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DESIGN, SYNTHESIS AND MOLECULAR DOCKING STUDIES ON NOVEL CINNOLINE DERIVATIVES AS POTENTIAL ANTITUBERCULOSIS AGENTS

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ABSTRACT: The emerging need for the multidrug regimen of *M. tuberculosis* strains urged us to synthesize novice and potent anti-tubercular medicaments. Our interest in this work had afforded a series of novice cinnolines as a new structural category of antituberculosis agents. All 14 compounds were synthesized using the appropriate scheme, two-step reactions with the high yielding product. The newly synthesized cinnoline Compounds were examined for their *in-vitro* drug-sensitive *M. tuberculosis* H37Hv strain. To date, evaluation of anti-tubercular activity various drugs in the multidrug regimen is on going out of which INH highly effective component drug and is advised by WHO. Some of the derivatives were considered to be promising inhibitors of *M. tuberculosis*. For example, the most active compound (CN-14) exhibited 12.5 µg/ml inhibitions against drug-sensitive *M. tuberculosis* H37Rv strain.

INTRODUCTION: *Mycobacterium tuberculosis* (MTB), in which an intracellular bacterium causes Tuberculosis. TB is considered as a global health crisis by the WHO. The main reason for death in the case of TB is due to a lack of better treatment to fight against strains of TB. Tuberculosis occupied the third position of death in women and mostly in between the ages of 15-44. Most of the TB cases are from developing states. TB is a dreadful disease in which one-third of the world population is affected by MT [1]. Treatment of TB included multi-drug regimen (Isoniazid, rifampicin, pyrazinamide, ethambutol). It is a long and time-taking method that requires continuous monitoring for at least six months. Depending on the upton body immune system the reappearance of symptoms of TB varies from patient to patient.

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There is a deadly need to synthesize effective drugs with less cost and rapid cure within less period of time [2]. A heterocyclic compound having two nitrogen atoms is cinnoline, which is light brownish in color acts as the building block for anti-tubercular drugs, benzo [c], and cinnolines hantsch widmann system is possessing molecular formula of $C_8H_6N_2$.

Complex diazo compounds result in nitrogenous basic organic compounds. It is compatible with quinoline and isoquinoline in structure and is non-toxic in nature. The first man who discovered the synthesis is Von Richter in the year 1883, declared the eminence of the core nucleus of cinnoline [3]. Cinnoline nucleus has antimicrobial [4] antitumor [5] anti-inflammatory [6], anti-tubercular [7]. Unnisa and her coworker have done synthesis and evaluated for anti-tubercular activity with low MIC value. Finding the cinnoline as the main scope of Anti-tubercular drug, a new series of cinnoline frame-work was designed, synthesized and evaluated. The primary target of isoniazid (INH) is Myco-bacterium tuberculosis enoyl-acyl-ACP reductase (InhA) [8].

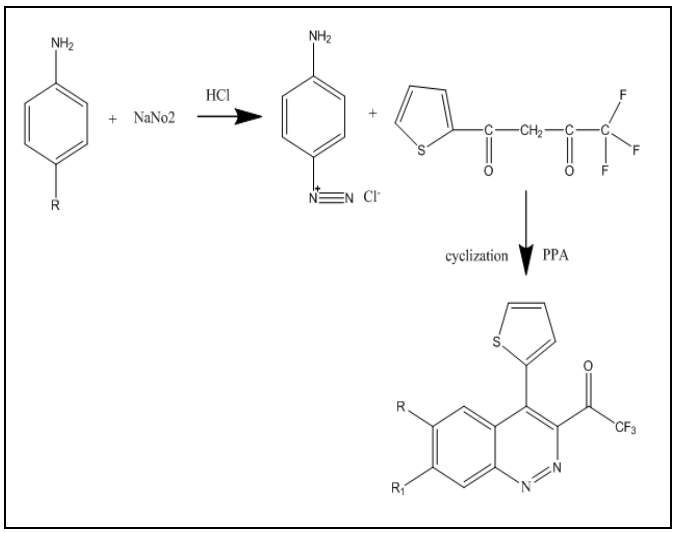


FIG. 1: SCHEME FOR SYNTHESIS OF CINNOLINE DERIVATIVES

MATERIALS AND METHODS:

Reagents and Chemicals: Various materials used for synthesis were purchased from respective vendors like sodium nitrate (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 (Loba Chemie, Mumbai, India). All reagents were analytical grades along with chemicals.

