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Design and synthesis of novel benzotriazole-based hybrids with enhanced antimicrobial, antimalarial, and antitubercular potentials

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A B S T R A C T

We have synthesized all drugs using previously identified active pharmacophores through molecular hybridization. This paper explains a simple method for making *N-((2-(piperazine-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline* analogs 5(A–L) through steps. We used mass spectrometry, ^{1}H NMR, and ^{13}C NMR to do a spectrum analysis to confirm the structure of the synthesized end products. We evaluated all synthesized compounds for their in vitro antimicrobial, antimalarial, and antitubercular activities. We have also examined the research on structure-activity relationships (SAR). Target chemicals demonstrate significant effectiveness against bacteria, fungal diseases, and malaria.

1. Introduction

Heterocycles containing a nitrogen atom provide intriguing medical and pharmacological effects. Nitrogen heterocycles, particularly those containing benzotriazole scaffolds, have been shown to exhibit a broad range of biological activities, making them valuable in medicinal chemistry. Recent studies underscore the diverse therapeutic potentials of nitrogen-containing heterocycles in antimicrobial, anticancer, and antimalarial applications. These scaffolds have been recognized as privileged structures in drug discovery, facilitating interactions with various biological targets and enhancing the pharmacological profile of novel therapeutic agents.[1-6] Benzotriazole is an important nucleus that has garnered the interest of medicinal scientists because of its diverse pharmacological effects. The facile functionalization of diverse ring locations in benzotriazole renders it a compelling synthetic precursor for developing and synthesizing novel pharmaceuticals. Benzotriazoles are a notable class of chemicals, many of which exhibit extensive pharmacological effects, including antitubercular, antibacterial, antihypertensive, anti-inflammatory, anticancer, anticonvulsant, and antioxidant properties.[7-8]

Benzotriazole scaffolds get a lot of attention because they have many medical and physiological benefits, such as their ability to lower blood pressure, widen blood vessels, protect neurons, open airways, and protect the liver. Researchers have investigated a variety of techniques for the synthesis of benzotriazole derivatives. Several techniques have garnered significant interest in recent years. Resistance to current antibacterial and antifungal medications has prompted the proliferation of antimicrobial agents as a primary focus of antibacterial research in recent years.[9-13] Consequently, the creation of innovative antimicrobial drugs is imperative to tackle this problem. It is essential to investigate novel antimicrobial agents with innovative modes of action to combat antibiotic resistance. The Plasmodium parasite, which causes malaria, continues to pose a significant threat in tropical and subtropical regions. The World Health Organization

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(WHO) believes that 50 percent of the global population is at risk of malaria infection. As a result of finding the natural molecule quinine, other heterocyclic scaffold compounds, like benzotriazole, have shown promise as antimalarials. Despite this, as drug resistance grows, especially against Artemisinin and its derivatives, we need new drugs, possibly including better benzotriazole derivatives, to make sure that therapies work.[14-20] Moreover, tuberculosis (TB) is among the most lethal illnesses, claiming over one million lives each year and infecting around one-third of the global population. For the past 50 years, TB therapy has depended on a prolonged, multidrug regimen. Recently, the treatment of Mycobacterium tuberculosis (M. TB) has employed antibiotics such as ciprofloxacin, Gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. The increasing resistance to these medicines highlights the pressing necessity for novel treatment approaches to address TB.[21] Over the last ten years, persistent efforts in TB therapy have resulted in the emergence of numerous promising compounds that have progressed to clinical trials. In addition to benzotriazole, other heterocyclic compounds, such as piperazine, are also being studied because they have a wide range of biological effects, such as pain-relieving, anti-inflammatory, antidepressant, antipsychotic, antianginal, and anticancer properties.[22-25]
Molecular hybridization is a recognized approach to medication creation and development. Using this method, many pharmacophores from bioactive natural or synthetic chemicals are combined into a single hybrid molecule. This often results in better affinity and potency compared to the original molecules. This approach can generate compounds with multiple modes of action, modified selectivity profiles, and diminished adverse effects, which is crucial in the development of novel anti-TB medicines.[26-30]

In recent years, the increase in antimicrobial resistance has propelled the quest for novel and more efficacious treatment agents. Benzotriazole derivatives, owing to their recognized bioactivity and capacity for modification, offer a viable answer to this issue. Their efficacy against resistant bacterial and fungal strains renders them promising candidates for further development as antimicrobial agents. Moreover, the rising incidence of malaria and TB has rendered the demand for novel medicines exceedingly urgent. The emergence of resistance to existing antimalarial compounds such as artemisinin and longstanding TB medications underscores the need for alternate treatments.[31-32] The benzotriazole framework, when integrated with additional bioactive entities via molecular hybridization, may provide an innovative strategy for addressing these disorders. The hybridization of benzotriazoles with other bioactive frameworks may yield innovative prospects for the development of highly effective anti-TB pharmaceuticals with enhanced efficacy and diminished resistance.

This study aims to design and synthesize new benzotriazole hybrid derivatives to evaluate their potential antimicrobial, antitubercular, and antimalarial properties. By exploring structure-activity relationships (SAR), we seek to identify potent compounds that can contribute to the growing need for effective treatments in these areas.

