Received: 23 February 2020 | Revised: 31 March 2020 | Accepted: 20 April 2020

DOI: 10.1002/jhet.4020

WILEY

ARTICLE

Synthesis, biological evaluation, and docking study of a series of 1,4-disubstituted 1,2,3-triazole derivatives with an indole-triazole-peptide conjugate

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Abstract

A series of new compounds containing an indole-triazole-peptide conjugate were designed as potential agents possessing the dual anti-bacterial and anti-cancer activities. Accordingly, 20 compounds were prepared via a multi-step synthesis involving the copper-catalyzed azide-alkyne cycloaddition (CuAAC) as a key step in moderate to high yield. All the synthesized compounds were purified by chromatographic techniques and characterized by IR, ^{1}H and ^{13}C NMR and mass spectral data. The synthesized derivatives were screened for their antimicrobial activities against one gram-positive (*Staphylococcus aureus*) and three gram-negative (*Escherichia coli*, *Klebsiella pneumonia*, and *Proteus vulgaris*) bacteria using an agar-well diffusion method. Most of the compounds showed moderate to reasonable antibacterial activities especially the compound **9e** that showed good activities against all the strains. The potential of DNA gyrase inhibitory activity of this compound was assessed by using molecular docking studies in silico carried out using Autodock Vina software. The low ΔG_{bind} value (−9.4 Kcal/mol) of compound **9e** suggested its good interactions with the target protein in silico. The cytotoxic activities of some of the compounds synthesized were evaluated via a MTT assay using the human lung cancer cell line A549. Several compounds showed promising activities among which compound **9b**, **9k,** and **9e** showed low IC_{50} values.

1 | INTRODUCTION

Due to the multidrug resistance of microorganisms, discovery of novel or new antibacterial agents is necessary. We designed new compounds having peptide triazole framework which can show both antibacterial and anticancer activity. This class of compounds possessing dual activities is expected to have promising medicinal importance due to their ability to suppress bacterial infection in cancer patients.[1] Indeed, the dual antibacterial and anticancer activities can benefit in various ways as for example by (a) controlling growth of cancer related bacterial infections, (b) protecting patients from the infection due to downplay of immune system, and (c) decreasing side effects of presently used medicine against cancer.[2] At present combination of antibiotics and anticancer drugs are used for the treatment of cancer patients. Thus compounds having dual activity[3] are beneficial. Herein we report the synthesis and biological evaluation of 20 new compounds for this purpose.

Derivatives of Ibuprofen, a well-known NSAID, possess a range of biological properties including antimicrobial,

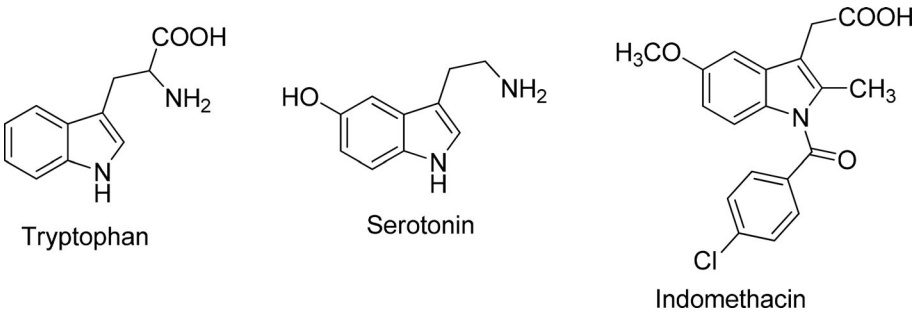


FIGURE 1 Examples of known molecules having the indole ring

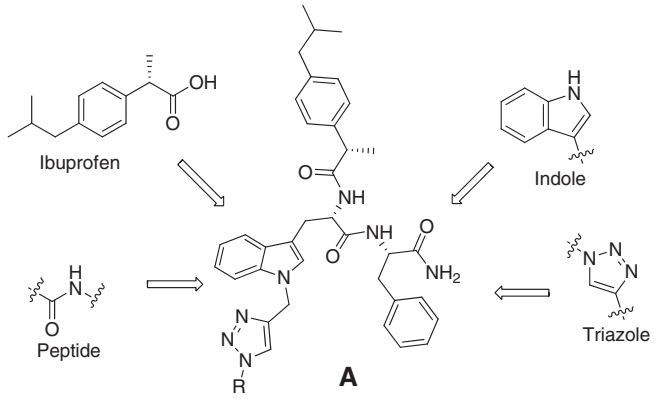


FIGURE 2 Design of new template **A** for the generation of library of compounds possessing the potential dual activities

antifungal, antiviral, and antitumor activities.[4–10] The 1,2,3-triazole framework is an interesting heterocyclic pharmacophore that attracted attention due to their fascinating biological activities.[11–21] The indole ring on the other hand is another attractive and privileged heterocyclic scaffold present in many natural products such as alkaloids, peptides, plant growth hormone, heteroauxin, the essential amino acid tryptophan, neurotransmitter serotonin or 5HT, and various synthetic compounds (Figure 1).[22–27]

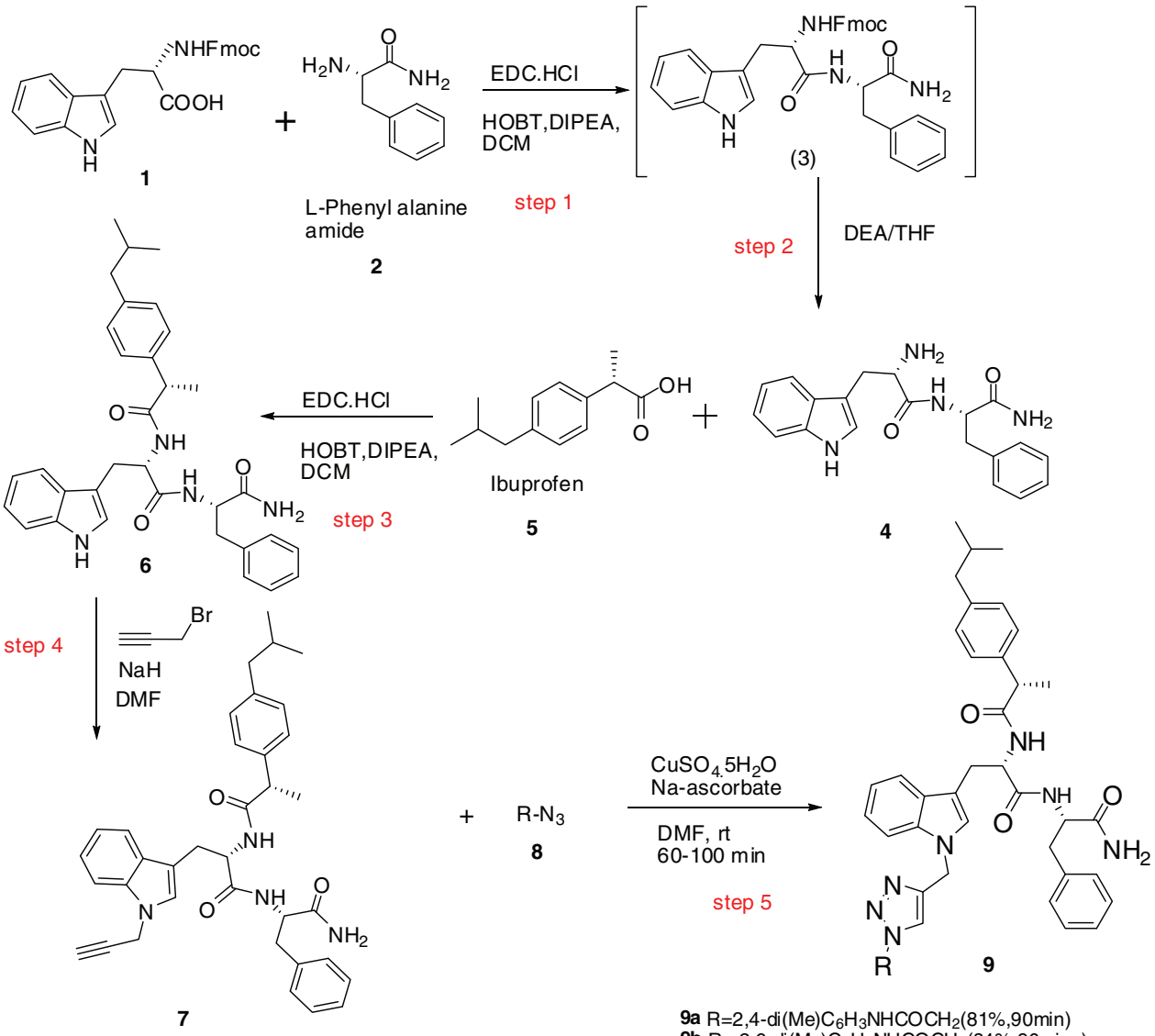
Anderson[28] has synthesized and demonstrated that 5-methyltryptophan can inhibit the growth of *Escherichia coli*. After development of genomic and proteomic technologies, it has been observed that smaller chain peptides can represent promising alternatives to conventional antibiotics and in other therapeutic field.[29–31] Taking into account of such positive aspects and in continuation of our research in the field of synthesis of small library of biologically active hybrid molecules we designed a new template **A** (Figure 2) which contains tripeptide derived from NSAID ibuprofen, indole and phenyl alanine amide with an additional 1,2,3-triazole moiety. One of our preliminary objectives was to establish a rapid synthesis of compounds based on **A** under mild conditions. So herein we represent preliminary results of our study.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Various methods are known for the synthesis of triazole and related derivatives including 1,2,3-triazoles.[32–41] Among these methods the use of CuAAC reaction has become a popular and well-known strategy for the construction of 1,2,3-triazole ring. The methodology involved the use of azides and appropriate alkynes as key starting materials. We adopted this strategy for the synthesis of our target compounds. Accordingly, the required alkyne **7** and azide **8** were prepared as shown in Scheme 1.

