Chemical Characterization and Therapeutic Evaluation of Condensed Cinnolo-Isothiazole Derivatives

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Abstract- **This study reports the synthesis of a series of substituted cinnoline derivatives condensed with an isothiazole moiety, yielding a new series of substituted cinnoline–isothiazole compounds (13a–13j). All synthesized compounds were obtained in good yields and high purity and were evaluated for their antibacterial and antifungal activities. The methodology, experimental procedures, and biological evaluation of ten different substituted cinnoline–isothiazole derivatives are described through a multistep reaction scheme. Structural characterization of the synthesized compounds was carried out using spectroscopic techniques, including IR, 1H NMR, and mass spectrometry. Biological evaluation revealed that several compounds exhibited promising antimicrobial activity. In particular, chloro-substituted derivatives (13DSDg) afforded the highest synthetic yield, while compounds 13DSDc, 13DSDd, 13DSDf, and 13DSDi showed hit compounds against antibacterial activity and antifungal activity.**

Index Terms- **Cinnoline–isothiazole derivatives, Antibacterial, and Anti-fungal**

I. INTRODUCTION

Cinnoline, a benzofused heterocycle containing two nitrogen atoms (Fig. 1), has attracted considerable attention since its initial synthesis in the late 19th century. The cinnoline ring system was discovered in 1883 by Von Richer [1-5]. Who in the course of experiments designed to convert o-nitro phenyl propionic acid into o-hydroxy acetophenone found that the diazonium chloride derived from o-amino phenyl propionic acid which was transformed in a ring on heating into a nitrogenous derivative. The new ring system so formed was named cinnoline (I). Cinnoline is an aromatic heterocyclic compound with the molecular formula $C_8H_6N_2$. It is isomeric with phthalazine and its alternative name is benzopyridazine. Cinnolines are cinnoline derivatives. A classic organic reaction for synthesizing cinnoline, is a Widman-Stoermer synthesis. A ring closing reaction of an α-vinyl aniline with hydrochloric acid and sodium nitrite [6-11].

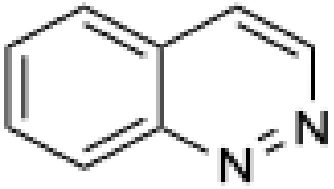

Fig. 1: Structure of Cinnoline

Isothiazole, a five-membered heterocyclic ring containing both nitrogen and sulfur atoms, is recognized for its incorporation into numerous biologically active compounds. Its distinct electronic and steric features contribute to diverse pharmacological properties, such as antimicrobial, anti-inflammatory, and enzyme inhibitory activities. The integration of an isothiazole moieties into drug candidates has yielded compounds with improved potency and selectivity [12-15].

The condensation of cinnoline with an isothiazole moiety to form cinnoline–isothiazole derivatives represents an innovative approach to hybrid heterocyclic frameworks that may synergize the beneficial biological attributes of both parent scaffolds. This fusion generates structurally unique molecules with multifaceted chemical nature, offering new opportunities for therapeutic exploration. Recent synthetic advances have enabled the efficient preparation of substituted cinnoline–isothiazole compounds, which have been characterized by spectroscopic techniques and assessed for their antimicrobial efficacy. Notably, chloro-substituted derivatives within this class have exhibited enhanced antibacterial and antifungal activities, comparable to

established standard drugs, highlighting their promise as scaffolds for novel antimicrobial agents [16,17].

Overall, cinnoline–isothiazole derivatives embody a compelling class of heterocyclic compounds with significant potential to contribute to the development of new therapeutic agents addressing the growing challenges of microbial resistance and fungal infections. Continued investigation into their synthesis, structural diversity, and biological evaluation is essential to fully realize their medicinal potential.

