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Synthesis, Antitubercular Activity of Novel Quinoxaline Derivatives

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Quinoxaline derivatives were synthesized and evaluated for antitubercular studies. All the synthesized compounds exhibited an interesting activity profile against the strain. The results revealed that the activity is considerably affected by various substituents. The compounds with quinolone substitution exhibited better antitubercular activity. The compounds **2c, 2d** and **2e and 2i, 2j and 2k** with ciprofloxacin, norfloxacin and sparfloxacin with sulphonamide and isoniazid substitution exhibited good percentage inhibition.

Keyword: Quinoxaline, Antitubercular activity, Sulphanilamide, Isoniazid.

1. Introduction

Tuberculosis is one of the most common infectious diseases known to human. One-third of the world population is infected with *Mycobacterium tuberculosis* and the World Health Organization (WHO) estimates that within the next twenty years approximately thirty million people will be infected with the bacillus [1]. With the global spread of HIV, similar increase in the incidence rate of Tuberculosis (TB) and mortality are to be feared [2]. Co-infection with TB and HIV can increase the risk of death twice when compared to death due to the later alone [3]. As resistant strains of *Mycobacterium tuberculosis* have slowly emerged, treatment failures also emerge. The current frontline therapy for tuberculosis consists of administering three or more different drugs (usually isoniazid, rifampin, pyrazinamide and ethambutol) over extended periods of time [4]. Problems due to multidrug-resistant TB arise and it becomes necessary to develop new therapeutic agents in order to treat the new forms of the disease.

Quinoxaline nucleus is an imperative scaffold that is not only synthetically important but also possesses a wide range of promising biological activities. This ring is reported to possess antitubercular activity [5–7]. A literature survey showed that over 500 quinoxaline derivatives were tested by the TAACF program, (Tuberculosis Antimicrobial Acquisition and Coordinating Facility) including simple substituted quinoxalines and their corresponding 1,4-di-*N*-oxides [8, 9]. Many of these compounds possess excellent antitubercular activity. Among the various heterocyclic compounds, quinoxalines form an attractive biologically active molecule as these are a part of various antibiotics such as echinomycin, levomycin, and actinoleutin [10, 11]. The antitubercular activity for Mannich bases of quinoxaline against *Mycobacterium tuberculosis* has been reported [12].

2. Material and Methods

2.1 General

All chemicals were purchased from Sigma Aldrich (India). Uncorrected melting points were determined using a Sigma scientific apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-500 instrument (300 MHz, Bruker) using TMS as an internal standard and DMSO-d_6 as solvent. Mass spectra were recorded on a GCMS QP 5000 Shimadzu. Elemental analysis was performed on Perkin Elmer 240 CHN analyzer. IR was recorded on ABB Bomem FTIR Spectrometer MB104 with KBr pellet. Intermediate quinoxaline-2,3-dione (**1a**) was synthesized based on reported procedure [13].

2.1.1..Synthesisof4-(3-Oxo-3,4-Dihydroquin oxalin-2(1H)-liydeneamino) benzenesulphona mide (1b):

3.42gm of Quinoxaline 2,3 dione and 3gm of sulphanilamide/isoniazid were taken in a RBF. To it 10ml of DMF and few drops of glacial acetic acid were added and the reaction mixture was refluxed for 3–5 h. The reaction mixture was poured on crushed ice or ice-cold water. The separated product was filtered out, washed and recrystallised from ethanol

2.1.2 General Procedure for the Synthesis of Mannich Bases (2c-2n)

Equimolar quantities of (0.01mol) (E)-3-(phenylimino)-3,4-dihydro quinoxaline-2(1H)-one and amines were taken in RBF. 50ml of glacial acetic acid and 1ml of formaldehyde were poured in to RBF and refluxed for 6-9hrs based on the substituted amines