2. Results and Discussion

2.1. Chemistry

The current study presents the design and synthesis of *N-((2-(piperazine-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline* analogs 5(A-L) using reductive amination of *tert-butyl 4-(3-formyl-1H-benzo[d][1, 2, 3]triazol-2(3H)-yl)piperazine-1-carboxylate* (3) and various amines 4(A-L) was followed by the deprotection of N-Boc derivatives of piperazines 5(A-L) (**Scheme 1**). We used tert-butyl *4-(3-formylbenzotriazol-2-yl)piperazine-1-carboxylate* (3) and 3-chloroaniline (5E) as model substrates to find the best reaction conditions. We then looked at how temperature, catalysts, and solvents affected the reactions (see **Table I**).

Table 1. Optimization of the reaction conditions for the synthesis of *tert-butyl 4-(3-(((3-chlorophenyl)amino)methyl)benzotriazole-2-yl)piperazine-1-carboxylate* (5E)

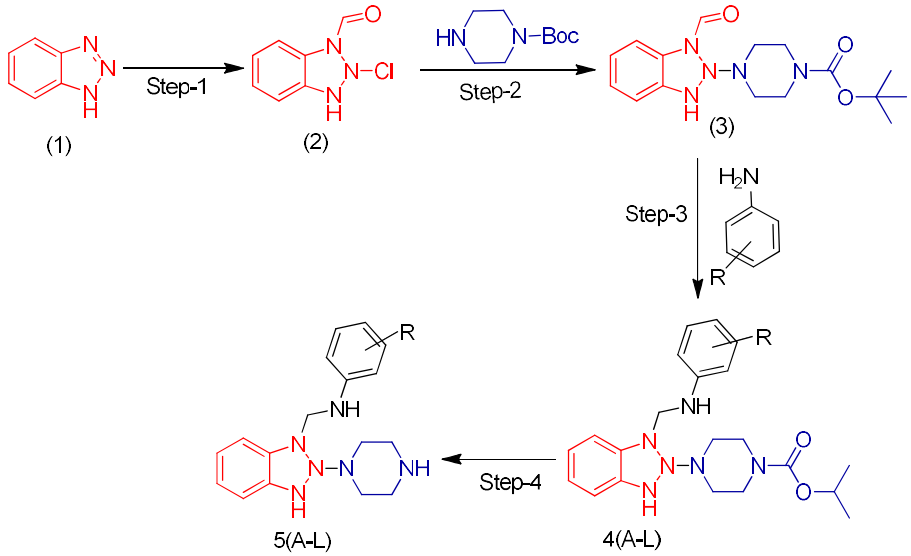
Entry	Catalyst	Solvent	Temp (°C)	Time	Yield a (%)
1	$NaCNBH_3$ and Acetic acid	Methanol	25	1h	85
2	$NaCNBH_3$ and Acetic acid	THF	25	1h	71
3	$NaCNBH_3$ and Acetic acid	Ethanol	25	1h	79
4	$NaBH_4$	2,2,2-trifluoroethanol	25	1h	55
5	$NaBH_4$ and Acetic acid	Methanol	25	2h	70
6	$NaBH_4$ and Acetic acid	THF	25	2h	66
7	$NaBH_4$ and Acetic acid	Ethanol	25	2h	69
8	$NaBH(OAc)_3$ and Acetic acid	THF	25	2h	59
9	$NaBH(OAc)_3$ and Acetic acid	Dichloroethane	25	2h	65
10	$NaCNBH_3$ and Acetic acid	Methanol	40	1h	85
11	$NaCNBH_3$ and Acetic acid	Methanol	50	1h	75
12	$NaCNBH_3$ and Acetic acid	Methanol	60	1h	71

a = Isolated yield

The optimization of this reductive examination was essential for achieving high yields and selectivity for the target products. Comprehensive spectrum analysis using mass spectrometry, ^1H NMR, and ^{13}C NMR techniques verified the radiochemistry of the synthesized benzotriazoles. Mass spectrometry confirmed molecular weights, aiding in the validation of the anticipated chemical structures. The ^1H NMR spectra showed clear signals that made it easier to find proton environments. This supported the arrangement of the substituents around the core of the benzotriazole. The ^{13}C NMR spectra

also helped us understand the carbon framework, supporting the proposed structure by showing specific chemical shifts connected to different carbon locations in the benzotriazole ring and its substituents.

We employed Infrared (IR) spectroscopy to identify essential functional groups, thereby reinforcing the regiochemistry. The molecular structure's functional groups, such as NH, C=N, and C-H, exhibited distinct absorption bands that matched the intended molecular design. Using spectrum data to get a clear picture of regiochemistry showed that the patterns of substitution in the benzotriazole derivatives matched the expected chemical structures.



Scheme 1. Synthesis of Benzotriazole Hybrid Derivatives

In a model process, we originally used standard reductive amination conditions, specifically $NaCNBH_3$ and acetic acid in methanol at ambient temperature. This made it possible to make *tert-butyl 4-(3-((3-chlorophenyl)amino)methyl)benzotriazole-2-yl)piperazine-1-carboxylate* (5E) effectively, with a 70% yield in one hour (**Table 1**). We repeated the process with several solvents, including THF and ethanol, to enhance the yield and optimize the reaction conditions. However, Table I recorded only moderate to excellent yields in THF and ethanol, indicating that methanol was the optimal solvent for this process. Subsequently, we assessed other reducing agents under the same reaction circumstances. The use of $NaBH_4$ as a catalyst in 2,2,2-trifluoroethanol yielded a significant amount of compound (5E) (Table I). The NaBHP and acetic acid system was also tested in methanol, THF, and ethanol, but there was no significant increase in product yield, resulting in only moderate yields in all cases (**Table 1**).

