Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2025, 14(2): 240-248

(International Peer Reviewed Journal)

One-pot two-step facile synthesis of new 2-Arylamino-5-(2-methyl quinazol-4-yl)-thio 1,3,4-thiadiazole hybrids as antimicrobial agents

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Accepted on 20th March, 2025

ABSTRACT

Quinazoline derivatives of thiadiazoles refers to a class of chemical compounds where a thiadizole ring attached to a quinoline ring, creating a molecule with potential biological activity often studied for its potential applications in medicines, including anti-inflammatory, anti-cancer, and antimicrobial properties (both anti-fungal and anti-bacterial) due to combined characteristics of both the quinazoline and thiadiazole moieties. These compounds consist of a quinazoline ring (a bicyclic aromatic ring) with a thiadiazole ring attached at a specific position, allowing for further modifications with different substituents with fine-tune biological activities. These derivatives exhibit diverse pharmacological activity including anti-leishmanial, anti-bacterial, anti-fungal, anti-cancer, etc. Keeping these views in mind I also have synthesized Quinazoline derivatives of thiadiazoles to enhance the uses of these derivatives. A one–pot, efficient and high-atom economic protocol involving the reaction between 2-Aryl-5-mercapto-1,3,4-thiadiazole with 2-methylamino-4-chloro quinazoline in Dimethyl formamide (DMF) as a solvent on a steam bath for 3 hrs, 2-Arylamino-5-(2-methylquinazol-4-yl)-thio 1,3,4-thiadiazole was developed. The final compounds were screened for their antimicrobial activities against Phytophthora infestans and Collicotricum falcatum and antitubercular activity against mycobacterium tuberculosis strain $H_{37}Ra$. The melting points were observed in open capillary tube and are uncorrected. The structures of the newly synthesized compounds were confirmed by IR on Perkin-Elmer 881 in KBr, and NMR spectroscopy (^{1}HNMR), and (^{13}C NMR) spectral data and elemental analysis. The results were compared with standard drugs tested under similar conditions. Some of these compounds showed promising antimicrobial activities.

Keywords: Quinozoline, Thiadiazoles, Dimethyl Formamide (DMF), Antifungal and antitubercular activities, NMR and IR data.

INTRODUCTION

1,3,4-Thiadiazoles were first described in 1882 by Fischer and further developed by Busch and his co-workers. The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in the field of Thiadiazoles. Thiadiazole carrying mercepto, hydroxyl and amino substituent's possess many good activities against microorganisms.

The literature of 1,3,4-thiadiazoles has been extensively reviewed. The 120-page survey by Almandin [1] is the definite work up to 1952 and is followed by Pushkarevsky review [2] in 1961 and the by S. G. Kukukguzel and co-workers [3] more modern treatment up to 1967. The specialist periodical reports of the chemical society on organic compounds of sulfur partially cover the literature [4-7] between 1970 and 1981.

