., 2020; Mubassir et al., 2025). In recent years, pharmacological interest has shifted toward developing hybrid molecules that incorporate multiple pharmacophores in a single molecular structure to generate synergistic effects (Dalal & Mekky, 2022; Tsacheva et al., 2023). Although each moiety has its own significance, few studies have integrated them into a single system (Abed & Ghanim, 2019). Thus, this research focuses on designing and synthesizing a new set of multifunctional tetrazole hybrids based on azo-Schiff base intermediates via a time-optimized, eco-friendly synthetic route. The main aim of the research is to apply the principles of green chemistry by using ethanol as a green reaction medium to substantially reduce reaction time, thereby increasing the overall effectiveness of the reaction. To determine the structural identity of the synthesized scaffolds, this work characterizes model scaffolds spectroscopically using FT-IR, ^{1}H-NMR, and ^{13}C-NMR. Their antimicrobial activity against model Gram-positive and Gram-negative microbes will also be assessed for the new hybrids, which will give more data about the structure-activity relationship (SAR) and the biological activity of these complex heterocyclic systems under the best conditions of synthesis.

2. Experimental

2.1. Materials

All chemicals and reagents were of analytical grade and used without further purification as supplied. The starting materials used were 4-aminoacetophenone (99%, Merck) and Maleic anhydride (99%, Merck), which were used in the first steps of the synthetic process. The aromatic aldehydes used in the following condensation reactions were: 2-methoxybenzaldehyde (85%, Aldrich), 2,4-dihydroxybenzaldehyde (98% Energy Chemical), 2,4-dimethoxybenzaldehyde (98% Aladdin Reagents), and 4-bromobenzaldehyde. The main solvent used for the synthesis and recrystallization processes was absolute ethanol (99%, Scharlau).

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2.2. Instrumentation

The tetrazole derivatives synthesized were characterized using the following instruments:

1. A Digital Melting Point device (Advanced SMP3) was used to determine the melting points of the synthesized compounds. The experiment was carried out in the Department of Chemistry laboratory at the College of Education, University of Diyala.
2. Fourier Transform Infrared (FTIR) spectroscopy of the produced compounds was used to determine the functional groups. A Shimadzu FT-IR 8400S spectrophotometer was used to analyze the samples, first prepared as KBr pellets. The spectral data were recorded in the 4000-400 cm^{-1} range. Early measurements were conducted at the University of Diyala, Department of Chemistry, in the College of Education of Pure Sciences, and further measurements were carried out at the PBC Center in Baghdad. Structural assignments were performed on a Shimadzu IRAffinity-1 instrument, using characteristic absorption bands.
3. Spectrophotometers ^{1}H-NMR and ^{13}C-NMR spectra were obtained in a Bruker spectrometer at 400 MHz. Several compounds were tested at the University of Tehran, in the Islamic Republic of Iran. The observed chemical shifts (δ) were in ppm relative to internal standards and the suggested molecular structures, as confirmed by the spectral data analysis.
4. Thin-layer chromatography (TLC) using silica gel G-coated aluminum plates, visible under a UV lamp (254 nm), was used to evaluate the reaction's progress and the final products' purity.

2.3. Azo-Schiff Base Derivatives Synthesis

Target azo-Schiff bases were synthesized in a stepwise method with the first intermediate A being made. N-(4-acetylphenyl) maleimide (A) was prepared by mixing 4-aminoacetophenone (2.75 g, 0.020 mol) with maleic anhydride (2.0 g, 0.0204 mol) in 100% ethanol. The yellow solid was obtained by heating the mixture under reflux at 70-78 °C for 3- 4 hours (Al-Azzawi & Huseeni, 2022). The product was filtered and recrystallized from ethanol. A (0.01 mol) (2.15g) was refluxed with 30 mL of 100% ethanol in the presence of hydrazine hydrate (80%, 0.5ml) to form N(4-acetylphenyl) maleimide

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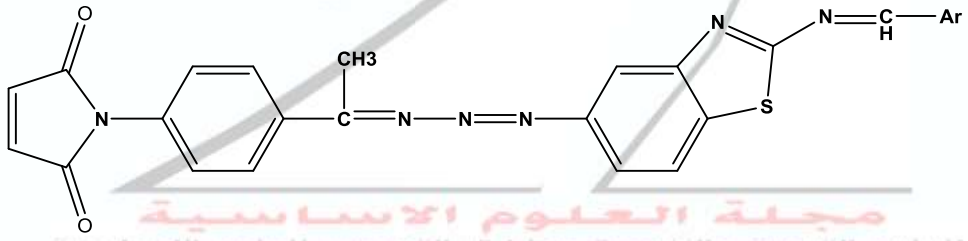
hydrazone (B) (Al-Mola & Al-Sabawi, 2025). The mixture was cooled in an ice bath, filtered, and recrystallized to achieve total crystallization. The azo intermediate, N -(4 -(1 -(2 -(6-aminobenzothiazol-2-yl) diazenyl) hydrazono) ethyl) phenyl) maleimide (C) was obtained by diazotizing the amino group of the two-end phenyl maleimide. 0.279 g of B (1 mmol, MW = 279 g/mol) was dissolved in 85% phosphoric acid (H_3PO_4), cooled down to 0-5 ℃, and a nitrating solution of NaNO2 (0.069 g, 10 mmol) and HNO3 (0.0417 mL) was added dropwise. Adding diazonium salt (0.152 g, 10 mmol) and p-aminobenzothiazole (0.152 g, 10 mmol) gave an orange precipitate, which was dissolved in 10 mL of ice water (Al-Joboury et al., 2021). The Azo-Schiff bases desired were finally formed by condensing the respective substituted aromatic aldehyde (1 mmol) with carbon (0.570 g, 1 mmol) in the presence of an acid. The reactants were suspended in 20 mL of 100% ethanol and 2-3 drops of glacial acetic acid and refluxed for 6-10 hours. The reaction was carried out, and crushed ice was added to the solution (Mohammed & Hasan, 2022). Filtering, washing the product with distilled water, and recrystallizing in 100% ethanol were used to obtain the pure target compounds.