TABLE 1: LIST OF SYNTHESIZED COMPOUNDS

S. no.	R_1	R_2
1	NO_2	-
2	NH_2	-
3	CH_3	-
4	Cl	-
5	Br	-
6	I	-
7	COOH	-
8	OH	-
9	HSO_3	-
10	NH_2SO_2	-
11	Cl	NO_2
12	CH_3O	Cl
13	F	Cl
14	Cl	CF_3

TABLE 2: PHYSICAL PROPERTIES OF CINNOLINE COMPOUNDS

S. no.	Name of compound	Molecular formula	Molecular weight	Melting point	Boiling point	Perc yield
1.	CN-1	$C_{14}H_6F_3N_3O_3S$	353.28	123-125	81	78
2	CN-2	$C_{14}H_8F_3N_3OS$	323.29	105-108	89	76
3	CN-3	$C_{15}H_9F_3N_2OS$	322.30	115-118	83.	71
4	CN-4	$C_{14}H_6ClF_3N_2OS$	387.17	130-132	87	69
5	CN-5	$C_{14}H_6BrF_3N_2OS$	385.17	100-103	71	67
6	CN-6	$C_{14}H_6F_3IN_2OS$	433.92	106-108	90	68
7	CN-7	$C_{15}H_7F_3N_2O_3S$	352.29	112-114	97	77
8	CN-8	$C_{14}H_7F_3N_2O_2S$	324.29	125-126	88	72
9	CN-9	$C_{14}H_7F_3N_2O_4S_2$	387.72	121-124	107	75
10	CN-10	$C_{14}H_8F_3N_3O_3S_2$	385.0	208-210	105	78
11	CN-11	$C_{14}H_5ClF_3N_3O_3S$	387.73	211-213	121	79
12	CN-12	$C_{15}H_8ClF_3N2O_2S$	371.98	120-123	89	77
13	CN-13	$C_{14}H_5ClF_4N_2OS$	360.72	156-159	84	76
14	CN-14	$C_{15}H_5ClF_6N_2OS$	410.72	120-122	86	75

TABLE 3: IUPAC NAMING OF SYNTHESIZED COMPOUNDS

S. no.	IUPAC name of the compounds
1	2,2,2-trifluoro-1-(6-nitro-4-(thiophen-2-yl)cinnolin-3-yl)ethanone
2	1-(6-amino-4-(thiophen-2-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
3	2,2,2-trifluoro-1-(6-methyl-4-(thiophen-2-yl)cinnolin-3-yl)ethanone
4	1-(6-chloro-4-(thiophen-3-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
5	1-(6-bromo-4-(thiophen-2-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
6	2,2,2-trifluoro-1-(6-iodo-4-(thiophen-2-yl)cinnolin-3-yl)ethanone
7	4-(thiophen-2-yl)-3-(2,2,2-trifluoroacetyl)cinnoline-6-carboxylic acid
8	2,2,2-trifluoro-1-(6-hydroxy-4-(thiophen-2-yl)cinnolin-3-yl)ethanone
9	4-(thiophen-2-yl)-3-(2,2,2-trifluoroacetyl)cinnoline-6-sulfonic acid
10	4-(thiophen-2-yl)-3-(2,2,2-trifluoroacetyl)cinnoline-6-sulfonamide
11	1-(6-chloro-7-nitro-4-(thiophen-2-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
12	1-(7-chloro-6-methoxy-4-(thiophen-3-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
13	1-(7-chloro-6-fluoro-4-(thiophen-3-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone
14	1-(6-chloro-4-(thiophen-3-yl)-7-(trifluoromethyl)cinnolin-3-yl)-2,2,2-trifluoroethanone