We then tested $NaBH(OAc)_3$ and acetic acid using THF and dichloroethane (DCE) as solvents. However, the results were not as efficient as with $NaCNBH_3$ and acetic acid (Table I). Thus, $NaCNBH_3$ and acetic acid in methanol at room temperature were determined to be the optimized reaction condition. Furthermore, increasing the temperature from room temperature (RT) to 60°C resulted in a decreased product yield (Table 1). Therefore, the optimized conditions for this reaction are $NaCNBH_3$ and acetic acid in methanol at room temperature.

Subsequently, we evaluated $NaBH(OAc)_3$ and acetic acid using THF and dichloroethane (DCE) as solvents. Nevertheless, the outcomes were not as effective as those obtained with $NaCNBH_3$ and acetic acid (**Table 1**). Consequently, $NaCNBH_3$ and acetic acid in methanol at ambient temperature were identified as the optimal reaction conditions. Moreover, elevating the temperature from room temperature (RT) to 60 °C led to a reduction in product yield (**Table 1**). The optimal conditions for this reaction are $NaCNBH_3$ and acetic acid in methanol at ambient temperature. The optimal conditions established for compound (5E) were effectively utilized in the reactions of *tert-butyl4-(3-formylbenzotriazol-2-yl)piperazine-1-carboxylate* (3) with various amines in the presence of $NaCNBH_3$ and acetic acid in methanol at ambient temperature, resulting in the corresponding tert-butyl *4-(3-((phenylamino)methyl)benzotriazol-2-yl)piperazine-1-carboxylate* derivatives 4(A-L) in good to excellent yields within one hour. To evaluate the applicability of this approach, we examined several aniline derivatives, and the reactions progressed seamlessly, producing outstanding results in every instance. Finally, *N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline* derivatives 5(A-L) were synthesized by deprotection of N-Boc from tert-butyl *4-(3-((phenylamino)methyl) benzotriazole-2-yl)piperazine-1-carboxylate* derivatives 4(A-L) using 4M HCl in 1,4-dioxane (Table II). After completion of the reaction, the mixture was basified with aqueous sodium bicarbonate and extracted with dichloromethane (DCM). The DCM layer was evaporated under a vacuum to obtain the pure product 5(A-L).

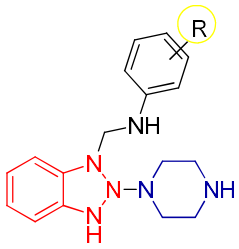


Table 2. Preparation of various benzotriazole hybrid piperazine derivatives 5(A-L)

Compd Code	R	Time (h)	Yield (%)	M.P. (°C)
5A	3-CH_3, -4F	2	85	190-194
5B	3,4-$(OCH_3)_2$	2	71	195-199
5C	3,4-$(F)_2$	2	79	185-189
5D	3-Cl, 4F	2	55	188-192
5E	3-Cl	2	70	196-200
5F	2,4-$(OCH_3)_2$	2	66	204-208
5G	4-Cl	2	69	201-205
5H	3-OCH_3	2	59	197-199
5I	3-CH_3	2	65	194-196
5J	4-CH_3	2	85	197-198
5K	4-OCH_3	2	75	194-196
5L	3,5-$(OCH_3)_2$	2	71	203-204

a = Isolated yields

All synthesized products were easily purified by trituration with n-pentane. The purity of the synthesized molecules was confirmed using TLC and elemental analysis. The structures of the final products were well characterized using spectral analysis methods, including IR, Mass, ^{1}H-NMR, and ^{13}C-NMR. The best results, in terms of both yield and reaction time, were achieved at room temperature.

2.1. Antibacterial Activity

All the synthesized benzotriazole hybrid piperazine compounds (5A–L) were tested for their antibacterial activity in vitro (Table 3). The bioassay results show that most of the benzotriazole compounds were pretty good at killing the bacteria that were tested, about the same as regular medicines. Most of the compounds that were tested were more effective against Gram-positive bacteria (S. aureus) than the common antibiotic Ampicillin (MIC 100 µg/mL), but 51% less effective than Chloramphenicol (MIC 50 µg/mL) and Ciprofloxacin (MIC 50 µg/mL).

Table 3

Antibacterial and antifungal activity (MICs, µg/ml)

Compound	Antibacterial activity (MICs, µg/ml)				Antifungal activity (MICs, µg/ml)		
	Gram-Positive Bacteria	Gram Negative Bacteria					
	S.A. (MTCC 96)	S.P. (MTCC 442)	E.C. (MTCC 443)	P.A. (MTCC 1688)	C.A. (MTCC 227)	A.N. (MTCC 282)	A.C. (MTCC 1323)
5A	100	125	125	200	500	>1000	>1000
5B	100	200	250	200	1000	1000	1000
5C	200	200	100	250	1000	1000	1000
5D	100	100	125	250	>1000	1000	1000
5E	125	125	100	100	500	500	500
5F	250	100	62.5	125	1000	1000	1000
5G	100	125	100	200	500	>1000	>1000
5H	200	100	250	100	1000	500	500
5I	125	250	62.5	100	500	1000	1000
5J	100	200	250	200	500	500	500
5K	100	250	125	100	250	500	500
5L	100	100	250	200	1000	500	500
Ampicillin	250	100	100	100	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

