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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Mohan Babu Bommagani, Sudhakar Mokenapelli, Jayaprakash Rao Yerrabelli, Sathish Kumar Boda & Prasad Rao Chitneni (2020): Novel 4-(1H-1,2,3-triazol-4-yl)methoxy)cinnolines as potent antibacterial agents: Synthesis and molecular docking study, Synthetic Communications, DOI: 10.1080/00397911.2020.1728333

To link to this article: https://doi.org/10.1080/00397911.2020.1728333

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https://doi.org/10.1080/00397911.2020.1728333

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Novel 4-(1H-1,2,3-triazol-4-yl)methoxy)cinnolines as potent antibacterial agents: Synthesis and molecular docking study

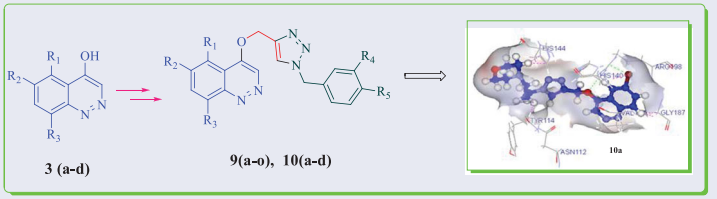
Mohan Babu Bommagani, Sudhakar Mokenapelli, Jayaprakash Rao Yerrabelli, Sathish Kumar Boda, and Prasad Rao Chitneni

Natural Products Laboratory, Department of Chemistry, Osmania University, Hyderabad, Telangana, India

ABSTRACT

A new series of cinnoline-1,2,3-triazole derivatives were designed and synthesized by adopting Cu(1) catalyzed regeoselective1,3-dipolar cycloaddition reaction of terminal alkyne and azide. The *in vitro* antibacterial activity of all these compounds revealed that compounds **9d**, **10a**, **10b**, and **10c** are more potent antibacterial agents. Among the series, compound 4-(3-(4-((cinnolin-4-yloxy)-methyl)-1H-1,2,3-triazol-1-yl)propyl)morpholine (**10b**) exhibited the most potent antibacterial activity against all tested gram-positive and gram-negative bacterial strains. Furthermore, molecular docking studies were also performed to understand the binding interactions of the most active analogs **9d**, **10a, 10b**, and **10c** with Elastase of *Pseudomonas aeruginosa* (PDB: 1U4G). The results indicated that these classes of compounds have potential antibacterial activity, especially the compound **10b** may serve as a promising antibacterial lead compound that could be further optimized for the further development of antibacterial drugs.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 22 September 2019

KEYWORDS
Anti-bacterial activity; cinnolines; click reaction; molecular docking studies; triazoles

Introduction

Bacterial infections are one of the most common causes of chronic infections and mortality against human health throughout the world. Antimicrobial agents, the "miracle drugs," are considered to be the principal agents to combat infectious diseases. Moreover, antibiotics have become less effective against certain illnesses because of their toxic reactions and also due to the surfacing of drug-resistant bacteria. For the last two decades, rapid progress in synthetic organic chemistry is associated with a search for new drug-like

CONTACT Chitneni Prasad Rao prasadraoou@yahoo.com Natural Products Laboratory, Department of Chemistry, Osmania University, Hyderabad 500007, Telangana, India.

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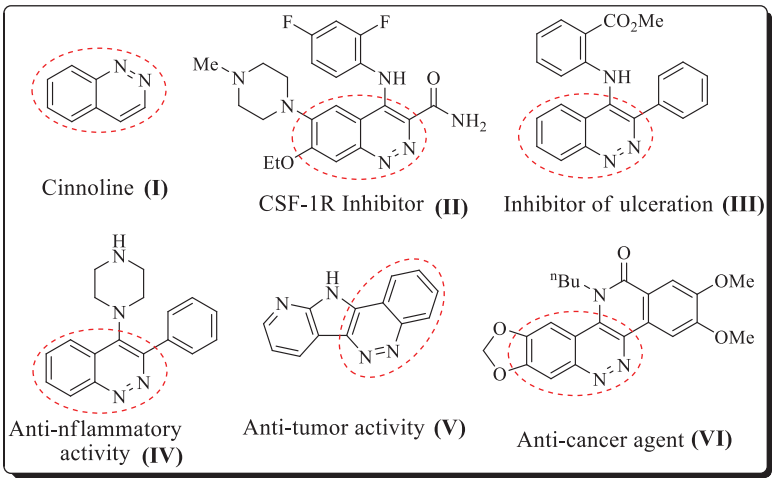


Figure 1. Some of the biologically active cinnoline derivatives.

