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Cinnoline Derivatives as Antibacterial Agent and Antimycobacterial Agent: Synthesis, Microbial Evaluation and Molecular Docking Study

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ABSTRACT

Fourteen Novel cinnoline library compounds were designed, synthesized through a facile approach, and allowed for screening for anti-bacterial activity and anti-tubercular activity. The titled compounds were entirely synthesized by replacing alkyl groups, sulphonyl, halo groups in the 6th & 7th position of cinnoline moiety. The enlightenment of structure was done by FTIR HNMR along with elemental analysis and further docked for Structural activity. The newly synthesized Cinnoline Compounds were examined for their in vitro drug-sensitive M tuberculosis H37Hv strain. All the compounds have shown MIC between >100-12.5 μg /ml. In this investigation, we Evaluated all the compounds for Anti-bacterial activity. The main compounds were initially tested in vitro for Anti-bacterial activity against gram-positive and gram-negative bacteria by using the Disk plate method. The most active Compound 10 exhibited 12.5 μg /ml inhibitions against drug-sensitive M Tuberculosis H37Rv strain. Among all synthesized compounds CN-7 was found to be a Hit compound with MIC value 12.5 ug/ml Against E Coli.

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INTRODUCTION

The main challenge in the world now a day is about infectious diseases and the pathogens which are resistant to drugs that are known (Wiederhold, 2017). Anti-bacterial agent (Cinnolines) is discovered through this development which inhibits DNA gyrase (Lewgowd and Stanczak, 2007). Mycobacterium Tuberculosis (MTB) which an intracellular bacterium causes Tuberculosis. According to WHO, TB was considered as a global health crisis. Tuberculosis was the reason for deaths in women mostly between the ages of 15-44. Most of the reported TB cases are from countries that are under development.TB is one of the dreadful diseases which affected one-third of the world's present population (World Health Organization, 2017). Well Treatment of TB includes a multidrug regimen(isoniazid, rifampicin, pyrazinamide, ethambutol). Treatment requires time as well as continuous monitoring of at least six months. Depending on the Upton body's immune system, the reappearance of symptoms of TB varies from patient to patient. There is a deadly need to synthesize effective drugs with less cost and rapid cure within less time (Fan *et al.*, 2018). The cinnoline core has anti-bacterial (Vargas *et al.*, 2008), antitumor (Satyanarayana *et al.*, 2008), antifungal (Pavadai *et al.*, 2012), and anti-inflammatory activities (Chaudhary *et al.*, 2014). Cinnolines also exhibit antituberculosis activity (Ramalingam *et al.*, 2006), and also possess anaesthetizing (Gomtsyan *et al.*, 2005) and even as a sedative activity (Alvarado *et al.*, 2006). Provoked by the synthesis of cinoxacin (Figure 1) by Giamarellou and Jackson (1975) evaluation of its anti-bacterial activity driven our research proposal to synthesize new compounds of scheme-1 with high yield and better potency (Tonk *et al.*, 2012).

