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Design, Synthesis, and Biological Evaluation of 1,2,3-Triazole-Based Carbamate Derivatives as Potential Anti-Inflammatory and Antimicrobial Agents

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Abstract

A novel series of substituted phenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl) methyl carbamate derivatives (6a–6i) were synthesized via a multistep synthetic route starting from aryl azides and terminal alkynes using copper-catalyzed azide-alkyne cycloaddition (CuAAC). The synthesized compounds were characterized by their physicochemical properties, including melting point, yield, and molecular weight. Anti-inflammatory activity was evaluated using the protein denaturation method, where compounds 6b, 6c, 6f, and 6h exhibited significant inhibition, with 6c showing activity comparable to standard diclofenac sodium. Antimicrobial activity was assessed using the agar well diffusion method against *B. cereus, E. coli, P. aeruginosa, S. aureus,* and *E. faecalis*. Compounds 6b, 6d, 6e, 6h, and 6i demonstrated selective antibacterial activity, with 6b displaying broad-spectrum inhibition. The results suggest that the 1,2,3-triazole-carbamate hybrids, particularly 6b and 6c, possess promising anti-inflammatory and antimicrobial potential and warrant further pharmacological exploration.

Keywords: 1,2,3-triazole, Antimicrobial, anti-inflammatory, IR, NMR, and Mass, etc.

1. Introduction

1,2,3-Triazoles, five-membered nitrogen-containing heterocyclic systems, play a crucial role in both organic and medicinal chemistry, primarily due to their synthesis through click chemistry. This method has a wide range of applications, spanning agriculture, industry, pharmaceuticals, and molecular design. Additionally, the compounds produced typically achieve high yields and are straightforward to isolate[1]. A literature survey revealed that triazole derivatives, an important group of heterocyclic compounds, have been extensively studied in recent years[2].1,2,3-Triazole and its derivatives have gained significant attention over the past few decades due to their valuable chemotherapeutic properties[3]. 1,2,3-triazole are found to be potent anti-inflammatory[4], antiplasmodial[5], antiparasitic[6], Antitubercular[7], antimalarial[8], anticonvulsant[9], analgesic[10] , antimicrobial[11], antineoplastic[12], antiviral [13], anticancer [14] activity and anti-proliferative [15].Extensive research has demonstrated that 1,2,3-triazole derivatives exhibit a broad spectrum of bioactivities including anti-inflammatory[16], antimicrobial[17], antiviral, anticancer, antiparasitic, antimalarial, and anticonvulsant effects. Their ability to interact with various biological targets, good metabolic stability, and favourable pharmacokinetic properties make them attractive candidates for drug development.

In light of these findings, our research focuses on the synthesis of a new series of substituted phenyl (2,3-dihydro-3-aryl-1,2,3-triazol-1-yl)methyl carbamate derivatives (6a–6i). These compounds were synthesized through a multi-step synthetic route involving click chemistry, esterification, hydrazide formation, diazotization, and carbamate derivatization using substituted phenols. The synthesized compounds were characterized by their physicochemical properties and evaluated for anti-inflammatory activity via protein denaturation assay and antimicrobial activity through zone of inhibition studies against selected bacterial strains. This study aims to explore the potential of triazole-carbamate hybrids as promising leads in the development of anti-inflammatory and antimicrobial agents.

2. Chemistry:

Synthesis of substituted azido benzene 1 was prepared as per available literature in good yield

. The azido benzene when react with acetylene in the presence of copper iodide and base in water as solvent for 24hr at room temperature it gives phenyl-1H-1,2,3- triazole derivatives 2. Next this triazole derivative react with ethyl 2-chloroacetate in presence of sodium ethoxide, it yields phenyl-1,2,3-triazole-1-yl-acetate derivatives 3. The reaction of compound 3 with hydrazine hydrate gives phenyl-1,2,3-triazole-1-yl-acetohydrazide derivatives 4 in good yield. The phenyl-1,2,3-triazole-1-yl-acetohydrazide 4 reacts with nitrous acid (HNO2) to form the corresponding acyl azide-containing triazole derivative 5. This acyl azide derivative under reflux condition in toluene react with substituted phenols to give methylcarbamate derivatives 6 in good yield.