II. MATERIALS AND METHODS

2. Synthesis of substituted condensed cinnolo isothiazole series

2.1 Preparation of substituted hydrazono (cyano) acetamide (4a -j)

[R: a = o-NO_2, b = p-NO_2, c = p- Cl, d = p- Br, e = 3,4-di-nitro, f = 2-Me, g = 3- Chloro, h = 2- Fluoro, i = 2,3 di Chloro, j = 3- Nitro]

The substituted aniline (0.195 mol) was dissolved in a mixture of conc. HCl (7.5 ml) and water (7.5 ml) and cooled to 0-5°C in an ice bath. To this, a cold saturated solution of sodium nitrite (0.19 mol) was added slowly. Soon after the addition, fumes of nitrous acid were liberated, and a pinch of sulfamic acid/thiourea was added and stirred until the fumes ceased. The diazonium salt thus formed was filtered into a cooled solution of cyano acetamide (0.195 mol) in water (350 ml),10 gm CH_3COONa, and 15 ml alcohol. The mixture was stirred for 6 h at room temperature, and the resulting solid was collected and recrystallized from methanol (Fig. 2).

2.2 Synthesis of substituted aniline 4-amino cinnoline 3-carboxamide (5a-j)

Chlorobenzene (150 ml) was added to anhydrous $AlCl_3$ (0.111 mol), and nitrogen gas passed for half an hour. This mixture was added to the substituted phenyl hydrazono cyano acetamide, and nitrogen was bubbled through it for 10 min. The mixture was then refluxed for 2 h. The solution was cooled, and dilute HCl (20 ml) was added. It was then heated in a water bath, cooled, filtered, washed twice with dilute NaOH solution, and filtered. The product was recrystallized from methanol and water (10:1) (Fig. 2).

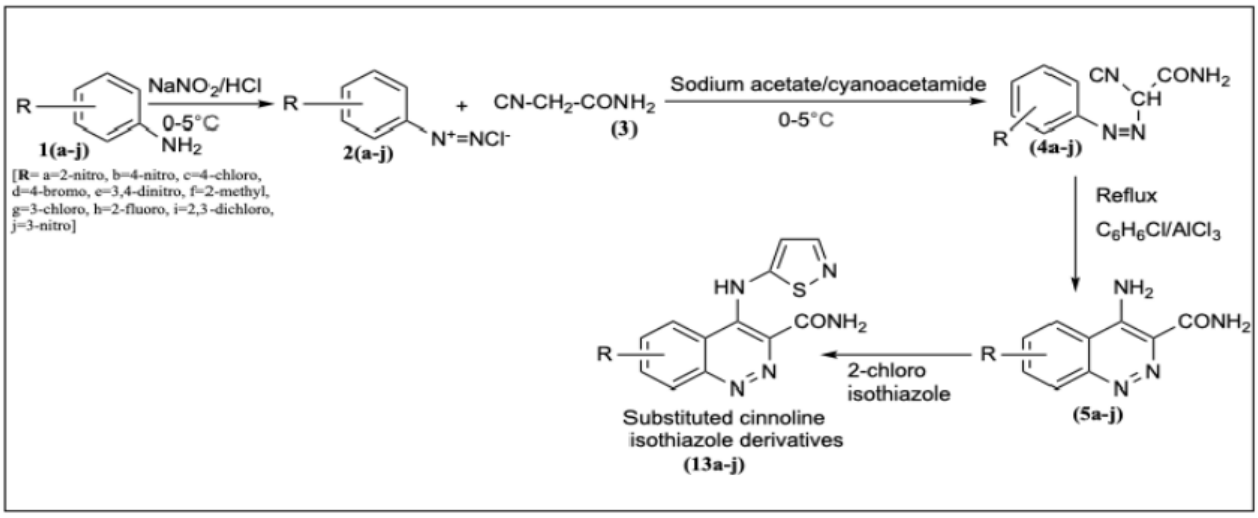

Fig. 2: Synthetic Reaction Scheme

2.3 Synthesis of substituted 4-(-5-amino- Isothiazole)-cinnoline -3-carboxamide 13(a-j)

The substituted 4-amino cinnoline-3-carboxamide (5a-j) and 2-chloro Isothiazole in DMF was refluxed for 2hrs, and poured in to crushed ice. The precipitate obtained was filtered, dried and recrystallized in methanol (Fig. 2).