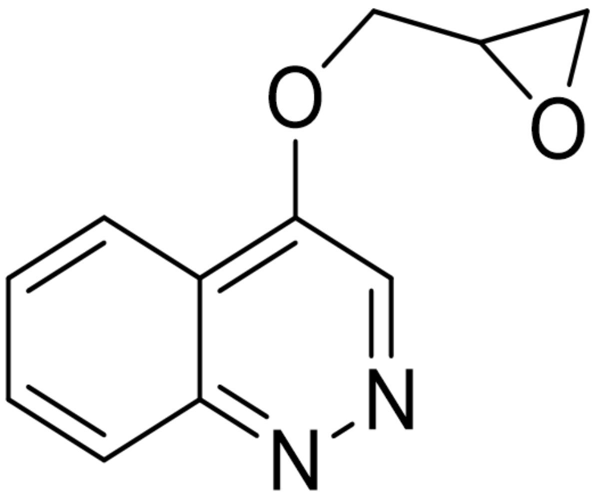

Figure 1: Structure of 4-(oxiran-2-ylmethoxy) cinnoline

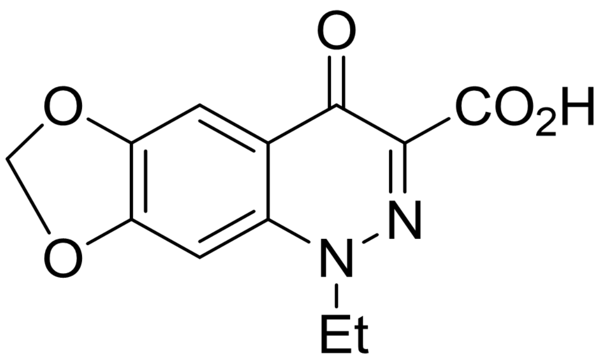

Figure 2: Structure of cinnoxacin

In drug discovery, cinnolines are most commonly used by a slight modification of an already existing one. As per published articles, lipophilicity is the major reason for activity in cinnoline. Many kinds of literature support the activity of cinnoline. In the light of previously published articles, cinnolines are revealed as efficient analogue which intrigued us to design and synthesize new derivatives. Besides, cinnolines have been remarkably active against E.coli (Bekhit, 2001). Because of the interest in an exploited anti-bacterial activity. Cinnolines paved its way towards the research path (Barraja *et al.*, 1999). These findings envisaged us to construct a novel molecular framework that contains cinnoline ring systems in the matrix with the hope of developing a compound that possesses better anti-bacterial activity. The breakthrough development of cinnoline moiety has intrigued us to synthesis A new series of cinnoline frameworks and evaluated for antimycobacterial activity, and the primary target of isoniazid (INH) is Mycobacterium tuberculosis enoyl-acyl-ACP reductase (InhA) (Hu *et al.*, 2017).

Provoked by the synthesis of cinoxacin (Figures 1 and 2) by Giamarellou and Jackson (1975) and evaluation of its anti-bacterial activity driven our research proposal to synthesize new compounds of scheme-1 with high yield and better potency.

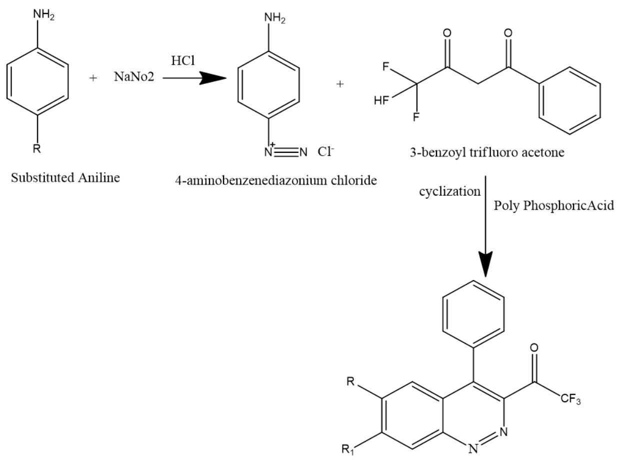

Figure 3: Scheme for the synthesis of cinnoline derivatives

Chemistry

In these studies, Novel cinnoline compounds are designed and synthesized (Figure 3). The strategy of Synthesized compounds were given in Scheme -1. Afforded compounds CN (1-14) were reacted with different substituted aniline in the presence of sodium nitrite and Hcl.

The diazonium salt formed is allowed for cyclization reaction through 3-benzoyl trifluoro acetone in the presence of polyphosphoric acid.

The purity of compound checked through TLC, and FTIR and proton NMR confirmed *the structures* of synthesized compounds.

Experimental protocols

The various materials used in the synthesis purchased from respective vendors like sodium nitrate (Merck, Hyderabad, India), 3- benzoyl trifluoro acetone (Merck, Hyderabad, India), (para Nitro *Aniline* (Loba Chemie, Mumbai, India), polyphosphoric acid (Otto Chem, Mumbai, India), *Sulfuric* acid (Loba Chemie, Mumbai, India), agar, beeswax, tragacanth gum (LobaChemie, Mumbai, India).

All reagents were analytical grades along with chemicals.

Synthesis of 2,2,2-trifluoro-1-(6-Substituted-4-phenyl cinnolin-3-yl)ethanone (CN1-14)

Substituted anilines (R1, R2) (0.1 mmol) was added to 5ml of Hcl (200ml) in cooled condition. To this sodium nitrite solution was added with stirring while the temperature is maintained below 5°c. To the diazonium salt (0.1Mol) of 3-benzoyl trifluoro acetone and of 2g of phosphoric acid was allowed to condense for 1hr.