compounds with desired properties. The discovery, development, and application of natural drugs have been carried out for thousands of years. One of the most fruitful paradigms for the discovery of new bioactive chemical entities is to start with established structural cores, known to be part of other bioactive molecules.[1] Cinnoline moiety, most commonly found in fluorescent chemicals, biologically active molecules, and other functional materials.[2–4] None of the cinnoline (**1,**1,2-diazanaphtalene or benzo[c] − 1,2-diazine), derivatives are found in nature. Hence, cinnolines were designed as analogs to quinoline and isoquinoline derivatives as they are isosteric to quinoline and isoquinolines. Richter and coworkers synthesized cinnoline derivatives for the first time in 1883.[5] Later on, its biological properties have been reported in the literature.[6,7] Recently, a series of cinnoline derivatives were reported as phosphodiesterase 10 A (PDE10A) inhibitors[8] and HNE inhibitors.[9] Cinnolines are known to exhibit antibacterial,[10] anti-inflammatory (**IV**),[11] antithrombotic,[12] anti-antimalarial,[13] anti-leukemic,[14] anti-tumor (**V**),[15] and CNS activities[16] (Figure 1). Owing to the significant biological activity, the chemistry of cinnoline has gained the enormous interest of medicinal chemists.

On the other hand, triazole derivatives have also gained much attention in heterocyclic chemistry due to their interesting chemical and structural properties and have been over the past years found to be wide applications in medicinal chemistry.[17] The 1,2,3-triazole heterocyclic scaffold plays an important role in agrochemical and pharmaceuticals containing anti-inflammatory,[18] anti-proliferative,[19] antiviral,[20] anti-HIV,[21] anticancer,[22] fungicidal,[23] and insecticidal[24] activity (Figure 2). Therefore, the amenable biological importance of these cinnolines and the medicinal importance of triazole heterocyclic moiety directed our attention to design and synthesize the cinnoline-4-substituted-1,2,3-triazole hybrid derivatives to evaluate their antibacterial activity.

Results and discussion

Chemistry

The present investigation focuses on the development of novel 4-(1*H*-1,2,3-triazol-4-yl)methoxy)cinnoline conjugates, starting from commercially available 2-aminobenzoic

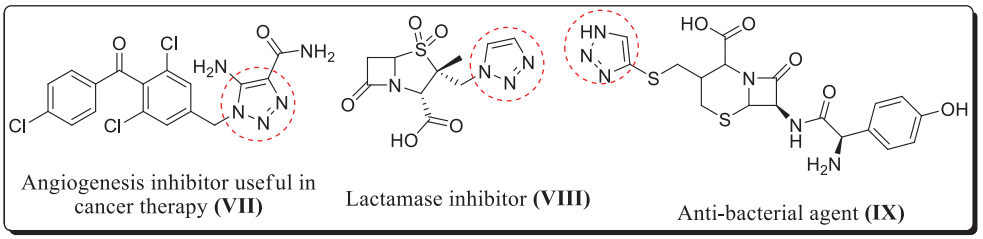
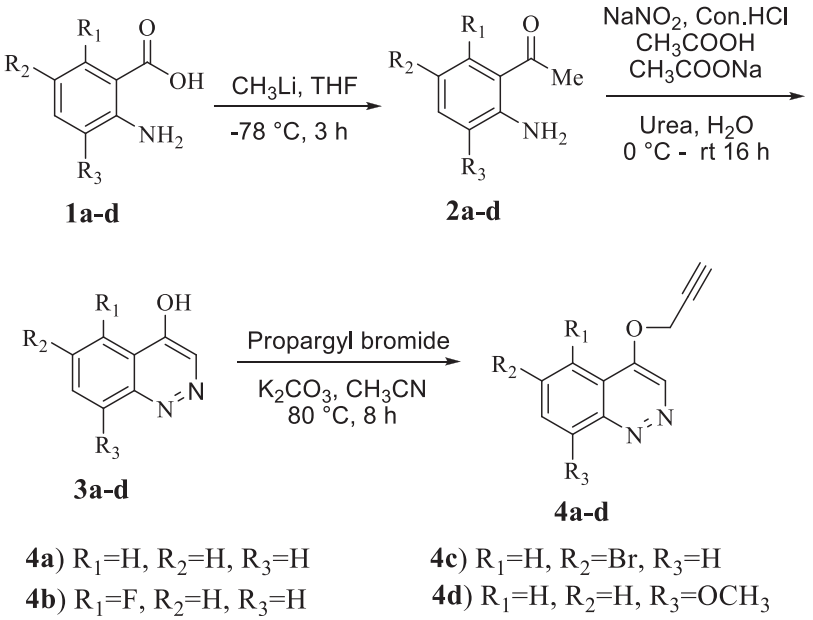


Figure 2. Some of the biologically active 1,2,3-triazole derivatives.