8-Nitro-4-(-5-amino Isothiazole)cinnoline-3-carboxamide ($13DSD_a$): Yield 55.89%; M.P 212-214°C; IR (KBr, cm-1) 3462.1 (NH stretching),

3342.5 (NH_2), 3246.2 (C-H stretching), 1611.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 1385.6 (NO_2 stretching), 1113.0 (C=F stretching), 1652.3 (C=N stretching), 1362.1 (C-N), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 8.96 (2H, d, of cinnolines), 6.52 (2H,m, Isothiazole), 9.20 (1H, s, of NH), 9.2 (2H, s, of $CONH_2$), Mass (m/z) 339mHz.

6-Nitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_b$): Yield 67.98%; M.P 105-107°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1552.1 (C=N), 1551.2 (NO_2 asymmetric), 1350.5 (nitro symmetric), 1224.3 (C-N), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 4.96 (2H, d, of cinnolines), 3.52 (2H,m, Isothiazole), 10.20 (1H, s, of NH), 9.5 (2H, s, of $CONH_2$), Mass (m/z) 342mHz.

6-Chloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_c$): Yield 57.34%; M.P 184-186°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 687.9 (C-Cl), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 7.90 (2H, d, of cinnolines), 7.53 (2H,m, Isothiazole), 11.23 (1H, s, of NH), 9.4 (2H, s, of $CONH_2$), Mass (m/z) 332mHz.

6-Bromo-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_d$): Yield 45.08%; M.P 158-160°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 1285.4 (C-N), 650 (C-Br), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 6.96 (2H, d, of cinnolines), 7.55 (2H,m, Isothiazole), 11.26 (1H, s, of NH), 9.0 (2H, s, of $CONH_2$), Mass (m/z) 332mHz.

6,7-dinitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_e$): Yield 61.14%; M.P 151-153°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 1528.7 (NO_2 asymmetric stretching), 1350.1 (NO_2 symmetric stretching)), 1267.8 (C-N), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 7.96 (2H, d, of cinnolines), 7.52 (2H,m, Isothiazole), 12.20 (1H, s, of NH), 8.9 (2H, s, of $CONH_2$), Mass (m/z) 341mHz.

8-Methyl-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_f$): Yield 54.78%; M.P 154-156°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 2862 (CH_3), 1253.8 (C-N stretching), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 4.96 (2H, d, of cinnolines), 6.52 (2H,m, Isothiazole), 12.20 (1H, s, of NH), 9.8 (2H, s, of $CONH_2$), Mass (m/z) 343mHz.

7-Chloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_g$): Yield 70.39%; M.P 166-168°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1556.3 (C=N), 1278.2 (C-N), 742.8 (C-Cl), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 6.97 (2H, d, of cinnolines), 7.42 (2H,m, Isothiazole), 8.20 (1H, s, of NH), 7.9 (2H, s, of $CONH_2$), Mass (m/z) 332mHz.

8-Fluoro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_h$): Yield 66.61%; M.P 148-150°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 1287.8 (C-N), 111.9 (C-F Stretching), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 6.96 (2H, d, of cinnolines), 7.32 (2H,m, Isothiazole), 8.20 (1H, s, of NH), 9.1 (2H, s, of $CONH_2$), Mass (m/z) 345mHz.

7,8-Dichloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_i$): Yield 58.82%; M.P 217-219°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (NH_2), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 678.4 (C-Cl), 1113.0 (C=S stretching), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 7.96 (2H, d, of cinnolines), 7.52 (2H,m, Isothiazole), 11.20 (1H, s, of NH), 9.9 (2H, s, of $CONH_2$), Mass (m/z) 342mHz.