The reaction progress was continuously monitored by TLC and then allowed recrystallization using ethanol, and finally, the reaction. Compounds CN (1–14) were prepared by a similar procedure by substituting the R alkyl group (Table 1).

The structure of the compound (1-14) has been confirmed based on analytical and spectral IR, 1H NMR, and Mass data. Synthesized compound properties. Physical properties and IUPAC names are illustrated (Table 1) (Awad *et al.*, 2011).

2,2,2-trifluoro-1-(6-nitro-4-phenylcinnolin-3-yl)ethanone(CN-1)

Yield 61%; M p; 159; IR (KBr, cm-1)1535 (N=N), 800 (C-S), 1609.31 (C=N Stretching),1385.6 (NO2 stretching),1601(C=O), 2862 (CH_3),1215 (C-F),1021.12 (N-N Stretching), 1H-NMR (CDCl3) 8.70 (s,1H,Ar), 8.26 (d,1H,Ar), 8.53 (d,1H,Ar), 7.40-7.52 (m,5H,Ar) *m/z: 347.05* C, 55.34; H, 2.32; F, 16.41; N, 12.10; O, 13.82

1-(6-amino-4-phenyl cinnolin-3-yl)-2,2,2-trifluoroethanone(CN-2)

Yield 66%; M p; 185 IR(KBr, cm1) 3199.33 (NH stretching), 1535(N=N), 800 (C-S), 1609.31 (C=N Stretching),1601 (C=O), 2862(CH_3),1215 (C-F),1021.12 (N-N Stretching),1H-NMR (CDCl3), 7. 92 (d,1H,Ar), 7.16 (t,1H,Ar), 6.92 (s,1H,Ar), 6.25 (s,1H,NH_2), 7.40-7.53 (m,5H,Ar) m/z: 317.08 C, 60.57; H, 3.18; F, 17.96; N, 13.24; O, 5.04

2,2,2-trifluoro-1-(6-methyl-4-phenylcinnolin-3-yl)ethanone(CN-3)

Yield 65%; Mp; 197; IR (KBr,cm; 1316.28 (NHstretching), 746 (C-Cl),1535 (N=N), 800 (C-S), 1609.31 (C = N Stretching),1601 (C=O), 2862 (CH_3), 1215 (C-F), 1021.12 (N-NStretching), 1H-NMR (CDCl3) 8.01 (d,1H,Ar), 7.40-7.58 (m,7H,Ar), 2.32 (s,1H,CH_3) m/z: 316.28, C, 64.56; H, 3.51; F, 18.02; N, 8.86; O, 5.06.

1-(6-chloro-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone(CN-4)

Yield 68%; Mp; 212; IR (KBr,cm1) 1316.28 (NHstretching), 746 (C-Cl),1535 (N=N), 800(C-S),1609.31(C=NStretching), 1601(C=O), 2862(CH_3), 1215(C-F), 1021.12 (N-NStretching) 1H-NMR (CDCl3) 8.01 (d,1H,Ar), 7.74 (t,2H,Ar), 7 .40-7.53 (m,5H,Ar), m/z: 336.70, C, 57.08; H, 2.39; Cl, 10.53; F, 16.93; N, 8.32; O, 4.75

1-(6-bromo-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone(CN-5)

Yield 64%; Mp; 221; IR (KBr,cm1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601(C=O), 2862 (CH_3), 650 (C-Br), 1215 (C-F), 1021.12 (N-NStretching), 1H-NMR (CDCl3) 4.207.95-8.01 (m,2H,Ar), 7.86 (t,1H,Ar), 7 .40-7.52 (m,5H,Ar) m/z: 381.25, C, 50.42; H, 2.12; Br, 20.96; F, 14.95; N, 7.35; ,

2,2,2-trifluoro-1-(6-iodo-4-phenylcinnolin-3-yl)ethanone(CN-6)

Yield %57; Mp; 165; IR (KBr,cm1) 1316.28 (NHstretching), 746(C-Cl), 1535(N=N), 800(C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1100 (C-I), 1215 (C-F), 1021.12 (N-NStretching) 1H-NMR (CDCl3) 8.10 (t,2H,Ar), 7.85 (d,1H,Ar), 7 .40-7.52 (m,5H,Ar) C16H8F3IN2O, m/z: 428.15, C, 44.88; H, 1.88; F, 13.31; I, 29.64; N, 6.54; O, 3.74

