Novel 1, 3, 4 - thiadiazole derivatives synthesis by MAOS

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Abstract- 1,3,4-thiadiazole nucleus is therapeutically interesting drug candidate as anti-inflammatory, antimicrobial ,anticonvulsant, antihypertensive, analgesic, antiepileptic, antiviral, antineoplastic and antitubercular agents. Therefore thiadiazole derivatives IVa-k were synthesized. The structures of the synthesized compounds were confirmed by spectral data and elemental analysis. The synthesized compounds were screened for antifungal activity by using Minimum Inhibitory Concentration (MIC) by serial dilution method against *Staphylococcus aureus* ATCC 9144, *Becillus Cereus* ATCC *11778, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853. , Aspergillus niger and Aspergillus flavus.*

Index Terms- Quinoline-4- carboxylic acid, thiosemicarbazide, phosphorous oxychloride, pyridine, CS_2 , phenol isothiocyanates, chloroform and concentrated H_2SO_4 , liq. ammonia MAOS, TLC technique, Antimicrobial activity, Minimum Inhibitory Concentration (MIC) by serial dilution method.

I. INTRODUCTION

The problem of multi-drug resistant microorganisms has reached on alarming level around the world. So for the treatment of microbial infections; the synthesis of new anti-infectious compounds has become an urgent need. Widespread antibiotic resistance, the emergence of new pathogens in addition to the resurgence of old ones, and the lack of effective new therapeutics exacerbate the problems of antimicrobial resistance[1].

There are number of five membered heterocyclic containing nitrogen and sulphur atom, have turned out to be a potential chemotherapeutic and pharmacotherapeutic agents but the interesting biological activities of a novel heterocyclic compound like thiadiazole has stimulated considerable research work. The biological profile of 1, 3, 4-Thiadiazole derivatives is very extensive. The broad and potent activities of thiadiazole categories such as anti-inflammatory[2-3], antimicrobial[4-6] ,anticonvulsant[7-10], antihypertensive[11-13], analgesic[14], antiepileptic, antiviral[15], antineoplastic and antitubercular agents[16], carbonic anhydrase inhibiting effect[17], anti-depressant[18], anti-oxidant properties[19], it also plays a prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-ketoacids. Furthermore, 1,3,4-thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N2C2S moiety[20]. They find applications as antibacterials, antitumor agents, pesticides, herbicides, dyes, lubricants, and analytical reagents[21-25].

Since thiadiazole nucleus is present as a core structural component in an array of drug and their derivatives has established them as pharmacologically significant scaffolds. In this study, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives for various pharmacological activities.

Microwave assisted organic synthesis (MAOS) continues to affect synthetic chemistry significantly by enabling rapid, reproducible and scaleable chemistry development with improvement in yield and quality of products [26]. Microwave heating is able to heat the target compounds without heating the entire furnace or oil bath, which saves time and energy. It is also able to heat sufficiently thin objects throughout their volume, in theory producing more uniform heating [27-30]. Microwave assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes. This technology has made an impact in several areas of drug discovery related to organic synthesis [31].

II. EXPERIMENTAL SECTION

Materials and methods

Materials

The reaction was carried out with analytical reagent grade chemicals and were used as received without further purification. The glasswares used were made of pyrex glass. NMR spectra were recorded on a Bruker Advance DPX-400400 FT spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. Silica gel-G was used for TLC. Melting points were determined by open glass capillary method and are uncorrected. The chemical shifts were reported in δ units relative to TMS used as an internal standard. Both microbial studies (antibacterial and antifungal activities) were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method.

Synthesis of compounds

I. Synthesis of 5- Quinolin -4- yl- [1, 3, 4] thiadiazol -2- yl amine:

Appropriate substituted quinoline-4- carboxylic acid (0.05 M) and thiosemicarbazide (0.05 M) were taken into a beaker to this phosphorous oxychloride (25mL) was added and made paste. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the microwave irradiation at 480 W for 3-6 min, with a pulse rate of 30 sec, each in a domestic microwave oven. The solvent was removed by distillation and residue was cooled and triturated with crushed ice. The resultant product was filtered, washed with small

portions of cold water and dried. It was purified by recrystallization from hot alcohol.