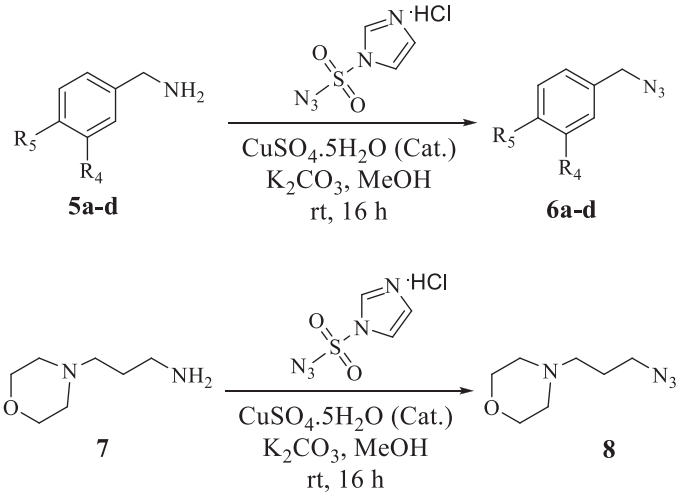


Scheme 1. Synthesis of alkyne partners **4a–d**.

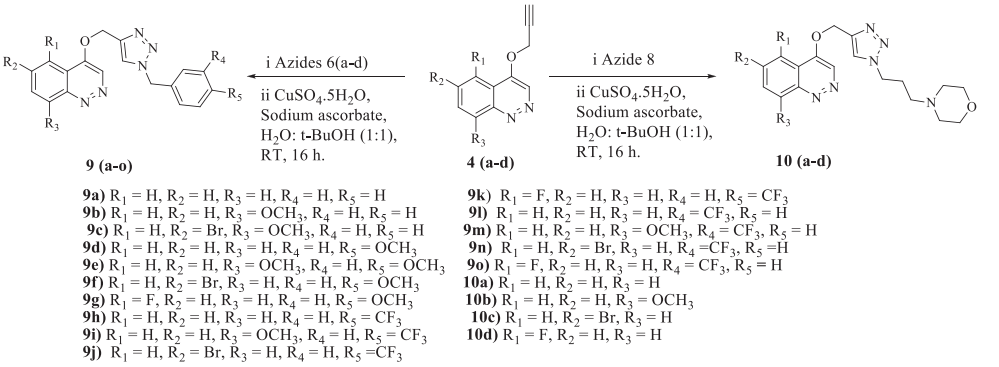
acid derivatives **1a–d** using 1,3-dipolar cycloaddition adopted with "Click reaction" as the key step.[25] Initially, the alkyne coupling partners **4a–d** were prepared in a stepwise manner starting from 2-aminobenzoic acid derivatives **1a–d** which were treated with a solution of methyllithium to provide 2-aminoacetophenones **2a–d** in moderate to good yields.[26] The aminoketones **2a–d** were further converted into the desired 4-hydroxy-cinnolines **3a–d** in good yields by diazotization/cyclization reaction.[27] Propargylation of the free hydroxyl group in **3a–d** with propargyl bromide in the presence of anhydrous K_2CO_3 in acetonitrile provided propargyl-cinnolines **4a–d** (Scheme 1).

The azide coupling partners (azidomethyl)benzenes **6a–d** and 4-(3-azidopropyl)morpholine (**8**) were prepared from corresponding amines **5a–d** and **7** using 1 *H*-imidazole-1-sulfonyl azide hydrochloride in the presence of $CuSO_4{\cdot}5H_2O$ in MeOH as shown in Scheme 2.[28,29]

Finally, the "Click reaction" was employed as the key step for the preparation of target compounds as outlined in Scheme 3. The reaction of azides **6a–d** and **8** with 4-(prop-2-yn-1-yloxy)cinnolines **4a–d** individually was carried out in the presence of catalytic amount of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in H_2O:*t*-BuOH (1:1 ratio) to



Scheme 2. Synthesis of azide partners **6a–d** and **8**.



Scheme 3. Synthesis of cinnoline-1,4-disubstituted-1,2,3- triazoles **9a–o** and **10a–d**.

render the corresponding cinnoline-4-substituted-1,2,3-triazole conjugates **9a–o** and **10a–d** as final products in moderate to good yields in the range of 38.9% to 68.9%. The plausible reaction mechanism for the formation of triazole ring was shown in Figure 3 although it is a known plausible reaction mechanism for triazole formation in literature.[30]

All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and Mass spectral analysis. The structure of 4-(prop-2-yn-1-yloxy-)cinnolines (**4a**) is explored in ^{1}H NMR spectra, the characteristic propargylic protons appeared at showed at δ 2.51 ppm as triplet and methylene protons appeared as doublet at δ 5.47 ppm, whereas the compound **9a**, the triazole proton of **9a** appeared as a singlet at δ 7.80 ppm, –OCH_2 appeared as singlet at δ 5.76 ppm and *N*-CH_2 appeared as singlet at δ 5.55 ppm, then again ^{13}C NMR showed carbon signals between δ 51.67 and δ 171.13 ppm that explored the presence of cinnoline as well as a –OCH_2 and 1,2,3-triazole ring. Moreover, the Mass spectral analysis showed that the molecular ion peak corresponding to the molecular mass of compound **9a**. Similarly, for compound **10a**, the characteristic proton of the newly formed triazole ring is appeared as a singlet at δ