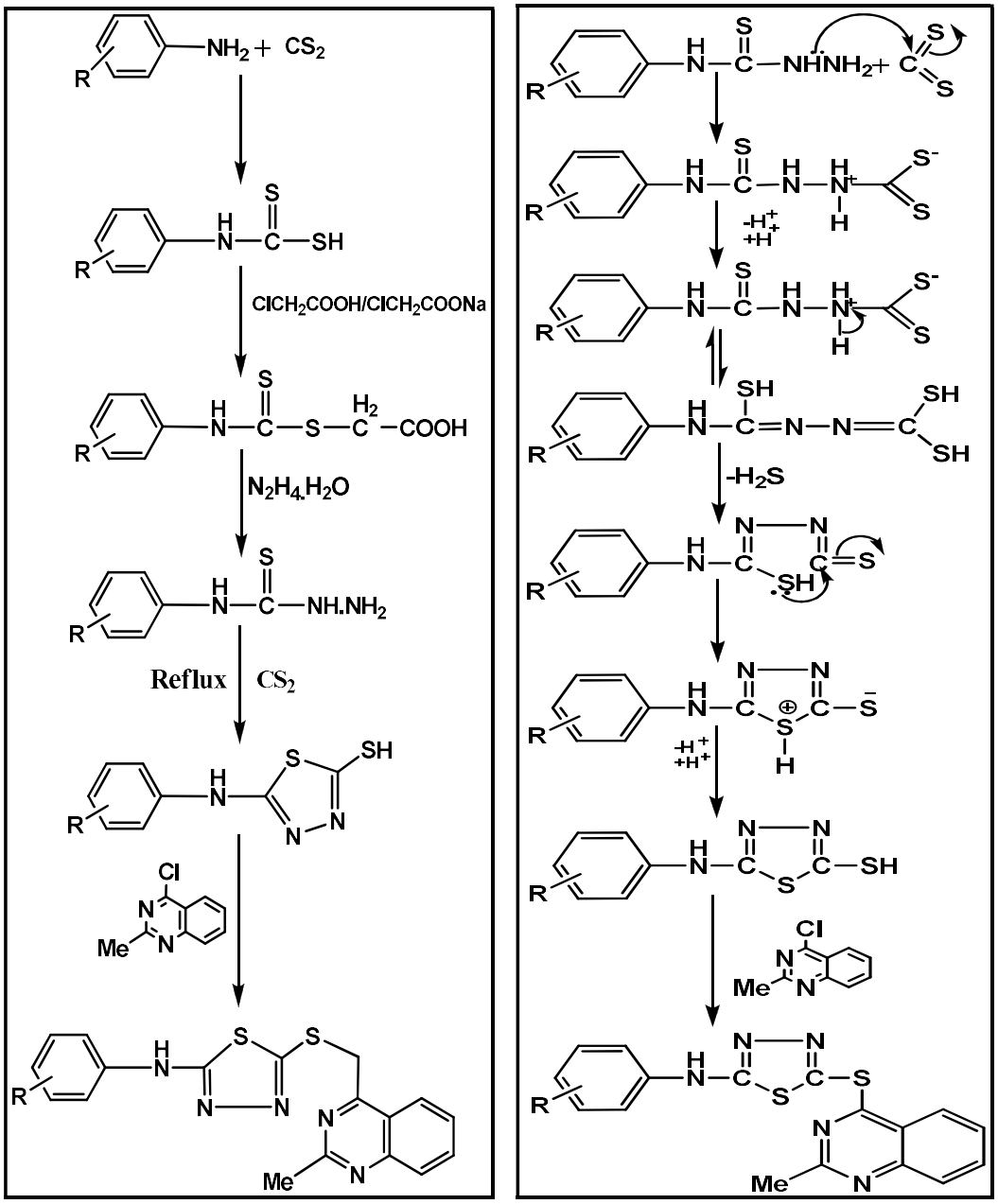
A brief review appeared recently [8, 9] and much useful information can also be obtained from the reference series 'Advances in Heterocyclic Chemistry' and 'Physical method of Heterocyclic Chemistry'. F. Rahim *et al*., [10] prepared unsubstituted 1,3,4-thiadiazole by transforming 2-amino-1,3,4-thiadiazole in to the 2-Bromo derivatives by Sandmeyer reaction and by reducing the Adams catalyst. The same compounds were obtained by bisthioformylation of hydrazine with sodium dithioformate, followed by spontaneous cyclization [11]. A. Aghcheli *et al*., [12] have recently described a suitable method for synthesizing 1,3,4-thiadizole by condensing N, N-dimethyl Formamide and N, N-diformyl hydrazine in the presence of phosgene. O. Gupta and Coworkers [13, 14] prepared several 2,5-dialkyl 1,3,4-thiadiazoles derivatives by reacting 1,2-diacyl hydrazines with phosphorous pentasulphide.

The quinazoline is an important heterocyclic moiety found in the basic skeleton of many natural products [15]. Substituted quinolines are potentially important compounds as they have potent anti-inflammatory, antiasthmatic, antibacterial, antimalarial activity and also have industrial applications [16-18].