II. Synthesis of 4 -(5- Isothiocyanato- [1, 3, 4] thiadiazol -2- yl) – quinoline:

Mixture of I (9.5mmol) was dissolved in pyridine (7.2mmol) and iodine (6.0mmol) at 0-5^{o}C. It was dissolved to stir for 20min and then carbondisulphide (5.5mmol) was added to the above reaction mixture at 0-5^{o}C. Resulted reaction mixture was allowed to stir for 4hr at 0-5^{o}C and the reaction was monitored by TLC. After completion of reaction excess of CS_2 and pyridine were removed by vacuum distillation to obtain crude product.

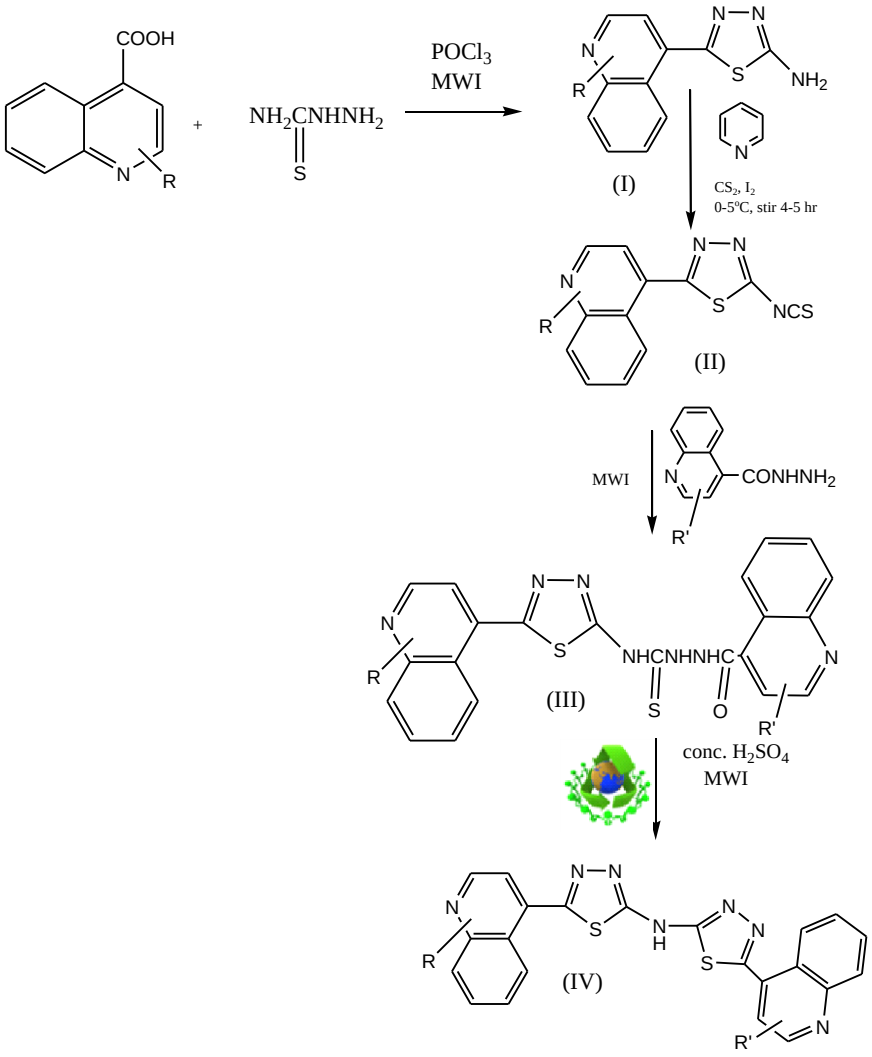
III. Synthesis of 5-quinolin -4– yl- [1, 3, 4,] thiadiazole -2- isonicotinoylthiosemicarbazide:

When a mixture of compound (II) (0.15 mole) and substituted phenol isothiocyanates (0.15 mole) dissolved in few drops of absolute ethanol was subjected to microwave irradiation at 160W for 5 min then compound (III) was the product. After completion of the reaction, reaction mixture was concentrated and kept overnight at room temperature. The needle shaped crystals of thiosemicarbazides was obtained with an excellent yield.

IV. Synthesis of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol -2- yl) – amine:

Compound (III) (0.10 mole) was dissolved in chloroform and concentrated H_2SO_4 (0.10 mole) and subjected to microwave irradiation in the resonance cavity of the microwave power system for 1.30 minutes and neutralized with concentrated liq. ammonia. . After completion of reaction, the mixture was poured into crushed ice, the solid separated was filtered, washed with water and re-crystallized from methanol yielded the pure compound.

Scheme 1



Characterization of the synthesized compounds

Compound IV(a-k):

Compound IV(a)

Yield:82 %; m.p:96 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.87-7.48 (m, 6H, ArH), 4.07 (s, 1H, - NH-), 8.60-7.20 (m, 6H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:150.5, 148.6, 143.7, 129.2, 127.6, 126.5, 126.3, 119.3 ; EIMS: (m/z): 439.07 (M+). Anal. calcd. For $C_{22}H_{13}N_7S_2$ C: 60.12 , H: 2.98 , N: 22.31 , S: 14.59 %

Compound IV(b)

Yield:90 %; m.p:112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.07-7.33 (m, 5H, ArH), 4.02 (s, 1H, - NH-), 8.68-7.26 (m, 6H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:156.2, 150.5, 149.3, 148.6, 145.2, 143.7, 130.3, 129.2, 128.1, 127.6, 127.4, 126.5, 126.3, 124.6, 120.1, 119.3 ; EIMS: (m/z): 473.03 (M+). Anal. calcd. For $C_{22}H_{12}ClN_7S_2$ C: 55.75 , H: 2.55 ,Cl: 7.48, N: 20.69 , S: 13.53 %

Compound IV(c)

Yield:94 %; m.p:120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.02-7.38 (m, 5H, ArH), 4.04 (s, 1H, - NH-), 2.57 (s, 3H, CH_3), 8.88-7.42 (m, 6H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:159.8, 150.5, 148.6, 148.5, 143.7, 142.9, 129.2, 129.0, 128.6, 127.6, 127.1, 126.5, 126.3, 125.2, 124.5, 121.3, 119.3, 21.6 ; EIMS: (m/z): 439.07 (M+). Anal. calcd. For $C_{23}H_{15}N_7S_2$ C: 60.91 , H: 3.33 , N: 21.62 , S: 14.14 %

Compound IV(d)

Yield:90 %; m.p:92 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.88-7.62 (m, 6H, ArH), 4.07 (s, 1H, - NH-), 2.75 (s, 3H, CH_3), 8.05-7.36 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:159.8, 150.5, 148.6, 148.5, 143.7, 142.9, 129.2, 129.0, 128.6, 127.6, 127.1, 126.5, 126.3, 125.2, 124.5, 121.3, 119.3, 21.6 ; EIMS: (m/z): 439.07 (M+). Anal. calcd. For $C_{23}H_{15}N_7S_2$ C: 60.91 , H: 3.33 , N: 21.62 , S: 14.14 %

Compound IV(e)

