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Research Article

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Synthesis, *In Vitro* Antitubercular Activity and 3D-QSAR of Novel Quinoxaline Derivatives

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Twenty new quinoxalines bearing azetidinone and thiazolidinone groups were synthesized by cyclocondensation of Schiff bases of quinoxaline-2, 3-dione and were characterized with several analytical tools. They were tested against *Mycobacterium tuberculosis* H37Rv at a concentration of 10 μg/mL by Microplate Alamar Blue Assay method. Quinoxaline derivatives with 2-chloro, dimethylamino and nitro substitutions exhibited *in vitro* activity, comparable to that of the drug, isoniazid. Three-dimensional quantitative structure–activity relationship studies indicated that electrostatic and steric field descriptors could explain the observed activity. The developed model fits the data well and has good predictive capability (r^2 = 0.81, q^2 = 0.71, F = 27.06, r^2_pred = 0.84, r^2_m = 0.84, r^2 BS = 0.80). Electronegative groups play an important role in the antitubercular activity.

Key words: azetidinone, antitubercular activity, thiazolidinones, three-dimensional, electron withdrawing groups, quantitative structure–activity relationship, quinoxaline

Abbreviations: 3D-QSAR, three-dimensional quantitative structure–activity relationship; CFU, colony-forming units; MIC, minimum inhibitory concentration; MLR, multiple linear regression.

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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 20 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 is to be feared (2). Coinfection with TB and HIV can increase the risk of death twice when compared with death because of the later alone (3). As resistant strains of *M. tuberculosis* have slowly emerged, treatment failures also emerge. The current front-line therapy for tuberculosis consists of administering three or more different drugs (usually isoniazid, rifampin, pyrazinamide and ethambutol) over extended periods of time (4). Problems because of multi-drug-resistant TB arise, and it becomes necessary to develop new therapeutic agents 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 Tuberculosis Antimicrobial Acquisition and Coordinating Facility program 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 *M. tuberculosis* has been reported (12).

Azetidinones and thiazolidinones are structural subunit of penicillin. Azetidinone is a four-membered nitrogen containing heterocycle possessing powerful antimicrobial (13–15), anti-inflammatory (16) and antitubercular activities (17,18). Thiazolidinone is an interesting heterocycle with various pharmacological activities. They are reported to possess a wide range of biological activities including antibacterial, antifungal, antiHIV, etc. (19).

Based on this logic, an attempt to synthesize some novel compounds containing quinoxaline ring fused to azetidinones and thiazolidinones and study their antitubercular activity. With the aim to establish the influence of substitutions on the antitubercular activity, 3D-quantitative structure–activity relationship (3D-QSAR) was developed. Quantitative structure–activity relationship helps to understand the structural features that are necessary for the antitubercular activity of compounds, and it serves as a guide in the design of more potent molecules. Use of QSAR for understanding antibacterial, antifungal and antiTB activities of small molecules has been well documented (20–25).

Materials and Methods

Instruments

All chemicals were purchased from Sigma Aldrich (Bangalore, India). Uncorrected melting points were determined using a Sigma

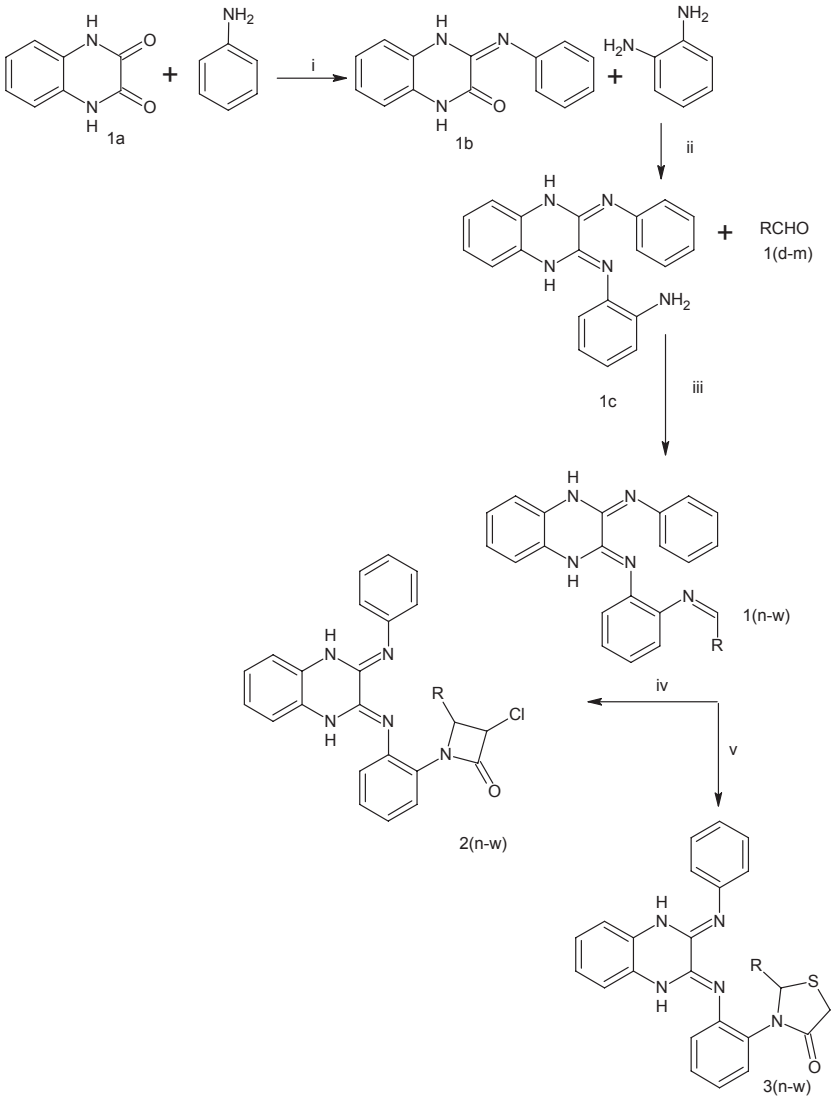
scientific apparatus (Coimbatore, India). ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-500 instrument (300 MHz; Bruker, Mumbai, India) using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent. Mass spectra were recorded on a GCMS QP 5000 Shimadzu (Shimadzu Analytical (India) Pvt. Ltd, Mumbai, India). Elemental analysis was performed on Perkin Elmer 240 CHN analyzer (Perkin Elmer Life Sciences Inc., Boston, MA, USA). IR was recorded on ABB Bomem FTIR Spectrometer MB104 with KBr pellet (ABB Bomem FTIR, Faridabad, India).