3. Materials and Methods:

3.1. General Information: The common reagents and substrates were obtained from commercial suppliers and used without further purification. 1H NMR was measured on a Bruker Avance-300, Varian Unity-400 MHz, and Avance New-500 MHz, and 13C NMR was measured with a Varian Unity-400 MHz (100 MHz) and with Avance New-500 MHz (125 MHz), as specified and referred as the internal standard to TMS (tetramethylsilane). High-resolution mass spectra (HRMS) were performed on a high-resolution magnetic sector mass spectrometer. Melting points were recorded on a Buchi 535 melting point apparatus and are uncorrected. TLC analysis was performed on Merck silica gel 60 F254 plates. Column chromatography was performed on silica gel (100−200 mesh) from Merck.

3.2. Synthesis of p-substituted 1-phenyl-4H-1,2,3-triazol-1-ium (2):

Azide **(1)** (1.0 mmol), Et_3N (0.2 mmol), water (1 mL), and CuI (0.1 mmol) were introduced one after the other to a flask fitted with a stirring bar. Acetylene gas was added from a balloon after the atmosphere was removed using a vacuum pump, and the mixture was agitated for 24 hours at room temperature. Following the completion of the reaction, the mixture was rinsed with brine (10 mL) and ethyl acetate (25 mL) was added to dissolve the result. After being dried over anhydrous Na_2SO_4, the organic layer was filtered. After the solvent was removed under reduced pressure, the residue was purified by flash chromatography to give p-substituted 1-phenyl-4H-1,2,3-triazol-1-ium **(2)** product.

3.3. Synthesis of ethyl [3-(4-substituted phenyl)-2,3-dihydro-1H-1,2,3-triazol-1- yl]acetate (3):

To a slurry of p-substituted 1-phenyl-4H-1,2,3-triazol-1-ium **(2)** (50 mg,0.116 mmol) in sodium ethoxide (50 mL) was added chloromethyl propanoate (30 mg, 0.535 mmol) followed by water (0.5 mL) and the mass was reflux for 18 hrs. Subsequently the reaction mixture was poured into cold water, acidified with 1 N HCl to a pH of 3–4; and the precipitated solid was filtered and triturated with ether followed by n–hexane to give a off-white solid product **(3).**

3.4.2-[3-(4-substituted phenyl)-2,3-dihydro-1H-1,2,3-triazol-1-yl] aceto hydrazide 4) :

A mixture of the appropriate ethyl [3-(4-substituted phenyl)-2,3-dihydro-1H-1,2,3-triazol-1-yl] acetate **(3) (**0.1mol), hydrazine hydrate (0.25mol), and 30ml of 95% ethanol was heated under reflux for 6h. The solvent was removed on a rotary vacuum evaporator and the residue was poured into 200ml of cold water. The solid that formed was collected, washed with ice-cold water, and recrystallized from ethanol.

3.5.1-azido-2-(2,3-dihydro-3-p-tolyl-1,2,3-triazol-1-yl) ethenone (5):

A 2-[3-(4-substituted phenyl)-2,3-dihydro-1H-1,2,3-triazol-1-yl] acetohydrazide **(4)** (0.1mol) was suspended in a mixture of dioxane (30ml) and acetic acid(30ml) and cooled to 0° C in freezing mixture. An ice-cold solution of sodium nitrite (2.12g) in water (10ml) was introduced into it in small portions with vigorous stirring. The temp of the reaction mixture was maintained below 2°C. After the complete addition, the reaction mixture was allowed to stay at room temp for 30min and the pale-yellow solid that separated was collected, washed with cold water.