4-phenyl-3-(2,2,2-trifluoroacetyl)cinnoline-6-carboxylic acid (CN-7)

Yield %65; Mp; 197; IR (KBr,cm1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching),1601 (C=O), 2862 (CH_3), 1215 (C-F), 1300(COOH), 1021.12 (N-NStretching) 10.5 (s,1H,OH), 1H-NMR (CDCl3) 8.61 (s,2H,Ar), 8.31 (d,1H,Ar), 7 .40-7.52 (m,5H,Ar) C17H9F3N2O3 m/z: 346.26, C, 58.97; H, 2.62; F, 16.46; N, 8.09; O, 13.86

2,2,2-trifluoro-1-(6-hydroxy-4-phenylcinnolin-3-yl)ethanone(CN-8)

Yield %57; Mp; 150; 1316.28 (NHstretching), 746 (C-Cl),1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 3200 (OH), 1021.12 (N-NStretching) 1H-NMR (CDCl3), 8.05 (d,1H,Ar), 7 .40-7.52 (m,5H, Ar, 7.03 (s,1H,Ar), 5.31 (s,1H,OH) C16H9F3N2O2 m/z: 318.25, C, 60.38; H, 2.85; F, 17.91; N, 8.80; O, 10.05

4-phenyl-3-(2,2,2-trifluoroacetyl)cinnoline-6-sulfonic acid (CN-9)

Yield %66; Mp; 206; IR (KBr,cm-1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 1350 (HSO3), 1021.12 (N-NStretching), 8.36-8.41 (m,3H,Ar), 7 .40-7.52 (m,5H,Ar), 2.1 (s,1H,OH), C16H9F3N2O4S, m/z: 382.02 C, 50.27; H, 2.37; F, 14.91; N, 7.33; O, 16.74; S, 8.39

4-phenyl-3-(2,2,2-trifluoroacetyl)cinnoline-6-sulfonamide(C N-10)

Yield %61; Mp; 221; IR (KBr,cm-1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1370 (SO2NH2), 1215 (C-F), 1021.12 (N-NStretching)) 8.41-8.36 (m,3H,Ar), 2.1(s ,1H,NH_2), 7 .40-7.52 (m,5H,Ar) C16H10F3N3O3S m/z: 381.33 C, 50.40; H, 2.64; F, 14.95; N, 11.02; O, 12.59; S, 8.41

1-(6-chloro-7-nitro-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone(CN-11)

Yield %67; Mp; 239,316.28 (NHstretching), 746(C-Cl), 1535(N=N), 800(C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 1021.12 (N-NStretching) *H-NMR (CDCl3)* 1 (s,1H,Ar), 7.91 (s,1H,Ar), 7 .40-7.52 (m,5H,Ar) C16H7ClF3N3O3 m/z: 381.69, C, 50.35; H, 1.85; Cl, 9.29; F, 14.93; N, 11.01; O, 12.58

1-(6-chloro-4-phenyl-7-(trifluoromethyl)cinnolin-3-yl)-2,2,2-trifluoroethanone(CN-12)

Yield %53; Mp; 169; 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 1021.12 (N-NStretching) 1H-NMR (CDCl3) 8.75 (s,1H,Ar), 7.96 (s,1H,Ar), 7 .40-7.52 (m,5H,Ar) C17H7ClF6N2O, m/z: 404.69 C, 50.45; H, 1.74; Cl, 8.76; F, 28.17; N, 6.92; O, 3.95

1-(7-chloro-6-fluoro-4-phenylcinnolin-3-yl)-2,2,2trifluoroethanone(CN13)

Yield %52; Mp; 187; IR (KBr,cm-1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 1021.12 (N-NStretching), 8.35 (d,1H,Ar), 7.37-7.52 (m,6H,Ar); C16H7ClF4N2O, m/z: 354.69C, 54.18; H, 1.99; Cl, 10.00; F, 21.43; N, 7.90; O, 4.51

1-(7-chloro-6-methoxy-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone(CN-14)