2.2 Anti-mycobacterial Activity

Antitubercular activity was evaluated against *Mycobacterium tuberculosis* H37 Rv ATCC27294 using Microplate Alamar Blue Assay [14]. The test was performed in black, clear-bottomed, 96-well microplates (black view plates; Packard Instrument Company, Meriden, Conn. USA) in order to minimize the background fluorescence. Initial drug dilutions were prepared in dimethylsulfoxide, and subsequent two fold dilutions were performed in 0.1 mL of 7H9GC media in the microplates. 0.1mL of 2.5 $\times 10^{6}$ CFU/mL of *Mycobacterium tuberculosis* H37 Rv in 7H9GC was added to each well of the 96 well microtitre plate containing the test compounds. Three control wells containing drug and medium, bacteria and medium and medium alone were prepared. All microtitre plates were incubated at 37 °C. On the seventh day of incubation, Alamar Blue dye solution (20mL Alamar Blue solution and 12.5 mL of 20% Tween 80) was added to all the wells and plates were re-incubated at 37 °C for 24 h. Fluorescence was measured in a Victor II multilabel fluorometer (Perkin Elmer Life Sciences Inc., Boston, MA). MIC was determined from the colour change.

3. Results and Discussion

As a part of our research, we have studied the effect of different substitutions on the quinoxaline ring for their anti tubercular activity. The synthetic route is shown in Scheme 1. The preparation of quinoxaline-2,3-dione (**1a**) was carried out as previously reported. Reaction of **1a** with isoniazid/sulphanilamide resulted in the formation of **1b/1b1.** This compound 1b/1b1 underwent N-Mannich reaction with different primary amines (**1c-1n**) to yield title compounds **2c-2n**. During the course of the reaction, the synthesis of Mannich bases (**2c-2n**) produced good yields (68.00 - 94.00%). All the compounds were characterized by IR, ^{1}H and ^{13}C NMR, MS, and elemental analyses. The formation of mannich base is confirmed by the appearance of N-CH_2 bond. The absorption peak at 1105-1459 cm^{-1} is due the presence of CH_2 group. The IR spectra of compounds showed absorption bands due to stretching vibrations of N-H, C=O and C-N at 3686-3771cm^{-1},1590-1698 cm^{-1} and 1527-1614cm^{-1} respectively. In ^{1}H NMR studies the chemical shift and multiplicity patterns correlated well with the proposed structures. Thus the ^{1}H NMR showed a singlet at δ 5.18 ppm corresponding to formation of N-CH_2-N while that of the NH-Ar signal appeared at δ 4.62 ppm. We confirmed the aromatic protons by the appearance of multiplets at δ 7.04- 8.49 ppm whereas the multiplets at δ 4.27-4.43 ppm confirmed the presence of 4 hydrogens of

piperazine. The ^{13}C NMR of **4a** revealed 32 carbon atoms with C=O having highest signal at δ 200.57 ppm while two CH_2 of cyclopropane appeared at δ 5.84 and δ 5.31 ppm. The remaining carbons showed signals ranging from δ 196.82 to δ 36.43. All the synthesized compounds exhibited an interesting activity profile against the tested mycobacterial strain. The Minimum Inhibitory Concentration (MIC) was determined for compounds **2c–2n** against the *M. tuberculosis* strain H37Rv using the micro plate Alamar Blue assay (MABA). The results of the antitubercular activity are presented in Table 1. All the synthesized compounds exhibited an interesting activity profile against the strain. The results revealed that the activity is considerably affected by various substituents. The compounds with quinolone substitution exhibited better antitubercular activity. The compounds **2c, 2d** and **2e and 2i, 2j and 2k** with ciprofloxacin, norfloxacin and sparfloxacin with sulphonamide and isoniazid substitution exhibited good percentage inhibition.