N-(4-acetyphenyl)maleimide hydrazone azo-benzothiazole Schiff base

Figure 1. Chemical structure of the intermediate azo benzothiazole Schiff base derivatives

2.4. General Procedure for the Synthesis of Tetrazole Derivatives (T1–T15)

The corresponding Schiff bases were converted to tetrazole derivatives by an ice-cold cycloaddition with glacial acetic acid in the presence of sodium azide. The reaction was carried out in the presence of a catalyst, ammonium chloride, and the reaction conditions were held constant. This technique has been successful in making fifteen derivatives. In particular, 0.195 g (3.0

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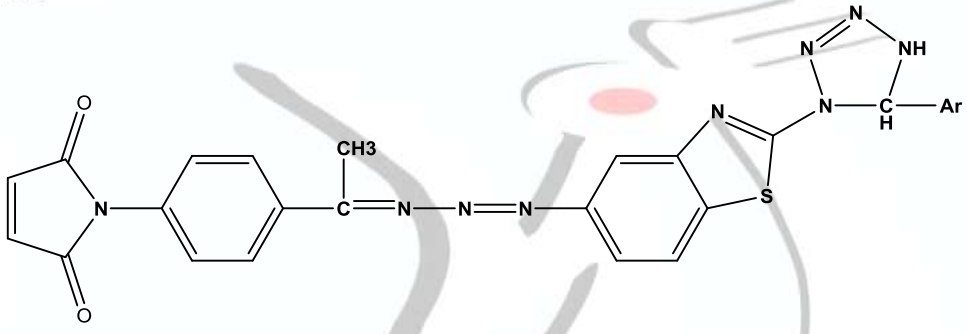
mmol) sodium azide was placed in 10 mL of glacial acetic acid in a round-bottom flask with a reflux condenser. Stirring and mild heating helped in this disintegration. Ammonium chloride (0.054 g (1.0 mmol) was put in as a catalyst, and the corresponding Schiff base (0.054 g (1.0 mmol) was stirred as much as possible (Sabri & Jumaa, 2026). The reaction was monitored by thin-layer chromatography (TLC) at 70-90 °C. Crushed ice was used to heat and cool the mixture, and the tetrazole derivative was precipitated. It was then filtered and dried using cold distilled water to remove inorganic salts and acid. Pure tetrazole derivatives were also obtained by recrystallization of ethanol, as well as crude products (Preetham et al., 2022).



1-(4-(E)-(1-(2-(benzothiazol-2-yl)diazenyl)ethylidene)phenyl)isoindoline-1,3-dione-2-yl)-5-(aryl)-1Htetrazole

Figure 2. General chemical structure of the synthesized tetrazole hybrids containing imide, azo, and azomethine linkages

2.5. Evaluation of antibacterial activity

The Gram-positive *Staphylococcus aureus and Staphylococcus epidermidis*, and the Gram-negative *Klebsiella pneumoniae and Escherichia coli* bacteria, were assessed for in vitro antibacterial activity using the agar well diffusion technique. The bacterial suspensions were diluted to a 0.5 McFarland standard (around 1.5×10^8 CFU/mL) and inoculated on Mueller-Hinton agar plates. A sterile cork borer was used to cut 6 mm-diameter wells. The synthesized compounds were dissolved in dimethyl sulfoxide (DMSO), and 100 µL of each solution was added to each well. A standard antibacterial agent (ciprofloxacin) was used, and DMSO was used to mitigate negative effects. Each experiment was done thrice, and during incubation at 35- 37 °C, the inhibition zone diameters were measured in millimeters (mm) after

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24 h (Balouiri et al., 2016; Gonelimali et al., 2018; Sadiq & Yildirim, 2024). Those compounds that did not exhibit inhibition zones were declared inactive.

3. Results and discussion

3.1. Synthetic strategy and chemical rationale

The multi-step synthesis was designed to produce a molecular hybrid of four pharmacophores incorporating the maleimide scaffold, azo linkage, benzothiazole group, and tetrazole heterocycle, as shown in Scheme 1. The synthetic pathway was performed in a systematic step-wise process:

I. N-substituted Maleimide (A) using Dehydration Cyclization

The nucleophilic acyl substitution and subsequent dehydration cyclization of maleic anhydride with 4-aminoacetophenone in refluxing absolute ethanol initiated this synthesis. Mechanistically, the primary amine of the free pair reacts with the electrophilic carbonyl center of the anhydride to open the ring, therefore creating a maleamic acid intermediate. This is followed by a series of intramolecular cyclizations, resulting in the loss of H_2O and the formation of a stable imide. This intermediate contains an acetyl handle, which is reactive and is then functionalized in a nucleophilic reaction.