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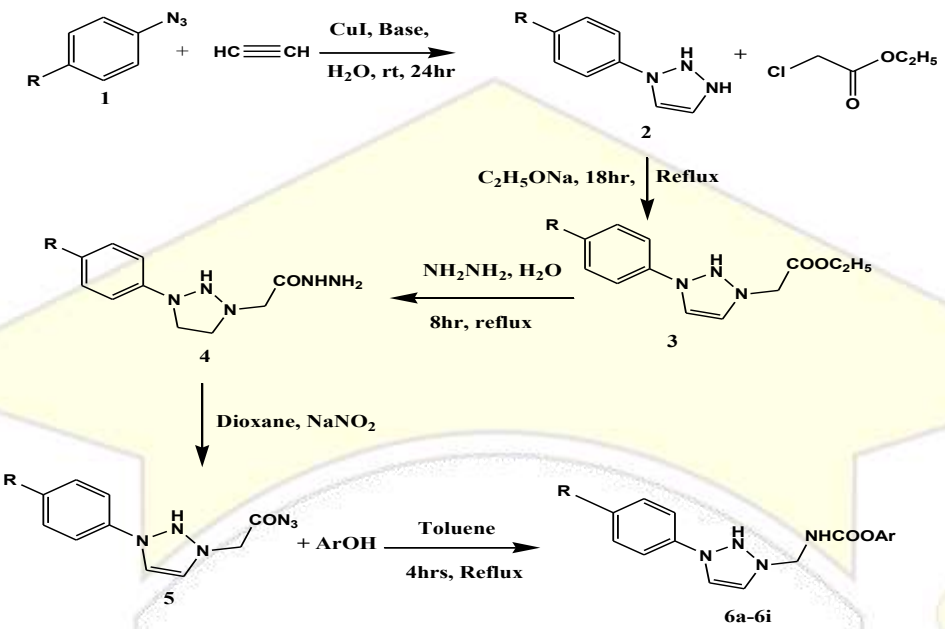
3.6. Synthesis of substituted phenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl) methyl carbamate derivatives (6a-6i):

A suspension of 1-azido-2-(2,3-dihydro-3-p-tolyl-1,2,3-triazol-1-yl) ethenone **(5)** react with substituted phenols in a toluene as a solvent was refluxed on a steam bath for 4hr. The progress of reaction was monitor by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure and then diluted with water. The product **(6)** that separated was collected and crystallized from benzene-pet ether. (Scheme 1)

Scheme 1



Scheme 1: Synthesis of substituted triazole derivatives

3.7.Evaluation of Anti-inflammatory activity By Anti-denaturation assay method

The denaturation of protein as one of the causes as inflammation is well documented. Production of auto-antigen in certain rheumatic diseases may be due to in vivo denaturation of proteins. A number of anti inflammatory drugs are known to inhibit the denaturation of protein. Based on thatwe have employed protein denaturation as in vitro screening model for anti-inflammatory compounds.(Sangita C et al 2012). Procedure The experiment was carried out with minor modification. The standard drug and extract was dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test Solution (4ml) containing different concentrations of drugwas mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 37°C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in waterbath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition ofdenaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition of denaturation was calculated by using followingformula.

$$\text{Percentage of inhibition} = \frac{(A\ \text{Test} - A\ \text{Control})}{(A\ \text{Test})} \times 100$$

At = O.D. of test solutionAc = O.D. of control

3.8. Evaluation of Antibacterial Activity

The antibacterial activity of the synthesized compounds (6a–6i) was evaluated using the **agar well diffusion method**. Nutrient agar plates were prepared and seeded with standardized inocula (approximately 1×10^6 CFU/mL) of five bacterial strains: *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*.Wells of 6

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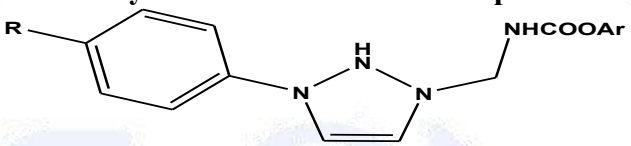
mm diameter were punched in the agar and filled with 100 µL of each test compound solution (concentration: 1 mg/mL in DMSO). Plates were incubated at 37 ± 1°C for 24 hours. The **zone of inhibition** was measured in millimeters (mm) and recorded as mean ± SD from triplicate experiments. **Gentamycin** (10 µg/mL) served as the **positive control**, and **DMSO** as the **negative control**. The absence of inhibition around the wells was considered as **no activity**.

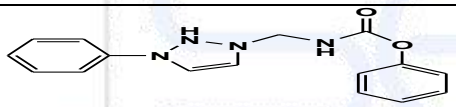
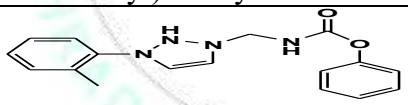
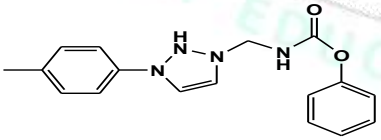
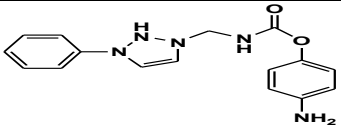
4. Results and Discussion