7-Nitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide ($13DSD_j$): Yield 62.45%; M.P 197-199°C; IR (KBr, cm-1) 3466.1 (NH stretching), 3341.5 (Symmetric N-H), 3236.2 (C-H stretching), 1631.9 (C=O stretching), 1470.6 (aromatic C=C stretching), 1352.1 (NO_2), 1285.7 (C-N stretching), 861.6 (Isothiazole), 1H NMR ($CDCl_3$ δ in ppm) 7.87 (2H, d, of cinnolines), 7.66 (2H,m, Isothiazole), 11.24

(1H, s, of NH), 9.2 (2H, s, of $CONH_2$), Mass (m/z) 311mHz

III. RESULTS AND DISCUSSION

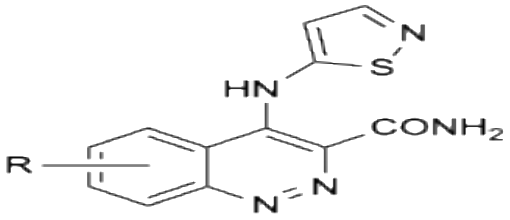

Fig. 3: Substituted Cinnoline Isothiazole Derivatives 13(a –j)

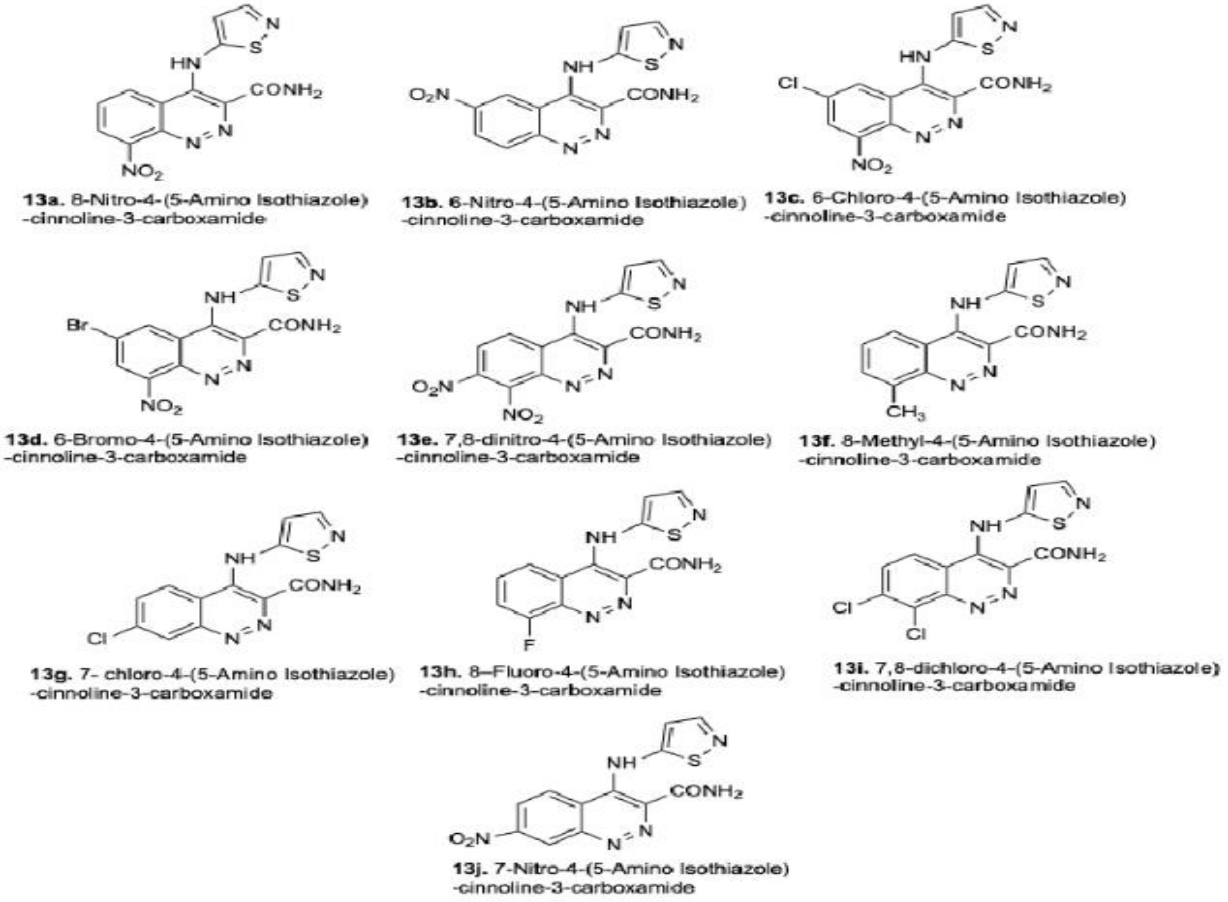

Fig. 4: Structures of substituted 4-(-5-amino-isothiazole)-cinnoline-3-carboxamide derivatives

The synthesis of substituted cinnoline pyrazine derivatives by the method described above resulted in products with good yields (Fig. 4).