Initially, the S-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl) amino)-3-(1*H*-indole-3-yl)propanoic acid (**1**) and (2S)-2-amino-3-phenylpropanamide (**2**) were reacted in the presence of coupling reagents, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and hydroxyl benzotriazole, *N*,*N*-diisopropylethylamine in dichloromethane (DCM). The corresponding product, that is, the peptide **3** was obtained as a white solid in 80% yield. The compound **3** on deprotection of the FMOC group in the presence of diethylamine in tetrahydrofuran afforded the desired amine **4** that was isolated as a white solid in 78% yield. The amine **4** was then allowed to couple with the ibuprofen **5** in the presence of EDC.HCl, HOBT, and DIPEA in DCM to give product **6** as a white solid in 86% yield. Finally, the regioselective *N*-propargylation of the indole ring of compound **6** was performed using propargyl bromide in the presence of sodium hydride in DMF to give the desired terminal alkyne **7** as a white solid in 88% yield. After successful synthesis of the terminal alkyne **7**, the organic azides **8** were prepared from the corresponding primary amines following two different routes reported earlier.[42] The terminal alkyne **7** was then allowed to couple with a series of azides **8** in the presence of $CuSO_4.5H_2O$ and sodium ascorbate at room temperature using DMF as a solvent to afford the desired target molecules **9** in 75%-91% yield. All the synthesized target compounds were purified by column chromatographic techniques and characterized by IR, ^1H and ^{13}C NMR and mass spectral data.



8a R=2,4-di(Me)$C_6H_3NHCOCH_2$
8b R= 2,6-di(Me)$C_6H_3NHCOCH_2$
8c R= 2-$NO_2C_6H_4NHCOCH_2$
8d R= 3-$NO_2C_6H_4NHCOCH_2$
8e R= 2-$ClC_6H_4NHCOCH_2$
8f R= 3-$ClC_6H_4NHCOCH_2$
8g R= 4-$ClC_6H_4NHCOCH_2$
8h R= 2-$CH_3C_6H_4NHCOCH_2$
8i R=$C_6H_5NHCOCH_2$
8j R=C_6H_5
8k R= 2-$NO_2C_6H_4$
8l R= 3-$NO_2C_6H_4$
8m R= 4MeO-2-$NO_2C_6H_3NHCOCH_2$
8n R= 4MeO-2-$NO_2C_6H_4$
8o R= 3-$COOHC_6H_4$
8p R= 4-$COOHC_6H_4$
8q R= 4-$COOCH_3C_6H_4NHCOCH_2$
8r R= $C_6H_5CH_2$
8s R=C_7H_{15}
8t R=4-$NO_2C_6H_4$

9a R=2,4-di(Me)$C_6H_3NHCOCH_2$(81%,90min)
9b R= 2,6-di(Me)$C_6H_3NHCOCH_2$(84%,90mins)
9c R= 2-$NO_2C_6H_4NHCOCH_2$(84%,80mins)
9d R= 3-$NO_2C_6H_4NHCOCH_2$(90%,90mins)
9e R= 2-$ClC_6H_4NHCOCH_2$(78%,90mins)
9f R= 3-$ClC_6H_4NHCOCH_2$(87%,90mins)
9g R= 4-$ClC_6H_4NHCOCH_2$(83%,80mins)
9h R= 2-$CH_3C_6H_4NHCOCH_2$(84%,90mins)
9i R=$C_6H_5NHCOCH_2$(90%,90mins)
9j R=C_6H_5(90%,100mins)
9k R= 2-$NO_2C_6H_4$(79%,90mins)
9l R= 3-$NO_2C_6H_4$(83%,90mins)
9m R= 4MeO-2-$NO_2C_6H_3NHCOCH_2$(86%,100mins)
9n R= 4MeO-2-$NO_2C_6H_4$(82%,80mins)
9o R= 3-$COOHC_6H_4$(88%,80mins)
9p R= 4-$COOHC_6H_4$(79%,100mins)
9q R= 4-$COOCH_3C_6H_4NHCOCH_2$(75%,90mins)
9r R= $C_6H_5CH_2$(89%,85mins)
9s R=C_7H_{15} (80%,90mins)
9t R=4-$NO_2C_6H_4$(85%,80mins)

SCHEME 1 Synthesis of peptide based novel compounds **9**

The partial representation of ^1H and ^{13}C NMR spectral data of compound **9a** are presented in Figure 3 where the key characteristic signals are depicted in red and green color. This compound possesses three -NH- and one —NH_2 groups that appeared at 3386, 3281, and 3212 cm^{-1} in the corresponding IR spectra. Additionally, the four amide

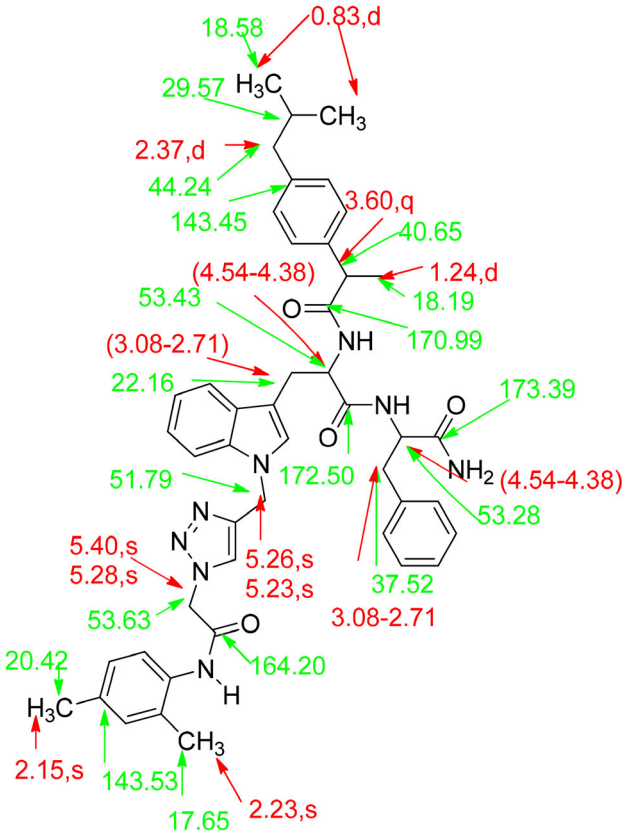


FIGURE 3 Partial representation of ^{1}H (red) and ^{13}C NMR (green) spectral data of compound **9a**

carbonyl groups appeared at 1670, 1669, 1645, and 1640 cm^{-1} in the IR spectra.

2.2 | Biology

2.2.1 | Antibacterial activity

All the synthesized compounds were screened for their antimicrobial activities against one gram-positive (*Staphylococcus aureus*) and three gram-negative (*E. coli*, *Klebsiella pneumonia*, and *Proteus vulgaris*) bacteria using an agar-well diffusion method and amoxicillin was used as a reference compound in this assay. The results, that is, the Zone of inhibition (mm) and MIC values (μg/mL) obtained are presented in Table 1. Most of the compounds showed moderate to reasonable activities against all strains. Indeed, the compound **9e** was identified as the most promising among these compounds as it showed good activity against both Gram-positive and Gram-negative bacterial species. Indeed, the compound **9e** showed significant inhibitory activity against *E. coli* with MIC of 25 μg/mL and was comparable to the reference compound Amoxycillin. Among other compounds **9a**, **9c,** and **9n** also showed activities against Gram-positive and Gram-negative bacteria. Particularly, the MIC of **9a** and **9n** was found to be 25 μg/mL against *E. coli* and *S. aureus,* respectively. Additionally, compound **9b** and **9k** also showed good activity against gram-negative strain. Nevertheless, the structure activity relationship (SAR) summary of anti-bacterial activities of compound **9** is presented in Figure 4. It is evident that the activity was varied with the change of position and nature of "R" group attached to the benzene ring connected to the 1,2,3-triazole moiety via a —$NHCOCH_2$— linker. For example, good activity was observed when the R group presented 2,4-dimethyl or *ortho*-nitro, *ortho*-chloro, or *para*-carboxylic acid moiety whereas activity was reduced when R group was at meta-position representing a nitro or chloro or carboxylic acid.

2.2.2 | Anti-cancer activity

Having evaluated the antibacterial activities of synthesized compounds we then tested the anti-cancer activities of these compounds in vitro against the human cancer cell line, that is, A549 (lung adenocarcinoma epithelial cell line) using a colorimetric MTT assay and doxorubicin as the standard drug. Compounds with promising (>50%) activities were taken for determination of IC_{50} values. Results of the active compounds are presented in Table 2. The compound **9b** and **9k** showed good activity whereas **9c**, **9e**, **9h**, **9m**, **9o,** and **9j** showed moderate activity. The SAR summary of anti-cancer activities of compound **9** against A549 cell line is presented in Figure 5.

A graphical representation of concentration dependent cytotoxic activity of some selected compounds along with that of reference compound doxorubicin is shown in Figure 6. It is evident that all these compounds showed uniform and consistent increase of cytotoxicity with the increase of their concentrations.

Overall, among all compounds synthesized the compound **9e** was found to be the most promising one in terms of anti-cancer as well as anti-bacterial activities.

2.3 | Molecular docking studies analysis

Next, the potential of DNA gyrase inhibitory activity of compound **9e** was assessed by using molecular docking studies in silico carried out using Autodock Vina software. Indeed, the binding affinity **9e** molecule toward DNA-gyrase cleavage complex of *S. aureus* organism's DNA binding site surrounded by the protein residues were analyzed using the molecular docking studies. The binding affinity of the molecule showed strong interactions with the DNA active site and results are shown in Table 3.