Thiadiazole and their derivatives have been used from ancient time while their synthetic strategy, physical and chemical properties have studied extensively. They have not only application in medicine [19, 20], and agriculture [21-24] but also widely used as proficient electron acceptor. Functional materials play important role in the field of organic electronics, in which thiadiazole have been reported [25]. They have been used as ligands for the coordination of paramagnetic cations. Some derivatives of thiadiazole exhibit antiferromagnetic interactions while other also possesses photoconductivity. Thiadiazole derivative possesses strong biological activities and thus are extensively used in the field of pesticides and medicine.

Leishmaniasis is a severing disease which is initiated by leishmania genus and belongs to family *Trypanosomatidea*. This disease is categorized into three types: visceral commonly called Kala-azar, mucocutaneous and Cutaneous. The most dangerous form is visceral in which vital organs are targeted by the parasite. Long time fever, hyper gammaglobulinemia, pancytopenia, and splenomegaly are the properties of such severe visceral leishmaniasis. The patient is affected in very short span of time and can cause death if untreated. Leishmaniasis is transferred through female sandflies and its bites can affect liver, spleen and bone marrow. The parasites of leishmaniasis have two morphological forms which are amastigotes and promastigotes. Each year 1.5 million people affected from cutaneous while 500,000 new cases appear from visceral leishmaniasis. Seventy (**70**) countries of the world affected by cutaneous leishmaniasis and major cases occur in Afghanistan, Pakistan, Saudi Arabia, Brazil and Syria. Allopurinol and rifampicin showed activity in experimental systems, but proved disappointing in clinical trials. Treatment of visceral leishmania is limited because of drug resistance and keeping that in mind, quinoline based derivatives have been synthesized and evaluated for their antileishmanial and found to be most active. Quinazoline-based gold complexes were synthesized, by Catherine Hemmert and subjected for antileishmanial activity, which showed good *in vivo* activity. A series of nitro-substituted thiadiazole derivatives were synthesized and evaluated for their antileishmanial activity. Compound given has high potency when compared with other analogs. Leishmaniasis can be treat by using tolerated drugs. Currently, glucantime, pentostam, pentamidine and amphotericin are the drugs which are used for treatment of leishmaniasis. However, treatment with these current drugs suffers from numerous limitations like toxicity, cost, parenteral administration, and banquet of drug resistance, and reverts in HIV–Leishmania co-infected patients. Therefore, there is still a horrible need for novel effective and anodyne drugs in the absence of a forthcoming vaccine.

Keeping in view the biological importance of these classes of heterocycles *i.e* quinoline and thiadiazole, in this study we are going to report the synthesis of quinazoline-based thiadiazole hybrid analogs, their *in vitro* leishmanicidal activity and molecular docking.



Scheme-I **Scheme-II**

R = 4-OH, 4-NO_2, 3-Cl, 3-CH_3, 2-NO_2, 2-CH_3, 4-Cl, 2-F 3-NO_2, 2-Cl, 4-F, 4-CH_3

Scheme I and II. Synthetic route and plausible Mechanism of the formation Quinozoline Thiadiazole derivatives

MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8201 PC Spectrophotometer (νmax in cm^{-1}), ^{1}H NMR and ^{13}C NMR spectra in DMSO-d6

on a Bruker DRX–300 (300 MHz) spectrometer using TMS as a internal reference (Chemical shifts in Delta, ppm). All the reagents used were AR grade; analyses were performed on an elemental Vario EL III Carlo Erba 1108 C H N analyzer. Elemental (C, H, N) analysis data are within the acceptable limits (±0.4%) between calculated and observed values. Antifungal activity was performed in agar-agar medium and the Antitubercular activity is Micobacterium tuberculosis strain $H_{37}Ra$ Low stein Jensens medium in CDRI Lucknow. The purity of compounds was checked by thin layer chromatography on silica gel plate using ether and ethyl acetate as solvents and iodine chamber was used as a developing chamber.

General procedure: A solution of substituted Thiadiazoles derivatives mixed with calculated amount of quinazoline ring in to 1:1 ration in a solution of DMF. The mixture was refluxed for 2-3 h on a steam bath. It was cooled and the solid which separated was filtered, dried and recrystallized from ethanol.