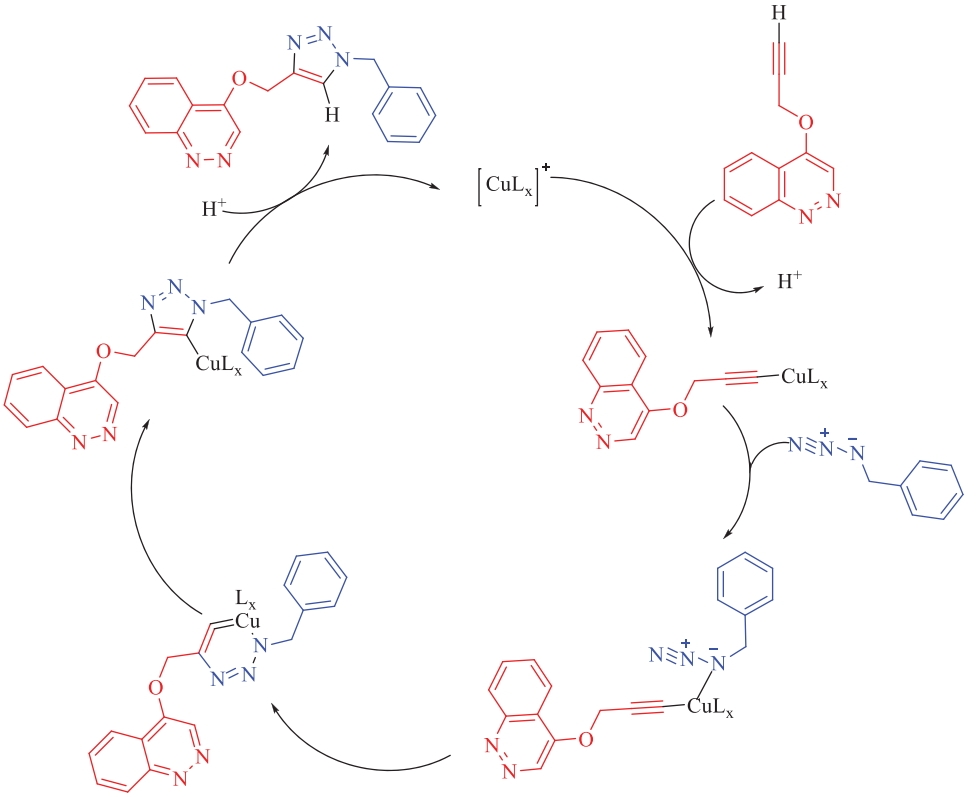


Figure 3. Plausible mechanism of 1,3-dipolar cycloaddition product formation.

7.51 ppm, whereas the $-OCH_2$ which was attached cinnoline ring resonated at δ 4.39 ppm, and the marpholine part of $-OCH_2$'s appeared at δ 3.63 ppm. Besides the ^{13}C NMR, Mass spectral analysis data confirmed that the formation of compound 10a from the reaction of **4a** and compound **8** in t-Butanol and water 1:1 ratio in the presence of $CuSO_4$.

Biological activity

Antibacterial activity

Inoculation of *Pseudomonas aeruginosa* (gram-negative), *Escherichia coli* (*E. coli*) (gram-negative), *Bacillus subtilis* (gram-positive), and *Staphylococcus aureus* (gram-positive) all microbes obtain from Microbial Type Culture Collection –MTCC. In auto calved LB broth media and Incubate overnight at 37°C in a shaker for Bacterial growth. From that, 0.3 mL of bacterial culture was taken and inoculated using spreader on freshly prepared auto calved agar plates, i.e., Petri dishes. After drying the plates, a 5-mm sample disc, which was dissolved in DMSO solvent, was kept on microbial plate along with positive controls NX (Norfloxacin) for *Staphylococcus* and *Pseudomonas*, and OF (ofloxacin) for *Bacillus* and *E. coli*, which were incubated overnight at 37°C in BOD incubator. After overnight incubation, zone of inhibition is measured using a measuring scale.

Table 1. Anti-bacterial activity of compounds **9a–o** and **10a–d**.[a]

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*Bacillus subtilis*	*Staphylococcus aureus*	*Pseudomonas Aeruginosa*	*Escherichia coli*
9a	–	–	–	–
9b	–	–	–	–
9c	–	–	–	–
9d	4.1	4.5	3.8	4.2
9e	–	–	–	–
9f	–	–	–	–
9g	3.1	–	–	4.0
9h	–	–	–	–
9i	–	–	–	–
9j	–	–	–	–
9k	3.0	3.0	–	–
9l	–	–	–	–
9m	–	–	–	–
9n	3.0	–	–	–
9o	–	–	–	–
10a	3.5	4.2	4.0	3.7
10b	5.2	5.5	5.6	4.8
10c	4.0	4.6	3.1	3.8
10d	3.9	3.5	–eth]	–
Norfloxacin	6.1	6	6.4	7

[a]Zone of inhibition (mm) 10 µg/mL concentrations.