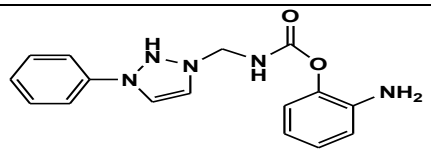
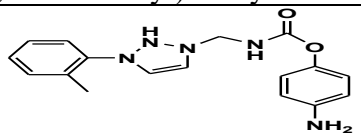
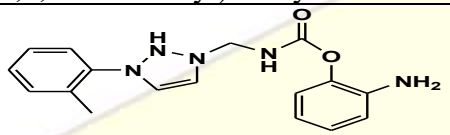
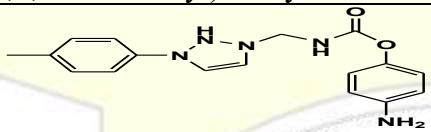
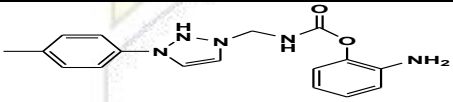
4.1. Physicochemical data of Compound 6a-6i

All synthesized compounds (6a–6i) are white crystalline solids, indicating purity and consistent crystallinity across the series. The molecular weights (M.W.) ranged from 296 to 325 g/mol, with minor variations attributed to the presence of different substituents such as amino or methyl groups on the phenyl rings. The percent yields (Y%) varied significantly, from 43% (6a) to 76% (6d). Compounds with electron-donating amino groups, particularly at the para position (e.g., 6d), tended to give higher yields, possibly due to better reactivity during cyclization or carbamate formation.The melting points (M.P.) of the compounds ranged between 135–166°C. A general trend of increased melting point is observed with more substituted or bulkier molecules, particularly compounds containing amino and methyl groups, such as 6g (165°C) and 6h (166°C). This may be due to enhanced intermolecular hydrogen bonding or steric packing in the solid state.Notably, compounds 6f–6i, which possess both amino and methyl substitutions on the aromatic ring, show relatively higher melting points, suggesting greater thermal stability compared to unsubstituted analogs.Overall, the data reflect successful synthesis of a structurally similar series of 1,2,3-triazole derivatives with consistent physicochemical profiles and moderate to good yields, supporting their suitability for further biological evaluation.

Table 2: Physicochemical data of Compound 6a-6i



Comp.	Structure and Chemical name	M.F.	M.W.	Y%	M.P.	Colour
6a	 phenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl) methyl carbamate	$C_{16}H_{16}N_4O_2$	296	43	137	White
6b	 phenyl (2,3-dihydro-3-o-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{18}N_4O_2$	310	47	135	White
6c	 phenyl (2,3-dihydro-3-p-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{18}N_4O_2$	310	59	151	White
6d	 4-aminophenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{16}H_{17}N_5O_2$	311	76	156	White

6e	 2-aminophenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{16}H_{17}N_5O_2$	311	52	158	White
6f	 4-aminophenyl (2,3-dihydro-3-o-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{19}N_5O_2$	325	57	161	White
6g	 2-aminophenyl (2,3-dihydro-3-o-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{19}N_5O_2$	325	56	165	White
6h	 4-aminophenyl (2,3-dihydro-3-p-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{19}N_5O_2$	325	52	166	White
6i	 2-aminophenyl (2,3-dihydro-3-p-tolyl-1,2,3-triazol-1-yl)methylcarbamate	$C_{17}H_{19}N_5O_2$	325	69	163	White

4.2. Spectral data of compound 6a-6i

The synthesized compounds 6a–6i were characterized by IR, mass spectrometry (MS), and ^{1}H NMR spectroscopy, confirming their expected structures as substituted phenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl) methyl carbamates.

All compounds showed characteristic absorption bands confirming the presence of key functional groups. The broad band at ~3485 cm^{-1} corresponds to the -NH stretching vibration of the carbamate group. The bands at 2929 cm^{-1} and 1978 cm^{-1} are attributed to aliphatic -CH stretching vibrations. The sharp peak at 1747 cm^{-1} confirms the carbamate carbonyl (-C=O) group. Additionally, the band near 1649 cm^{-1} indicates N-H bending, while aromatic C=C stretching appears around 1421 cm^{-1}, consistent with the phenyl substitutions on the triazole ring. The MS spectra exhibited prominent molecular ion peaks $[M+H]^+$ around m/z 325 with isotopic peaks at 326, 327, and 328, supporting the molecular weight of the synthesized compounds and suggesting successful substitution patterns in the series. The base peak at m/z 325 confirms the expected molecular formula and purity.