II. Nucleophilic addition-elimination to create Hydrazones (B)

Intermediate (A) was reacted with hydrazine hydrate in ethanol. This is a nucleophilic addition-elimination reaction that attacks the carbonyl (C=O) to form a stable azomethine (C=N) bond. Integrating these nitrogen centers into the bioisosteric replacement plan was predicted to enhance ligand-receptor affinity and the pharmacological properties of the entire ligand.

III. Diazotization and electrophilic Azo-Coupling (C & D)

The primary amino group was then transformed to a highly reactive diazonium cation in a solution of mineral acid (HNO_3) using $NaNO_2$. This diazotization was maintained at 0- 5 °C to prevent the volatile diazonium salt from releasing nitrogen at elevated temperatures. This was followed by the electrophilic aromatic substitution (SEAr), i.e., an azo-coupling reaction with 2-aminobenzothiazole. The ensuing azo-bridged (-N=N-), increases the conjugative range of the aromatic system, decreasing the HOMO-LUMO

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gap and increasing the stability of the molecule and the power of the chromophoric activity.

IV. [3+2] Regioselective Cycloaddition to Tetrazole (T15)

The last architectural assembly was a [3+2] dipolar cycloaddition of the azo-Schiff base (D) and the azide anion (N_3^-). Lewis acid promoters are the azide and NH_4Cl. The acetic acid is an anhydrous protic catalyst, and the azide is also a 1, 3-dipole and reacts with the electrophilic carbon of the azomethine group. The result of this cyclization is the tetrazole ring, a five-membered nitrogen heterocycle, that is metabolically stable, with the carboxylic acid isomer of which is a potential bioisostere.

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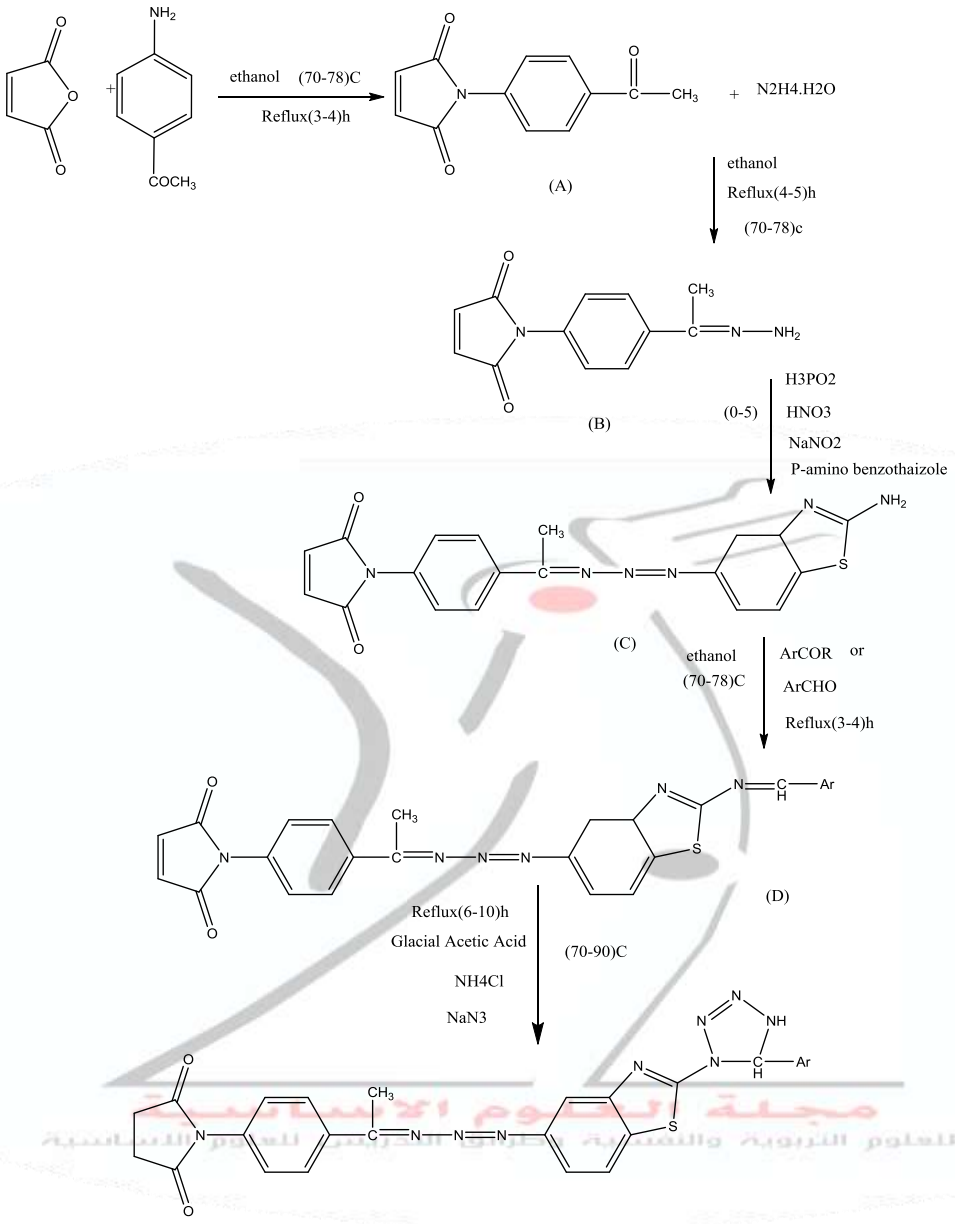