Synthesis of 4-substituted Cinnoline Derivatives: Dissolve (0.1 mole) of Substituted aniline in a mixture of 5 ml of HCl (200 ml) and cooled to 0-5°C in an ice bath, and add a solution sodium nitrite in a (26 ml) of water in a small portion and maintain the temperature below 5 °C. Filter and recrystalize the crude extract with ethanol then (0.1 mole) reflux condenser, add (0.1 mol) of thenoyl trifluoride of 2 g of phosphoric acid and condense for 1 h. The reaction progress was continuously monitored by TLC and then allowed recrystallization using ethanol, and finally reaction mixture was added to the ice cold water and stirred well. Filter the solution using a glass funnel, drain well and wash the solid for 5-6 times with cold water, spread the solid upon absorbing filter paper and then allow it to dry overnight and collect the solid product [9]. **Scheme 1** Compounds CN (1–14) were prepared by a similar procedure by substituting R alkyl group **Table 1**. The structures of the compounds (1-14) have been confirmed on the basis of analytical and spectral IR, 1H NMR and Mass data. Synthesized compounds properties physical properties and IUPAC names are illustrated in **Table 2** and **3**.

2, 2, 2-trifluoro-1- (6-nitro-4- (thiophen-2-yl) cinnolin-3-yl) ethanone (CN-1): Yield 78%, Mp:123-125 IR (KBr) K_{max} in (cm) IR (KBr, cm^{-1}) 3199.33 (NH stretching), 800 (C-S),1251(C-F), 1609.31 (C=N is stretching), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 1601(C=O), 1535(N=N), 1H NMR (DMSO-d6, 300 MHz, d ppm) 8.80 (s, 1H.Ar H), 8.53 (t, 1H, Ar H), 8.27 (d, 1H, Ar H), 7.68 (d, 1H, thenoyl ring), 7.41 (t,1H,thenoyl ring), 7.16 (t, 1H, thenoyl ring) MS, m/z (%), 353(M+) Anal. Calcd. For $C_{14}H_6F_3N_3O_3S$: C, 47.60; H, 1.71; N, 11.89%.

1-(6-amino-4-(thiophen-2-yl)cinnolin-3-yl)-2,2,2-trifluoroethanol (CN-2): Yield 76%, M p:105-108 IR (KBr) K_{max} in (cm) IR (KBr, cm^{-1}) 3199.33 (NH stretching), 1535(N=N), 800 (C-S), 1251(C-F), 1601 (C=O), (1609.31 (C=N is stretching), 1601 (C=O), (1248.69 (OH bending), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 3199.33 (NH_2 stretching), 1H NMR (DMSO-d6, 300 MHz, d ppm) 8.80 (s,1H.Ar H), 8.53 (t, 1H, Ar H),8.27 (d, 1H, Ar H), 7.68 (d, 1H, thenoyl ring), 7.41 (t, 1H, thenoyl ring), 7.16 (t,1H,thenoyl ring), 6.26 (d, 2H, NH_2) MS, m/z (%), 32 3(M+) Anal. Calcd. For $C_{14}H_8F_3N_3OS$: C, 52.01; H, 2.41; N, 13.00%; O, 4.95; S, 9.92%.

2, 2, 2-trifluoro-1- (6-methyl-4-(thiophen-2-yl) cinnolin-3-yl) ethanone (CN-3): Yield 71% M p; 115-118; IR (KBr, cm^{-1}) 3199.33 (NH stretching), 1535 (N=N),800 (C-S), 1609.31 (C=N stretching), 1601 (C=O), 2862(CH_3), 1021.12(N-N Stretching), 758.85 (DI subs benzene), 3199.33 (NH_2 stretching) 1H NMR (DMSO-d6, 300 MHz, d ppm), 2.33 (Ss, 3H, CH_3), 7.16 (t,1H, thenoyl), 7.41 (d,1H, thenoyl), 7.52 (s,1H, Ar H),8.03 (d,1H,Ar H), 7.58 (m, 1H, Ar H). MS, m/z (%), 341.98 (M+) Anal. Calcd. for $C_{14}H_6ClF_3N_2OS$: C, 49.06; H, 1.71; Cl, 10.34%; O, 4.67; S, 9.36%.

1-(6-chloro-4-(thiophen-3-yl) cinnolin -3-yl)-2, 2, 2-trifluoroethanone(CN-4): Yield: 69; M p; 130-132IR (KBr) K_{max} in (cm) 3199.33 (NH stretching), 800 (C-S),1251 (C-F), 1601 (C=O), 1535 (N=N), (1609.31 (C=N stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 850 (C-Cl), 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.03 (d, 1H, Ar), 7.68-7.773 (3H, m, Ar), 7.41 (d, 1H, thenoyl),7.6 (t,1H,thenoyl). MS, m/z (%), 322 (M+) Anal. Calcd. for $C_{15}H_9F_3N_2OS$: C, 55.90; H, 2.81; N, 8.69%; O, 4.96; S, 9.95%.