TABLE 1 Antibacterial activities of compound **9**

S. no.	Compound	Zone of inhibition[a] (mm) and MIC[b] (μg/mL)			
		***S. aureus* gram (+ve)**	***E. coli* gram (−ve)**	***K. pneumoniae* gram (−ve)**	***P. vulgaris* gram −ve)**
1	**9a**	12 ± 0.3 (>200)	17 ± 0.57 (25)	13 ± 0.4 (>200)	13 ± 0.5 (150)
2	**9b**	14 ± 0.57 (>200)	15 ± 1.0 (>200)	15 ± 0.57 (50)	13 ± 0.57 (150)
3	**9c**	14 ± 1.52 (>200)	16 ± 0.57 (>200)	15 ± 1.0 (50)	12 ± 0.57 (150)
4	**9d**	11 ± 0.5 (>200)	12 ± 0.4 (>200)	13 ± 0.57 (150)	11 ± 0.3 (>200)
5	**9e**	16 ± 1.0 (200)	16 ± 0.57 (25)	14 ± 0.57 (100)	14 ± 1.0 (100)
6	**9f**	11 ± 0.5 (>200)	13 ± 0.57 (>200)	14 ± 1.0 (100)	14 ± 0.3 (100)
7	**9g**	12 ± 0.4 (150)	12 ± 0.5 (>200)	15 ± 1.0 (100)	15 ± 0.5 (50)
8	**9h**	14 ± 0.57 (50)	14 ± 1.0 (50)	13 ± 0.4 (>200)	12 ± 0.5 (150)
9	**9i**	13 ± 0.57 (100)	15 ± 1.0 (50)	13 ± 0.57 (>200)	13 ± 0.57 (150)
10	**9j**	13 ± 1.0 (100)	14 ± 0.57 (50)	13 ± 0.4 (150)	13 ± 0.3 (150)
11	**9k**	12 ± 0.4 (>200)	16 ± 1.52 (50)	12 ± 0.4 (>200)	12 ± 0.57 (150)
12	**9l**	11 ± 0.5 (>200)	10 ± 0.4 (>200)	13 ± 1.0 (150)	11 ± 0.57 (>200)
13	**9m**	12 ± 0.57 (150)	15 ± 0.57 (50)	13 ± 1.0 (150)	10 ± 0.3 (>200)
14	**9n**	15 ± 1.0 (25)	13 ± 0.57 (>200)	14 ± 1.0 (100)	10 ± 0.5 (>200)
15	**9o**	12 ± 0.3 (150)	12 ± 0.5 (>200)	13 ± 1.52 (>200)	12 ± 1.0 (150)
16	**9p**	10 ± 0.57 (>200)	16 ± 1.0 (50)	12 ± 0.5 (>200)	14 ± 0.4 (100)
17	**9r**	13 ± 0.4 (100)	15 ± 1.0 (100)	14 ± 0.57 (50)	13 ± 0.5 (150)
18	**9s**	12 ± 0.5 (>200)	15 ± 1.52 (150)	12 ± 0.5 (>200)	12 ± 0.57 (150)
19	Amoxycillin	28 ± 0.3 (25)	29 ± 0.5 (25)	31 ± 0.2 (25)	27 ± 0.6 (25)

Note: Data are means (n = 3) ± SD of three replicates.

Abbreviations: *E. coli*, *Escherichia coli; K. pneumoniae*, *Klebsiella pneumonia*; *P. vulgaris*, *Proteus vulgaris; S. aureus, Staphylococcus aureus*.

[a]Zone of inhibition was calculated for stock solution at 0.4 mg/50 μL.

[b]Minimal inhibitory concentration (MIC) values of the particular compounds are given within the brackets.

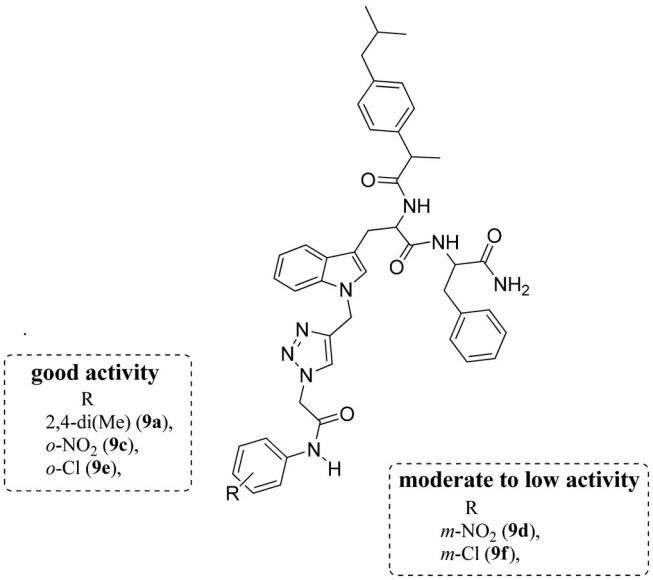


FIGURE 4 SAR summary of anti-bacterial activity of compound **9**

TABLE 2 Cytoxicity (IC_{50} values) of compound **9** against A549 cell line

S. no.	Compound	IC_{50} (μg/mL) A549
1	**9b**	17.35
2	**9c**	31.95
3	**9e**	25.81
4	**9h**	28.52
5	**9j**	38.68
6	**9k**	15.25
7	**9m**	34.02
8	**9o**	36.85
9	Doxorubicin	4.39

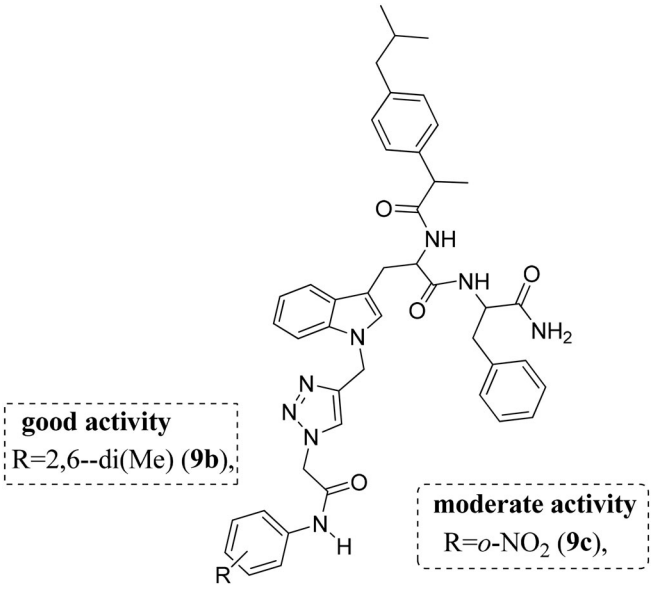


FIGURE 5 SAR summary of anti-cancer activity of compound **9** against A549 cell line

The crystal structure of the DNA-gyrase cleavage complex of *S. aureus* (PDB_ID: 5CDQ) has been consider for the docking the molecule **9e** molecule. The crystal structure contains an inhibitor Moxifloxacin intercalation in the major groove of E and F chains of DNA. The DNA binding protein with A and C chains are stabilizing the binding of the DNA with the bound Moxifloxacin.

The molecule **9e** docked in the intercalation location of DNA of the DNA-gyrase complex (Figure 7). The molecule bound to the DNA was stabilized by the hydrogen bonds, hydrophobic interactions, and π-π interaction. The 3-phenylpropane group of the inhibitor molecule showed π-π interaction. Adenine ring (DA-2013) of the E chain, Guanine (DG-2009) of the F chain bases and the propane

TABLE 3 Docking score of the compound **9e**

Molecule	Binding affinity (in kcal/mol)
9e	−9.4

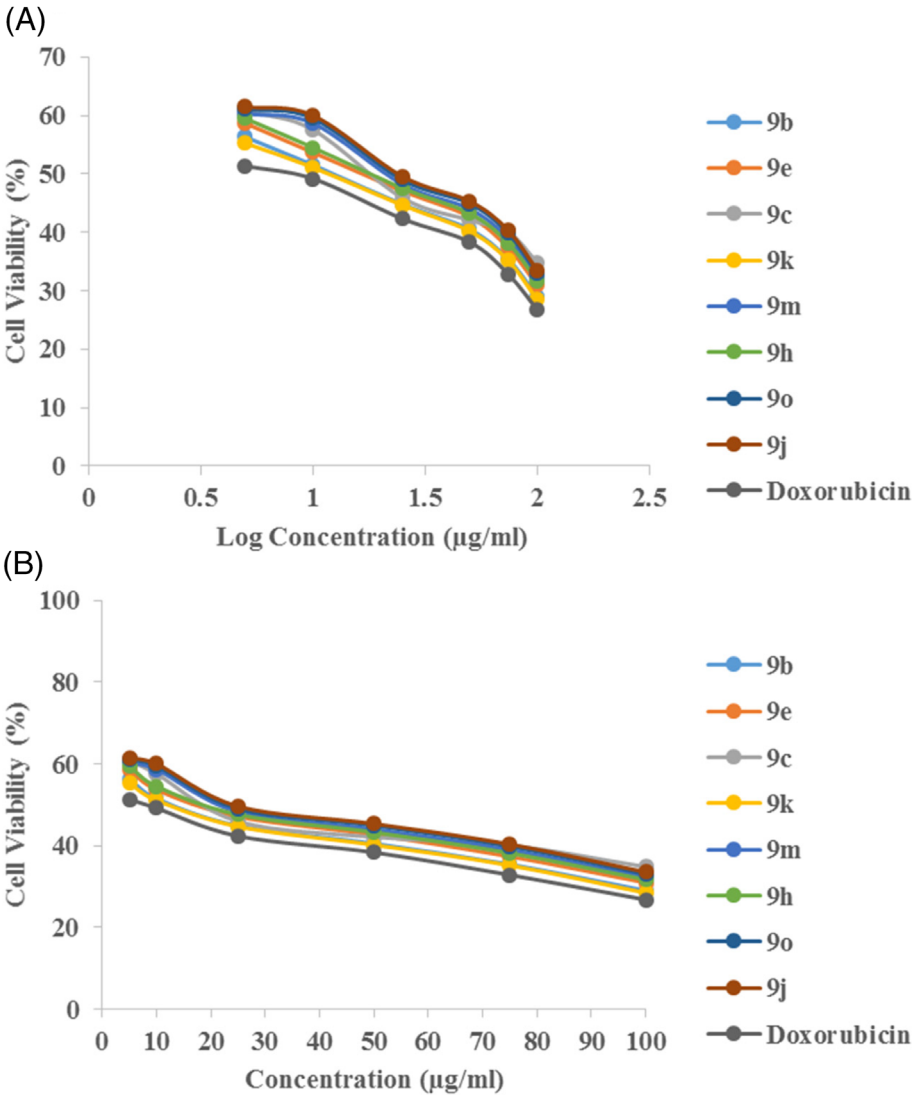


FIGURE 6 Concentration-dependent cytotoxic activity of selected compounds and doxorubicin