Yield:92 %; m.p:98 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.09-7.33 (m, 5H, ArH), 4.03 (s, 1H, - NH-), 2.55 (s, 3H, CH_3), 8.05-7.40 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:159.8, 156.2, 149.3, 148.5, 145.2, 142.9, 130.3, 129.0, 128.6, 128.1, 127.4, 127.1, 126.5, 125.2, 124.6, 124.5, 121.3, 120.1, 21.6; EIMS: (m/z): 487.04 (M+). Anal. calcd. For $C_{23}H_{14}ClN_7S_2$ C: 56.61 , H: 2.89 , Cl: 7.27, N: 20.09 , S: 13.14 %

Compound IV(f)

Yield:96 %; m.p:116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.05-7.34 (m, 5H, ArH), 4. 7 (s, 1H, - NH-), 2.62 (s, 3H, CH_3), 8.02-7.28 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:159.8, 148.5, 142.9, 129.0, 128.6, 127.1, 125.2, 124.5, 121.3, 21.6 ; EIMS: (m/z): 467.10 (M+). Anal. calcd. For $C_{24}H_{17}N_7S_2$ C: 61.65 , H: 3.66 , N: 20.97 , S: 13.72 %

Compound IV(g)

Yield:98 %; m.p: 110^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.85-7.47 (m, 6H, ArH), 4.4 (s, 1H, - NH-), 8.09-7.52 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:156.2, 150.5, 149.3, 148.6, 145.2, 143.7, 130.3, 129.2, 128.1, 127.6, 127.4, 126.5, 126.3, 124.6, 120.1, 119.3; EIMS: (m/z): 4737.03 (M+). Anal. calcd. For $C_{22}H_{12}ClN_7S_2$ C: 55.75 , H: 2.55 , Cl: 7.48, N: 20.69 , S: 13.53 %

Compound IV(h)

Yield:79 %; m.p:82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.02-7.58 (m, 5H, ArH), 4.9 (s, 1H, - NH-), 8.03-7.33 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:156.2, 149.3, 145.2, 130.3, 128.1, 127.4, 126.5, 124.6, 120.1 ; EIMS: (m/z): 506.99 (M+). Anal. calcd. For $C_{22}H_{11}Cl_2N_7S_2$ C: 51.97 , H: 2.18 , Cl: 13.95, N: 19.29 , S: 12.61 %

Compound IV(i)

Yield:76 %; m.p:90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.02-7.36 (m, 5H, ArH), 2.55 (s, 3H, CH_3), 4.4 (s, 1H, - NH-), 8.10-7.48 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:159.8,156.2, 149.3, 148.5, 145.2, 142.9, 130.3, 129.0, 128.6, 128.1, 127.4, 127.1, 126.5, 125.2, 124.6, 124.5, 121.3, 120.1, 21.9; EIMS: (m/z): 487. 04 (M+). Anal. calcd. For $C_{23}H_{14}ClN_7S_2$ C: 56.61 , H: 2.89 , Cl: 7.27, N: 20.09 , S: 13.14 %

Compound IV(j)

Yield:73 %; m.p:118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.02-7.36 (m, 6H, ArH), 4.0 (s, 1H, - NH-), 7.93-7.36 (m, 4H, ArH), 8.02-7.38 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:158.1, 150.5, 148.8, 148.6, 144.9, 143.7, 137.8, 132.4, 129.4, 129.2, 128.5, 127.6, 126.5, 126.3, 123.4, 119.3, 118.1; EIMS: (m/z): 549.06 (M+). Anal. calcd. For $C_{28}H_{16}ClN_7S_2$ C: 61.14 , H: 2.93 , Cl: 6.45, N: 17.82 , S: 11.66 %

Compound IV(k)

Yield:77 %; m.p:89 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ :8.05-7.47 (m, 5H, ArH), 4.9 (s, 1H, - NH-),7.97-7.39 (m, 4H, ArH), 8.05-7.40 (m, 5H, ArH); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ:158.1, 156.2, 149.3, 148.8, 145.2, 144.9, 137.8, 132.4, 130.3, 129.4, 129.2, 128.5, 128.1, 127.6, 127.4, 126.5, 126.3, 124.6, 123.4, 120.1, 118.1; EIMS: (m/z): 583.02 (M+). Anal. calcd. For $C_{28}H_{15}Cl_2N_7S_2$ C: 57.54 , H: 2.59 , Cl: 12.13, N: 16.77 , S: 10.97 %