Compound IUPAC Name	Comp. No.	Physical nature	M.P (in °C)	Yield (in %)
8-Nitro-4-(-5-amino Isothiazole)cinnoline-3-carboxamide	13DSD$_a$	Pale brown crystals	212-214	55.89

6-Nitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_b$	Dark Yellow crystals	105-107	67.98
6-Chloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_c$	Green crystals	184-186	57.34
6-Bromo-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_d$	Light green-brown crystals	158-160	45.08
6,7-dinitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_e$	Dark orange crystals	151-153	61.14
8-Methyl-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_f$	Dark red crystals	154-156	54.78
7-Chloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_g$	Golden violet crystals	166-168	70.39
8-Fluoro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_h$	Light brown crystals	148-150	66.61
7,8-Dichloro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_i$	Off white crystals	217-219	58.82
7-Nitro-4-(-5-amino-Isothiazole)cinnoline-3-carboxamide	$13DSD_j$	Orange Crystals	197-199	62.45

Table. I: Physical data of substituted 4(-5-amino-pyrazine)-cinnoline-3-carboxamide derivatives 13(a-j)

IV. RESULTS OF BIOLOGICAL EVALUATION (SCHEME – 13a-j)

4.1 Anti-bacterial activity studies

S.No.	Compound No.	Diameter of zone of inhibition (mm)			
		P. aeruginosa	E. coli	B.subtilis	S. aureus
1	$13DSD_a$	11	14	15	13
2	$13DSD_b$	16	13	15	14
3	$13DSD_c$	21	19	21	21
4	$13DSD_d$	20	19	20	20
5	$13DSD_e$	12	17	14	16
6	$13DSD_f$	18	19	17	20
7	$13DSD_g$	16	14	17	18
8	$13DSD_h$	16	12	14	15
9	$13DSD_i$	20	21	20	20
10	$13DSD_j$	12	14	15	13
11	Norfloxacin (10µg)	21	23	24	22
12	THF	0	0	0	0

Table. II: Data for anti-bacterial activities of synthesized compounds using Disk Diffusion MethAll the synthesized substituted cinnoline Isothiazole derivatives were tested at 50µg level and shown moderate to good antibacterial activity, among the tested compounds $13DSD_c$, $13DSD_d$, $13DSD_f$ and $13DSD_i$ showed significant activity while other compounds showed moderate activity in comparison with the standard drug norfloxacin.

S.No.	Compound No. ↓	S.aureus						B.subtilis						E.coli						P.aeruglnosa					
	Dilutions	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	$13DSD_a$	-	-	+	+	+	+	-	-	+	+	+	+	-	-	+	+	+	+	-	-	-	+	+	+
2	$13DSD_b$	-	-	-	+	+	+	-	-	-	+	+	+	-	-	+	+	+	+	-	-	-	+	+	+
3	$13DSD_c$	-	-	-	-	+	+	-	-	-	+	+	+	-	-	-	-	+	+	-	-	-	-	+	+
4	$13DSD_d$	-	-	-	+	+	+	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	+	+
5	$13DSD_e$	-	-	+	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+
6	$13DSD_f$	-	-	-	-	-	+	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	+	+
7	$13DSD_g$	-	-	+	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+	-	-	+	+	+	+
8	$13DSD_h$	-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	-	+	+	-	-	-	+	+	+
9	$13DSD_i$	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	+	+
10	$13DSD_j$	-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+	-	-	+	+	+	+
11	Norfloxacin	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	+	+	+
12	+ve control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	-ve control	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

'+' indicates the presence of growth and '–' indicates the absence of growth.