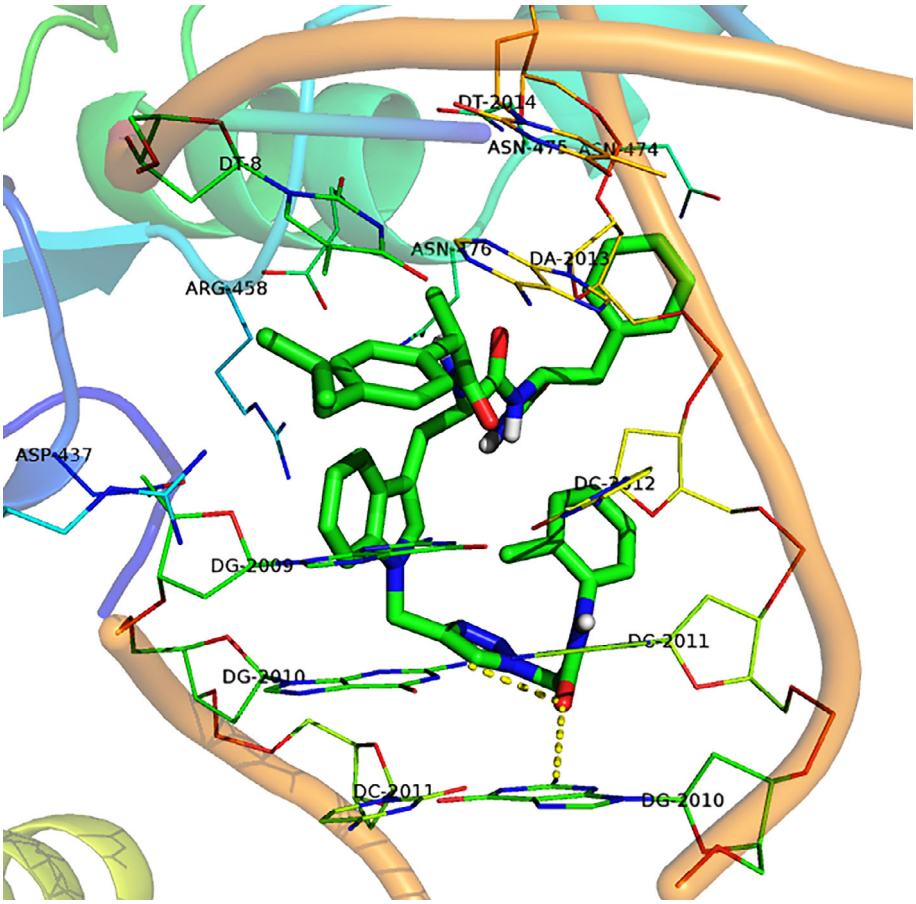


FIGURE 7 Molecule **9e** docked in the active site of the DNA-gyrase cleavage complex of *Staphylococcus aureus* (PDB_ID:5CDQ). Inhibitor molecule shown in green color stick style and the DNA side chains and amino acid side chains are shown in line style

showed CH-π interactions with Thymine ring (DT-8) of chain F. The peptide carbonyl oxygen of molecule showed bifurcated hydrogen bonds with the NH_2 of the Guanine ring (DG-2010) of E chain and F chains. The binding affinity of the molecule with DNA gyrase was observed as −9.4 Kcal/mol. The interaction of DNA bases and the amino acid side-chains in protein are shown in Figure 7.

3 | CONCLUSIONS

In conclusion, a series of new compounds containing an indole-triazole-peptide conjugate were designed that were expected to possess the dual anti-bacterial and anticancer activities. Accordingly, 20 compounds were prepared via a multi-step synthesis involving the copper-catalyzed azide-alkyne cycloaddition (CuAAC) as a key step in moderate to high yield. All the synthesized compounds were purified by chromatographic techniques and characterized by IR, ^{1}H and ^{13}C NMR and mass spectral data. The synthesized derivatives were screened for their antimicrobial activities against one gram-positive (*S. aureus*) and three gram-negative (*E. coli*, *K. pneumoniae*, and *P. vulgaris*) bacteria using an agar-well diffusion method. Most of the compounds showed moderate to reasonable antibacterial activities especially the compound **9e** that showed good activities against all the strains. The potential of DNA gyrase inhibitory activity of this compound was assessed by using molecular docking studies in silico carried out using Autodock Vina software. The low ΔG_{bind} value (−9.4 Kcal/mol) of compound **9e** suggested its good interactions with the target protein in silico. The cytotoxic activities of some of the compounds synthesized were evaluated via a MTT assay using the human lung cancer cell line A549. Several compounds showed promising activities among which compound **9b**, **9k,** and **9e** showed low IC_{50} values. Overall, the compound **9e** appeared to be promising among all the compounds synthesized and tested. Thus the indole-triazole-peptide based framework presented here could be a template for the identification and development of novel and potential agents having antibacterial/anticancer dual activities.

4 | EXPERIMENTAL

4.1 | Chemistry

Commercially available chemicals were used directly without further distillation and recrystallization. Cintex

melting point apparatus was used to check melting point following open glass capillary method. Perkin-Elmer IR spectrometer was used to record IR spectra using KBr pellets. Bruker ACF-300 machine or a Varian 300 or 400 MHz spectrometer were used to record ^{1}H and ^{13}CMR using DMSO-d_6, as solvent tetramethylsilane as an internal reference. Jelol JMC D-300 mass spectrometer was used to record mass spectra of synthesized compounds. Progress of reactions was monitored routinely by TLC (thin layer chromatography) in a regular interval. Crude final compounds were purified by column chromatography using silica gel (100-200 mesh, SRL, India).

4.2 | General procedure for synthesis of 4

(1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (6.74 g, 35.16 mmol), and hydroxybenzotriazole (4.75 g, 35.16 mmol), was added to a well-stirred solution of **1** (10.0 g, 23.44 mmol) in DCM (200 mL) and stirred the contents for 5 minutes at RT, then L-phenyl alanine amide (**2**) (23.44 mmol) was added to the above stirred solution followed by *N*,*N*-diisopropylethylamine (6.2 mL) addition at RT, maintained reaction mixture at RT for 4-5 hours. The progress of the reaction was monitored by at regular intervals by checking TLC, after completion of the reaction, the reaction mixture was quenched in 35% of ammonium chloride solution and extracted with DCM (3 × 100 mL), the organic layer was washed with water and brine solution, dried over anhydrous sodium sulfate, filtered and evaporated under vacuum thus crude product **3** obtained was dissolved in THF (200 mL), added diethyl amine to this stirred the contents for 3-4 hours. at RT, after completion of the reaction, evaporated the solvent completely and diethyl ether was added to the residue. After stirring for 30 minutes the mixture was filtered, thus the compound **4** was isolated.

4.3 | General procedure for synthesis of 6

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride (EDC.HCl) (25.44 mmol) and 1-hydroxybenzotriazole (HOBT) (25.44 mmol) was added to a well-stirred solution of **4** (16.96 mmol) in DCM (60 mL) and stirred the contents for 5 minutes at RT, then Ibuprofen **5**(16.96 mmol) was added to the above stirred solution followed by *N*,*N*-diisopropyl ethylamine (DIPEA) (4.5 mL) addition at RT, maintained reaction mixture at RT for 4-5 hours the progress of the reaction was monitored at regular intervals by checking TLC. After completion of the reaction the reaction mixture was quenched in 35% of ammonium chloride solution and extracted with DCM (3 × 50 mL), the organic layer was washed with water and brine solution, combined organic layer and evaporated solvent under vacuum, thus the compound **6** were isolated.

4.4 | General procedure for synthesis of 7

To a stirred solution of compound **6** (14.86 mmol) in DMF (80 mL) added sodium hydride.

(29.70 mmol) lot wise at 5-10°C, stirred the contents for 5 minutes, and followed by propargyl bromide (20.79 mmol) addition, this reaction mixture was maintained for 2-4 hours at RT. The progress of the reaction was monitored at regular intervals by checking TLC. After completion of the reaction, reaction mixture was quenched in a crushed ice, thus solid was separated, filtered the solid under vacuum, washed with n-hexane and dried the solid under vacuum for 4 hours. The compound **7** purified by column chromatography by using silica gel (100-200 mesh) with MeOH/DCM to get desired product.