1a. 4-(5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2-ylamino)phenol: Yield: (61%), White solid (EtOH); m.p 135^{0}C; IR: 3220(O-H arom ring stretching), 3010(C-H arom ring), 2905(C-H aliph ring), 1610(C=N stretching), 1459(C=C stretching), 1095(C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.70(m, 8H, arom proton), 5.35 (s,1H, O-H proton), 4.0 (s 1H imine proton), 4.46 (s 2H methylene proton) 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 116.3, 121.0, 122.1, 122.8, 126.5, 128.9, 131.4, 133.6, 148.9, 149.5, 152.1, 159.0, 161.8, 170.8 Anal. Clacd for $C_{18}H_{15}N_2OS_2$; Elemental Analysis: C, 56.67; H, 3.96; N, 18.36; O, 4.19; S, 16.81.

1b. 2-(5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2-ylamino)phenol: Yield: (56%), White solid (EtOH); m.p 130^{0}C; IR: 3210(O-H arom ring stretching), 3005(C-H arom ring), 2915(C-H aliph ring), 1610(C=N stretching), 1450(C=C stretching), 1075(C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.46 (m, 8H, arom proton), 5.35 (s,1H, O-H proton), 4.0 (s 1H imine proton), 4.46 (s 2H methylene proton) 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 112.0, 116.3, 120.3, 122.0, 122.4, 122.8, 126.4, 128.3, 131.5, 134.6, 144.2, 149.2, 152.8, 159.3, 161.0, 170.1 Anal. Clacd for $C_{18}H_{15}N_2OS_2$; Elemental Analysis: C, 56.67; H, 3.96; N, 18.36; O, 4.19; S, 16.81.

1c. N-(2-chlorophenyl)-5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2 amine: Yield: (72%), Brown solid (EtOH); m.p 160^{0}C; IR: 2995(C-H arom ring), 2865(C-H aliph ring), 1620 (C=N stretching), 1445(C=C stretching), 1090(C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.20-6.75 (m, 8H, arom proton), 4.46 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 122.0, 122.3, 122.5, 122.9, 125.3, 126.5, 127.3, 128.0, 130.4, 131.8, 136.4, 149.3, 152.5, 159.6, 161.2, 170.2, Anal. Clacd for $C_{18}H_{14}N_5S_2Cl$; Elemental Analysis: C, 54.06; H, 3.53; Cl, 8.87; N, 17.51; S, 16.04.

1d. N-(3-chlorophenyl)-5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2 amine : Yield: (69%), Dark Brown solid (EtOH); m.p 168^{0}C; IR: 3000 (C-H arom ring), 2900(C-H aliph ring), 1605 (C=N stretching), 1450(C=C stretching), 1075 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.20-6.75 (m, 8H, arom proton), 4.46 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 122.0, 122.3, 122.5, 122.9, 125.3, 126.5, 127.3, 128.0, 130.4, 131.8, 136.4, 149.3, 152.5, 159.6, 161.2, 170.2, Anal. Clacd for $C_{18}H_{14}N_5S_2Cl$; Elemental Analysis: C, 54.06; H, 3.53; Cl, 8.87; N, 17.51; S, 16.04.

1e. N-(4-chlorophenyl)-5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2 amine: Yield: (69%), White solid (EtOH); m.p 150^{0}C; IR: 3000 (C-H arom ring), 2900(C-H aliph ring), 1595 (C=N stretching), 1460(C=C stretching), 1065 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-7.24 (m, 8H, arom proton), 4.46 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 122.0, 122.3, 122.8, 126.3, 127.3, 128.0, 129.4, 131.8, 138.4, 149.4, 152.8, 159.5, 161.9, 170.0, Anal. Clacd for $C_{18}H_{14}N_5S_2Cl$; Elemental Analysis: C, 54.06; H, 3.53; Cl, 8.87; N, 17.51; S, 16.04.