All the synthesized compounds were screened for their ability in *in vitro* assays for their anti-bacterial[31] activity against two different gram-positive bacterial strains [*B. subtilis*; *S. aureus*] and two gram-negative bacterial strains [*P. aeruginosa*; *E. coli*]. The strains used for the activity procured from IMT, Chandigarah. Cultures of test organisms were maintained on nutrient agar (bacterial) subcultured in Petri dishes prior to testing. The compounds are tested at concentrations of 10 µg/mL using DMSO as a solvent. The zone of inhibition (in mm) was compared with standard drug Norfloxacin. The results are given in Table 1. Among all, the compounds **9d, 10a 10b,** and **10c** have shown an excellent zone of inhibition against *P. aeruginosa* bacterial strain, and these compounds also have shown good bacterial activity. The compound **9d** has shown 4.0 mm zone of inhibition against *E. coli* bacterial strain. Remaining derivative compounds have shown moderate antibacterial activity. Morpholine moiety containing Cinnoline-triazole conjugates as the side chain exhibited enhanced activity when compared to other molecules.

Molecular docking studies

Exploration of the molecular interaction of the compounds was performed through molecular docking studies. To study the molecular interaction of compounds, crystallographic data of Elastase of *P. aeruginosa* (PDB:1U4G) was retrieved from Protein Data Bank (DOI: 10.2210/pdb1U4G/pdb). The docking study of antibacterial active compounds **9d**, **10a**, **10b,** and **10c** with Elastase revealed the high docking score (LibDock)[32] and binding affinity, in the range of 110.706–129.425, as compared to known antibiotic drug. Norflaxacin 135.922 (Table 2). The best conformations with H-bond interactions obtained for docked compounds are shown in Figure 4. These results indicate that most of the compounds bound within the binding site pocket of reference

Table 2. Details of LibDock score and ligand interaction data revealed through molecular docking of title derivatives on Elastase of *Pseudomonas aeruginosa* (PDB: 1U4G).

Compound	Lib Dock score	Interacting atoms	Bond distance	No. of H-bonds
9a	110.706	A:ARG198:HH12–16a:O11	2.360000	1
		16a:H32–A:ARG198:HH12	1.606000	
		16a:H29–A:GLY187:CA	2.191000	
		16a:H31–A:HIS140:ND1	2.083000	
10a	116.347	A:ARG198:HH12–19a:O11	2.322000	1
		19a:H35–A:TYR114:HA	1.696000	
		19a:C3–A:VAL137:HG23	2.043000	
10b	129.425	A:GLY187:HN–19b:O24	2.467000	2
		A:ARG198:HH12–19b:N21	2.261000	
		19b:H36–A:ARG198:HH22	1.553000	
		19b:H44–A:GLY187:HA2	1.461000	
		19b:O24–A:GLY187:N	2.285000	
10c	123.732	A:HIS140:HD1–19c:Br27	2.320000	2
		A:ARG198:HH12–19c:O11	2.000000	
		19c:H29–A:GLY187:CA	1.985000	
		19c:H29–A:GLY187:HA1	1.372000	
		19c:H37–A:TYR114:HA	1.541000	
		19c:H41–A:HIS144:CG	2.139000	
Norflaxacin	135.922	A:GLY187:HN–Nor:N6	2.369000	3
		A:ASN112:HD22–Nor:O2	2.410000	
		A:ASN112:HD22–Nor:O3	0.860000	
		Nor:H41–A:HIS140:NE2	1.740000	

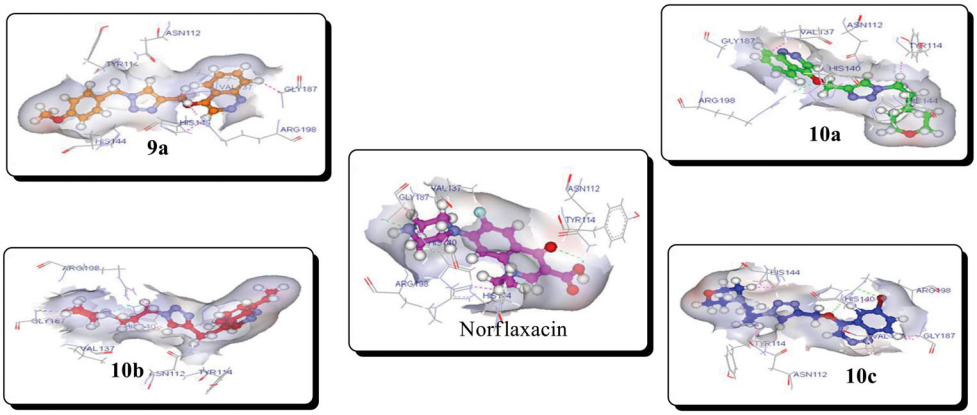


Figure 4. Receptor-ligand hydrogen bonds (green color) and bumps (pink color) of compounds **9d, 10a, 10b, 10c** and norfloxacinwith active site residues of Elastase of *Pseudomonas aeruginosa* (PDB: 1U4G).