Compound **2c**. Yeild: 0.80 g (78%). mp.148 ˚C. IR (ν max/cm^{-1}, KBr): 3467.09 (N–H), 1691.60 (C=O), 1610.95 (C=N). ^1H NMR [300 MHz, CH3OH-d_4]: 1.12-1.51 (m, 4H, CH_2 of cyclopropyl H), 3.03-3.51 (m, 1H, CH of cyclopropyl-H), 4.42-4.62 (m, 8H, piperazinyl H), 4.74 (s, 1H, NH-Ar), 6.03 (s, 2H, N-CH_2-N), 6.69-7.31 (m, 12H, aromatic H), 11.024 (s, 1H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 200.57 (C=O), 196.82 (COOH), 163.49 (C=N), 148.76 (C=C), 141.32 (N-C=O), 1 143.81, 141.96, 139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15, 126.82, 123.37, 122.72, 120.12, 119.01, 112.63, 110.17, 105.82, 103.64 (18 aromatic carbons), 112.47 (C=C-COOH), 65.31 (N-CH_2-N), 51.65,48.97, 47.83, 45.31 (4 carbon of piperazine), 36.43 (CH of cyclopropane), 5.84, 5.31 (CH_2 of cyclopropane). Compound **2d**. Yeild: 0.84 g (83%). mp.140 ˚C. IR (ν max/cm^{-1}, KBr): 3322.15 (N–H), 1590.94 (C=O), 1515.07 (C=N). ^1H NMR [300 MHz, $CDCl_3$-d_4]: 1.321 (t, J=6.4Hz, 3H, CH_3 of C_2H_5), 4.41 (q, J=7 Hz, 2H, CH_2 of C_2H_5), 4.12-4.36 (m, 8H, piperazinyl H), 4.74 (s, 1H, NH-Ar), 6.64 (s, 2H, N-CH_2-N), 7.16-7.88 (m, 12H, aromatic H), 11.024 (s, 1H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 201.21 (C=O), 197.62 (COOH), 163.39 (C=N), 148.06 (C=C), 142.32 (N-C=O), 143.64, 142.78, 139.34, 136.81, 136.20, 135.16, 133.68, 131.67, 129.43, 127.46, 123.35, 122.64, 121.21, 119.20, 112.64, 110.25, 106.03, 103.63 (18 aromatic carbons), 112.57 (C=C-COOH), 64.94 (N-CH_2-N), 61.76 (N-CH_2), 57.08 (CH_3 of C_2H_5), 51.72, 49.14, 47.69, 45.43 (4 carbon of piperazine), 14.91 (CH_2 of C_2H_5).

Compound **2e**. Yeild: 0.86 g (85%). mp.186 ˚C. IR (ν max/cm^{-1}, KBr): 3320.15 (N–H), 1686.36 (C=O), 1602.17 (C=N). ^1H NMR [300 MHz, $CDCl_3$-d_4]: 1.15-1.48 (m, 4H, CH_2 of cyclopropyl H), 2.67-3.33 (m, 1H, CH of cyclopropyl-H), 4.16-4.66 (m, 8H, piperazinyl H), 4.74 (s, 1H, NH-Ar), 6.62 (s, 2H, N-CH_2-N), 7.46-7.88 (m, 11H, aromatic H), 11.25 (s, 1H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 200.91 (C=O), 196.69 (COOH), 163.53 (C=N), 149.13 (C=C), 141.32 (N-C=O), 143.81, 141.96, 139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15, 126.82, 123.37, 122.72, 120.12, 119.01, 112.63, 110.17, 105.82, 103.64 (18 aromatic carbons), 114.63 (C=C-COOH), 64.26 (N-CH_2-N), 51.56, 48.46, 47.69, 45.54 (4 carbon of piperazine), 36.56 (CH of cyclopropane), 5.84, 5.31 (CH_2 of cyclopropane).

Compound **2f** Yeild: 0.95 g (92%). mp.120 ˚C. IR (ν max/cm^{-1}, KBr): 3479.39 (N–H), 1624.08 (C=O), 1597.02 (C=N). ^1H NMR [300 MHz, $CDCl_3$-d_4]: 4.21-4.39 (m, 8H, piperazinyl H), 4.42 (s, 1H, NH of piperazine), 4.66 (s, 1H, NH-Ar), 6.03 (s, 2H, N-CH_2-N), 7.16-7.88 (m, 9H, aromatic H). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 163.49 (C=N), 147.32 (N-C=O), 143.81, 141.96, 139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15 122.72, 120.12, 119.01 (12 aromatic carbons), 65.31 (N-CH_2-N), 51.65, 48.97, 47.83, 45.31 (4 carbon of piperazine).