Ar= 4-OH-3-OCH3-Ar-CHO , 4-Cl-Ar-CHO , 4-OH-Ar-COCH3 , 4-OCH3-ArCHO , 2-OH-Naph-CHO , Ar-CHO
2,2-(OH)2-Ar-CHO , 2,4-(OCH3)-Ar-CHO , 4-NO2-Ar-COCH3 , 4-Br-Ar-CHO , 4-Cl-Ar-COCH3
4-OH-Ar-CHO , 4-NO2-ArCHO , 2-OH-Ar-CHO , Ar-COCH3

Scheme 1. Synthetic pathway for the preparation of the new tetrazole hybrids incorporating azo-methine and imide moieties

3.2. Physical and synthetic evaluation

Table 1 summarizes the physical constants and synthetic results of the synthesized tetrazole derivatives (T1–T15). As expected, the pathway

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alteration upon progressive conversion from the azo-Schiff bases to the final tetrazole architecture affords clear changes in solid physical states, narrow m.p.s, and remarkably different hues; all good signs of complete chemical transformation and product purity.

1. Substituent electronic effect

The electronic character of the aromatic ring substituents had a great impact on the synthetic efficiency and yields of the target tetrazoles (T1-T15):

- Electron-Withdrawing Groups (EWGs): Derivatives that included strong EWGs (the nitro group $-NO_2$ in T9 and T13, as well as the halogen group -Cl in T2, -Br in T10) gave high yields of up to 92%. This is attributed to the inductive effect (-I), which reduces the electron density of the azomethine (C=N) bond. This increases the electrophilicity of the carbon atom, making nucleophilic attack by the azide ion (N3 -) easier in the cycloaddition step.
- Electron-Donating Groups (EDGs): Hydroxyl (-OH in T3, T12, T14) and methoxy ($-OCH_3$ in T4, T8) groups, which serve as electron donors either through resonance or induction, were also found to give excellent yields (81-95%). Surprisingly, the highest yield (95%) was obtained in T1 (which had both -OH and $-OCH_3$). This shows that the catalytic conditions (acetic acid/ ammonium chloride) were effective in overcoming the deactivating electronic resistance, resulting in high conversion rates despite the electron-rich.

2. Mechanical stability and mechanical characterization

The purity of the compounds and thermal profile of the compounds can be a powerful source of information on the physicochemical properties of the compounds:

- All the derivatives' melting points (m.p.) are sharp and defined, and this means that the purification and re-crystallization processes employed are very efficient.
- Many of the tetrazoles that were synthesized were thermally stable with melting points of 200 and above. In particular, T10 melted at the highest temperature of 233-235. This thermal resilience is likely due to strong intermolecular forces (such as H-bonding in hydroxy derivatives) and

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intermolecular stacking of the large conjugated benzothiazole, azo, and maleimide systems.

3. Optical Inference and Chromophoric System

The visual appearance of the products (Yellowish Orange to Dark-Reddish Brown) is direct evidence of the effectiveness of the formation of the extended conjugation system:

- The color difference is specifically brought about by the effect of the substituent on the transitions that are the transitions in the $\pi \rightarrow \pi *$.
- The azo-bridge and tetrazole-benzothiazole moiety combination results in a wide delocalized resonance system. This decreases the energy gap between the Highest Occupied Molecular orbital (HOMO) and the Lowest Unoccupied Molecular orbital (LUMO), making light absorptions occur at longer wavelengths (bathochromic shift).
- It was established that T1 and T11 were deep reddish-brown, indicating stronger conjugation, which is why such compounds can be used as stable organic dyes or advanced biological probes.

Table 1. Physicochemical data, electronic nature, and synthetic results for target tetrazoles (T1-T15)

Comp.	Substituent Name	Electronic Nature	Yield (%)	M.P. (℃)	Appearance
T1	2-hydroxy-4-methoxybenzaldehyde	EDG	95%	208–210	Dark-Reddish Brown
T2	4-chlorobenzaldehyde	EWG	91%	203–205	Brownish Orange
T3	4-hydroxyacetophenone	Strong EDG	81%	207–209	Light Orange
T4	4-methoxybenzaldehyde	EDG	89%	188–190	Crimson Red
T5	2-hydroxynaphthaldehyde	Mixed	87%	195–197	Yellowish Green
T6	benzaldehyde	Neutral	85%	158–160	Reddish Orange
T7	2,4-dihydroxybenzaldehyde	EDG	92%	210–212	Medium Brown
T8	2,4-dimethoxybenzaldehyde	EDG	87%	172–175	Dark Orange Brown
T9	4-nitroacetophenone	Strong EWG	82%	209–211	Yellow Orange
T10	4-bromobenzaldehyde	EWG	87%	233–235	Dark Brown
T11	4-chloroacetophenone	EWG	87%	144–148	Deep Reddish Brown

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T12	4-hydroxybenzaldehyde	Strong EDG	85%	203–205	Light Orange
T13	4-nitrobenzaldehyda	Strong EWG	92%	225–227	Pale Orange
T14	2-hydroxybenzaldehyde	EDG	87%	216–218	Yellowish Orange
T15	acetophenone	Neutral	82%	202–205	Pale Yellowish Orange