Yield %51; Mp; 182; IR (KBr,cm-1) 1316.28 (NHstretching), 746 (C-Cl), 1535 (N=N), 800 (C-S), 1609.31 (C=NStretching), 1601 (C=O), 2862 (CH_3), 1215 (C-F), 1021.12 (N-NStretching) C17H10ClF3N2O2 m/z: 366.72 C, 55.68; H, 2.75; Cl, 9.67; F, 15.54; N, 7.64; O, 8.731H-NMR (CDCl3) 8.35 (s,1H,Ar), 7 .40-7.52 (m,5H,Ar), 6.87 (s,1H,Ar), 3.62 (s,3H,CH_3)

Molecular Docking Studies

Structure-based drug design and molecular studies

Ligand docking studies were performed by Molegro Virtual Docker (MolegromApS, Aarhus C, and Denmark). Fourteen compounds selected from the search of a new ligand for GyrB ATPase (A domain of DNA Gyrase) inhibitor as a novel anti-bacterial drug-like candidate. The target Protein selected for docking studies is DNA Gyrase Subunit B (PDB ID: 4BAE). In the antimycobacterial activity, the target proteins selected for docking are DHFrase A (PDB ID:2CIG). The structures were drawn using Chem Draw version 12.0 and saved in mol format after minimization of energy. The structures were drawn using Chem Draw version 12.0 and saved in *mol* format after the minimization of energy. The 3D structures of target proteins were downloaded from the protein data bank PDB format. The selected chain in the target protein imported into the workspace. The present docking study was carried out first by creating a suitable surface, and binding pockets were predicted, and then ligand was allowed to be imported into the workspace. A grid generated the co-crystallized ligand in the binding pocket. Docking was carried out by setting some of the parameters like *the selection* of ligand*,* score function*,* binding site*,* algorithm search*,* No of runs*,* maximum interactions, population size*,* energy threshold*,* maximum steps*,* neighbour distance factor*,* pose clustering (Thomsen and Christensen, 2006). The resulting docking score (moldock) of the ligand was allowed to compare against the crystallized ligand of protein present in ciprofloxacin, final docking results recorded in (Table 2) (Figure 4).

In silico pharmacokinetics(ADME)properties

The designed compounds are well predicted for their physicochemical properties using Swiss ADME online software. In the general human body, the receptor's pharmacokinetic properties are based on molecular properties. Lipinski introduced this rule for predicting the bioavailability of drugs like Molecule and some physicochemical properties. The Clog P value (1.92 to +5.31)*,* Molecular weight *(*316.28-404.69)*,* H bond donors *(*not more than 1)*,* HBA *(*not more than 9)*,* rotatable bonds *(*4 or fewer*)* polar surface area (equal to or & 1t;111.39 Å). Drugs can easily cross the BBB in the log p-value between 1.65 and 2.86. According to John, the drugs possessing log p-value 1.5 to 2.5 can cross the BBB easily (Daina *et al.*, 2017). According to silico ADME report, all the synthesized signalling compounds obeyed Lipinski's rule of five; as a result, these obtained compounds can absorb orally, and it can reach its desired target site by crossing the BBB (Table 3).

Antimicrobial Activity

All the synthesized compounds were evaluated by disk plate method according to standard proce-

Table 1: Physical properties of Synthesized Compounds

S. No.	Compound	R	R^1	Name of the compound(iupac)	Molecular formula	Molecular weight	Melting point	% yield
1	CN-1	NO_2	-	2,2,2-trifluoro-1-(6-nitro-4-phenylcinnolin-3-yl)ethanone	C16H8F3N3O3	347.25	159	61
2	CN-2	NH_2	-	1-(6-amino-4-phenyl quinoline-3-yl)-2,2,2-trifluoroethanol	C16H10F3N3O	317.27	185	66
3	CN-3	CH_3	-	2,2,2-trifluoro-1-(6-methyl-4-phenylcinnolin-3-yl)ethanone	C17H11F3N2O	316.28	197	65
4	CN-4	Cl	-	1-(6-chloro-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone	C16H8ClF3N2O	336.70	212	68
5	CN-5	Br	-	1-(6-bromo-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone	C16H8BrF3N2O	381.15	221	64
6	CN-6	I	-	2,2,2-trifluoro-1-(6-iodo-4-phenylcinnolin-3-yl)ethanone	C16H8F3IN2O	428.15	165	57
7	CN-7	COOH	-	4-phenyl-3-(2,2,2-trifluoroacetyl)cinnoline-6-carboxylic acid	C17H9F3N2O3	346.26	197	65
8	CN-8	OH	-	2,2,2-trifluoro-1-(6-hydroxy-4-phenylcinnolin-3-yl)ethanone	C16H9F3N2O2	318.25	150	57
9	CN-9	SO_3H	-	phenyl3(2,2,2trifluoroacetyl) cinnoline-6- sulfonic acid	C16H9F3N2O4S	382.02	206	66
10	CN-10	SO_2NH_2	-	4-phenyl-3-(2,2,2-trifluoroacetyl)cinnoline-6-sulfonamide	C16H10F3N3O3S	381.33	221	61
11	CN-11	Cl	NO_2	1-(6-chloro-7-nitro-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone	C16H7ClF3N3O3	381.69	239	67
12	CN-12	Cl	CF_3	1-(6-chloro-4-phenyl-7-(trifluoromethyl)cinnolin-3-yl)-2,2,2-trifluoroethanone	C17H7ClF6N2O	404.69	169	53
13	CN-13	F	Cl	1-(7-chloro-6-fluoro-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone	C16H7ClF4N2O	354.69	187	52
14	CN-14	OCH_3	-	1-(7-chloro-6-methoxy-4-phenylcinnolin-3-yl)-2,2,2-trifluoroethanone	C17H10ClF3N2O2	366.72	182	51