4.5 | General procedure for synthesis of 9

A mixture of azide **8** (1 mmol), an appropriate terminal alkyne **7** (1 mmol), copper sulfate pentahydrate (49.92 mg, 0.20 mmol) and sodium ascorbate (39.62 mg, 0.20 mmol) in DMF (3 mL) was stirred vigorously for 10-30 minutes. The progress of the reaction was monitored by checking TLC at regular interval. After completion of the reaction, the reaction mixture was quenched in crushed ice. The solid separated was filtered, dried, and purified by column chromatography on silica gel using dichloromethane/methanol to give desired product.

4.5.1 | 2-Amino-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-3-(1*H*-indol-3-yl) propanamide (4)

Pale yellow colored solid; m.p.: 146°C-151°C; R_f: 0.5 (Methanol: DCM 1:9); MS *m/z* 351.18 ($M+1^+$, 105%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.92 (s, 1H), 8.02 (d, 6.4 Hz, 1H), 7.57-7.51 (m, 2H), 7.36 (d, 7.6 Hz, 1H), 7.21-6.98 (m, 9H), 3.47 (d, 4 Hz, 1H), 3.15-2.84 (m, 3H), 2.70-2.50 (m, 1H), 1.98-1.72 (m, 2H). $^{13}CNMR$ (DMSO-d_6, 100 MHz) 174.23, 172.81, 137.49, 136.33, 129.36, 127.98, 127.49, 126.28, 123.90, 120.95, 118.47, 118.31, 111.42, 110.51, 55.37, 52.83, 37.82, 30.52.

4.5.2 | (S)-N-((S)-1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1*H*-indol-3-yl)-2-((S)-2-(4-isobutyl phenyl)propanamido) propanamide (6)

Pale yellow colored solid; m.p.: 225°C-230°C; R_f: 0.6 (Methanol: DCM 1:9); MS *m/z* 539.30 ($M+1^+$, 100%); ^{1}H NMR (DMSO- d_6, 400 MHz) δ 10.74 (s, 1H), 8.03 (d, 8 Hz, 1H), 7.92-7.87 (m, 1H), 7.59-7.45 (m, 1H), 7.32 (d, 5.8 Hz, 5H), 7.30-6.90 (m, 10H), 4.55-4.37 (m, 2H), 3.64-3.56 (m, 1H), 3.11-2.90 (m, 4H), 2.37 (d, 7.2 Hz, 2H), 1.8-1.74 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.83 (d, 6.4 Hz, 6H).^{13}CNMR (DMSO-d_6, 100 MHz) δ 173.27, 172.53, 171.07, 156.93, 137.58, 137.07, 136.02, 133.08, 129.11, 129.06, 128.34, 127.92, 127.48, 126.58, 126.50, 126.10, 125.34, 123.50, 120.81, 118.18, 111.24, 110.15, 105.63, 55.11, 53.64, 53.39, 44.64, 37.55, 27.68, 18.55.

4.5.3 | (S)-N-((S)-1-Amino-1-oxo-3-phenylpropan-2-yl)-2-((S)-2-(4-isobutylphenyl) propanamido)-3-(1-(prop-2-yn-1-yl)-1*H*-indol-3-yl)propanamide (7)

Pale yellow colored solid; m.p.: 214°C-218°C; R_f: 0.65 (Methanol: DCM 1:9); MS *m/z* 577.31 ($M+1^+$, 100%); ^{1}H NMR (DMSO- d_6, 400 MHz) δ 8.07 (d, 6.4 Hz, 1H), 7.95-7.89 (m, 1H), 7.62 (d, 7.6 Hz, 1H), 7.48-7.41 (m, 1H), 7.33-7.20 (m, 3H), 7.18-6.97 (m, 10H), 6.86 (s, 1H), 5.00 (s, 1H), 4.83 (s, 1H), 4.57-4.39 (m, 2H), 3.61 (q, 7.2 Hz, 1H), 3.36 (s, 1H), 3.11-2.73 (m, 4H), 2.38 (d, 7.6 Hz, 2H), 1.80-1.75 (m, 1H), 1.28-1.17 (m, 3H), 0.84 (d, 6.4 Hz, 6H).^{13}CNMR (DMSO-d_6, 100 MHz) δ 173.27, 172.53, 171.07, 156.93, 137.58, 137.07, 136.02, 133.08, 129.11, 129.06, 128.34, 127.92, 127.48, 126.58, 126.50, 126.10, 125.34, 123.50, 120.81, 118.18, 111.24, 110.15, 105.63, 55.11, 53.64, 53.39, 44.64, 37.55, 27.68, 18.55.

4.5.4 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-(2-((2,4-dimethylphenyl) amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl) methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl)propanamido) propanamide (9a)

Off white colored solid; m.p.: 224°C-228°C; R_f: 0.54 (Methanol: DCM 1:9); MS *m/z* 781.41 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3386, 3281, 3212, 2950, 2375, 2317, 1670, 1669, 1645, 1640, 1540, 1226, 1045, 745, 695. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.97 (s, 1H), 8.07 (t, 8 Hz, 1H), 7.9-7.89 (m, 2H), 7.60-7.44 (m, 2H), 7.25-6.90 (m, 17H), 5.40 (s, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 5.23 (s, 1H), 4.54-4.38 (m, 2H), 3.60 (q, 7.2 Hz, 1H), 3.08-2.71 (m, 4H), 2.37 (d, 7.2 Hz, 2H), 2.23 (s, 3H), 2.15 (s, 3H), 1.80-1.73 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.83 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.39, 172.50, 170.99, 164.20, 143.53, 143.45, 139.21, 139.06, 139.00, 137.72, 137.61, 136.04, 134.61, 134.59, 132.83, 131.44, 130.88, 129.21, 129.07, 128.63, 128.04, 128.00, 127.94, 127.80, 127.03, 126.94, 126.82, 126.72, 126.49, 126.22, 126.12, 124.70, 121.08, 118.56, 110.27, 110.04, 53.63, 53.43, 53.28, 51.79, 44.24, 40.65, 37.52, 29.57, 22.16, 20.42, 18.58, 18.20, 17.65.

4.5.5 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-(2-((2,6-dimethylphenyl) amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl) methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl) propanamido)propanamide (9b)

Off white colored solid; m.p.: 225°C-230°C; R_f: 0.54 (Methanol: DCM 1:9); MS *m/z* 781.41 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3382, 3283, 3209, 2955, 2378, 2313, 1669, 1664, 1642, 1638, 1539, 1228, 1049, 740, 698. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.1-7.9 (m, 3H), 7.60-6.90 (m, 20H), 5.40 (s, 1H), 5.29 (s, 1H), 5.27 (s, 1H), 5.23 (s, 1H), 4.54-4.36 (m, 2H), 3.60 (q, 6.8 Hz, 1H), 3.02-2.73 (m, 4H), 2.37 (d, 6.8 Hz, 2H), 2.11 (s, 6H), 1.80-1.74 (m, 1H), 1.24 (d, 6.8 Hz, 3H), 0.82 (d, 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.40, 172.61, 170.99, 163.93, 143.53, 143.46, 139.22, 139.06, 139.02, 137.71, 137.60, 135.02, 134.13, 129.21, 129.07, 128.64, 128.56, 128.00, 127.94, 127.70, 127.03, 126.95, 126.85, 126.70, 126.22, 124.60, 121.08, 121.04, 118.62, 118.56, 110.03, 53.62, 53.53, 53.28, 51.52, 44.23, 40.66, 37.53, 29.56, 22.16, 18.61, 18.19, 17.95.

4.5.6 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-((2-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)propanamide (9c)

Off white colored solid; m.p.: 199°C-203°C; R_f: 0.58 (Methanol: DCM 1:9); MS *m/z* 798.37 ($M+1^+$, 100%); IR(ν_{max} in cm^{-1}): 3282, 3176, 1672, 1640, 1511, 1354, 1222, 1053, 737, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.08 (t, 8 Hz, 1H), 7.99-7.87 (m, 3H), 7.74-7.66 (m, 2H), 7.6-7.52 (m, 1H), 7.48-7.38 (m, 2H), 7.34-6.90 (m, 15H), 5.40 (s, 1H), 5.35 (s, 1H), 5.33 (s, 1H), 5.23 (s, 1H), 4.54-4.38 (m, 2H), 3.60 (q, 7.2 Hz, 1H), 3.07-2.73 (m, 4H), 2.37 (d, 7.2 Hz, 2H), 1.82-1.73 (m, 1H), 1.25 (d, 6.8 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.40, 172.62, 171.01, 164.87, 143.58, 142.27, 139.07,

139.01, 137.71, 137.61, 134.13, 130.31, 129.21, 129.07, 128.63, 128.00, 127.94, 127.03, 126.95, 126.82, 126.72, 126.22, 125.82, 125.44, 125.04, 124.79, 124.68, 121.07, 118.57, 110.30, 110.07, 109.79, 53.63, 53.53, 53.45, 51.84, 44.23, 40.62, 37.53, 29.55, 22.16, 18.57, 18.19.

4.5.7 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-((3-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)propanamide (9d)

Off white colored solid; m.p.: 197°C-201°C; R_f: 0.56 (Methanol: DCM 1:9); MS *m/z* 798.37 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3285, 3172, 1670, 1642, 1513, 1353, 1224, 1054, 738, 693. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.57 (s, 1H), 8.10-7.86 (m, 4H), 7.65-7.45 (m, 3H), 7.34-6.90 (m, 16H), 5.42 (s, 1H), 5.33 (s, 1H), 5.30 (s, 1H), 5.24 (s, 1H), 4.54-4.35 (m, 2H), 3.64-3.55 (m, 1H), 3.07-2.73 (m, 4H), 2.36 (d, 7.2 Hz, 2H), 1.81-1.7;0 (m, 1H), 1.24 (d, 7.6 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.65, 171.93, 170.73, 166.30, 141.71, 139.19, 139.01, 137.72, 136.55, 130.40, 129.22, 128.62, 128.00, 127.01, 126.94, 125.53, 125.48, 121.21, 121.10, 114.46, 113.80, 113.32, 110.09, 109.15, 53.62, 53.44, 52.07, 51.58, 44.21, 40.65, 37.53, 29.55, 22.15, 18.57, 18.18.