and similar binding pattern with binding site amino acid residues. All the docked compounds have a significant binding affinity on selected target infers that these compounds are very active and can be potential leads against antibacterial. Docking analysis of all the compounds with the Elastase of *P. aeruginosa* revealed that the compound **10b** fitted well in the active site pocket, showing the best docking score of 129.425, which is closest to Norflaxacin which has a docking score of 135.922. From Figure 4, it is revealed that two hydrogen bonds and three close contacts are formed between compound **10b** with the protein. The first hydrogen bond is formed with the amino acid Gly187 of the Elastase. This bond is formed between the hydrogen atom of nitrogen

molecule of the amino acid Gly187 with the 24th oxygen atom of the compound **10b** (GLY187:HN-10b:O24) with a hydrogen bond distance of 2.467 Å, and the second hydrogen bond formed in between ARG198:HH12-10b:N21 with a hydrogen bond distance 2.261 Å. In addition to that, the compound **10b** also formed three close contacts with Arg198 and Gly187 amino acid residues of the target protein.

Conclusions

In conclusion, we have developed simple and efficient method for the synthesis of novel 4-((1-alkyl-1*H*-1,2,3-triazol-4-yl)methoxy)cinnolines **9a–o** and **10a–d**. All the synthesized compounds are screened for their antibacterial activity. Among the series of compounds, halogen-containing groups and electron-donating group ($-OCH_3$) on either of cinnoline/aromatic moiety derivatives **(9d, 9g,** and **9k)** have enhanced the anti-bacterial activity. Moreover, it is clear that the morpholine side chain containing cinnoline-triazole derivatives **(10a–c)** has more potent anti-bacterial activity. Molecular docking analysis of these compounds also well supported the experimental screening results of four different bacterial strains. Among all those compounds, **10a** fitted well in the active site pocket of Elastase of *P. aeruginosa*, showing the best docking score of 129.425. The potent antibacterial activity of these cinnoline-triazole derivatives suggests that they are potential candidates for further development of new antibiotic drugs.

Experimental

Instrumentation and chemicals

All chemicals used were of laboratory grade and used without further purification. Melting points of compounds were determined in open capillary tubes in a silicon oil bath using a Veego melting point apparatus and are uncorrected. The purity of compounds was monitored using TLC on silica F254 coated aluminum plates (Merck) as adsorbent and U.V. light and iodine as visualizing agents. ^1H and ^{13}C NMR spectra were recorded on Varian mercury TH-300 operating at 400 MHz (^1H NMR) and 101.6 MHz (^{13}C NMR) using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard (Chemical shift in ppm).

General procedure for synthesis of 4-(1H-1,2,3-triazol-yl)methoxy)cinnoline conjugates (9a–o and 10a–d)

To the stirred suspension of 4-(prop-2-yn-1-yloxy)cinnoline (**4a–d**) (0.81 mmol) in H_2O:*t*-BuOH (1:1 ratio) in 50 mL round bottom flask, azidomethyl benzene (**6a–d/8**) were added (1.22 mmol), followed by addition of sodium ascorbate (4.07 mmol), and $CuSO_4.5H_2O$ (1.63 mmol). The resulting mixture was stirred at room temperature for 6–6 h, then the reaction mixture was diluted with H_2O (10 mL) and extracted into DCM (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered off, concentrated, and purified using Flash chromatography to afford respective desired compounds **9a–o/10a–d** in moderate to good yields.

4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)cinnoline (9a)

Yield (46.5%), *m.p.* 120–130 °C. Brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1 H, Ar), 8.11 (d, $J = 8.0$ Hz, 1 H, **Ar**), 7.96 (d, $J = 8.8$ Hz, 1 H, **Ar**), 7.83 (d, $J = 7.2$ Hz, 2 H, **Ar**), 7.49 (t, $J = 7.6$ Hz, 1 H, **Ar**), 7.33 (t, $J = 7.2$ Hz, 3 H, **Ar**), 7.26 (d, $J = 6.8$ Hz, 2 H, **Ar**), 5.76 (s, 2 H, **–OCH2**), 5.55 (s, 2 H, **–NCH2**).^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.7, 140.5, 140.4, 134.1, 134.0, 129.2, 128.9, 128.1, 125.7, 125.1, 124.6, 122.5, 115.6, 54.4, 51.6. ESI-MS: *m/z* 318.0 $[M + H]^+$. Anal. Calcd for ($C_{18}H_{15}N_5O$). C: 68.13; H: 4.76; N: 22.07. Found. C: 68.20; H: 4.41; N: 22.20%.