Table 1: Solvent optimization for the synthesis of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol – 2- yl) - amine

Entry	Solvent	Microwave (min)	Product yield %
1	Ethanol	10.00	45
2	Nitromethane	2.00	50
3	Chloroform	1.30	96
4	Methanol	15.00	33
5	Water	20.00	20

As the results from **table 1,** it was revealed that the yield of the product was found to be excellent in the case of chloroform while it is poor with other solvents such as ethanol, nitromethane, methane and water.

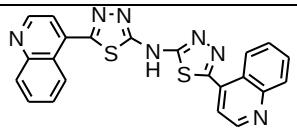
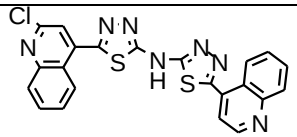
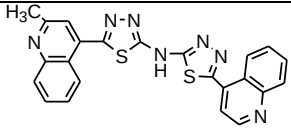
Table 2: Catalyst optimization for the synthesis of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol – 2- yl) – amine

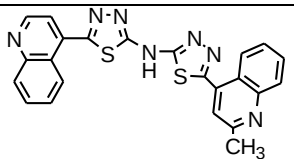
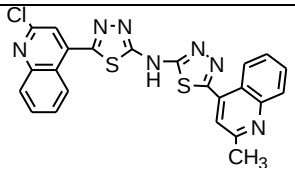
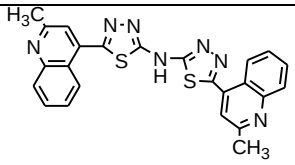
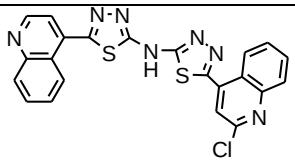
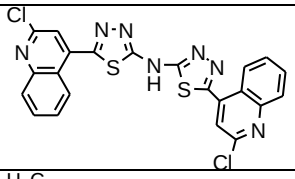
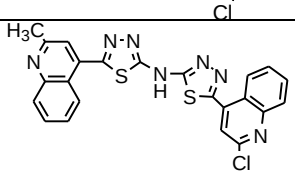
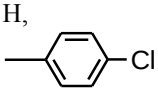
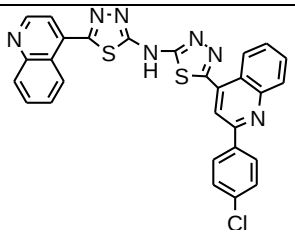
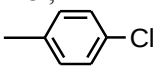
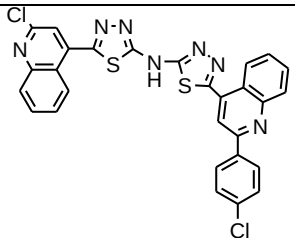
Entry	Solvent	Catalyst	Product Yield%
1	$CHCl_3$	H_2SO_4	90
2	$CHCl_3$	$POCl_3$	43
3	$CHCl_3$	H_3PO_4	11
4	$CHCl_3$	PPA	46

It was demonstrated from **Table 2** that though the yield of the product increases to an appreciable quantity in different catalytic systems, interestingly solvent $CHCl_3$ and catalyst H_2SO_4 was found to be the most efficient in the reported synthetic protocol. This efficient method for the synthesis of the potential protocol is in context of green chemistry involving microwave irradiation technique, which is the most convenient way to form the substituted of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol – 2- yl) – amine. **IV(a-k)**