4.5.8 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-(2-((2-chlorophenyl)amino)-2-oxo ethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl) propanamido)propanamide (9e)

Light yellow colored solid; m.p.: 208°C-211°C; R_f: 0.60 (Methanol: DCM 1:9); MS *m/z* 787.34 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3403, 3284, 3199, 2957, 2380, 2314, 1674, 1666, 1643, 1547, 1464, 1263, 739, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.08 (t, 8 Hz, 1H), 8.00-7.94 (m, 2H), 7.89 (s, 1H), 7.71 (d, 8 Hz, 1H), 7.60-7.44 (m, 3H), 7.34-6.90 (m, 16H), 5.40 (s, 1H), 5.37 (s, 1H), 5.35 (s, 1H), 5.23 (s, 1H), 4.52-4.38 (m, 2H), 3.60 (q, 7.2 Hz, 1H), 3.03-2.73 (m, 4H), 2.37 (d, 7.2 Hz, 2H), 1.82-1.75 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.30, 172.50, 170.90, 164.79, 143.52, 139.01, 137.74, 137.71, 137.60, 137.09, 136.88, 135.66, 135.52, 134.08, 133.85, 129.39, 129.57, 129.21, 129.12, 129.07, 128.56, 127.94, 127.03, 126.95, 126.87, 126.81, 126.71, 126.62, 126.22, 126.18, 126.14, 126.11, 125.77, 124.81, 124.71, 121.07, 118.57, 110.29, 110.05, 109.87, 53.63, 53.54, 53.43, 51.83, 44.20, 40.63, 37.53, 29.56, 22.16, 18.58, 18.19.

4.5.9 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-(2-((3-chlorophenyl)amino)-2-oxo ethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl) propanamido)propanamide (9f)

Off colored solid; m.p.: 210°C-215°C; R_f: 0.60 (Methanol: DCM 1:9); MS *m/z* 787.34 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3401, 3282, 3199, 2955, 2379, 2312, 1673, 1665, 1642, 1546, 1463, 1262, 737, 692. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.10-7.74 (m, 4H), 7.61-6.90 (m, 20H), 5.41 (s, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 5.24 (s, 1H), 4.53-4.38 (m, 2H), 3.60 (q, 6.8 Hz, 1H), 3.07-2.71 (m, 4H), 2.36 (d, 6.8 Hz, 2H), 1.80-1.73 (m, 1H), 1.25 (d, 7.2 Hz, 3H), 0.82 (d, 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.38, 172.60, 170.38, 164.56, 143.64, 139.76, 139.08, 137.71, 135.67, 135.52, 133.14, 130.61, 129.21, 129.07, 128.63, 127.81, 127.93, 127.01, 126.94, 126.22, 126.11, 124.77, 124.66, 123.47, 118.66, 118.57, 117.57, 110.31, 110.07, 53.62, 53.53, 53.30, 52.07, 44.22, 40.65, 37.53, 29.56, 22.16, 18.56, 18.18.

4.5.10 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-(2-((4-chlorophenyl)amino)-2-oxo ethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl) propanamido)propanamide (9g)

Pale yellow colored solid; m.p.: 211°C-216°C; R_f: 0.62 (Methanol: DCM 1:9); MS *m/z* 787.34 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3400, 3281, 3198, 2954, 2378, 2311, 1672, 1664, 1641, 1545, 1462, 1261, 736, 691. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.10-7.88 (m, 3H), 7.60-6.55 (m, 21H), 5.40 (s, 1H), 5.26 (s, 1H), 5.24 (d, 2.4 Hz, 1H), 4.52-4.38 (m, 2H), 3.63-3.57 (m, 1H), 3.06-2.71 (m, 4H), 2.36 (d, 7.2 Hz, 2H), 1.80-1.73 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.60, 172.51, 170.99, 164.56, 139.76, 133.14, 130.61, 129.21, 129.07, 128.63, 127.99, 127.93, 127.02, 126.94, 124.66, 123.47, 118.66, 118.57, 117.57, 52.07, 44.23, 37.53, 29.56, 22.16, 18.56, 18.18.

4.5.11 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-oxo-2-(o-tolylamino)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl) propanamide (9h)

Off white colored solid; m.p.: 210°C-214°C; R_f: 0.56 (Methanol: DCM 1:9); MS *m/z* 767.40 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3381, 3282, 3207, 2954, 2376, 2312, 1668, 1664, 1641, 1638, 1539, 1228, 1048, 740, 697. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.75 (s, 1H), 8.10-7.91 (m, 3H), 7.6-6.90 (m, 20H),

5.4 (s, 1H), 5.30 (d, 8.8 Hz, 1H), 5.23 (s, 1H), 4.56-4.36 (m, 2H), 3.60 (q, 7.2 Hz, 1H), 3.10-2.71 (m, 4H), 2.37 (d, 6.8 Hz, 2H), 2.20 (s, 3H), 1.82-1.72 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.55, 171.94, 170.98, 164.27, 143.47, 139.01, 138.95, 137.67, 137.02, 135.97, 135.44, 130.38, 129.21, 129.08, 128.64, 128.56, 127.99, 127.94, 127.02, 126.99, 126.94, 126.85, 126.11, 123.47, 121.05, 118.11, 109.99, 109.40, 53.29, 52.90, 52.81, 51.82, 44.22, 40.39, 37.53, 29.57, 22.16, 18.54, 18.16, 17.73.

4.5.12 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-oxo-2-(o-tolylamino)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl) propanamide (9i)

Pale yellow colored solid; m.p.: 196°C-200°C; R_f: 0.54 (Methanol: DCM 1:9); MS *m/z* 753.38 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3398, 3284, 2954, 1667, 1604, 1549, 1228, 1051, 735, 695. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.07 (t, 7.6 Hz, 1H), 7.99-7.89 (m, 2H), 7.60-7.44 (m, 4H), 7.33-6.91 (m, 18H), 5.40 (s, 1H), 5.26 (s, 1H), 5.24 (s, 2H), 4.54-4.37 (m, 2H), 3.60 (q, 6.8 Hz, 1H), 3.08-2.67 (m, 4H), 2.37 (d, 7.2 Hz, 2H), 1.80-1.72 (m, 1H), 1.24 (d, 7.6 Hz, 3H), 0.82 (d, 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.39, 172.36, 170.99, 164.07, 143.82, 139.07, 139.00, 137.95, 137.60, 136.89, 136.87, 135.25, 134.91, 134.13, 129.21, 129.07, 128.86, 128.63, 128.00, 127.94, 127.03, 126.95, 126.11, 124.78, 123.72, 121.05, 119.14, 113.88, 11.30, 109.79, 53.63, 53.28, 52.97, 52.10, 44.22, 40.65, 37.53, 29.57, 22.16, 18.55, 18.19.

4.5.13 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)propanamide (9j)

Off white colored solid; m.p.: 180°C-188°C; R_f: 0.60 (Methanol: DCM 1:9); MS *m/z* 696.36 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3365, 3286, 3200, 2926, 2380, 2315, 1706, 1676, 1642, 1339, 1222, 1032, 851, 742, 695. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.58 (s, 1H), 8.45 (s, 1H), 8.11-8.01 (m, 2H), 7.88-7.80 (m, 2H), 7.64-7.44 (m, 5H), 7.37-6.85 (m, 13H), 5.49 (s, 1H), 5.33 (s, 1H), 4.59-4.37 (m, 2H), 3.63-3.50 (m, 1H), 3.10-2.72 (m, 4H), 2.36-2.37 (m, 2H), 1.78-1.66 (m, 1H), 1.23 (d, 6.8 Hz, 3H), 0.82-0.77 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.49, 172.63, 171.05, 145.14, 144.87, 139.17, 139.00, 138.94, 137.63, 136.49, 136.44, 135.64, 129.80, 129.76, 129.20, 129.05, 128.62, 128.51, 128.16, 128.00, 127.93, 126.94, 126.84, 126.79, 126.10, 121.26, 121.19, 121.15, 119.92, 119.85, 118.67, 110.61, 110.29, 109.74, 53.66, 53.59, 53.46, 44.19, 40.67, 37.50, 29.55, 22.14, 18.37, 17.97.

4.5.14 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)-1*H*-indol-3-yl)propanamide (9k)

Yellow colored solid; m.p.: 194°C-198°C; R_f: 0.62 (Methanol: DCM 1:9); MS *m/z* 741.35 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3357, 3280, 3209, 2925, 2427, 1677, 1640, 1636, 1517, 1310, 1220, 1031, 851, 789, 696. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.51 (s, 1H), 8.38 (s, 1H), 8.20-7.96 (m, 3H), 7.89-7.47 (m, 5H), 7.35-6.90 (m, 13H), 5.51 (s, 1H), 5.34 (s, 1H), 4.57-4.38 (m, 2H), 3.58 (q, 7.2 Hz, 1H), 3.10-2.67 (m, 4H), 2.36-2.31 (m, 2H), 1.80-1.71 (m, 1H), 1.25 (d, 3.2 Hz, 3H), 0.83-0.78 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.27, 172.62, 171.02, 144.71, 139.19, 139.01, 137.74, 137.62, 135.69, 135.59, 134.29, 134.24, 129.20, 129.05, 128.62, 128.56, 128.00, 127.94, 127.32, 127.29, 126.97, 126.89, 126.11, 125.45, 124.43, 121.18, 118.68, 110.33, 55.43, 53.56, 51.06, 44.20, 40.50, 37.52, 31.25, 29.55, 29.50, 22.14, 18.49, 18.03.