1-(6-bromo-4-(thiophen-2-yl)cinnolin-3-yl)-2,2,2-trifluoroethanone (CN-5): Yield: 67; M p: 100-103; IR (KBr) K_{max} in (cm) 691(Br), 800 (C-S), 1535 (N=N), 1609.31 (C=N stretching), 1601 (C=O), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 3199.33 (NH_2 stretching), 1H NMR (DMSO-d6, 300 MHz, d ppm), 7.16 (t,1H,Ar),7.68-7.873 (2H, m, Ar), 7.41 (d,1H,thenoyl),7.68 (d, 1H, thenoyl). MS, m/z (%), 322(M+) Anal. Calcd. for $C_{14}H_6BrF_3N_2OS$: C, 43.43; H, 1.56; Br, 20.64, F, 14.74, N, 7.24%; O, 4.13; S, 8.28%.

2, 2, 2-trifluoro-1- (6-iodo-4 -(thiophen-2-yl) cinnolin-3-yl) ethanone (CN-6): Yield: 68; MP: 106-108; IR (KBr) K_{max} in (cm) 680.01(C-S), 1251 (C-F), 1601 (C=O), 1609.31 (C=N is stretching), 1535 (N=N), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.10 (m, 2H, Ar H),7.85 (d, 1H, Ar H), 7.68 (d, 1H, thenoyl),7.40 (d, 1H, thenoyl), 7.16 (t, 1H, thenoyl), MS, m/z (%), 433.92 (M+) Anal. Calcd. for $C_{14}H_6F_3IN_2OS$: C, 38.73; H, 1.39, F, 13.13, I, 29.23, N, 6.45%; O, 3, 69; S, 7.39%.

4-(thiophen -2-yl)-3-(2, 2, 2-trifluoroacetyl) cinnoline-6-carboxylic acid (CN-7): Yield: 77; M p: 112-114; IR (KBr) K_{max} in (cm), 690 (C-Br), 1252 (C=S), 1609.31 (C=N stretching), 1535 (N=N), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2 stretching), 1H NMR (DMSO-d6, 300 MHz, d ppm), 7.16 (t,1H,Ar), 7.68-7.873 (2H, m, Ar), 7.41 (d, 1H, thenoyl), 7.68 (d,1H,thenoyl). MS, m/z (%), 322 (M+) Anal. Calcd. for $C_{14}H_6BrF_3N_2OS$: C, 43.43; H, 1.56; Br, 20.64, F, 14.74, N, 7.24%; O, 4.13; S, 8.28 %.

2, 2, 2-trifluoro-1-(6-hydroxy-4-(thiophen-2-yl) cinnolin-3-yl)ethanone(CN-8): Yield:72;M p:125-126; IR (KBr) K_{max} in (cm) 1248.69 (OH bending), 1535 (N=N), 800 (C-S), 1609.31 (C=N stretching), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2 stretching), 1H NMR (DMSO-d6, 300 MHz, d ppm), 7.03 (S, 1H, Ar),7.16 (t, 1H, Ar), 7.31-7.43 (2H, m, Ar), 8.04 (d, 1H, Ar), 7.68 (d, 1H, thenoyl). MS, m/z (%), 324 (M+) Anal. Calcd. For $C_{14}H_7F_3N_2O_2S$: C, 51.85.43; H, 2.18; Br, 20.64, F, 17.58, N, 8.64%; O, 9.87; S, 9.89%.

4-(thiophen-2-yl) -3-(2, 2, 2-trifluoroacetyl) cinnoline-6-sulfonic acid (CN-9): Yield: 75; M.P; 121-124; IR (KBr) K_{max} in (cm) 460 (SO_3), 800 (C-S), 1609.31 (C=N stretching), 1535 (N=N), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2 stretching) 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.36-8.41 (m, 3H, Ar), 7.68 (d, 1H, thenoyl), 7.41 (1H, t, thenoyl), 7.16 (t, 1H, thenoyl). MS, m/z (%), 387(M+) Anal. Calcd. for $C_{14}H_7F_3N_2O_4S_2$: C, 43.30; H, 1.82; F, 14.68, N, 7.21%; O, 16.48; S, 16.51%.