Compound **2g**. Yeild: 0.94 g (91%). mp110 ˚C. IR (ν max/cm^{-1}, KBr): 3602.04 (N–H), 1624.86 (C=O), 1585.55 (C=N). ^1H NMR [300 MHz, $CDCl_3$-d_4]: 2.18 (s, 3H, CH_3 of piperazine), 4.21-4.54 (m, 7H, piperazinyl H), 4.66 (s, 1H, NH-Ar), 6.62 (s, 2H, N-CH_2-N), 7.26-7.78 (m, 9H, aromatic H). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 163.49 (C=N), 141.32 (N-C=O), 143.81, 141.96,

139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15 122.72, 120.12, 119.01 (12 aromatic carbons), 65.31 (N-CH_2-N), 51.65,48.97, 47.83, 45.31 (4 carbon of piperazine), 43.44 (1 carbon of N-methyl of piperazine).

Compound **2h**. Yeild: 0.81 g (82%). mp 116 ˚C. IR (ν max/cm^{-1}, KBr): 3402.36 (N–H), 1632.52 (C=O), 1614.55 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 2.68,2.72,2.81,2.92 (s, 8H, of morpholine), 4.74 (s, 1H, NH-Ar), 6.64 (s, 2H, N-CH_2-N), 7.16-7.78 (m, 9H, aromatic H). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 163.49 (C=N), 141.32 (N-C=O), 143.81, 141.96, 139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15 122.72, 120.12, 119.01 (12 aromatic carbons), 65.31 (N-CH_2-N), 66.86, 64.25, 51.11, 51.87 (4 carbon of morpholine).

Compound **2i**. Yeild: 0.75 g (72%). mp.152 ˚C. IR (ν max/cm^{-1}, KBr): 3400.51 (N–H), 1628.34 (C=O), 1579.74 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 1.15-1.45 (m, 4H, CH_2 of cyclopropyl H), 3.54-3.98 (m, 1H, CH of cyclopropyl-H), 4.16-4.66 (m, 8H, piperazinyl H), 4.74 (s, 1H, NH-Ar), 6.03 (s, 2H, N-CH_2-N), 7.16-7.78 (m, 11H, aromatic H), 11.02 (s, 1H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 200.57 (C=O), 196.82 (COOH), 163.49 (C=N), 148.76(C=C), 141.32 (N-C=O), 143.81, 141.96, 139.42, 137.58, 136.41, 135.11, 133.74, 132.22, 129.15, 126.82, 123.37, 122.72, 120.12, 119.01, 112.63, 110.17, 105.82, 103.64 (18 aromatic carbons), 112.47 (C=C-COOH), 65.31 (N-CH_2-N), 51.65,48.97, 47.83, 45.31 (4 carbon of piperazine), 36.43 (CH of cyclopropane), 5.84, 5.31 (CH_2 of cyclopropane).

Compound **2j**. Yeild: 0.76 g(75%). mp.141 ˚C. IR (ν max/cm^{-1}, KBr): 3300.25 (N–H), 1608.44 (C=O), 1596.54 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 1.03 (t, J=6.4Hz, 3H, CH_3 of C_2H_5), 4.29 (q, J=7 Hz, 2H, CH_2 of C_2H_5), 4.31-4.48 (m, 8H, piperazinyl H), 4.66 (s, 1H, NH-Ar), 6.03 (s, 2H, N-CH_2-N), 7.16-7.78 (m, 11H, aromatic H), 11.02 (s, ^{1}H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 200.21 (C=O), 196.53 (COOH), 164.21 (C=N), 148.12 (C=C), 142.06 (N-C=O), 143.21, 142.06, 139.61, 137.64, 136.74, 135.46, 134.21, 132.26, 129.12, 126.78, 123.43, 122.69, 120.26, 119.31, 112.36, 110.16, 105.87, 103.44 (18 aromatic carbons), 112.32 (C=C-COOH), 65.24 (N-CH_2-N), 56.74 (CH_3 of C_2H_5), 51.62, 48.74, 47.78, 45.29 (4 carbon of piperazine), 14.83 (CH_2 of C_2H_5).