dure (Gfeller *et al.*, 2014). Antibacterial activity is screened against *Bacillus subtilis* MTCC 441, *S. Aureus* ATCC 96, *E.coli* ATCC 8739, *K.pneumoniae* MTCC 109, (Table 4).Minimum inhibitory concentration (MIC) was determined and tabulated in (Table 4).

The standard drug used was ciprofloxacin. Experimental results revealed that all the cinnoline candidates had shown activity between range 12.5-100 μg/ml.

According to antimicrobial activity result, the main reason for the activity in compound-7 is because of the presence of Carboxylic group, which increases the lipophilic nature. In compound-11 electron, negative group chlorine enhanced the antimicrobial activity with MIC of 12.5 μg/ml.

Antimycobacterial Activity

MIC calculation of compounds 1–14 against M. tuberculosis was conducted with microplate Alamar blue assay (MABAMABA reports reveal that *the introduction* of sulfonamide moiety increased the antimycobacterial with *a MIC value* of 12. 5μg/ml.

Compound-11 had also shown remarkable activity

Table 2: Molecular docking reports for compounds CN (1-14) against protein DNA Gyrase B & DHFrase A

S.No	Binding Energy(Kcal/mol) PDB code: 4BAE	Residue involving H-bond	Binding Energy(Kcal/mol) PDB code: 2CIGDHRase	Residue involving H-bond
CN -1	-100.372		-138.979	Ala,Arg,Ser,Val
CN -2	-101.048	-	-128.048	-
CN -3	-93.015	-	-123.015	-
CN -4	-93.844	-	-113.844	-
CN -5	-93.672	-	-121.672	-
CN -6	-118.364	-	-108.364	-
CN -7	-135.44	Asn52	-139.382	Arg,Gly,Gln
CN -8	-105.21	-	-105.21	—
CN -9	-107.12	-	-107.12	—
CN-10	-101.22	–	-141.678	Ala,IIe,Asp,Tyr,Ser
CN -11	-128.534	Asn 52-	-139.666	Gln,Val,Arg
CN-12	-127.469	Ile 84,hr 169	-127.469	-
CN-13	-101.924	-	-101.924	–
CN-14	-101.821	-	-101.821	–