3.3. FT-IR spectroscopic analysis

The synthesized tetrazole hybrids were confirmed structurally by FT-IR spectroscopy, as exemplified by the spectrum of compound T1 (Figure 3), and the typical bands and their electronic assignments are summarized in Table 2. the T1 spectrum shows definitely the chemical combined contribution of the substituents; the appearance of the band at 3325 cm^{-1} with the O-H was much broader than that of free hydroxyl groups, therefore the presence of a strong intramolecular hydrogen bond with the tetrazole nitrogen in it. The effect of such an interaction is to decrease the force constant (k) of the bond and decrease the vibrational frequency. The broad absorption bands in the region of 3232-3547 cm^{-1} are ascribed to the stretching vibrations of the (N-H) and (O-H). The large broadening and the bathochromic shift of these peaks, particularly in the derivatives T5 and T12, are diagnostic evidence of intramolecular hydrogen bonding. This interaction occurs between the phenolic hydroxyl protons and the nitrogen lone pairs of the heterocyclic core, thereby reducing the force constant (k) and the vibrational frequency. The imide scaffold was also formed, as evidenced by the diagnostic carbonyl bands (C=O) that were found within 1680-1716 cm^{-1}. The variation of these values is mainly dictated by the mesomeric effect; the more the system is conjugated, the more the electrons are delocalized to the aromatic ring, the lower the single-bond nature of the C=O moiety, and the lower the frequency of the stretching band, as Hooke's Law predicts. The appearance of the bands of (C=N) azomethine at 1543-1683^{-1} area proves the effective condensation into the intermediates of the Schiff bases (Field et al., 2020). These frequencies are highly sensitive to substituent effects, with electron-withdrawing groups (EWGs) generally increasing bond order by withdrawing electron density from the nitrogen center. The azo linkage

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(N=N) was identified by vibrations in the 1533-1600 cm^{-1} region. The aromatic bands are often coupled to the aromatic (C=C) modes, suggesting a large conjugation system that stabilizes the chromophoric system. The homogeneity of the heterocyclic structure was also confirmed by the presence of the thiazole ring of the heterocyclic structure; the presence of the (C-S) stretching was observed between 428 and 640 $cm^{-1,}$ as seen in compounds T5, T7, and T12, which are consistent with literature values for thiazole derivatives (Shukla et al., 2024).

Table 2. Characteristic FT-IR absorption bands (cm^{-1}) and vibrational assignments of the synthesized tetrazole derivatives

Comp.	N-H / O-H Stretching	Carbonyl (C=O)	Azomethine (C=N)	Aromatic / Azo	Others
1	٣٣٢٥	١٧١٦	١٥٤٣	١٦٠٠	C−H_{Ar} 3028-3132, C−H_{Al} 2808-2897
2	٣٣٥٢	١٦٨١	١٦٥٤	١٥٣٩	C−H_{Ar} 3105, C-S 513-547
5	٣٢٣٤-٣٥٤٧	١٧٠٨	١٦٣٧	١٥٣٣	C−O 1273, S−C 428-623
7	٣٢٣٢-٣٤٦٩	١٦٨٠	١٦٣٩	١٥٣٩-1566	C−O 1274, C−S 476-640
10	٣٣٣٨-3414	١٧١٠	١٦٥٣ - 1683	١٥٣٣-1597	C−H_{Ar} 3107-3194, C−H_{Al} 2924
12	3338-3414	1712	1683	1533-1595	C−H_{Ar} 3105, C−H_{Al} 2980, C−S 592-640

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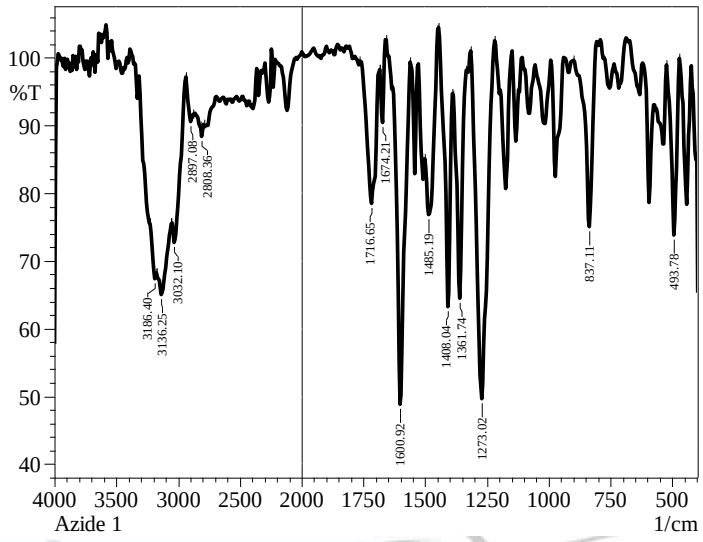

Figure 3. FT-IR spectrum of compound T1 showing the characteristic vibrational modes of the hybrid scaffold

3.4. ¹H-NMR spectroscopic analysis

The synthesized tetrazoles were further investigated by structural analysis using ¹H-NMR spectroscopy in DMSO-d_6, and the key chemical shifts and integration values are outlined in Table 3. The main diagnostic point in all the spectra is the singlet at the characteristic 10.7- 11.0 ppm, which is the NH proton of the tetrazole ring. This high level of de-shielding of this proton is a direct consequence of the strong inductive effect (-I) of the four electronegative nitrogen atoms in the heterocyclic ring, which decreases the number of electrons around the hydrogen nucleus. In derivatives that contained a phenolic moiety (as in T1, T7, and T12), there was an additional singlet (or broad singlet) between the OH proton at 9.0 -10.0 ppm. The downfield shift of the hydroxyl signal in these compounds is ascribed to the synergistic effects of the electron-withdrawing aromatic system and intramolecular hydrogen bonding, which further de-shields the proton. The aromatic protons appeared as complex multiplets and doublets in the range 6.6 - 8.1 ppm. Electron-withdrawing groups, including -N=N-, C=N, and C=O, result in a significant shift (downfield) to the core aromatic signals. The compounds T5 and T10 showed a typical AA'BB' splitting phenomenon, which validates a symmetrical para-substitution of the benzene