4-(thiophen-2-yl) -3-(2, 2, 2-trifluoroacetyl) cinnoline-6 -sulfonamide(CN-10): Yield; 78; M.P: 208-210; IR (KBr) K_{max} in (cm) 1166 (SO_2NH_2), 800 (C-S), 1609.31 (C=N is stretching), 1535 (N=N), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2, stretching) 1HNMR (DMSO-d6, 300 MHz, dppm), 8.368.41 (m, 3H, Ar), 7.68 (d,1H,thenoyl), 7.41 (1H, t, thenoyl), 7.16 (t, 1H, thenoyl), 2.01 (S, 1H, NH_2) MS, m/z (%), 387(M+) Anal. Calcd. for $C_{14}H_8F_3N_3O_3S_2$: C, 43.41; H, 2.08; F, 14.71, N, 10.85%; O, 12.39; S, 16.56 %.

1-(6-chloro-7-nitro -4-(thiophen-2 -yl)cinnolin-3-yl) -2, 2, 2-trifluoroethanone(CN-11): Yield; 79; Mp: 211-213; IR (KBr) K_{max} in (cm) 800 (C-S), 1609.31 (C=N is stretching), 1535 (N=N), 1600.21 (C=OStr), 1359.79(NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2 stretching) 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.36-8.41 (m, 3H, Ar), 7.68 (d, 1H, thenoyl), 7.41 (1H, t, thenoyl), 7.16 (t,1H,thenoyl), 2.01 (s, 2H, NH2) MS, m/z (%), 387 (M+) Anal. Calcd. for $C_{14}H_5ClF_3N_3O_3S$: C, 43.37; H, 1.30; Cl, 9.14; F, 14.71, N, 10.85%; O, 12.39; S, 8.27%.

1-(7- chloro-6 -methoxy-4- (thiophen-3-yl) cinnolin-3-yl)-2, 2, 2-trifluoroethanone (CN-12): Yield: 77; M.P: 120-123; IR (KBr) K_{max} in (cm) Cl, CH 30 800 (C-S), 601(C-Cl), 1535 (N=N), 1609.31 (C=N stretching), 1359.79 (NO_2 stretching), 1248.69 (OH bending), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1393.32 (NO_2 stretching), 3199.33 (NH_2 stretching) 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.36 (s,1H,Ar), 7.68 (d,1H,thenoyl), 7.41 (1H, d, thenoyl), 6.96 (s, 1H, Ar), 7.16 (t, 1H, thenoyl), 3.82.01 (s, 3H, CH_3) MS, m/z (%), 371(M+) Anal. Calcd. for $C_{15}H_8ClF_3N_2O_2S$: C, 48.33; H, 2.16; Cl, 9.51; F, 15.29, N, 7.92%; O, 8.58; S, 8.60%.

1-(7-chloro-6- fluoro-4-(thiophen-3-yl) cinnolin-3-yl)-2, 2, 2-trifluoroethanone(CN-13): Yield:76 M p:156-159; IR (KBr) K_{max} in (cm) 601 (C-Cl), 800 (C-S), 1251 (C-F), 1535 (N=N), 1609.31 (C=N is stretching), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1H NMR (DMSO-d6, 300 MHz, d ppm), 8.36 (d, 1H, Ar), 7.68 (d, 1H, thenoyl), 7.37-7.39 (t, 2H, Ar), 7.16 (t, 1H, thenoyl), MS, m/z (%), 371(M+) Anal. Calcd. for $C_{14}H_5ClF_4N_2OS$: C, 46.62; H, 1.40; Cl, 9.83; F, 21.07, N %.