The ^{1}H NMR data show characteristic signals for the triazole and substituted phenyl rings. A singlet at δ 2.21 ppm (3H) corresponds to the methyl substituent in tolyl derivatives. The singlet at δ 4.48 ppm (2H) corresponds to the methylene (-CH_2-) protons adjacent to the carbamate nitrogen. Aromatic and triazole protons appear in the region δ 6.09–7.16 ppm with complex splitting patterns (doublets and double doublets), consistent with substituted phenyl rings and triazole protons. The splitting constants (J = 7.5–8.3 Hz) are typical for aromatic protons in ortho and meta positions. Overall, the spectral data collectively support the successful synthesis of the target carbamate derivatives (6a–6i), confirming the expected substitution on the triazole

and phenyl rings. The consistency across the series indicates structural integrity and high purity of the compounds, correlating well with the observed physicochemical properties.(Table 2)

Table 2: Spectral data of compound 6f

IR Spectrum Data	3485 (-NH Str), 2929 (-CH=H Str), 1978 (-CH Str), 1747 (-C=O Str), 1649 (-NH B), 1421 (Ar C=C Str)
MS Data m/z (%)	[M+H]+ 325 (100%), 326 (20.6%), 327 (2.4%), 328 (0.2%)
^{1}H NMR Data	"^{1}H NMR: δ 2.21 (3H, s), 4.48 (2H, s), 6.09-6.27 (2H, 6.15 (d, *J* = 7.9 Hz), 6.21 (d, *J* = 7.9 Hz)), 6.87-7.16 (8H, 6.94 (ddd, *J* = 8.1, 1.1, 0.5 Hz), 6.96 (ddd, *J* = 8.3, 7.5, 1.1 Hz), 6.97 (ddd, *J* = 8.1, 7.5, 1.6 Hz), 7.00 (ddd, *J* = 8.2, 1.4, 0.5 Hz), 7.02 (ddd, *J* = 8.3, 1.6, 0.5 Hz), 7.10 (ddd, *J* = 8.2, 1.5, 0.5 Hz))"

4.3. Evaluation of anti-inflammatory activity

The inhibition of protein denaturation is a widely accepted method for evaluating the anti-inflammatory potential of compounds, as denatured proteins can trigger inflammatory responses. In this study, synthesized compounds (6a–6i) were assessed for their ability to prevent heat-induced denaturation of albumin at concentrations ranging from 100 to 500 µg/mL, with **diclofenac sodium** serving as a standard reference. Among the tested compounds, **6c and 6b** demonstrated the most potent activity, showing concentration-dependent inhibition, with **6c reaching 79.24% inhibition** at 500 µg/mL, closely approaching **diclofenac (69.55%).** Compound **6f** also exhibited significant inhibition (67.45%), indicating strong anti-inflammatory potential. Compounds **6g and 6e**, on the other hand, showed comparatively lower activity, with **6g** maintaining nearly constant and minimal inhibition across all concentrations, suggesting weak or negligible interaction with denatured protein structures. Interestingly, some compounds such as **6a, 6h, and 6i** also displayed moderate but consistent increases in activity with rising concentrations, indicating a dose-responsive anti-inflammatory behaviour.

Overall, the results suggest that certain compounds, particularly **6c, 6b, and 6f**, have promising protein stabilization properties, potentially due to functional groups capable of hydrogen bonding or hydrophobic interactions with albumin, thereby preventing denaturation. These findings highlight their potential as anti-inflammatory agents.(Table 3)

Table 3: Anti-inflammatory activity of compound 6a-6i

Compound Code	Concentration in µg/ml					
	100	**200**	**300**	**400**	**500**	**100**
6a	8.08	21.87	31.53	35.02	38.53	41.04
6b	19.12	21.31	37.06	42.32	64.28	78.90
6c	21.01	33.43	45.34	57.56	65.73	79.24
6d	19.21	23.66	35.21	46.94	49.26	51.67
6e	16.41	17.88	37.45	39.06	42.34	44.69
6f	18.45	33.39	45.65	49.13	55.39	67.45
6g	25.43	22.21	22.46	22.93	22.48	22.50
6h	29.89	29.44	32.68	34.26	45.25	56.70
6i	16.09	23.07	33.21	36.95	39.54	43.60
Diclofenac Sodium	**19.51**	**27.01**	**45.75**	**47.73**	**65.31**	**69.55**

4.4. Evaluation of antibacterial activity

The antimicrobial efficacy of the synthesized compounds (6a–6i) was evaluated by measuring the **zone of inhibition** against a panel of Gram-positive and Gram-negative bacteria: *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus*

faecalis. **Gentamycin** served as the standard antibiotic control, showing strong and broad-spectrum activity with inhibition zones ranging from 17–19 mm. Among the tested compounds, **6b, 6d, 6e, 6h**, and **6i** exhibited selective antimicrobial activity, while **6a, 6c, 6f**, and **6g** showed no activity against any strain tested.