1f. N-(4-fluorophenyl)-5-((2-methylquinazolin-4-yl)methylthio)-1,3,4-thiadiazol-2-amine: Yield: (58%), Dark Brown solid (EtOH); m.p 210^{0}C; IR: 3030 (C-H arom ring), 2890(C-H aliph ring), 1620 (C=N stretching), 1475(C=C stretching), 1055 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-7.31 (m, 8H, arom proton), 4.46 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 116.0, 120.3, 122.1, 122.8, 126.3, 128.0, 131.4, 136.8, 149.1, 152.0, 157.5, 159.5, 161.2, 170.2, Anal. Clacd for $C_{18}H_{14}N_5S_2F$; Elemental Analysis: C, 56.38; H, 3.68; F, 4.95; N, 18.26; S, 16.72.

1g. 5-((2-methylquinazolin-4-yl)methylthio)-N-(2-nitrophenyl)-1,3,4-thiadiazol-2-amine: Yield: (58%), Yellow solid (EtOH); m.p 121^{0}C; IR: 3020 (C-H arom ring), 2920(C-H aliph ring), 1600 (C=N stretching), 1550 (asymmetric streaching of NO_2 group), 1465(C=C stretching), 1050 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.15-6.88 (m, 8H, arom proton), 4.86 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 110.2, 119.3, 122.1, 122.8, 125.3, 126.4, 128.4, 129.8, 131.4, 137.3, 144.5, 149.5, 152.2, 159.7, 161.0, 170.5, Anal. Clacd for $C_{18}H_{14}N_6S_2O_2$; Elemental Analysis: C, 52.67; H, 3.44; N, 20.47; O, 7.80; S, 15.62.

1h. 5-((2-methylquinazolin-4-yl)methylthio)-N-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine: Yield: (58%), Yellow solid (EtOH); m.p 130^{0}C; IR: 3025 (C-H arom ring), 2930(C-H aliph ring), 1610 (C=N stretching), 1535 (asymmetric streaching of NO_2 group), 1450(C=C stretching), 1065 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-7.48 (m, 8H, arom proton), 4.86 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 109.2, 113.5, 122.1, 122.8, 123.7, 126.8, 128.7, 130.8, 131.5, 143.3, 148.7, 149.5, 152.5, 159.0, 161.2, 170.1, Anal. Clacd for $C_{18}H_{14}N_6S_2O_2$; Elemental Analysis: C, 52.67; H, 3.44; N, 20.47; O, 7.80; S, 15.62.

1i. 5-((2-methylquinazolin-4-yl)methylthio)-N-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine: Yield: (58%), Light Yellow solid (EtOH); m.p 125^{0}C; IR: 3015 (C-H arom ring), 2900(C-H aliph ring), 1600 (C=N stretching), 1540 (asymmetric streaching of NO_2 group), 1435(C=C stretching), 1045 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.89 (m, 8H, arom proton), 4.86 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 119.2, 122.1, 122.8, 124.1, 126.3, 128.2, 131.8, 137.5, 146.3, 149.2, 152.7, 159.2, 161.5, 170.3, Anal. Clacd for $C_{18}H_{14}N_6S_2O_2$; Elemental Analysis: C, 52.67; H, 3.44; N, 20.47; O, 7.80; S, 15.62.

1j. 5-((2-methylquinazolin-4-yl)methylthio)-N-o-tolyl-1,3,4-thiadiazol-2-amine: Yield: (73%), White crystelline solid (EtOH); m.p 142^{0}C; IR: 3005 (C-H arom ring), 2910 (C-H aliph ring), 1605 (C=N stretching), 1435(C=C stretching), 1045 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.51 (m, 8H, arom proton), 4.86 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton pyrimidine ring), 2.12 (s, 3H methyl proton aniline ring); ^{13}C NMR (δ ppm): δ 17.2, 25.2, 39.0, 122.1, 122.8, 123.2, 123.7, 126.2, 126.8, 128.5, 129.3, 131.2, 131.7, 142.5, 149.5, 152.1, 159.2, 161.3, 170.4, Anal. Clacd for $C_{19}H_{17}N_5S_2$; Elemental Analysis: C, 60.13; H, 4.52; N, 18.45; S, 16.90.