1-(6-chloro-4-(thiophen-3-yl)-7-(trifluoromethyl) cinnolin-3-yl)-2, 2, 2-trifluoroethanone(CN-14): Yield: 75 M.P: 120122; IR (KBr) K_{max} in (cm)

711.45, 601(C-Cl), 800 (C-S), 1251 (C-F), 1535 (N=N), 1609.31 (C=N is stretching), 1021.12 (N-N Stretching), cinnolin ring (889), 758.85 (DI subs benzene), 1H NMR (DMSO-d6), 8.75 (s,1H,Ar), 7.95-7.98 (d.2H, Ar), 7.72 (t, 1H, Ar), 7.22 (d, 1H, Ar). m/z (%), 409.97(M+) Anal. Calcd. for $C_{15}H_5C_lF_6N_2OS$: C, 43.86; H, 1.23; Cl, 8.63; F, 27.75; N, 6.82; O, 3.90; S, 7.81%.

TABLE 4: MIC OF ANTI TUBERCULAR ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound	MIC (µg/ml)
CN-1	50
CN-2	25
CN-3	25
CN-4	100
CN-5	50
CN-6	100
CN-7	12.5
CN-8	50
CN-9	25
CN-10	12.5
CN-11	100
CN-12	50
CN-13	25
CN-14	12.5

Anti-tubercular Activity: The MABA method is used to evaluate Antitubercular activity synthesized compounds against *M. tuberculosis*. Generally, in this method, stable reagents are used, and moreover, this method is non-toxic and maintains better relations with proportional and BACTEC radiometric method. During the incubation process, in the process of reduction of evaporation to the stable well plate, 200 µl of deionized sterile water is added. Serial dilution of done on the plate itself and middle brook 79 H broth was added to 96 well plates. The concentration of the drug was maintained at 100-0.8 µg/mL.

Paraffin is used to cover and seal the plates and then incubated at 37 ºC for 5 days. To the plate, before incubation of 24 h, 25 µl of 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added. Blue color indicates that there is no bacterial growth, while pink color indicates the growth of bacteria [10]. Finally, the MIC of compounds was determined based on the prevention of color change from blue to pink. Owing to Mycobacterial study, Compound-14 has proven outstanding activity with MIC less than 12.5 µg/mL due to the Introduction of fluorine group at 7th position. In addition, Compound-7 also shown excellent MIC of 12.5 µg/mL. Noteworthy results are obtained by all synthesized compounds with less MIC value, and the results are depicted in **Table 4**.

TABLE 5: MOLECULAR DOCKING REPORTS FOR COMPOUNDS CN (1-14) AGAINST PROTEIN DHFRASE A

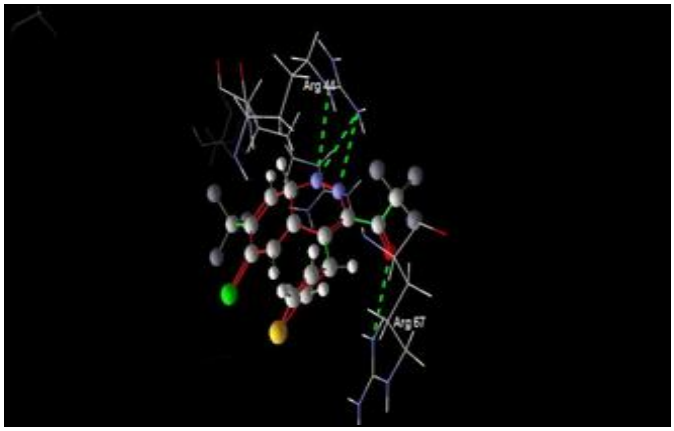
S. no.	PDB Code	Binding energy (KCAL/MOL)	Residue involving H-Bond
CN-1	PDB:2CIG	-129.372	
CN-2	PDB:2CIG	-129.048	-
CN-3	PDB:2CIG	-129.173	-
CN-4	PDB:2CIG	-128.694	-
CN-5	PDB:2CIG	-128.364	-
CN-6	PDB:2CIG	-128.364	-
CN-7	PDB:2CIG	-144.587	Gln-98, Gly-97, Arg-45, 44, 44,
CN-8	PDB:2CIG	-105.21	-
CN-9	PDB:2CIG	-127.38	-
CN-10	PDB:2CIG	-143.814	Ala-126, Arg-16, Gly-17, Gly-18, Gln-98, Val-97, Gly-96, Val-46
CN-11	PDB:2CIG	-134.645	-
CN-12	PDB:2CIG	-121.01	-
CN-13	PDB:2CIG	-111.21	-
CN-14	PDB:2CIG	-146.921	Arg-44, 67