4.5.15 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)-1*H*-indol-3-yl)propanamide (9l)

Light brown colored solid; m.p.: 195°C-197°C; R_f: 0.62 (Methanol: DCM 1:9); MS *m/z* 741.35 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3401, 3281, 2980, 2379, 1709, 1678, 1642, 1540, 1283, 1110, 1028, 855, 741, 699. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.8-8.60 (m, 2H), 8.38-8.27 (m, 2H), 8.13-7.99 (m, 2H), 7.85-7.49 (m, 3H), 7.38-6.75 (m, 14H), 5.52 (s, 1H), 5.39 (s, 1H), 4.57-4.39 (m, 2H), 3.55 (q, 7.2 Hz, 1H), 3.11-2.71 (m, 4H), 2.28 (dd, 6.8 Hz, 38 Hz, 2H), 1.75-1.64 (m, 1H), 1.22 (d, 6.8 Hz, 3H), 0.82-0.74 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.64, 172.55, 170.88, 148.40, 138.98, 137.98, 137.74, 137.05, 136.96, 135.58, 131.46, 131.39, 129.20, 129.05, 128.58, 128.38, 127.99, 127.93, 126.91, 126.71, 125.88, 122.97, 121.84, 121.61, 121.19, 114.62, 110.67, 110.45, 53.64, 53.42, 52.95, 44.12, 37.51, 29.54, 22.08, 18.39, 17.73.

4.5.16 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(2-((4-methoxy-2-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)propanamide (9m)

Pale yellow colored solid; m.p.: 225°C-230°C; R_f: 0.56 (Methanol: DCM 1:9); MS *m/z* 828.38 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3366, 3290, 3197, 2925, 1639, 1542, 1463, 1238, 1038, 804, 740. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.42 (s, 1H), 8.31 (s, 1H), 8.12-7.96 (m, 3H), 7.74-7.61

(m, 3H), 7.55-6.92 (m, 15H), 5.48 (s, 2H), 5.32 (s, 2H), 4.55-4.36 (m, 2H), 3.92 (s, 3H), 3.58 (q, 7.2 Hz, 1H), 3.09-2.69 (m, 4H), 2.36-2.31 (m, 2H), 1.79-1.72 (m, 1H), 1.24 (d, 6.4 Hz, 3H), 0.81 (t, 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.27, 172.52, 170.88, 160.16, 144.93, 144.45, 139.00, 138.90, 137.73, 137.65, 135.68, 135.59, 129.21, 129.05, 128.72, 128.68, 128.61, 128.11, 128.00, 127.94, 126.97, 126.90, 126.75, 124.70, 121.81, 121.75, 121.43, 119.30, 118.67, 110.50, 56.55, 53.65, 5360, 53.51, 44.21, 40.65, 37.52, 37.52, 29.56, 22.15, 18.50, 18.06.

4.5.17 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(4-methoxy-2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl) propanamide (9n)

Off white colored solid; m.p.: 208°C-212°C; R_f: 0.60 (Methanol: DCM 1:9); MS *m/z* 771.36 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3366, 3291, 3197, 2925, 1639, 1542, 1463, 1238, 1038, 804, 741. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.41 (s, 1H), 8.31 (s, 1H), 8.09-7.93 (m, 2H), 7.74-7.39 (m, 6H), 7.33-6.92 (m, 13H), 5.48 (s, 1H), 5.32 (s, 1H), 4.54-4.39 (m, 2H), 3.91 (s, 3H), 3.58 (q, 7.2 Hz, 1H), 3.09-2.71 (m, 4H), 2.36-2.32 (m, 2H), 1.79-1.70 (m, 1H), 1.24 (d, 6.8 Hz, 3H), 0.81 (t, 7.6 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.60, 17.02, 170.88, 160.17, 144.93, 144.43, 144.22, 139.20, 139.03, 137.73, 137.62, 129.21, 129.05, 128.73, 128.61, 128.58, 128.00, 127.93, 126.7, 126.90, 121.16, 119.30, 118.66, 110.50, 56.55, 53.64, 53.56, 53.44, 44.22, 40.64, 37.52, 29.56, 22.14, 18.50 18.06.

4.5.18 | 3-(4-((3-(3-((1-Amino-1-oxo-3-phenylpropan-2-yl)amino)-2-(2-(4-isobutylphenyl) propanamido)-3-oxopropyl)-1*H*-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (9o)

Off white colored solid; m.p.: 207°C-210°C; R_f: 0.50 (Methanol: DCM 1:9); MS *m/z* 718.44 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3392, 3281, 3198, 2425, 1673, 1637, 1540, 1338, 1218, 1029, 928, 739, 699. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.80 (s, 1H), 8.23-7.90 (m, 4H), 7.62-6.90 (m, 19H), 5.50 (s, 1H), 5.31 (s, 1H), 4.58-4.38 (m, 2H), 3.59 (q, 7.2 Hz, 1H), 3.07-2.75 (m, 4H), 2.36 (d, 6.8 Hz, 2H), 1.82-1.70 (m, 1H), 1.23 (d, 6.2 Hz, 3H), 0.83 (d, 5.6 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.46, 173.27, 171.02, 166.58, 141.31, 139.16, 137.58, 135.95, 130.77, 129.23, 129.08, 128.64, 125.56, 128.00, 127.94, 127.19, 127.01, 126.85, 126.22, 126.12, 123.46, 118.12, 111.13, 110.09, 109.82, 53.62, 53.49, 53.26, 44.22, 40.65, 37.59, 29.56, 22.18, 18.61, 17.98.

4.5.19 | 4-(4-((3-(3-((1-Amino-1-oxo-3-phenylpropan-2-yl)amino)-2-(2-(4-isobutylphenyl) propanamido)-3-oxopropyl)-1*H*-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (9p)

Pale yellow colored solid; m.p.: 208°C-212°C; R_f: 0.52 (Methanol: DCM 1:9); MS *m/z* 740.35 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3401, 3292, 3210, 2953, 1709, 1673, 1641, 1540, 1284, 1180, 1109, 855, 740, 696. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.81(s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.14-7.92 (m, 6H), 7.64-7.49 (m, 2H), 7.34-6.83 (m, 13H), 5.51 (s, 1H), 5.35 (s, 1H), 4.58-4.39 (m, 2H), 3.55 (q, 6.8 Hz, 1H), 3.10-2.72 (m, 4H), 2.30 (dd, 7.2 Hz, 2H), 1.79-1.66 (m, 1H), 1.24-1.22 (m, 3H), 0.82-0.75 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.27, 172.58, 172.71, 169.88, 144.02, 137.76, 137.63, 136.45, 135.14, 133.77, 133.60, 130.93, 130.91, 129.20, 129.05, 128.59, 128.48, 128.19, 128.00, 127.94, 126.94, 126.82, 125.32, 119.78, 119.61, 119.54, 118.71, 111.47, 110.71, 109.74, 53.64, 53.20, 52.71, 4.22, 40.65, 37.51, 29.52, 22.13, 18.29, 17.93.

4.5.20 | Methyl-4-(2-(4-((3-(3-((1-amino-1-oxo-3-phenylpropan-2-yl)amino)-2-(2-(4-isobutyl phenyl)propanamido)-3-oxopropyl)-1*H*-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamido)benzoate (9q)

Pale yellow colored solid; m.p.: 235°C-239°C; R_f: 0.50 (Methanol: DCM 1:9); MS *m/z* 811.39 (M+1$^+$, 100%); IR (ν_{max} in cm^{-1}): 3402, 3291, 3211, 2954, 1708, 1672, 1641, 1540, 1283, 1179, 1109, 855, 739, 695. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.08 (t, 8 Hz, 1H), 7.96-7.90 (m, 4H), 7.67 (d, 8.8 Hz, 2H), 7.61-7.45 (m, 2H), 7.27-6.91 (m, 15H), 5.41 (s, 1H), 5.30 (d, 8.8 Hz, 2H), 5.24 (s, 1H), 4.54-4.38 (m, 2H), 3.82 (s, 3H), 3.60 (q, 7.2 Hz, 1H), 3.05-2.73 (m, 4H), 2.36 (dd, 2.4 Hz, 7.2 Hz, 2H), 1.78-1.74 (m, 1H), 1.25 (d, 7.6 Hz, 3H), 0.82 (d, 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.40, 172.61, 170.99, 165.68, 164.78, 143.65, 142.70, 139.19, 138.99, 137.60, 135.53, 130.37, 129.21, 129.07, 128.62, 127.99, 127.94, 127.02, 126.95, 126.82, 126.71, 126.22, 126.10, 124.77, 124.44, 118.63, 110.31, 110.06, 109.86, 53.62, 53.53, 53.30, 52.17, 51.91, 44.22, 40.67, 37.53, 29.56, 22.15, 18.56, 18.19.

4.5.21 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-benzyl-1H-1,2,3-triazol-4-yl methyl)-1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl)propanamido) propanamide (9r)

Pale yellow colored solid; m.p.: 185°C-13°C; R_f: 0.64 (Methanol: DCM 1:9); MS *m/z* 710.38 (M+1$^+$, 100%); IR

(ν_{max} in cm^{-1}): 3395, 3289, 3203, 2379, 1677, 1635, 1510, 1318, 1036, 746, 698. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.07 (t, 8 Hz, 1H), 7.98-7.88 (m, 2H), 7.60-7.41 (m, 2H), 7.34-6.87 (m, 19H), 5.52 (s, 1H), 5.48 (s, 1H), 5.35 (s, 1H), 5.18 (s, 1H), 4.52-4.37 (m, 2H), 3.58 (q, 7.2 Hz, 1H), 3.03-2.73 (m, 4H), 2.38-2.32 (m, 2H), 1.79-1.73 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.82 (d, 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.28, 172.50, 171.91, 144.04, 139.17, 139.02, 137.60, 135.91, 135.63, 129.21, 129.07, 128.68, 128.64, 128.07, 127.99, 127.94, 127.87, 127.02, 126.92, 126.11, 123.26, 123.12, 121.07, 118.63, 118.58, 110.29, 109.81, 53.62, 53.54, 53.28, 52.71, 44.22, 40.70, 37.53, 29.57, 22.15, 18.51, 18.12.