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ring (Pavia et al., 2012). On the other hand, in compounds T1 and T12, there were some doublets upfield at a higher frequency at 6.6-6.8 ppm; this can be attributed to the mesomeric effect of a hydroxyl and methoxy group (+R), which augmented the electron density (shielding) of the ortho-protons. The integrity of the heterocyclic components was measured by specific signals, e.g., the CH-tetrazole proton in T10 that was found to be a specific singlet at 5.8 6.2 ppm, as depicted in Figure 4. The formation of the successful Schiff base linkage and the presence of substituents in the upfield region were supported by:

- A single sharp singlet at 1.9 - 2.5 ppm, which is the methyl group (CH_3) of the azomethine carbon (CH_3-C=N).
- A singlet at δ 3.7–3.9 ppm, T1, and attributed to the methoxy protons (-OCH_3).

The correct incorporation of these aliphatic signals, as compared to the aromatic protons, validates the identity, as well as the high purity of the tetrazole derivatives produced in the synthesis.

Table 3. ^{1}H-NMR chemical shifts (δ, ppm) and spectral assignments for the synthesized tetrazole derivatives in DMSO-d_6

Comp.	NH (Tetrazole)	Ar-H (Protons)	Other Aromatic / Phenolic	Aliphatic / Substituents
1	10.8-11.0 (s, 1H)	7.0-8.1 (m, 8H)	9.2-9.5 (s, 1H, OH)	6.6-6.8 (d, 2H), 3.7-3.9 (s, 3H, OCH_3), 2.3-2.5 (s, 3H, CH_3)
2	11.0 (s, 1H)	7.1-7.8 (m, 8H)	7.2-7.4 (d, 2H, p-Cl-Ph)	2.3-2.5 (s, 3H, CH_3)
5	11.0 (s, 1H)	7.05-7.35 (AA'BB', 2H)	7.40-7.80 (m, 8H)	1.9 (s, 3H, CH_3)
7	10.7 (s, 1H)	6.7-8.0 (m, 8H)	9.5-9.8 (br.s, 1H, OH)	2.50 (s, 3H, CH_3)
10	10.8-11.0 (br.s, 1H)	7.0-7.4 (AA'BB', 4H)	5.8-6.2 (s, 1H, CH_{tet})7.45-7.70 (m, 2H, Benzothiazole)6.70-6.90 (m, 2H)	7.70-8.00 (m, 4H, EWG-Ar)1.90-2.00 (s, 3H, CH_3)
12	10.9 (s, 1H)	7.0-8.0 (m, 8H)	9.0-9.2 (s, 1H, OH)	6.6-6.8 (d, 2H), 2.3-2.5 (s, 3H, CH_3)

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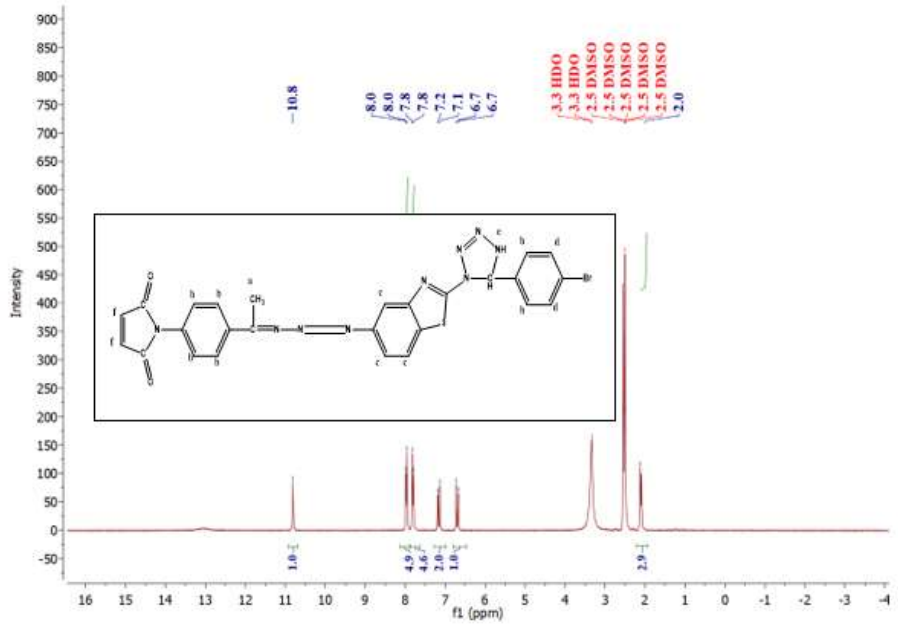

Figure 4. ^{1}H-NMR spectrum of compound T10 (in DMSO-d_6) showing the diagnostic singlet of the tetrazole CH proton at 5.8 -6.2 ppm, the characteristic AA'BB aromatic splitting pattern, and the deshielded tetrazole *NH* signal at 11.0 ppm