Molecular Docking Studies:

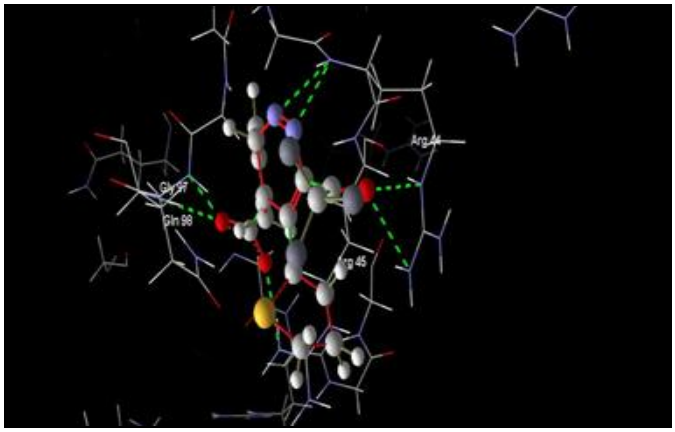
Structure-Based Drug Design and Molecular Studies: Ligand docking studies were performed by Molegro Virtual Docker (Molegro mApS, Aarhus C and Denmark). Fifteen compounds were selected in the search of new ligand for GyrB ATPase (a domine of DNA Gyrase) inhibitor as a novel antibacterial drug-like candidate. The structures were drawn using Chem Draw version 12.0 and saved in .mol format after the minimization of energy. The target proteins for docking studies are DNA Gyrase Subunit B (PDB ID: 2CIG).

The 3D structure of the target proteins was downloaded from the protein data bank PDB

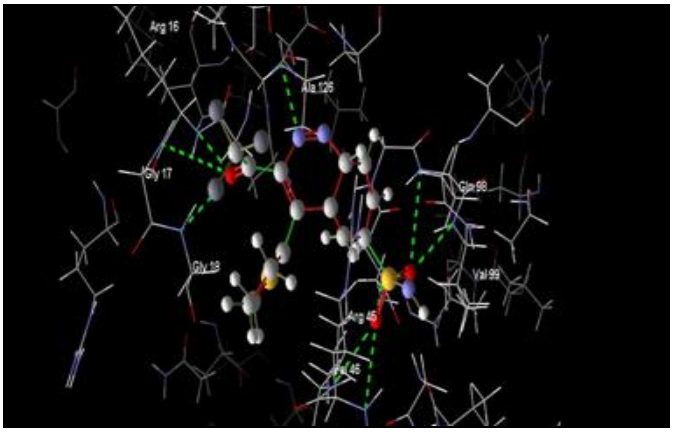
format. The selected chain in the target protein imported into the workspace. The surface was created, and binding pockets were predicted, and then ligands also imported to the workspace and prepared them for docking. The grid was generated around the binding pocket of co-crystallized ligand and docking was run after setting of parameters such as choosing which ligand to dock, choosing scoring function and defining binding site, choosing search algorithm and number of runs, maximum interaction, maximum population size, energy threshold, maximum steps, neighbor distance factor and pose clustering [11]. The docking scores (moldock) of the ligands are compared with co-crystallized ligand of the respective proteins, fin docking results recorded in **Table 5** and **Fig. 2**.



CN-14 (A)



CN-7 (B)



CN-10 (C)

FIG. 2: 2D PLOT OF LIGAND PROTEIN INTERACTION PROFILE BY MVD. VISUALIZATION OF HYDROGEN BOND INTERACTION BETWEEN 1A AND (A) DNA GYRASE B RECEPTOR (Arg-44, 67), (B) Gln-98, Gly-97, Arg-45, (c) Ala-126, Arg-16, Gly-17, Gly-18, Gln-98, Val-97, Gly-96, Val-46) (D) (Asp 79). HYDROGEN BONDS ARE MENTIONED IN DISCONTINUOUS LINE IN GREEN COLOUR