Table. III: Data of MIC for anti-bacterial activity

Dilutions	1	2	3	4	5	6
Conc. µg/ml	1000	500	250	125	62.5	31.25

Table. IV: Concentration of derivatives in different dilutions

Derivatives like $13DSD_c$, $13DSD_d$, $13DSD_f$, $13DSD_i$ showed higher activity than all. These compounds can be subjected to further studies for toxicity.

4.2 Antifungal Activity Studies

S. No.	Compound No.	Diameter of zone of inhibition (mm)	
		C. albicans	A. niger
1.	$13DSD_a$	10	11
2.	$13DSD_b$	12	12
3.	$13DSD_c$	18	19
4.	$13DSD_d$	19	19

5.	$13DSD_e$	11	12
6.	$13DSD_f$	18	17
7.	$13DSD_g$	11	15
8.	$13DSD_h$	12	15
9.	$13DSD_i$	18	18
10.	$13DSD_j$	13	12
11.	Griseofulvin (25µg)	23	24
12.	THF	0	0

Table. V: Data for antifungal activity of synthesized compounds using Disk diffusion method

All the Substituted Cinnoline Isothiazole derivatives were tested at 50µg level. From the anti-fungal activity studies, it is evident that the synthesized compounds showed moderate to good anti-fungal activity. Among the tested compounds $13DSD_c$, $13DSD_d$, $13DSD_f$, $13DSD_i$ have shown good activity against C. albicans and A.niger. While other compounds shown weak anti-fungal activity in comparison with the standard drug griseofulvin.

S.No.	Compound No.	Presence or absence of growth											
	↓	C. albicans						A. niger					
	Dilutions	1	2	3	4	5	6	1	2	3	4	5	6
1.	$13DSD_a$	-	-	+	+	+	+	-	-	+	+	+	+
2.	$13DSD_b$	-	-	-	+	+	+	-	-	-	+	+	+
3.	$13DSD_c$	-	-	-	-	+	+	-	-	-	-	+	+
4.	$13DSD_d$	-	-	-	+	+	+	-	-	-	+	+	+
5.	$13DSD_e$	-	-	+	+	+	+	-	-	-	-	+	+
6.	$13DSD_f$	-	-	-	+	+	+	-	-	-	-	+	+
7.	$13DSD_g$	-	-	-	-	+	+	-	-	-	-	+	+
8.	$13DSD_h$	-	-	-	+	+	+	-	-	-	+	+	+
9.	$13DSD_i$	-	-	-	-	+	+	-	-	-	-	+	+
10.	13DSDj	-	-	+	+	+	+	-	-	-	+	+	+
11.	+ve control	+	+	+	+	+	+	+	+	+	+	+	+
12.	-ve control	-	-	-	-	-	-	-	-	-	-	-	-

'+' Indicate presence of growth and '–' indicate absence of growth

Table. VI: Data of MIC for antifungal activity.

All the Synthesized compounds have shown anti-fungal activity to a certain extent. Among the tested compounds $13DSD_c$, $13DSD_f$ and $13DSD_i$ have shown good activity against C. albicans and A.niger. while other compounds show moderate activity.

V. CONCLUSION

The presented work represents the series of novel compounds synthesized using cinnoline ring which undergoes condensation process to produce ten substituted Cinnoline Isothiazole series. The compounds which are halogen substituted where chloro substitution gave the highest yield and potency towards antibacterial, and anti-fungal activity in comparison to the other compounds. All the synthesized compounds gave goo dpotency towards antibacterial and antifungal activity but out of all

$13DSD_c$, $13DSD_f$ and $13DSD_i$ have shown great potency against C. albicans and A.niger. Further, it would be interesting to obtain the possible mechanism of actio

VI. ACKNOWLEDGEMENT

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VII. CONFLICT OF INTEREST

The authors declare no conflict of interest.

VIII. AUTHOR'S CONTRIBUTION

Saxena V and Kumar P has designed the scheme and experimental work both synthetic and biological work was performed. Literature review and compilation of the work and making it get ready for the publication was completed by Kumar P. Lastly, Saravanan K has guided in the process.

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