Compound 5F, which has two methoxy groups on the phenyl ring, had moderate effectiveness against S. aureus growth at a minimum inhibitory concentration (MIC) of 250 µg/mL, making it like Ampicillin in this way. Also, compounds 5F, 5H, and 5L had equal effectiveness against *S. pyogenes* at a minimum inhibitory concentration (MIC) of 100 µg/mL, which is the same as ampicillin. However, they were 48% less effective than chloramphenicol (MIC 50 µg/mL) and ciprofloxacin (MIC 50 µg/mL). The residual compounds demonstrated modest efficacy against S. pneumoniae. The antibacterial activity of all synthesized compounds against the two Gram-negative pathogens, on the other hand, was very high. Compounds 5F and 5I (MIC 62.5 µg/mL) have shown superior efficacy against E. coli, exceeding that of ampicillin (MIC 100 µg/mL). Also, compounds 5C, 5E, and 5G were very effective against E. coli, with an MIC value of 100 µg/mL, which is about the same as ampicillin. Compounds 5E, 5H, 5I, and 5K (MIC 100 µg/mL) exhibited equivalent potency to ampicillin against *P. aeruginosa*, although shown 51% reduced efficacy compared to chloramphenicol (MIC 50 µg/mL). The residual compounds had modest efficacy against P. aeruginosa.

2.2. Antifungal Activity

The tested benzotriazole derivatives' antifungal activity showed that C. albicans was very sensitive to several drugs (**Table 3**). The derivatives 5A, 5E, 5G, and 5J had a minimum inhibitory concentration (MIC) of 500 εg/mL against C. albicans, which was about the same as Griseofulvin's MIC of 500 µg/mL. The MIC of compound 5K against C. albicans is 250 µg/mL, which is much higher than that of Griseofulvin. Furthermore, the most of compounds exhibited moderate inhibitory efficacy against A. niger and A. clavatus.

Table 4. The Antimalarial activity of compounds 4(A-L)

Compd	Mean IC50 values (µg/mL)
5A	0.85
5B	1.15
5C	1.02
5D	0.93
5E	1.10
5F	0.99
5G	0.91
5H	0.87
5I	0.83
5J	0.95
5K	0.89
5L	1.00

Table 5. The Antituberculosis activity of compounds 4(A-L)

Compound	Mean IC50 values (µg/mL)
5A	150
5B	450
5C	120
5D	400
5E	500
5F	100
5G	75
5H	90
5I	500
5J	300
5K	850
5L	550
Isoniazid	0.20
Rifampicin	0.25

2.3. Anti-Malarial Activity

We evaluated the in vitro anti-malarial efficacy of all synthesized compounds 5(A-L) against the Plasmodium falciparum 3D7 strain, which is susceptible to chloroquine. **Table 4** displays the average IC50 values. Most of the compounds had modest anti-malarial efficacy.

2.4. Anti-Tuberculosis Activity

We evaluated the in vitro anti-tuberculosis efficacy of all synthesized compounds 5(A-L) against the Mycobacterium tuberculosis H37Rv strain. We used isoniazid and rifampicin as reference medications. **Table 5** presents the experimental MIC values for these compounds. Among the evaluated compounds, compound 5G exhibited significant activity (50 µg/mL). The remaining drugs had modest anti-tubercular efficacy.

2.5. Structure-Activity Relationship (SAR)

SAR analysis suggests that small electron-donating groups (e.g., -OCH_3, -CH_3) improve antifungal and antibacterial activity, likely due to enhanced membrane permeability and increased interaction with microbial targets, Compounds bearing methoxy (-OCH_3) and methyl (-CH_3) groups on the arylamine ring generally exhibited enhanced antibacterial and antifungal activities. The electron-donating nature of these groups increases electron density on the aromatic ring, which likely improves the binding affinity of the compounds to the bacterial and fungal cell targets. For example, compounds 5F, 5H, and 5L, with methoxy groups at various positions, showed significant activity against *Staphylococcus aureus* and *Candida albicans*. On the other hand, electron-withdrawing halogen groups (e.g., -Cl, -F) increase the antimicrobial spectrum by improving interaction with bacterial enzymes, particularly in Gram-negative bacteria, Compounds with chloro (-Cl) and fluoro (-F) groups on the aromatic ring, such as 5C and 5E, demonstrated strong activity against *Escherichia coli* and *Pseudomonas aeruginosa*. The graphical SAR models (**Fig. 6**) illustrate how substituent modifications on the benzotriazole scaffold influence biological activity. These models highlight the optimal substitution patterns for maximizing antimicrobial potency and could guide further modifications to improve the activity of these hybrid derivatives.