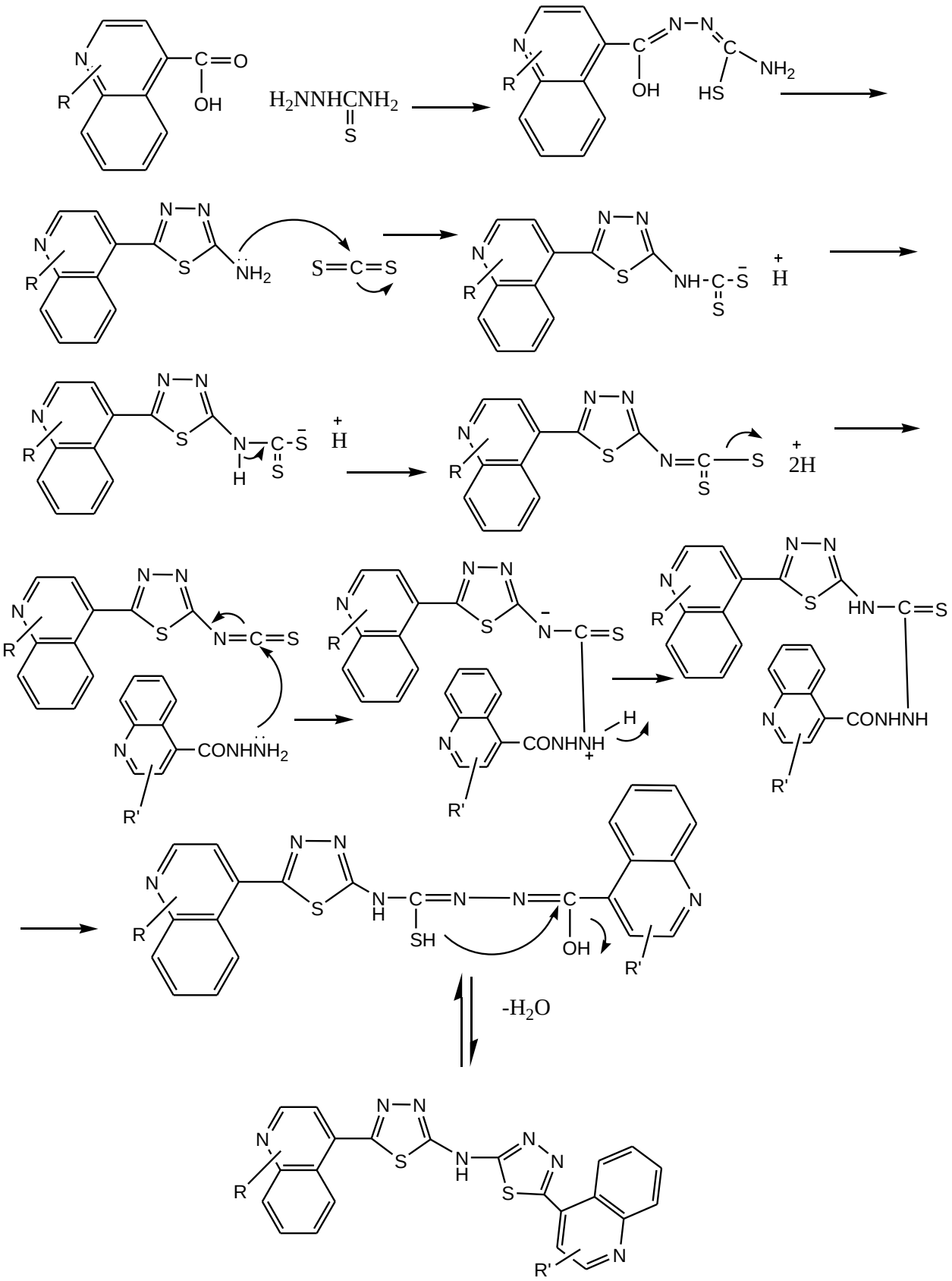
In an attempt to expand the scope of the reaction, a series of derivatives were synthesized using many variants of acids in the first step and acid hydrazide in the second step of the reaction. The results are summarized in **Table 3.**