4.5.22 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-3-(1-((1-heptyl-1H-1,2,3-triazol-4-yl) methyl) -1*H*-indol-3-yl)-2-(2-(4-isobutylphenyl)propanamido) propanamide (9s)

Pale yellow colored solid; m.p.: 175°C-179°C; R_f: 0.62 (Methanol: DCM 1:9); MS *m/z* 718.44 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3372, 3291, 2925, 1641, 1538, 1464, 1223, 1051, 739, 696. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.07-7.1 (m, 3H), 7.49-6.89 (m, 16H), 5.35 (s, 1H), 5.19 (s, 1H), 4.54-4.38 (m, 2H), 4.27-4.20 (m, 2H), 3.59 (q, 6.8 Hz, 1H), 3.07-2.73 (m, 4H), 2.36 (t, 7.2 Hz, 2H), 1.82-1.69 (m, 3H), 1.25-1.19 (m, 11H), 0.83-0.81 (m, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.25, 172.49, 171.01, 143.67, 139.19, 139.01, 138.95, 137.60, 136.96, 135.49, 129.21, 129.07, 128.63, 128.58, 127.90, 126.82, 126.10, 125.09, 122.90, 122.82, 121.03, 118.80, 118.54, 110.28, 109.79, 53.63, 53.54, 53.48, 53.32, 44.22, 40.80, 37.52, 31.01, 29.63, 29.57, 27.97, 29.53, 27.97, 25.74, 22.15, 22.91, 18.54, 18.08.

4.5.23 | N-(1-Amino-1-oxo-3-phenylpropan-2-yl)-2-(2-(4-isobutylphenyl)propanamido)-3-(1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl) propanamide (9t)

Brown colored solid; m.p.: 195°C-199°C; R_f: 0.60 (Methanol: DCM 1:9); MS *m/z* 741.35 ($M+1^+$, 100%); IR (ν_{max} in cm^{-1}): 3373, 3287, 3197, 2995, 1672, 1642, 1528, 1340, 1234, 1041, 853, 742, 693, 423. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.73 (s, 1H), 8.55 (s, 1H), 8.40-8.36 (m, 2H), 8.20-8.01 (m, 4H), 7.65-7.45 (m, 2H), 7.38-6.80 (m, 13H), 5.53 (s, 1H), 5.38 (s, 1H), 4.60-4.39 (m, 2H), 3.56 (q, 7.2 Hz, 1H), 3.11-2.72 (m, 4H), 2.35-2.24 (m, 2H), 1.74-1.65 (m, 1H), 1.24 (d, 7.2 Hz, 3H), 0.78 (dd, 6.4 Hz, 20.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.30, 172.64, 170.85, 146.60, 146.57, 145.98, 145.75, 140.69, 140.62, 139.12, 139.01, 137.75, 137.63, 135.63, 129.25, 129.19, 129.05, 128.59, 128.46, 128.21, 128.00, 126.92, 126.82, 126.22, 126.11, 125.46, 125.40, 121.68, 121.22, 120.45, 118.76, 118.74, 110.79, 110.52, 109.71, 53.62, 53.54, 51.30, 44.20, 40.59, 37.52, 29.53, 22.11, 18.26, 17.90.

4.6 | Antibacterial activity

4.6.1 | Test organisms and culture condition

Four bacterial strains including three Gram-negative and one Gram-positive were used for the determination of antibacterial activity of the synthesized compounds. All four bacterial strains were donated by Department of Microbiology, Osmania General Hospital, and Hyderabad. Standard microbiological methods were used to check purity of all bacterial strains. Mueller Hinton Agar (MHA) slants were used to store bacterial stock culture and temperature was well maintained by 4°C.

4.6.2 | Determination of antibacterial activity

Antibacterial activities of test compounds were performed by an agar-well diffusion method.[43,44] Amoxycillin was taken as the positive references at a concentration of 0.1 mg per 50 μL. DMSO was used as a negative control. The bacterial strains were reactivated from stock cultures by transferring into Mueller-Hinton broth and incubating at 37°C for 18 hours. A final inoculums containing 10^6 colonies forming units (1 x 10^6 CFU/mL) was added aseptically to MHA medium and poured into sterile petri dishes. Test compounds were dissolved in DMSO to prepare solution. 0.4 mg/50 μL was added to wells (8 mm in diameter) punched on agar surface. Plates were incubated overnight at 37°C and diameter of inhibition zone (DIZ) around each well was measured in mm. Each experiment was repeated three times (triplicates).

The anti-bacterial activity was investigated by determining the minimum inhibitory concentrations (MICs). MIC of compounds was assessed using the broth microdilution method.[45] Each test compound was dissolved in dimethyl sulfoxide (DMSO, Fisher Chemicals) to give a stock solution. Minimum Inhibitory Concentration (MIC) is the lowest concentration of an anti-microbial growth that will inhibit the visible growth of a microorganism after overnight incubation.

Compound preparation

Compounds were weighed individually 1 mg and dissolved in methanol for final stock concentration as 1 mg/mL as same sample, standard amoxicillin also prepared.

Culture preparation

Loop of culture was inoculated in 3 mL of nutrient broth and incubated at 37°C for overnight in shaking incubator.

Inoculum preparation

From overnight grown culture, 20 μL of culture was taken and inoculated in 1.5 mL of nutrient broth and added different concentrations of compound and was incubated at 37°C for overnight in an incubator.

Result

After 24 hours of compound treatment, tubes were observed and results were noted.

4.7 | In vitro cytotoxicity

DMEM (Dulbecco's modified Eagles medium), MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], trypsin, and EDTA Phosphate Buffered Saline (PBS) were purchased from Sigma Chemicals Co. (St. Louis, MO) and Fetal Bovine Serum (FBS) was purchased from Gibco. 25 and 75 cm^2 flask and 96 well plates were purchased from Eppendorf India.

The Cancer cell line A549 was purchased from NCCS, Pune and the cells were maintained in DMEM supplemented with 10% FBS and the antibiotics penicillin/streptomycin (0.5 mL^{-1}), in atmosphere of 5% CO_2/95% air at 37°C.

4.7.1 | MTT assay for cytotoxicity

Preparation of test compound

For MTT assay, each test compounds were weighed separately and dissolved in DMSO. With media make up the final concentration to 1 mg/mL and the cells were treated with series of concentrations from 10 to 100 μg/mL.

Principle

MTT Assay is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The assay depends both on the number of cells present and on the assumption that dead cells or their products do not reduce tetrazolium. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, dark purple colored formazan crystals. The cells are then solubilized with a DMSO and the released, solubilized formazan reagent is measured spectrophotometrically at 570 nm.

Procedure

Cell viability was evaluated by the MTT Assay[46] with three independent experiments with six concentrations of compounds in triplicates. Cells were trypsinized and perform the tryphan blue assay to know viable cells in cell suspension. Cells were counted by haemocytometer and seeded at density of 5.0×10^3 cells/well in 100 μL media in 96 well plate culture medium and incubated overnight at 37°C. After incubation, take off the old media and add fresh media 100 μL with different concentrations of test compound in wells in 96 plates. After 48 hours, discard the drug solution and add the fresh medic with MTT solution (0.5 $mg/mL^{-1)}$ was added to each well and plates were incubated at 37°C for 3 hours. At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula and concentration of test drug needed to inhibit cell growth by 50% values is generated from the dose-response curves for each cells using with origin software.

$$\%\,\text{Inhibition} = [(\text{Control} - \text{Treatment})/\text{Control}] \times 100.$$

4.8 | Docking study

Molecular docking studies were performed in order to predict the interaction of synthesized compounds with the binding sites of DNA-gyrase cleavage complex of *S. aureus* (Gram-positive bacteria) with PDB_ID:5CDQ is carried out using Autodock Vina software[47,48] open source molecular docking software.

4.8.1 | Docking method

Molecular docking studies of molecule **9e** into the crystal structures of DNA-gyrase cleavage complex of *S. aureus* (Gram-positive bacteria) with PDB_ID:5CDQ is carried out using Autodock Vina software,[47,48] open source molecular docking software. We have generated a grid box with desired parameters around the active site of DNA-gyrase cleavage complex of *S. aureus*[49] (PDB_ID:5CDQ) as centre: x = 40.123, y = −46.732, z = 64.933 and grid box size: x = 25, y = 39, z = 29 with 1 Å grid spacing. We generated

10 conformations in each docking output by using advanced Genetic algorithm method in vina Protein/DNA complex and molecule input preparations and docking output analysis were carried out using MGLTools-1.5.6 software.

ACKNOWLEDGMENT

The authors S. Srinivas and P. Neeraja are thankful to Alembic Pharmaceuticals Ltd, Hyderabad, India and DVR College of Engineering & Technology, Hyderabad, India for constant encouragement and support. We also thank to CFRD, Osmania University, Hyderabad, India and JNTU, Hyderabad, India.

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How to cite this article: Suryapeta S, Papigani N, Banothu V, Dubey PK, Mukkanti K, Pal S. Synthesis, biological evaluation, and docking study of a series of 1,4-disubstituted 1,2,3-triazole derivatives with an indole-triazole-peptide conjugate. *J Heterocyclic Chem*. 2020;1–16. https://doi.org/10.1002/jhet.4020