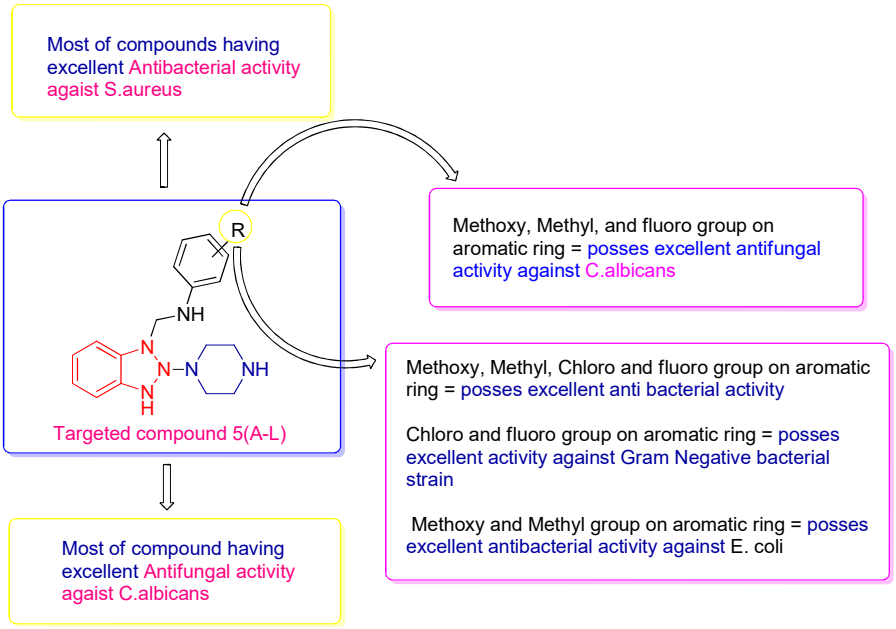


Fig. 6. The Structure-activity relationship (SAR) of Benzotriazole hybrid piperazine derivatives 5(A-L)

3. Conclusions

This work effectively synthesized and characterized a series of benzotriazole compounds with considerable potential for antibacterial, antimalarial, and antitubercular uses. The spectrum investigations, comprising NMR, IR, and mass spectrometry, validated the structural integrity and regiochemistry of each molecule. Biological tests showed that many of the synthesized compounds were very effective against both Gram-positive and Gram-negative bacteria. In some cases, these compounds were even more effective than traditional antibiotics. These benzotriazole compounds were also very good at killing fungi, especially *Candida albicans*. They were also somewhat effective at stopping Plasmodium falciparum and Mycobacterium tuberculosis, which shows that they could be used to treat malaria and tuberculosis. The research highlights the significance of benzotriazole as a multifunctional scaffold that, via molecular hybridization, may produce molecules with improved bioactivity and selectivity. The findings indicate that the additional optimization of substituents on the benzotriazole core may enhance effectiveness and diminish resistance, positioning these compounds as viable candidates for future therapeutic development. The results of this study add to the growing body of new treatments for infectious diseases and show that benzotriazole derivatives can help solve global health problems caused by antibiotic resistance. All derivatives also exhibited moderate anti-malarial and anti-tubercular activity. In the present study, compounds 5E, 5F, 5G, 5H, and 5I demonstrated highly potent activity against most of the tested bacteria and fungi.

4. Experimental

4.1. Materials and Methods

All reagents were utilized as they were received from commercial vendors without further purification. We measured the melting points (MP, °C) of all synthesized compounds in open capillaries using electrothermal equipment, without any corrections. The purity of the synthesized compounds was evaluated using precoated TLC plates (Merck Kieselgel F254),

with compound spots visualized under UV light. The FTIR spectra were recorded on a Shimadzu IR Affinity-1 spectrometer using KBr pellets, and the wave numbers (v max) were reported in cm^{-1}. The ^{1}H-NMR spectra were recorded using a Bruker Advance II NMR spectrometer running at 400MHz utilizing DMSO-d_6 as the solvent and tetramethyl silane (TMS) as the internal standard. Chemical shift (δ) values are denoted in parts per million (ppm), whereas coupling constants (J) are indicated in hertz (Hz). Mass spectra were obtained using the Waters Quadrupole Detector (TDQ).

4.2. General procedure

Synthesis of tert-butyl4-(1-formyl-1H-benzo[d][1,2,3]triazol-2(3H)-yl)piperazine-1-carboxylate derivative, 3

A stirred solution of 1-chlorobenzotriazole-3-carbaldehyde (1 equivalent) in 10 volumes of DMF was treated with 2.5 equivalents of K_2CO_3. The reaction mixture was stirred at room temperature for 20 minutes. Next, we added 2 equivalents of tert-butyl piperazine-1-carboxylate and heated the reaction mixture at 110 °C for 5 hours. Thin-layer chromatography (TLC) tracked the product's production. After the reaction was complete, we allowed the liquid to cool to ambient temperature and quenched it by introducing it to crushed ice. We extracted the solution using ethylene acetate. We desiccated the organic layer using sodium sulphate and evaporated the solvent to obtain the crude product. The crude product underwent purification using column chromatography employing 10% ethyl acetate in hexane as the eluent.
Synthesis of tert-butyl4-(1-((phenylamino)methyl)-1H-benzo[d][1,2,3]triazol-2(3H)-yl)piperazine-1-carboxylate derivative 4(A-L)

Adding phenylamine (1.2 equivalents) to a stirred solution of tert-butyl 4-(1-formyl-1H-benzo[d][1,2,3]triazol-2(3H)-yl)piperazine-1-carboxylate (1 equivalent) in methanol changed the chemical structure. Next, we added a catalytic quantity of acetic acid and agitated the reaction mixture for 1 hour at ambient temperature. Thin-layer chromatography (TLC) allowed for the observation of the intermediate development. After the reaction period, we cooled the mixture to 0 °C and agitated it for 10 minutes. Subsequently, $NaCNBH_3$ (2 equivalents) was added, and the reaction mixture was agitated at ambient temperature for one hour. After the reaction, we cooled the liquid with crushed ice and then extracted it using ethyl acetate. The crude product underwent purification using column chromatography.
Synthesis of N-((2-(piperazine-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline analogs 5(A-L)