***In-silico* Pharmacokinetics (ADME) Properties:** Now online software is introduced like Swiss ADME for predicting physicochemical properties of designed compounds [12]. In our body, the pharmaco-kinetics property of the receptor is dependent on the molecular properties of compounds. Some physical-chemical properties and bioavailability studies of compounds are predicted using lipinski rule. They are C_{log} P (1.92 to +5.31), Molecular weight (321.73–434.17D), H-bond donors (Not more than 2), HBA (not more than 9), rotatable bonds (4 or fewer) Polar Surface Area (equal to or <130Å) (Lipinski, 2004). Drugs can easily cross the BBB in the log p-value between 1.5 and 2.5. It was explained that Drugs possessing log p-value 1.5 to 2.5 could cross the BBB easily (Mikitsh J.L *et al.*, 2014). As per the *in-silico* ADME report, all the cinnoline compounds pass Lipinski's rule of five so these compounds will absorb orally, and it can reach its targeted site by crossing BBB **Table 6**.

It is enforced only to absorption by passive diffusion of title compounds through cell membranes but not to the drugs which absorb through the active transport process [13].

TABLE 6: *IN-SILICO* ADME PROPERTIES OF CINNOLINE COMPOUNDS

S. no.	M. wt	C log p	HBD	HBA	Nrotb	TpsA
1.	353.28	3.1	0	8	4	116.91 A^2
2.	323.2	3.21	1	6	3	97.11
3.	322.30	4.2	0	6	3	71.09
4.	342.72	4.31	0	6	3	71.09
5.	387.17	4.40	0	6	3	71.09A^2
6.	434.17	4.44	0	6	3	71.09
7.	352.29	3.34	1	8	4	108.39
8.	324.28	3.37	1	7	7	91.32
9.	405.37	1.92	2	10	4	137.08
10.	387.36	2.62	1	9	4	139.63
11	387.72	3.64	0	8	4	116.91
12.	344.74	4.49	0	6	3	63.25
13.	362.73	4.77	0	7	3	70.03
14.	410.72	5.31	0	9	4	7.09 A^2

Chemistry: The substituted diketone is the best versatile core for the synthesis of heterocyclic compounds. The titled compounds are synthesized According to the procedure reported in the literature [14, 15] **Scheme 1**. Calculated moles of aniline is treated with sodium nitrate in cooling conditions in the presence of 1N HCl to afford benzene diazonium salt. On further reaction with thenoyl trifluoro acetone in the presence of polyphosphoric acid on withstanding temperature undergoes cyclization to yield the substituted cinnoline compound as main adduct. CN1-14 mentioned in **Table 2** are yielded by treating with different substituted aniline to give new cinnoline Candidate.

DISCUSSION: New Cinnoline compounds are synthesized by the selected scheme, and Well-employed Anti-tubercular potency of Cinnolines was evaluated by MABA method. Fascinated by Cinnoline core and its prominence driven us to synthesize and evaluate Anti-tubercular activity. Previous literature data support the present work [16]. Novice series of cinnoline compounds are synthesized by substituting different groups at 6^{th} position. The compound-14 with halogen groups Cl and CF_3 at its 6^{th} and 7^{th} position with log p-value 3.6 resulted in striking activity with MIC 12.5 µg/mL when compared with standard drug isoniazid. Compound -7 bearing Carboxylic group at 6^{th} position also contributed remarkable activity of MIC 12.5 µg/mL due to its polarity it was also noticed that the sulfonamide group in Compound-10 of benzene ring showed marked anti-tubercular activity and intrigued us to note its MIC value.

The structural anti-tubercular activity relationship in the Compounds synthesized profound the inhibition of tuberculosis. The presence of a rigid bicyclic ring system is important for activity. The presence of thenoyl ring with trifluoro substitution plays an eminent role and is recommended for better prominent activity in **Table 5**. Nitro groups are preferred over amino groups due its lipophilicity. The striking results paved the way for researchers in the future for drug development in tuberculosis.

CONCLUSION: Finally, we have designed a potent inhibitor of Mtb H37Rv with MIC of 12.5 µg/ml having drug-like properties. It was owing to the anti tubercular evaluation of all synthesized compounds. Noteworthy results are tabulated. The method selected for this activity is MABA for determining the MIC value against H37Rv. The range of MIC value of all cinnoline compounds is found to be between 100 and 12.5 µg/ml (MIC) when compared with standard drug isoniazid. Cinnoline, no doubt, will pave the way for the better antimycobacterial drug in the future.

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CONFLICTS OF INTEREST: Authors don't have any Conflicts of interest.

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