Compound **2k**. Yeild: 0.81 g (80%). mp.194 ˚C. IR (ν max/cm^{-1}, KBr): 3086.16 (N–H), 1627.83 (C=O), 1527.83 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 0.87-0.93 (m, 4H, CH_2 of cyclopropyl H), 3.03-3.93 (m, 1H, CH of cyclopropyl-H), 4.01-4.66 (m, 8H, piperazinyl H), 4.74 (s, 1H, NH-Ar), 6.74 (s, 2H, N-CH_2-N), 7.44-7.78 (m, 11H, aromatic H), 11.02 (s, 1H, COOH). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 201.68(C=O), 197.32 (COOH), 162.82 (C=N), 149.12 (C=C), 141.46 (N-C=O), 143.62, 141.81, 139.46, 137.62, 136.27, 134.21, 133.61, 132.18, 129.41, 126.62, 123.42, 122.69, 120.11, 119.01, 112.63, 110.18, 105.82, 103.64 (18 aromatic carbons), 112.89 (C=C-COOH), 66.26 (N-CH_2-N), 51.56,48.81, 47.86, 45.37 (4 carbon of piperazine), 36.43 (CH of cyclopropane), 5.84, 5.31 (CH_2 of cyclopropane).

Compound **2l**. Yeild: 0.83g (83%). mp.114 ˚C. IR (ν max/cm^{-1}, KBr): 3467.09 (N–H), 1691.60 (C=O), 1610.95 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 4.18-4.42 (m, 8H, piperazinyl H), 4.36 (s, 1H, NH of piperazine), 4.61 (s, 1H, NH-Ar), 5.24 (s, 2H, N-CH_2-N), 7.21-8.48 (m, 8H, aromatic H). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 164.26 (C=N), 141.51 (N-C=O), 144.08, 141.82, 139.51, 137.63, 136.38, 135.18, 133.68, 132.42, 129.15 123.02, 120.19, 119.16 (12 aromatic carbons), 65.36 (N-CH_2-N), 51.36, 498.12, 47.68, 45.26 (4 carbon of piperazine).

Compound **2m**. mp.105 ˚C. IR (ν max/cm^{-1}, KBr): 3322.57 (N–H), 1615.07 (C=O), 1590.94 (C=N). ^{1}H NMR [300 MHz, CH3OH-d_4]: 2.18 (s, 3H, CH_3 of piperazine), 4.22-4.48 (m, 8H, piperazinyl H), 4.66 (s, ^{1}H, NH-Ar), 6.03 (s, 2H, N-CH_2-N), 7.27-7.49 (m, 8H, aromatic H). ^{13}C NMR [300 MHz, CH_3-OH-d_4]: 162.42 (C=N), 141.66 (N-C=O), 144.21, 142.16, 139.46, 137.68, 136.47, 134.94, 133.34, 132.41, 129.32 122.61, 120.76, 119.63 (12 aromatic carbons), 65.66 (N-CH_2-N), 51.42, 49.07, 47.61, 45.34 (4 carbon of piperazine), 43.62 (1 carbon of N-methyl of piperazine).

Compound **2n**. Yeild: 0.79 g (76%). mp.110 ˚C. IR (ν max/cm^{-1}, KBr): 3402.30 (N–H), 1632.52 (C=O), 1614.55 (C=N). ^{1}H NMR [300 MHz, $CDCl_3$-d_4]: 2.51, 2.58, 2.90, 2.98 (s, 8H, of morpholine), 4.66 (s, 1H, NH-Ar), 6.62 (s, 2H, N-CH_2-N), 7.16-7.78 (m, 8H, aromatic H). ^{13}C NMR [300 MHz, CH_3OH-d_4]: 162.82 (C=N), 143.21 (N-C=O), 144.36, 142.84, 139.24, 137.61, 136.54, 134.91, 133.62, 132.31, 129.18 122.27, 120.51, 119.11 (12 aromatic carbons), 65.36 (N-CH_2-N), 66.86, 64.25, 51.11, 51.87 (4 carbon of morpholine).

4. Conclusion:

Synthesis, spectral characterization, antitubercular activity of a new series of quinoxalines derivatives of is reported here. The *in vitro* antitubercular screening results of the title compounds, evidenced that compounds **2c, 2d** and **2e and 2i, 2j and 2k**, may be considered promising for the development of new antitubercular agents. The current findings can help chemists and pharmacists for further investigations in this field in search of potent antitubercular agents.