3.5. ^{13}C-NMR Spectroscopic Analysis

The carbon skeleton of the prepared derivatives was clearly identified through ^{13}C-NMR spectroscopy, and the chemical shifts observed (δ ppm) were found to be in excellent agreement with the molecular structures suggested in Table 4. The spectra showed sharp signals in the downfield region of 165-183 ppm, which are signals of the carbonyl carbons within the imide rings. It is worth noting that compound T5 had a distinctive signal at 180 ppm, which is the thiocarbonyl (C=S). This strong de-shielding of the carbon is due to the high electronegativity of the sulfur atom and the resonance stabilization of the thiourea moiety. By contrast, the imide carbonyls (C=O) of compounds T1, T2, T7, T10, and T12 were found at relatively high fields, and their position was also very sensitive to the electronic surroundings of the attached substituents. The Schiff base condensation was successful, as indicated by the appearance of signals in the range of 130-165 ppm. The location of these quaternary carbon (C_q) signals

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is determined by the electron density distribution around the C=N bond; compound T10 had a signal at 137 ppm, and T7 had a signal at 130 ppm as indicated by the presence of the attached aromatic/heterocyclic systems. The aromatic and heterocyclic carbons came out between 118 and 160 ppm. Carbons attached to the hydroxyl groups (C-OH) were detected with diagnostic peaks at 150 and 119 ppm (as in T5, T7, and T12) and carbons attached to the halogen groups (C-Cl and C-Br) were found in the expected ranges, due to the inductive effect (-I) of these substituents on the aryl ring. The presence of the clear signals of methyl (CH3) and methoxy (OCH3) groups was evident in the aliphatic region. The methyl group on the imine bond of T12 showed an extremely high shielding effect (27 ppm), suggesting a special electronic environment. All other derivatives had the standard methyl shifts between 20 and 35 ppm, and the methoxy signal of T1 was found at 55 ppm. The number of non-equivalent carbon signals in each spectrum matches the proposed molecular formulas, confirming the structural identity and high purity of the hybrids synthesized. Moreover, the solvent (DMSO-$_{d6}$) was used as an internal reference for the calibration of the observed chemical shifts (Kotlyar, 2021).

Table 4. ^{13}C-NMR chemical shifts (δ, ppm) and assignments for the synthesized tetrazole derivatives in DMSO-d_6

Comp.	C=O / (Carbonyl)	C=N (Imine)	Ar–C (Aromatic & Heterocyclic)	Aliphatic (CH_3 /OCH_3)
1	183 (Cimide), 178 (C=O)	160-165 (C=N)	150-152 (C–N, O), 141, 132, 130, 119 (Ar–C)	55 (OCH_3), 27 (CH_3)
2	167 (C=O,imide)	153 (C=N)	131 (Cq), 128 (Ph), 121 (Benzoth.), 118 (Ph–Cl)	35 (CH_3)
5	(170 - 167) (C1,C2, C=O)	155 (C4, C=N)	160 (C-N, O), 150 (C-OH), 148 , 140 , 138 , 122-134 (Ar-C)	22 (CH_3)
7	176 (C1, C2, C=O)	130 (C=N)	130 (CN, S), 119 (C–OH), 127, 124 (Ar–CH)	20-25 (CH_3)
10	167 (C=O,imide)	137 (Cq –C=N)	135 (Cq–S), 133 (Phmid), 130 (Phtet), 119 (C–Br)	27 (CH_3)
12	165 (C=O,imide)	130 (Cq –C=N)	130 (Ar–CH), 127 (Phmid), 122 (Benzoth.), 119 (Ar–C)	27 (CH_3)

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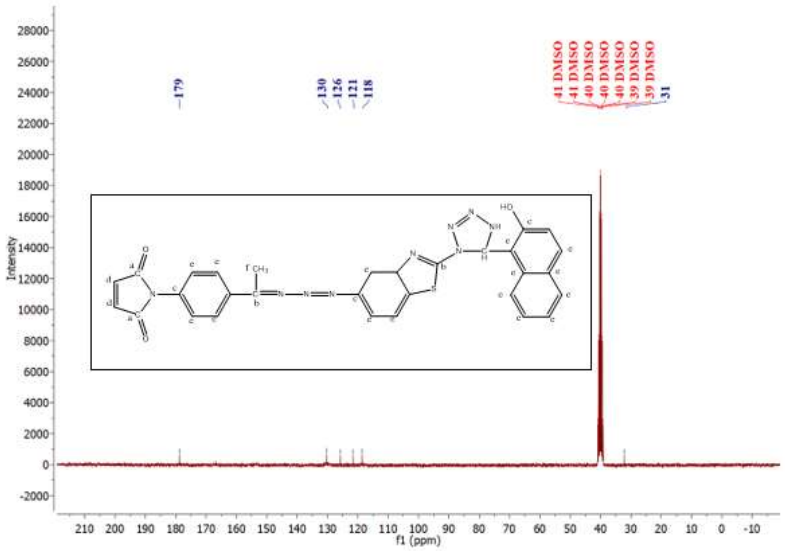

Figure 5. ^{13}C-NMR spectrum of compound T5 (in DMSO-d_6), highlighting the diagnostic thiocarbonyl signal at 180 ppm and the distinct resonance of the aromatic carbons