Full experimental details: characterization data and copies of ^{1} H, ^{13}C NMR and MS spectra for all novel synthesized compounds have been submitted along with the manuscript. This material can be found via the "Supplementary Content" section of this article's webpage.

Acknowledgments

Authors, Mohan Babu thanks to, Head Department of Chemistry, CFRD Osmania University, Hyderabad, Telangana, India for providing facilities.

ORCID

Sudhakar Mokenapelli http://orcid.org/0000-0001-9575-4830
Prasad Rao Chitneni http://orcid.org/0000-0003-0062-9856

References

[1] Matthew, E. W.; Scott, A. S.; Brent, R. S. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.
[2] Holland, D.; Jones, G.; Marshall, P. W.; Tringham, G. D. *J. Med. Chem.* **1976**, *19*, 1225–12258. DOI: 10.1021/jm00232a011.
[3] Barbara, P.; Cristina, C.; Chandrakant, S.; Virginia, S.; Alessandra, M.; Paola, B.; Girolamo, C.; Patrizia, D.; Anna, C. *ARKIVOC* **2014**, *5*, 384–398.
[4] Smith, C. R.; Dougan, D. R.; Komandla, M.; Kanouni, T.; Knight, B.; Lawson, J. D.; Sabat, M.; Taylor, E. R.; Vu, P.; Wyrick, C. *J. Med. Chem.* **2015**, *58*, 5437–5444. DOI: 10.1021/acs.jmedchem.5b00734.
[5] Richter, V. *Chem. Ber.* **1883**, *16*, 677–684. DOI: 10.1002/cber.188301601154.
[6] Jacobs, T. L. In *Heterocyclic Chemistry*, Gilchrist, T.L., Eds.; **1957**. Chapter 6.
[7] (a) Castle, R. N. New York, 1973.(b) Katritzky, A. R. In *Handbook of Heterocyclic Chemistry*; Katritzky, A. R., Ed. Pergamon Press: Oxford, 1985.
[8] Yang, H.; Murigi, F. N.; Wang, Z.; Li, J.; Jin, H.; Tu, Z. *Z. Bioorg. Med. Chem. Lett.* **2015**, *25*, 919–924. DOI: 10.1016/j.bmcl.2014.12.054.
[9] Jakhar, A.; Makrandi, J. K. *Indian J. Chem.* **2012**, 313–318.
[10] Ryu, C. K.; Lee, J. Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1850–1853. DOI: 10.1016/j.bmcl.2006.01.005.
[11] Tonk, R. K.; Bawa, S.; Chawla, G.; Deora, G. S.; Kumar, S.; Rathore, V.; Mulakayala, N.; Rajaram, A.; Kalle, A. M.; Afzal, O. *Eur. J. Med. Chem.* **2012**, *57*, 176–1784. DOI: 10.1016/j.ejmech.2012.08.045.
[12] Pinna, G. A.; Curzu, M. M.; Fraghi, P.; Gavini, E.; Amico, M. D. *Farmaco* **1996**, *51*, 653–664.
[13] Maria, P. G.; Igor, A. S.; Letizia, C.; Giovanna, C.; Agostino, C.; Gabriella, G.; Andrei, I. K. T.; Mark, Q.; Claudia, V. J. *Med. Chem.* **2016**, *31*, 628–635.