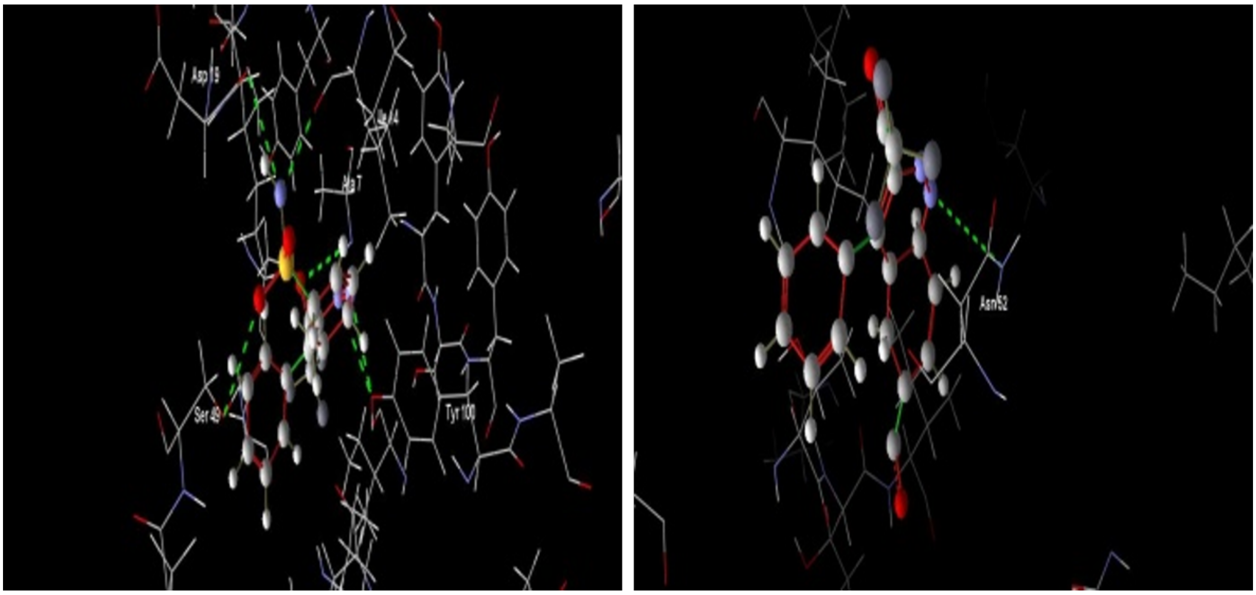

Figure 4: 2D plot of ligand-protein interaction profile by MVD. Visualization of hydrogen bond interaction between Compound-7 DNA Gyrase B Receptor (Ike 171, Thor 169), Compound-10 DHFrase A (Ala, IIe, Asp, Tyr, Ser). Hydrogen bonds are mentioned in discontinuous line in green colour.

Table 3: ***In silico*** **ADME properties of cinnoline compounds**

Compound Code	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	TPSA	Log $P_{o/w}$ (iLOGP)	BBB permanent
CN-1	347.25 g/mol	4	8	0	88.67 $Å^2$	2	NO
CN-2	317.27 g/mol	3	6	1	68.87 $Å^2$	2.01	YES
CN-3	316.28 g/mol	3	6	0	42.85 $Å^2$	2.69	YES
CN-4	336.70 g/mol	3	6	0	42.85 $Å^2$	2.78	NO
CN-5	381.15 g/mol	3	6	0	42.85 $Å^2$	2.85	NO
CN-6	428.15 g/mol	3	6	0	42.85 $Å^2$	2.84	YES
CN-7	346.26 g/mol	4	8	1	80.15 $Å^2$	1.95	NO
CN-8	318.25 g/mol	3	7	1	63.08 $Å^2$	2.09	YES
CN-9	382.02 g/mol	4	9	1	105.60 $Å^2$	1.65	NO
CN-10	381.33 g/mol	4	9	1	111.39 $Å^2$	1.69	NO
CN-11	381.69 g/mol	4	8	0	88.67 $Å^2$	2.12	NO
CN-12	404.69 g/mol	4	9	0	42.85 $Å^2$	2.87	NO
CN-13	354.69 g/mol	3	7	0	42.85 $Å^2$	2.66	NO
CN-14	366.72 g/mol	4	7	0	52.08 $Å^2$	2.86	NO

at the lowest MIC value due to *the chlorine atom* at its 6th position (Jones and Fuchs, 1976) .

Compound-7 has exhibited remarkable activity against standard drug isoniazid (Table 4).

RESULTS

The anti-bacterial activity was evaluated by the disk plate method for the compound (1-14). MIC values of all compounds are between 100 and 12. 5μg/ml. All compounds have shown promising activity, among all synthesized compounds, Compound-7 having a carboxyl group at 6th position *profounded* greater activity against gram -ve bacteria when compared with a standard drug with MIC 12. 5μg/ml against *E. coli.* Compound-11 also demonstrated as an outstanding compound possessing chlorine *atom* and *Nitro* group a 6th and 7th position with a better MIC value of 25 μg/ml against *E. Coli.* Compound-12 also showed the best activity with a MIC value of 25μg/ml, and also Significant MIC value is tabulated. Compounds are screened against M. *Tuberculosis* H37Rv by the MABA method. Surprisingly, all of the compounds reported MIC between 100 and 12.5 μg/ml. AN outstanding MIC value was noted for Compound-10 with 12. 5μg/ml.