5. Acknowledgements

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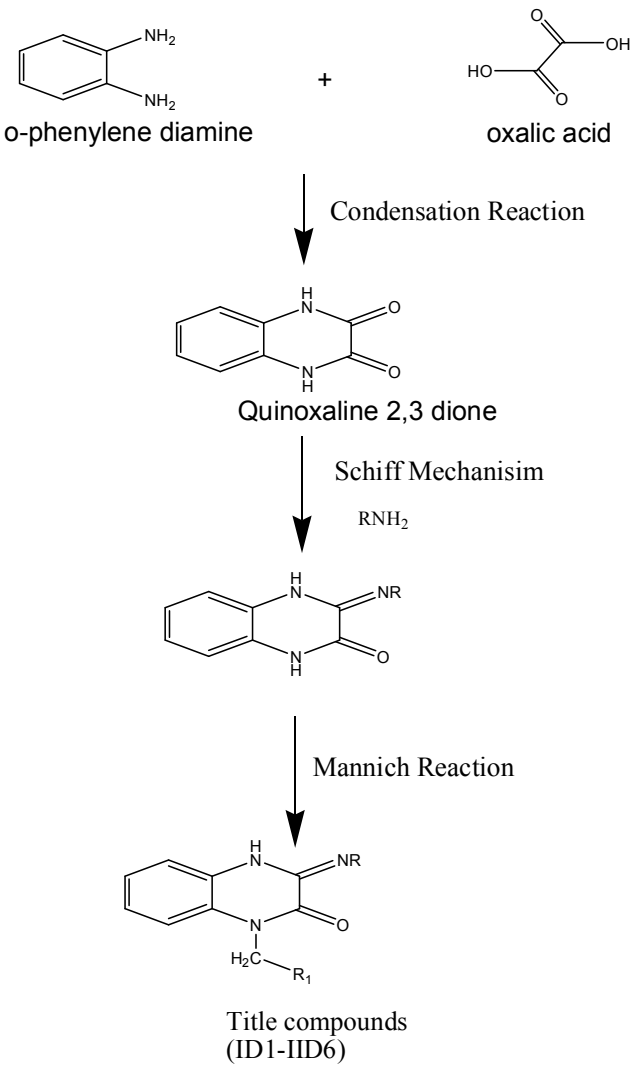
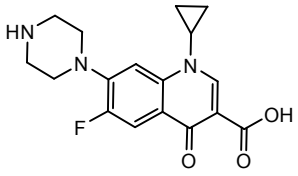
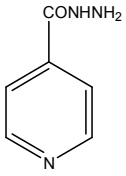
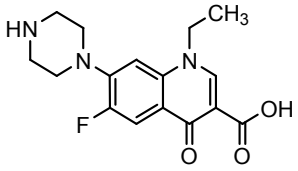
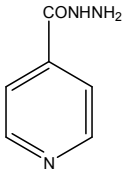
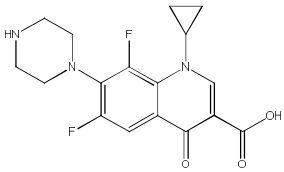
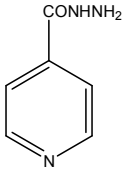
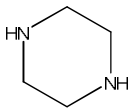
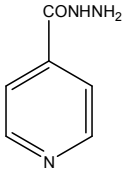
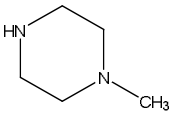
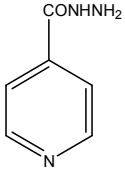
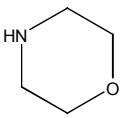
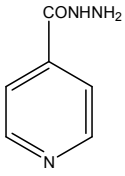
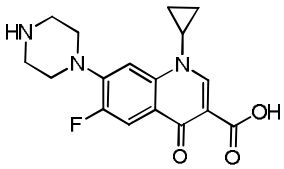
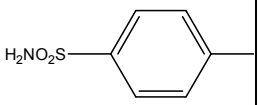
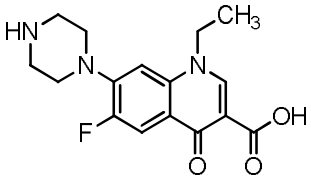
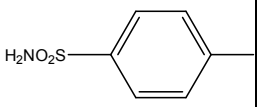
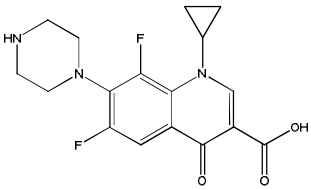
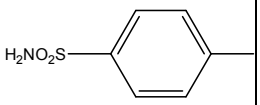
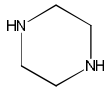
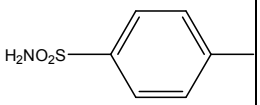
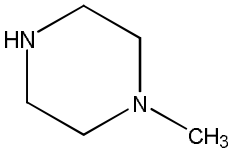
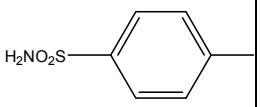
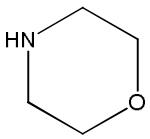
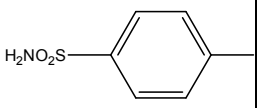