To a stirred solution of tert-butyl 4-(1-((phenylamino)methyl)-1H-benzo[d][1,2,3]A-L, which is a triazol-2(3H)-yl)piperazine-1-carboxylate derivative, was mixed with 10 vol. of 4M HCl in 1,4-dioxane at 0 °C. The HCl was added drop by drop. We agitated the reaction mixture for 2 hours at ambient temperature. Thin-layer chromatography (TLC) tracked the product's production. We evaporated the mixture to dryness upon completion of the reaction to obtain the crude product. We subsequently basified the reaction mixture with aqueous sodium bicarbonate and extracted it using dichloromethane (DCM). We evaporated the DCM layer under vacuum to obtain pure products 4 (A-L), and then refined them by trituration with n-pentane.

4.3 Physical and Spectral Data

tert-butyl 4-(1-formyl-1H-benzo[d][1,2,3]triazol-2(3H)-yl)piperazine-1-carboxylate derivative, (3)

Yield; 81%, m.p. 198 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H, CHO), 8.50 (s, 1H, NH), 7.80–7.84 (t, 1H, aromatic C-H), 7.68–7.72 (t, 1H, aromatic C-H), 7.39–7.42 (t, 1H, aromatic C-H), 3.64–3.66 (t, 4H, CH_2), 3.43–3.45 (t, 4H, CH_2), 1.49 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.35 (CH_3), 42.44 (CH_2), 47.20 (CH_2), 115.26, 116.13, 122.75, 124.81, 125.98, 126.31, 127.58, 127.77, 129.68, 131.02, 141.32, 157.76.IR (KBr): v 3371, 2947, 1643 (C=N), 1504, 1449, 1265, 1033, 941, 779 cm^{-1}.MS (ESI) m/z for (340.17): 341.69 $(M+H)^+$.

4-fluoro-3-methyl-N-((2-(piperazin-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline (5A)

Yield: 85% Melting Point (m.p.): 190–194 °C.^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H, NH), 8.34 (s, 1H, benzotriazole H), 7.93–7.91 (d, 1H, aromatic C-H), 7.86–7.84 (d, 1H, aromatic C-H), 7.71–7.67 (t, 1H, aromatic C-H), 7.49–7.45 (t, 1H, aromatic C-H), 6.90–6.85 (t, 1H, aromatic C-H), 6.64 (s, 1H, aromatic C-H), 4.38 (s, 2H, CH_2), 3.32 (s, 4H, CH_2), 2.12 (s, 4H, CH_2), 1.60 (s, 3H, CH_3).^{13}C NMR (100 MHz, DMSO): δ 14.35 (CH_3), 42.44 (CH_2), 47.20 (CH_2), 115.26 (aromatic C), 122.75, 124.81, 125.98, 127.58, 129.68. IR (KBr): v 3371 (NH), 1643 (C=N), 1504, 1265, 1033, 779 cm^{-1}.MS (ESI): m/z for (350.19): 351.5 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{23}FN_6$ (350.19): C 71.98%, H 6.62%, N 15.99%. Found: C 71.95%, H 6.61%, N 15.96%.

3,4-dimethoxy-N-((2-(piperazin-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline (5B)

Yield: 71% Melting Point (m.p.): 195–199 °C.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H, NH), 9.38 (s, 1H, benzotriazole H), 7.90–7.91 (d, 1H, aromatic C-H), 7.74–7.70 (t, 1H, aromatic C-H), 6.86–6.76 (m, 3H, aromatic C-H), 4.54 (s, 2H, CH_2), 3.62 (s, 6H, OCH_3), 3.30 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 42.10 (CH_2), 45.28 (CH_2), 51.40, 56.14 (OCH_3), 121.13, 122.76, 127.57.IR (KBr): v 3376 (NH), 1647 (C=N), 1544, 1268, 1039 cm^{-1}.MS (ESI): m/z for (378.21): 379.4 $(M+H)^+$.Elemental Analysis: Calculated for $C_{22}H_{26}N_4O_2$ (378.21): C 69.82%, H 6.92%, N 14.80%.Found: C 69.81%, H 6.90%, N 14.78%.

3,5-difluoro-N-((2-(piperazin-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline (5C)

Yield: 79%, Melting Point (m.p.): 185–189 °C.¹H NMR (400 MHz, MeOD): δ 8.79 (s, 1H, NH), 8.23–8.21 (d, 1H, aromatic C-H), 8.05–8.03 (d, 1H, aromatic C-H), 7.99–7.95 (t, 1H, aromatic C-H), 7.74–7.70 (t, 1H, aromatic C-H), 7.09–7.02 (m, 1H, aromatic C-H), 6.67–6.62 (m, 1H, aromatic C-H), 6.50–6.48 (d, 1H, aromatic C-H), 4.51 (s, 2H, CH_2), 4.15–4.12 (t, 4H, CH_2), 3.62–3.59 (t, 4H, CH_2).¹³C NMR (100 MHz, DMSO): δ 42.10 (CH_2), 45.48 (CH_2), 51.20, 103.62, 114.15, 115.46, 121.35, 122.64, 123.14, 127.35, 127.72, 129.51, 135.90, 137.19, 144.82, 147.18, 148.45, 155.45.IR (KBr): ν 3340 (NH), 2832, 1643 (C=N), 1550, 1435, 1265, 1033, 941 cm^{-1}.MS (ESI): m/z for (354.17): 355.2 $(M+H)^+$.Elemental Analysis: Calculated for $C_{17}H_{21}F_2N_5$ (354.17):C = 58.44%, H = 6.06%, F = 10.88%, N = 20.05%.Found: C = 58.40%, H = 6.10%, F = 10.90%, N = 20.00%.