DISCUSSION

The Mol Dock scores of the fourteen tested compounds range between -93 and -135 Docking studies were performed with anti-bacterial DNA gyrase B along with E. coli to understand the molecular activity of the compounds. According to docking studies carbonyl a group of Compound-7 interacted with Asn52 of nitrogen group compound-11 had shown interaction with Asn52 of nitrogen and oxygen atom compound-12 also shown three interactions.

Table 4: Anti-bacterial activity Zone of Inhibition data (mm) MIC data (μg/ml); MIC of Anti tubercular activity of Synthesized compounds

S.No	Anti-bacterial Activity MIC data (μg/ml)				Anti-bacterial activity Zone of Inhibition data (mm)				M.t MIC(μg/ml)
	B.s	S.a	E.c	k.p	B.s	S.a	E.c	k.p	m.t
CN-1	100	50	25	50	12	9	13	12	25
CN-2	50	100	50	100	10	11	13	14	100
CN-3	100	50	50	100	12	13	12	13	50
CN-4	50	100	25	50	10	11	14	13	100
CN-5	100	50	50	25	12	10	11	12	50
CN-6	50	50	25	50	13	14	18	11	100
CN-7	100	50	12.5	25	12	10	22	13	25
CN-8	50	100	50	100	12	11	14	11	50
CN-9	100	50	100	50	10	11	12	13	100
CN-10	50	100	100	50	13	12	13	14	12.5
CN-11	100	50	25	50	12	13	19	15	25
CN-12	50	25	25	50	11	12	14	11	50
CN-13	-	100	50	50	12	13	12	13	50
CN-14	50	100	100	50	11	10	13	11	100
Standard drugs Ciprofloxacin Isoniazid	3.7	3.8	3.5	3.5	25	25	25	25	6.5

Gram-positive: *Bacillus subtilis*, *Staphylococcus aureus*, Gram-negative: *Escherichia coli*, *Klebsiella pneumonia*; M.t: Mycobacterium tuberculosis H37Rv

Out of which two Interact with Ile 84 of an oxygen atom and another one with the 169 of nitrogen atoms. Based on the docking report Compound-7 was observed to be a potent compound against E Coli with possible interactions with the best docking score (Kannan *et al.*, 2018; Gautam and Chourasia, 2010). Docking studies with M. Tuberculosis DHFRase were performed to investigate the activity of the main compounds (Ramalingam *et al.*, 2006). Owing to the docking report of antimycobacterial activity, Ala-7 interacts with the oxygen atom of compound-10. All the synthesized compounds exhibited profound activity against microbes. Docking analysis supports anti-bacterial and antimycobacterial results.

Lead compound identification can be the best possible with the development of a cinnoline molecule by the optimization of pharmacodynamic and pharmacokinetic properties.

CONCLUSION

The present work depicts the significance of synthesized compounds with better activity against bacterial strains and mycobacterial strain when compared over the standard drug with a good percentage of yield. Novice cinnoline derivatives were synthesized possessing anti-bacterial activity and anti-tubercular activity. These derivatives had proven to be the best potent drug for fighting against microbes. The Mol Dock scores of the fourteen tested compounds range between -93 and - 135. All the synthesized compounds exhibited profound activity against microbes. Docking the analysis supports the anti-bacterial and antimycobacterial results. Lead compound identification can be the best possible with the development of signalling molecule by optimization of pharmacodynamic and pharmacokinetic properties. Titled compounds are afforded by substituting alkyl, halogen groups at 6th, and 7th position in the basic cinnoline moiety. Compound-7 had shown better activity with MIC 12. 5μg/ml against E. coli and compound-10 are found to be potent against Mycobacterial strain. In conclusion, the combination of two active rings displayed profound microbial activity.

Author Contribution

MP Evangelin proposed the study, constructed the study and performed the statistical analysis. K Balamurugan supervised, guided and managed the study. All authors organized the manuscript and this version of the article.

Ethics Approval and Consent to Participate

Not applicable.

Human and Animal Rights

No Animals/Humans were used for studies that are base of this research.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

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Conflict of Interest

The authors declare that there is no conflict of interest for this study.

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