[14] Stefanska, B.; Arciemiuk, M.; Bontemps-Gracz, M. M.; Dzieduszycka, M. *Bioorg. Med. Chem.* **2003**, *11*, 561–572. DOI: 10.1016/S0968-0896(02)00425-X.
[15] Bahner, C. T.; Rives, L. M.; McGaha, S. W.; Rutledge, D.; Ford, D.; Gooch, E.; Westberry, D.; Ziegler, D.; Ziegler, R. *Arzneimittelforschung.* **1981**, *31*, 404–412.
[16] KokaiTokkyoKoho, JpnJ. P 61280483. 1986 [*Chem. Abstr.* **1988**, 108 P131839].
[17] Hartmuth, C.; Kolb, K.; Barry, S. Drug Discov. Today 2003, *8*, 1128–1137. DOI: 10.1016/s1359-6446(03)02933-7.
[18] Shafi, S.; Mahboob, A. M.; Mulakayala, N.; Mulakayala, C.; Vanaja, G.; Kalle, A. M.; Pallu, R.; Alam, M. S. *Eur. J. Med. Chem.* **2012**, *49*, 324–331. DOI: 10.1016/j.ejmech.2012.01.032.
[19] Ying-Chao, D.; Yi-Chao, Z.; Xiao-Chen, L.; Meng-Meng, W.; Xian-Wei, Y.; Yuan-Yuan, G.; Gai-Zhi, L.; Jia-Xin, Z.; Hong-Min, L. *Eur. J. Med. Chem.* **2013**, *64*, 99–116.
[20] Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Eur. J. Med. Chem.* **2013**, *70*, 703–711. DOI: 10.1016/j.ejmech.2013.10.057.
[21] Pribut, N.; Veale, C. G. L.; Basson, A. E.; van Otterlo, W. A. L.; Pelly, S. C. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3700–3721. DOI: 10.1016/j.bmcl.2016.05.082.
[22] Yadav, P.; Lal, K.; Kumar, A.; Guru, S. K.; Jaglan, S.; Bhushan, S. *Eur. J. Med. Chem.* **2017**, *126*, 944–952. DOI: 10.1016/j.ejmech.2016.11.030.
[23] Wang, Z. J.; Gao, Y.; Hou, Y. L.; Zhang, C.; Yu, S. J.; Bian, Q.; Li, Z. M.; Zhao, W. G. *Eur. J. Med. Chem.* **2014**, *86*, 87–93. DOI: 10.1016/j.ejmech.2014.08.029.
[24] Aher, N. G.; Pore, V. S.; Mishra, N. N.; Kumar, A.; Shukla, P. K.; Sharma, A.; Bhat, M. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759–767. DOI: 10.1016/j.bmcl.2008.12.026.
[25] (a) Uttamchandani, M.; Lu, C. H. S.; Yao, S. Q. *Acc. Chem. Res.* **2009**, *42*, 1183–1192. DOI: 10.1021/ar9000586. (b) Kolb, H.; Finn, C.; Sharpless, M. G. K. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2004–2021. 2004. DOI: 10.1002/1521-3773(20010601)40:11<2004::aid-anie2004>3.3.co;2-x. (c) Lutz, J. F.; Zarafshani, Z. *Adv. Drug Deliv. Rev.* **2008**, *60*, 958–970. DOI: 10.1016/j.addr.2008.02.004. (d) Brissonnet, Y.; Mellet, C.; Morandat, S.; Moreno, M.; Deniaud, D.; Matthews, S.; Vidal, S.; Sestak, S.; Kirat, K.; Gouin, S. *J. Am. Chem. Soc.* **2013**, *135*, 18427–18435. DOI: 10.1021/ja406931w. (e) Bhaskar, K.; Naveen, P.; Perla, R.; Hasithashilpa, A.; Perumal, Y.; Anireddy, J. S.; Sravanthi, D. G.; Bathini, B. N. *RSC Adv.* **2017**, *7*, 11543–11549. DOI: 10.1039/C6RA27974K. (f) Bhaskar, K.; Perla, R.; Rayam, P.; Allaka, T. R.; Hasithashilpa, A.; Perumal, Y.; Balasubramanian, S.; Sravanthi, D. G.; Bathini, N.; Anireddy, B. J. S. *Chemistry Select* 2018, *3*, 5050. DOI: 10.1002/slct.201800459
[26] Juan, M. S.; Eduardo, B.; Vicente, G. F.; Vicente, G. *Org. Lett.* **2012**, *14*, 1444–1447.
[27] Barbagallo, E.; Legeay, C.; Rinaldi-Carmona, M.; Roux, P.; Vernhet, C. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 919–924. DOI: 10.1016/j.bmcl.2014.12.054
[28] Mohamed, R.; Aly, E. I. S.; Ali, S. H.; Abdel-Hafez, S. H. *Beilstein J. Org. Chem.* **2015**, *11*, 1922–1931. DOI: 10.3762/bjoc.11.208.
[29] (a) Ethan, D.; Borger, G.; Stic, R. V. *Org. Lett.* **2007**, *9*, 3797–3800. (b) Devine, W.; Woodring, J. L.; Swaminathan, U.; Amata, E.; Patel, G.; Erath, J.; Roncal, N. E.; Lee, P. J.; Leed, S. E.; Rodriguez, A.; et al. *J. Med. Chem.* **2015**, *58*, 5522–5531. DOI: 10.1021/acs.jmedchem.5b00515.
[30] Rostovtsev, V. V.; Luke, G. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. DOI: 10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4.
[31] Gomes, A. T.; Smânia, J. A.; Seidel, C.; Smâni, E. F. A.; Honda, N. K.; Roese, F. M.; Muzzi, R. M. *Braz. J. Microbiol.* **2003**, *34*, 194–202. DOI: 10.1590/S1517-83822003000300002.
[32] Cleidson, V.; Simone Machado, d. S.; Elza, F. A. S.; Artur, S. *Brazilian J. Microbiol.* **2007**, *38*, 369–380.