3-chloro-4-fluoro-N-((2-(piperazin-1-yl)-2,3-dihydro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)aniline (5D)

Yield: 55%, Melting Point (m.p.): 188–192 °C. ¹H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H, NH), 8.22–8.20 (d, 1H, aromatic C-H), 8.05–8.03 (d, 1H, aromatic C-H), 7.74–7.70 (t, 1H, aromatic C-H), 6.67–6.62 (m, 1H, aromatic C-H), 4.53 (s, 2H, CH_2), 4.17–4.12 (t, 4H, CH_2).¹³C NMR (100 MHz, DMSO): δ 42.10 (CH_2), 45.28, 114.25 (aromatic C), 117.60, 127.34. IR (KBr): ν 3356 (NH), 1627 (C=N), 1545, 1269, 1031 cm^{-1}.MS (ESI) m/z for (373.86): 374.4 $(M+H)^+$, 375.6 $(M+2H)^+$.Elemental Analysis: Calculated for $C_{19}H_{23}ClF\ N_4$ (373.86):C: 65.23%,H: 6.60%,N: 15.76%,Cl: 5.06%,F: 3.35%,Found:C: 65.10%,H: 6.55%,N: 15.75%,Cl: 5.05%,F: 3.30%.

3-Chloro-N-((2-(piperazin-1-yl)benzotriazol-3-yl)methyl)aniline, (5E)

Yield: 70%, Melting Point (m.p.): 196–200 °C.¹H NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H, NH), 8.18–8.20 (d, 1H, aromatic C-H), 7.98–7.92 (t, 1H, aromatic C-H), 7.70–7.65 (t, 1H, aromatic C-H), 7.09–7.01 (m, 2H, aromatic C-H), 6.65–6.61 (m, 2H, aromatic C-H), 6.52 (d, 1H, aromatic C-H), 4.56 (s, 2H, CH_2), 4.14–4.10 (t, 4H, CH_2), 3.62–3.60 (t, 4H, CH_2).¹³C NMR (100 MHz, DMSO): δ 42.15 (CH_2), 45.00, 51.10, 110.65, 114.20, 117.58, 120.60, 121.30, 123.42, 126.20, 127.60, 135.12, 149.00, 156.85.IR (KBr): ν 3320 (NH), 2960, 1620 (C=N), 1530, 1440, 1265, 1033, 945 cm^{-1}.MS (ESI): m/z = 354.2 $(M+H)^+$, 355.2 $(M+2H)^+$.Elemental Analysis: Calculated for $C_{17}H_{18}ClN_5$ (354.12): C 57.63%, H 5.12%, N 19.79%; Found: C 57.61%, H 5.10%, N 19.77%.

2,4-Dimethoxy-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5F)

Yield: 66%, Melting Point (m.p.): 204–208 °C.¹H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H, NH), 9.35 (s, 1H, benzotriazole H), 6.83–6.78 (m, 3H, aromatic C-H), 6.60 (s, 1H, aromatic C-H), 4.53 (s, 2H, CH_2), 3.60 (s, 6H, OCH_3).¹³C NMR (100 MHz, DMSO): δ 42.25 (CH_2), 45.60, 50.90, 55.70 (OCH_3), 101.20, 107.30.IR (KBr): ν 3340 (NH), 1625 (C=N), 1540, 1260, 1040 cm^{-1}.MS (ESI): m/z = 379.4 $(M+H)^+$.Elemental Analysis: Calculated for $C_{19}H_{23}N_5O_2$ (379.18): C 60.15%, H 6.10%, N 18.43%; Found: C 60.12%, H 6.09%, N 18.40%.

4-Chloro-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5G)

Yield: 69%, Melting Point (m.p.): 201–205 °C. ¹H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H, NH), 8.22–8.20 (d, 1H, aromatic C-H), 8.05–8.03 (d, 1H, aromatic C-H), 7.99–7.95 (t, 1H, aromatic C-H), 7.09–7.02 (m, 2H, aromatic C-H), 6.67–6.62 (m, 2H, aromatic C-H), 6.50–6.48 (d, 1H, aromatic C-H), 4.59 (s, 2H, CH_2), 4.17–4.12 (t, 4H, CH_2).¹³C NMR (100 MHz, DMSO): δ 42.20 (CH_2), 45.28, 114.19 (aromatic C), 121.23, 122.16, 123.34, 127.63.IR (KBr): ν 3346 (NH), 1629 (C=N), 1539, 1262, 1033 cm^{-1}.MS (ESI): m/z = 353.2 (M+H)+, 354.3 $(M+2H)^+$.Elemental Analysis: Calculated for $C_{17}H_{18}ClN_5$ (353.12): C 57.67%, H 5.12%, Cl 10.04%, N 19.80%; Found: C 57.65%, H 5.10%, Cl 10.02%, N 19.77%.