Table 3: M.W promoted synthesis of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol -2- yl) – amine

Entry	R and R'	Product	Time(min)	Yield (%)
1.	H		1.20	82
2.	2-Cl		1.15	90
3.	2-CH_3		1.15	94

4.	2'-CH_3		1.25	90
5.	2-Cl, 2'-CH_3		1.20	92
6.	2-CH_3, 2'-CH_3		1.30	96
7.	2'-Cl		1.20	98
8.	2-Cl, 2'-Cl		1.20	79
9.	2-CH_3, 2'-Cl		1.30	76
10.	H, 2' 		1.25	73
11.	2-Cl, 2' 		1.30	77

Plausible mechanism for the formation of Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol -2- yl) - amine



Antimicrobial activity:

Pharmacological evaluation is one of the most important factors for the determination of activity of compounds. Evaluation part of the work should be variable and easy to perform. Since last few years, prevalence of infectious diseases has increased to a great

extent. Antimicrobial agents are the most commonly used to treat the different types of infectious diseases. Few of the compounds were tested *in vitro* for antimicrobial activity at concentrations of 200 μg/mL. The data was compared to the standard ciprofloxacin for bacteria and fluconazole for fungi.

Antibacterial activity

For antibacterial studies microorganisms employed were *Staphylococcus aureus* ATCC 9144, *Becillus Cereus* ATCC *11778, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853.*

Antifungal activity

For an antifungal activity, *Aspergillus niger and Aspergillus flavus* were used as organism.

Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMF. Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 18–20 hrs at 35^0c. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity.

Table 4 : Antibacterial activity of compounds (IVa-k)

Compounds	**Microorganisms**			
	S. aureus	*B. Cereus*	*E.coli*	*P. aeruginosa*
IV(a)	13.00	11.33	15.47	14.22
IV(b)	13.31	12.33	14.62	13.38
IV(c)	12.21	10.40	14.22	12.83
IV(d)	12.10	11.20	13.67	12.80
IV(e)	13.20	11.33	14.50	13.22
IV(f)	11.13	10.00	13.50	12.25
IV(g)	15.22	14.20	18.40	16.13
IV(h)	16.23	15.56	20.48	18.47
IV(i)	14.22	12.83	15.56	13.50
IV(j)	16.20	14.68	17.51	15.40
IV(k)	18.40	15.87	20.65	16.15
Ciprofloxacin	26.52	24.58	28.31	25.83

Table 5 : Antifungal activity of compounds (IVa-k)

Compounds	**Microorganisms**	
	Aspergillus niger	*Aspergillus flavus*
IV(a)	14.68	12.34
IV(b)	16.44	14.42
IV(c)	13.29	10.81
IV(d)	12.53	10.90
IV(e)	15.48	13.35
IV(f)	10.92	10.73
IV(g)	17.67	15.52
IV(h)	18.77	16.71
IV(i)	16.53	14.62
IV(j)	18.71	17.53
IV(k)	19.80	18.68
Fluconazole	26.36	27.35

III. RESULTS AND DISCUSSION

The new derivatives thiadiazole were prepared following the reaction sequences depicted in Scheme 1. Initial compounds I was prepared from available quinoline-4- carboxylic acid and thiosemicarbazide, which was then converted to compound II using pyridine and CS_2, then to compound III by using substituted phenol isothiocyanate and finally to compound IV(a-k) by using chloroform and concentrated H_2SO_4. The synthesized compounds were screened for their antimicrobial activity and they were found to possess good antibacterial and antifungal activity.

IV. CONCLUSION

Bis – (5-quinolin -4– yl- [1, 3, 4,] thiadiazol -2- yl) – amine has proved to be a potential chemotherapeutic and pharmacotherapeutic agents. The microwave technique has continued to add further improvements on the performance of reactions to provide products more efficiently in higher yields, better quality in less reaction time and is ecofriendly in nature.

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