Scheme 1

Table 1: The *in-vitro* antitubercular activity of compounds **2n–w** and **3n–w** against *M. tuberculosis* H37Rv strain.

Compound code	R_1	R	Anti tubercular activity (MIC)
2c			2.5

2d			3.75
2e			3.75
2f			5.0
2g			5.0
2h			6.25

2i			3.75
2j			5.0
2k			5.0
2l			6.25
2m			5.0
2n			6.25

6. References

1. WHO. Weekly epidemiological record. 2003; 78: 121-128.
2. De Cock KM, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. Int J Tuberc Lung Dis 1999; 3: 457-465.
3. Gupta RA, Gupta AK, Soni LK, Kaskhedikar SG. Rationalization of physicochemical characters of oxazolyl thiosemicarbazone analogs towards multi-drug resistant tuberculosis. A QSAR approach. Eur. J. Med. Chem 2007; 42: 1109-1116.
4. Janin YL. Antituberculosis drugs: Ten years of research. Bioorg Med Chem 2007; 15: 2479-2513.
5. Esther V, Silvia PS, Lidia ML, Saioa A, Asunción B, Beatriz S, Raquel V, Ignacio A, Antonio M. Selective activity against Mycobacterium tuberculosis of new quinoxaline 1,4-di-N-oxides. Bioorg Med Chem 2009; 17: 385–389.
6. Esther V, Pablo RD, Eduardo AC, Antonio M. QSAR analysis for quinoxaline-2-carboxylate 1,4-di-N-oxides as anti-mycobacterial agents. J Mol Graph Model 2009; 28: 28–36.
7. Elsa M, Saioa A, Silvia P, Enrique T, Ignacio A, Antonio M. Synthesis and antimycobacterial activity of new quinoxaline-2-carboxamide 1,4-di-N-oxide derivatives. Eur J Med Chem; 45 2010; 4418-4426.
8. Carta A, Corona P, Loriga M. Quinoxaline 1, 4-dioxide: A versatile scaffold endowed with manifold activities. Curr Med Chem 2005; 12: 2259-2272.
9. Goldman RC, Laughon BE, Reynolds RC, Secrist JA, Maddry JA, Guie MA, Poffenberger AC, Kwong, CA, Ananthan S. Programs to facilitate tuberculosis drug discovery: The tuberculosis antimicrobial acquisition and coordinating facility. Infect Disord Drug Targets 2007; 7: 92-104.
10. Lee JS, Waring MJ. Interaction between synthetic analogues of quinoxaline antibiotics and nucleic acids. Changes in mechanism and specificity related to structural alterations. Biochem J 1978; 173: 129–144.
11. Bailey C, Michael JW. DNA recognition by quinoxaline antibiotics: use of base-modified DNA molecules to investigate determinants of sequence-specific binding of triostin and Tandam. Biochem J 1998; 330: 8187.
12. Ramalingam P, Ganapaty S, Babu RC. In vitro antitubercular and antimicrobial activities of 1-substituted quinoxaline-2,3(1H,4H)-diones. Bioorg Med Chem Lett 2010; 20: 406–408.