- **Compound 6b** displayed the broadest spectrum, notably inhibiting *B. cereus* (11 mm), *E. coli* (9 mm), *S. aureus* (10 mm), and *E. faecalis* (14 mm), albeit with mild activity.
- **Compound 6d** showed good activity against *S. aureus* (18 mm), moderate inhibition of *P. aeruginosa* (8 mm), and slight activity against *E. faecalis* (2 mm).
- **Compound 6e** was active against *P. aeruginosa*, *S. aureus*, and *E. faecalis*, with inhibition zones of 10 mm, 16 mm, and 10 mm, respectively.
- **Compounds 6h** and **6i** showed selective activity against *S. aureus*, with inhibition zones of 14 mm and 17 mm, respectively.

Overall, the data suggest **compound 6b** possesses mild broad-spectrum activity, while **6d, 6e, 6h, and 6i** exhibit **strain-specific antimicrobial effects**, particularly against *S. aureus*. These results indicate potential for structural optimization to enhance potency and spectrum. (Table 4)

Table 4: Zone of Inhibition of compound 6a-6i

Compound Code	B. cereus	E. coli	P. aeroginosa	S. aureus	E. faecalis
6a	No activity	No activity	No activity	No activity	No activity
6b	11±05	09±05	01±05	10±05	14±05
6c	No activity	No activity	No activity	No activity	No activity
6d	No activity	No activity	08±05	**18±05**	02±05
6e	No activity	No activity	10±05	**16±05**	10±05
6f	No activity	No activity	No activity	No activity	No activity
6g	No activity	No activity	No activity	No activity	No activity
6h	No activity	No activity	No activity	**14±05**	No activity
6i	No activity	No activity	No activity	**17±05**	No activity
Gentamycin	**17±05**	**18±05**	**18±05**	**19±05**	**18±05**

CONCLUSION

In this study, a series of novel substituted phenyl (2,3-dihydro-3-phenyl-1,2,3-triazol-1-yl) methyl carbamate derivatives (6a–6i) were successfully synthesized via a multi-step reaction pathway starting from aryl azides and progressing through the formation of triazolium salts, esters, hydrazides, and azido derivatives. The final carbamate derivatives were obtained by the reaction of intermediate azido compounds with various substituted phenols under reflux in toluene. The synthetic methodology was efficient and reproducible, with moderate to high yields (43–76%) and well-defined melting points (135–166°C), confirming the purity and stability of the final compounds. Physicochemical data revealed that the presence of electron-donating groups, especially amino or methyl substitutions on the aromatic rings, influenced the yield and melting point, with para-substituted analogues generally exhibiting better thermal stability and higher synthetic efficiency. The synthesized compounds were evaluated for anti-inflammatory potential using the protein denaturation assay. Compounds 6b, 6c, 6f, and 6h demonstrated significant inhibitory activity, with compound 6c exhibiting a comparable effect

to diclofenac sodium, indicating promising anti-inflammatory potential linked to the triazole-carbamate framework. In the antimicrobial assay, zone of inhibition studies showed that compound 6b displayed broad-spectrum antibacterial activity against B. cereus, E. coli, S. aureus, and E. faecalis, while compounds 6d, 6e, 6h, and 6i exhibited selective inhibition against P. aeruginosa and S. aureus. The observed antibacterial activity suggests that structural features such as electron-donating amino and methyl groups enhance microbial sensitivity, especially against Gram-positive organisms. Overall, the synthesized 1,2,3-triazole-carbamate hybrids demonstrated favorable physicochemical profiles, anti-inflammatory efficacy, and moderate to selective antimicrobial activity, making them promising candidates for further pharmacological exploration and potential lead compounds in the development of new anti-infective and anti-inflammatory agents.

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