3.6. Biological assessment and SAR discussion

To test the antibacterial action of the synthesized compounds (T1, T2, T5, T7, T10, and T12), the gram-positive (*S. aureus and S. epidermidis*) and gram-negative (*E. coli and K. pneumoniae*) strains of bacteria were used. The results show a strong concentration-dependent antibacterial effect, as shown in Table 5 and in the zone of inhibition in Figure 6. Positive controls (standard antibiotics such as Ceftriaxone, Erythromycin, and Azithromycin) were used to verify bacterial strain sensitivity. Compound T10 showed a remarkable inhibition zone of 22 mm against S. epidermidis, similar to Azithromycin (30 mm) at the same concentration, as shown in Table 5. This suggests that the tetrazole-benzothiazole backbone contains strong pharmacophores capable of mimicking conventional antibiotics. Conversely, only the solvent (DMSO) showed no inhibition (0 mm) by any strain, supporting the idea that the reported antibacterial effect is due only to the generated compounds and not the medium. A selectivity towards Gram-

positive bacteria, especially *S. epidermidis*, was observed. Mechanically, this can be attributed to the fact that Gram-positive bacteria have a simpler cell wall structure than the outer lipopolysaccharide membrane of Gram-negative strains. The hybrids produced have a greater capacity to enter the porous peptidoglycan layer, whereas the outer membrane of Gram-negative bacteria is a strong diffusion barrier that limits compound concentration within the cell. The high potency of compounds T10 and T12 is primarily due to the tetrazole ring. Tetrazole, a crucial bioisostere of the carboxyl group, has several advantages in medicinal chemistry:

- Compared to carboxylic acids, the tetrazole ring increases the lipophilic character of the molecule, which is needed to enter the lipid-dense bacterial cell membrane (Gao et al., 2019).
- The four hydrogen bonding sites on the four N atoms of the tetrazole ring allow the existence of many hydrogen bonding opportunities with bacterial molecular targets, including DNA gyrase or cell wall synthesis enzymes. (Farzandi et al., 2025).
- The tetrazole scaffold has longer metabolic stability, which means that the duration of action will be longer at the site of infection (Chandra et al., 2025).

The combination of the imide, azomethine, and tetrazole groups (T10) provides an optimal electronic environment against bacterial growth. Although the evidence presented in these findings, supported by the data in Table 5 and Figure 6, identifies these compounds as good antibacterial leads, future research incorporating molecular docking will be needed to determine the exact binding sites in bacterial targets.

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Table 5. Antibacterial activity of the selected tetrazole derivatives (T1, T2, T5, T7, T10, and T12) and standard antibiotics at different concentrations against Gram-positive and Gram-negative bacteria

Compound	Concentration	S.aureus	S.epidermidis	E.coli	K.Pneumonia
1	100	13	15	13	15
	50	8	11	10	10
	25	n.a	8	9	11
2	100	n.a	14	8	8
	50	n.a	10	n.a	7
	25	n.a	7	n.a	n.a
5	100	n.a	16	8	8
	50	n.a	12	7	9
	25	n.a	9	12	8
7	100	n.a	18	n.a	n.a
	50	n.a	14	n.a	n.a
	25	n.a	10	n.a	n.a
10	100	n.a	22	n.a	n.a
	50	n.a	17	n.a	n.a
	25	n.a	12	n.a	n.a
12	100	n.a	20	8	10
	50	n.a	15	n.a	n.a
	25	n.a	11	n.a	10
Ceftriaxone		30	n.a	20	20
Erythromycin		n.a	n.a	30	n.a
Azithromycin		n.a	30	n.a	n.a
DMSO		0	0	0	0

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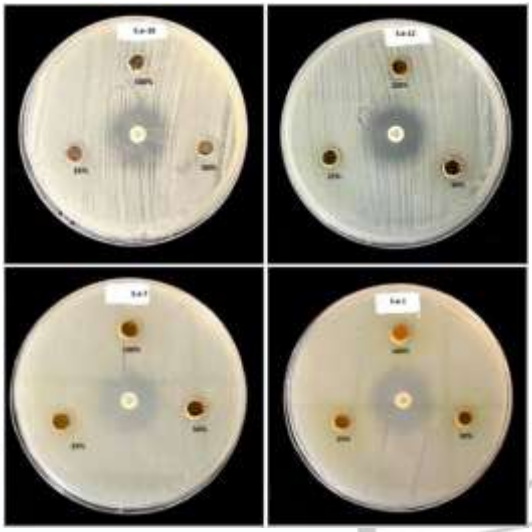

Figure 6. Inhibition zones of the synthesized tetrazole derivatives against *Staphylococcus epidermidis* at concentrations of 25, 50, 100%, showing the concentration-dependent antibacterial effect

4. Conclusion

A new class of nitrogen-containing tetrazole hybrids was produced effectively via an efficient, strategic route. The methodology was also more efficient, as the final products were attained in a significantly shorter time (6-10 hours) than those previously reported. This time advantage, along with the use of ethanol as a green solvent, highlights the research's sustainability. Although the last mechanism required glacial acetic acid, its use is well controlled as part of minimizing the chemical footprint. The integrity of the scaffolds and the successful incorporation of the different pharmacophores were confirmed by structural characterization of representative compounds by FT-IR and NMR spectroscopy. Their highly active antibacterial activity against resistant pathogens, combined with a friendly and time-saving synthetic pathway, makes the hybrids useful templates for future drug design. This study has shown that it is possible to obtain high-yield medicinal scaffolds without affecting the environment or economic aspects.

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