1k. 5-((2-methylquinazolin-4-yl)methylthio)-N-m-tolyl-1,3,4-thiadiazol-2-amine: Yield: (75%), White solid (EtOH); m.p 136^{0}C; IR: 3005 (C-H arom ring), 2910 (C-H aliph ring), 1605 (C=N stretching), 1435(C=C stretching), 1045 (C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.51 (m, 8H, arom proton), 4.86 (s 2H methylene proton), 4.0 (s 1H imine proton), 2.32 (s 3H methyl proton pyrimidine ring), 2.12 (s, 3H methyl proton aniline ring); ^{13}C NMR (δ ppm): δ 17.2, 25.2, 39.0, 122.1, 122.8, 123.2, 123.7, 126.2, 126.8, 128.5, 129.3, 131.2, 131.7, 142.5, 149.5, 152.1, 159.2, 161.3, 170.4, Anal. Clacd for $C_{19}H_{17}N_5S_2$; Elemental Analysis: C, 60.13; H, 4.52; N, 18.45; S, 16.90.

RESULTS AND DISCUSSION

The newly designed compounds have been synthesized as given in scheme 1. The thiadiazole were used as valuable intermediates for the preparation of the title compounds. In fact, these compounds with a carbonyl group function in their structure served as activated amine, used as a nucleophilic donor. A

solution of thiadiazole (2.0 gm) in absolute DMF (dimethyl formamide) was added to a boiling solution of quinazoline (2.0 gm). The mixture was refluxed for 2-3 hrs on a steam bath. furnished the final products **1-12**. The structures of the final products have been confirmed by elemental and spectral (IR, ^{1}H NMR & ^{13}C NMR) data. The IR: spectrum of **1** gave peaks at Yield: (61%), White solid (EtOH); m.p 135^{0}C; IR: 3220(O-H arom ring stretching), 3010(C-H arom ring), 2905(C-H aliph ring), 1610(C=N stretching), 1459(C=C stretching), 1095(C=S stretching) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.16-6.70(m, 8H, arom proton), 5.35 (s,1H, O-H proton), 4.0 (s 1H imine proton), 4.46 (s 2H methylene proton) 2.32 (s 3H methyl proton); ^{13}C NMR (δ ppm): δ 25.2, 39.0, 116.3, 121.0, 122.1, 122.8, 126.5, 128.9, 131.4, 133.6, 148.9, 149.5, 152.1, 159.0, 161.8, 170.8 Anal. Clacd for $C_{18}H_{15}N_2OS_2$; Elemental Analysis: C, 56.67; H, 3.96; N, 18.36; O, 4.19; S, 16.81, Similar pattern of spectral results were also obtained for rest all the compounds of this series. The results of antifungal testing revealed that all tested compounds showed moderate to good fungicidal activity against *Phytophthora infestans* and *Collicotricum falcatum* in the reference of Dithane M-45. Although most of the substituted thiadiazolo quinazoline derivatives showed antimicrobial activity, so keeping these views in mind, tested all the thiadiazolo quinazoline derivatives against Mycobacterium tuberculosis strain H_{37}Ra in Lowenstein Jensen's medium, but none of the tested compounds showed the better antitubercular activity.

The result was not very encouraging. The screening data of antifungal activity of this series of **c**ompounds show moderate activity. The Flouro substituted compounds scaffold possess notable activity on the both tested fungi. The most active compound which inhibit about **91 %** of fungal growth. The data of antimicrobial activity also revealed that compounds having polar substituent like, chloro, nitro and methoxy, imparts much toward antimicrobial power in this series of compounds. The results of the antifungal and antitubercular studies are listed in table 1 and table 2 respectively.

APPLICATION

In order to see the applicability of these newly synthesized Thiadiazolo-quinazoline compounds, we have tested them on biological screen. These compounds have been evaluated for their following two type of activity.