3-Methoxy-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5H)

Yield: 59%,Melting Point (m.p.): 197–199 °C. ¹H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H, NH), 8.22–8.20 (d, 1H, aromatic C-H), 8.05–8.03 (d, 1H, aromatic C-H), 7.99–7.95 (t, 1H, aromatic C-H), 7.09–7.02 (m, 2H, aromatic C-H), 6.67–6.62 (m, 2H, aromatic C-H), 6.50–6.48 (d, 1H, aromatic C-H), 4.51 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.61–3.62 (t, 4H, CH_2).¹³C NMR (100 MHz, DMSO): δ 42.10 (CH_2), 45.48, 51.20, 55.18 (OCH_3), 105.26, 109.42, 121.36, 122.67, 123.48.IR (KBr): ν 3345 (NH), 1622 (C=N), 1534, 1271, 1067 cm^{-1}.MS (ESI): m/z = 349.4 $(M+H)^+$.Elemental Analysis: Calculated for $C_{18}H_{21}N_5O$ (349.16): C 61.88%, H 6.06%, N 20.06%; Found: C 61.85%, H 6.05%, N 20.04%.

3-Methyl-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5I)

Yield: 65%, Melting Point (m.p.): 194–196 °C.¹H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H, NH), 8.34 (s, 1H, benzotriazole H), 7.93–7.91 (d, 1H, aromatic C-H), 7.86–7.84 (d, 1H, aromatic C-H), 7.71–7.67 (t, 1H, aromatic C-H), 7.49–7.45 (t, 1H, aromatic C-H), 6.90–6.85 (t, 1H, aromatic C-H), 4.38 (s, 2H, CH_2), 3.61–3.62 (t, 4H, CH_2), 2.12 (s, 3H, CH_3).¹³C NMR (100 MHz, DMSO): δ 20.51 (CH_3), 42.45 (CH_2), 47.28, 123.25, 124.55, 125.45, 127.85.IR (KBr): ν 3345 (NH), 1689 (C=N), 1536, 1264, 1038 cm^{-1}.MS (ESI): m/z = 333.4 (M+H)+.Elemental Analysis: Calculated for $C_{18}H_{22}N_5$ (333.17): C 64.85%, H 6.64%, N 22.35%; Found: C 64.82%, H 6.62%, N 22.32%.

4-Methyl-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5J)

Yield: 85%, Melting Point (m.p.): 197–198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H, NH), 8.34 (s, 1H, benzotriazole H), 7.93–7.91 (d, 1H, aromatic C-H), 7.86–7.84 (d, 1H, aromatic C-H), 7.71–7.67 (t, 1H, aromatic C-H), 7.52–7.48 (t, 1H, aromatic C-H), 6.64 (s, 1H, aromatic C-H), 4.38 (s, 2H, CH_2), 3.83 (s, 3H, CH_3), 3.62–3.64 (t, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 20.50 (CH_3), 42.40 (CH_2), 47.26, 123.15, 124.50, 125.85, 127.75. IR (KBr): ν 3340 (NH), 1643 (C=N), 1550, 1435, 1033 cm^{-1}.MS (ESI): m/z = 333.2 (M+H)$^+$. Elemental Analysis: Calculated for $C_{18}H_{21}N_5$ (333.17): C 64.85%, H 6.64%, N 22.35%; Found: C 64.82%, H 6.62%, N 22.32%.

4-Methoxy-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5K)

Yield: 75%, Melting Point (m.p.): 194–196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 1H, NH), 8.31 (s, 1H, benzotriazole H), 7.93–7.91 (d, 1H, aromatic C-H), 7.86–7.84 (d, 1H, aromatic C-H), 7.70–7.69 (t, 1H, aromatic C-H), 6.91–6.86 (t, 1H, aromatic C-H), 6.62 (s, 1H, aromatic C-H), 4.31 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO): δ 20.50 (CH_3), 42.40 (CH_2), 47.26, 51.56 (OCH_3), 123.15, 124.50. IR (KBr): ν 3326 (NH), 1626 (C=N), 1535, 1445, 1036 cm^{-1}.MS (ESI): m/z = 349.3 (M+H)$^+$. Elemental Analysis: Calculated for $C_{19}H_{23}N_5O$ (349.19): C 65.31%, H 6.63%, N 19.18%; Found: C 65.28%, H 6.61%, N 19.15%.

3,5-Dimethoxy-N-((2-(piperazin-1-yl)benzotriazole-3-yl)methyl)aniline, (5L)

Yield: 71%, Melting Point (m.p.): 203–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H, NH), 9.35 (s, 1H, benzotriazole H), 7.92–7.93 (d, 1H, aromatic C-H), 7.66–7.63 (t, 1H, aromatic C-H), 7.49–7.85 (t, 2H, aromatic C-H), 4.55 (s, 2H, CH_2), 3.59 (s, 6H, OCH_3).^{13}C NMR (100 MHz, DMSO): δ 42.10 (CH_2), 45.48, 51.20, 55.18 (OCH_3), 105.26, 109.42, 121.36. IR (KBr): ν 3376 (NH), 1647 (C=N), 1544, 1268, 1039 cm^{-1}.MS (ESI): m/z = 379.4 (M+H)$^+$. Elemental Analysis: Calculated for $C_{20}H_{24}N_5O_2$ (379.20): C 63.33%, H 6.38%, N 18.43%; Found: C 63.31%, H 6.36%, N 18.41%.

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