Antifungal screening: The newly synthesized compounds were screened for their antifungal activity against two species of fungi against *Phytophthora infestans* and *Collicotricum falcatum* in DMSO by poisoned food technique. The desired amount of the test material was taken in pre sterilized, cold Petri plates having 0.5 mL of acetate and 9.5 mL of the molten medium, the Petri plates were moved in round fashion to get a homogenous mixture of the contents. In the control set, 9.5 mL of the medium, 0.5 mL of acetone and distilled water equal in amount to the test material were taken; when the medium solidified one mycelial disc of the inoculums was aseptically inoculated upside down in the centre of each assay plate which were then incubated. The visual colony diameter of the test fungi in each assay was noted in mutually perpendicular direction at intervals of 24 to 168 h (i.e 7 days). The diameter of the inoculated fungal disc was subtracted from the apparent colony diameter to represent the mycelial growth. On the basis of growth recorded on 7th day of incubation, the fungicidal activity of test compounds was calculated in terms of present inhibition using the following formula.

$$\% \text{ inhibition of mycelial growth} = \frac{dc\text{-}dt}{dc} \times 100$$

Where, **dc** = Average diameter growth of the colony in control set on 7th day of incubation. **dt** = Average diameter growth of the colony in treatment set on 7th day of incubation.

A commercial drug, Dithane M-45 was also tested under similar conditions to compare the results of tested compounds. The data for the antifungal studies are listed in table 1.

Table 1. Antifungal studies of tested compounds and Dithane M-45

S. No	R	Average % Inhibition against Phytophthora Infectans at		
		1000ppm	100ppm	10ppm
1.	4-OH	63	35	18
2.	2-OH	60	41	26
3.	2-Cl	78	45	24
4.	3-Cl	70	50	34
5.	4-Cl	71	49	32
6.	4-F	91	63	40
7.	2-NO2	90	61	40
8.	3-NO_2	85	52	35
9.	4-NO_2	80	50	38
10.	2-CH_3	68	42	30
11.	4-CH_3	66	40	27
12.	2-OCH_3	80	49	36
13.	Dithane M-45	100	80	66

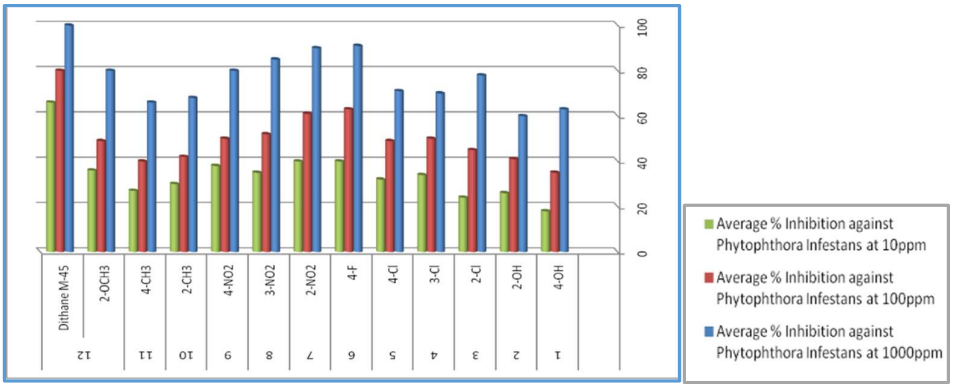


Figure 1. Fungicidal activity graph of compound 1-12 (Zone of inhibition in mm).

Antitubercular Activity: Although most of the substituted thiadiazolo-quinazoline derivatives showed antitubercular activity, so keeping these views in mind, we have tested all the thiadiazolo quinazoline derivatives against Mycobacterium tuberculosis strain $H_{37}Ra$ in Lowenstein Jensen's medium, but none of the tested compounds showed the better antitubercular activity.

Table 2. Antitubercular activity

S. No	R	M.I.C. ug mL^{-1}
1.	4-OH	60
2.	2-OH	72
3.	2-Cl	75
4.	3-Cl	72
5.	4-Cl	80
6.	4-F	98
7.	2-NO_2	76
8.	3-NO_2	70
9.	4-NO_2	89
10.	2-CH_3	62
11.	4-CH_3	59
12.	4-OCH_3	81
	Mycobacterium tuberculosis Strain H37Ra	100

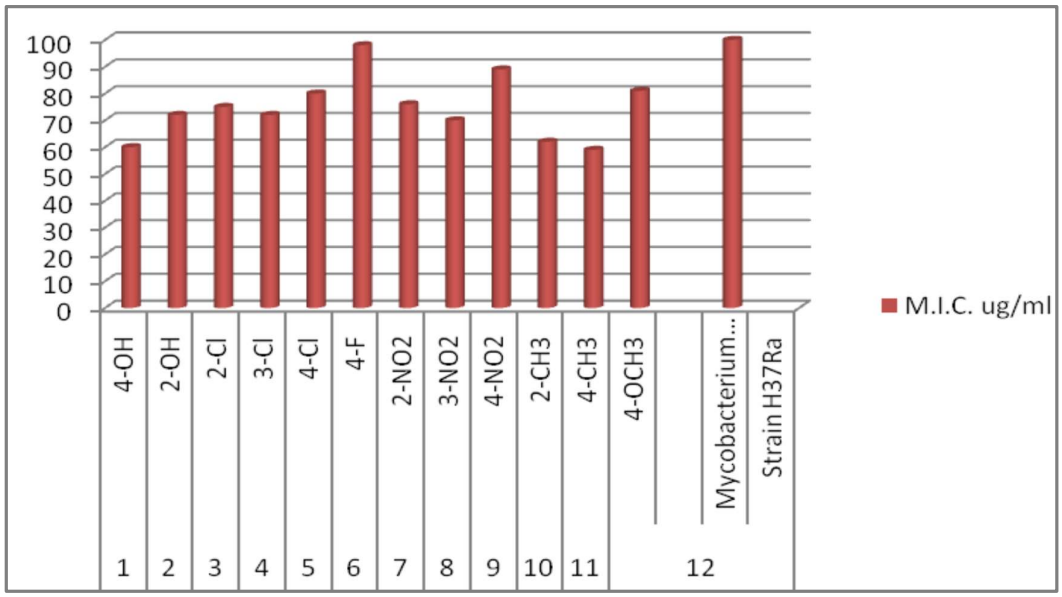


Figure 2. Antitubercular activity graph of compound 1-12 against Mycobacterium tuberculosis strain $H_{37}Ra$ (Zone of inhibition in MIC ug mL^{-1})

CONCLUSION

In the present investigation, series of new fused thiadiazolo quinazoline have been synthesized and screened for their antifungal and antibacterial activity. The activity reveals that the synthesized compounds possess moderate to good activity profile. The insights gained in this study will be useful for development of new anti-infective agents. Similar pattern of spectral results were also obtained for rest all the compounds of this series. The results of antifungal testing revealed that all tested compounds showed moderate to good fungicidal activity against *Phytophthora infestans* and *Collicotricum falcatum* in the reference of Dithane M-45. Although most of the substituted thiadiazolo quinazoline derivatives showed antitubercular activity, so keeping these views in mind, tested all the thiadiazolo quinazoline derivatives against Mycobacterium tuberculosis strain $H_{37}Ra$ in Lowenstein Jensen's medium, but none of the tested compounds showed the better antitubercular activity.

The result was not very encouraging. The screening data of antifungal activity of this series of **c**ompounds show moderate activity. The Flouro substituted compounds scaffold possess notable activity on the both tested fungi. The most active compound which inhibit about **91 %** of fungal growth. The data of antimicrobial activity also revealed that compounds having polar substituent like, chloro, Nitro, and methoxy, imparts much toward antimicrobial power in this series of compounds. The results of the antifungal and antitubercular studies are listed in table 1 and table 2 respectively.

ACKNOWLEDGMENT

The one of authors is thankful to the Chairman, Department of Chemistry, D. D. U. Gorakhpur University, Gorakhpur, for providing the facilities. They also thank to Chairman, Department of Botany, D. D. U. Gorakhpur University, for help in carrying antimicrobial activities. They also thank C D R I, Lucknow for antitubercular analysis and Chemistry Department, B. H. U., Varanasi, for IR, NMR spectral and elemental analysis. One of the authors, is thankful to U. G. C., New Delhi for financial assistantship.

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