Synthesis of compounds

The synthetic route is shown in Scheme 1. The yield of the compounds was not optimized. Intermediate quinoxaline-2,3-dione (**1a**) was synthesized based on reported procedure (26).

Compound **1a** (3.42 g, 2 mmol) was added to a mixture of aniline (1.85 mL) and ethanol (10 mL) and stirred magnetically at room temperature for 30 min. To this well-stirred mixture, few drops of glacial acetic acid were added, and the stirring was continued for further 10 min. Then, it was irradiated in microwave oven (400 W) for 2 min. The reaction mixture was poured into crushed ice. A solid was collected by filtration, washed with water and recrystallized from ethanol to yield 5.1 g of 3-((phenylimino)-3,4-dihydroquinoxaline)-one (**1b**) (yield 85%).

To a stirred solution of compound **1b** (2.37 g, 1 mmol) and *o*-phenylenediamine (1.08 g) in 10 mL of ethanol, few drops of glacial acetic acid were slowly added at room temperature. This mixture was irradiated with microwave oven for 2 min. The crude product was filtered off, washed with water, dried by applying vacuum and



Scheme 1: Reagent and conditions (i) and (ii) EtOH, glacial acetic acid, microwave 400 W, 2 min.; (iii) DMF, glacial acetic acid microwave 400 W, 45 seconds; (iv) chloroacetyl chloride, 1,2-dioxan, triethylamine microwave 400 W, 3 min; (v) thioglycolic acid, EtOH microwave 400 W, 4 mins.

recrystallized with ethanol to give 2.41 g of *N*-((E)-3-(phenylimino)-3,4-dihydroqunoxalin-2(1H)-ylidene)benzene-1,2-diamine(**1c**) (yield 74%).

Compound **1c** (3.27 g, 1 mmol) was dissolved in 10 mL of ethanol, and then, the required aromatic aldehyde (**1d–m**) was added. Then to this mixture, few drops of glacial acetic acid were added slowly and stirred with a magnetic stirrer for 30 min. It was kept in microwave oven for 3 min. The reaction was cooled to room temperature, washed with water, dried by $MgSO_4$ and filtered. The filtrate was evaporated to dryness to produce corresponding Schiff bases (**1n–w**) (yield ranges between 58% and 77%), and the residue was purified by silica gel column chromatography.

The Schiff base(s) **1n–w** (0.01 mmol) was dissolved in 1,2-dioxan, followed by the addition of chloroacetyl chloride (1.12 g, 0.01 mmol,) and triethylamine (1.01 g, 1 mmol) slowly in a round bottom flask. The reaction mixture was stirred for 1 h, and then, it was irradiated in a microwave oven for 3 min. The solid that appeared after the addition of water was filtered off and dried to get **2n–w** (yield varying between 11.48% and 80.01%). The residue was purified by silica gel column eluted with ethylacetate/petroleum ether (1:5) to yield respective azetidinones.

A mixture of Schiff base (s), **1n–w** (0.01 mmol), thioglycolic acid (1 mmol) and ethanol (10 mL) were irradiated in microwave oven for 4 min. The reaction mixture was poured into ice cooled water. The solid thus obtained was removed by filtration, and the residue was purified by silica gel column as mentioned above to afford **3n–w** (yield ranges between 64% and 88%). The chemical structures of the synthesized compounds were determined on the basis of IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

3-Choro-4-(2-hydroxyphenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2n)

Yield 52.66%, m.p. 270–272 °C; IR (υ_{max}, /cm, KBr): 3610 (Ar-OH), 3367 (N-H), 2960(C-H), 1741 (Azetidinone, C=O), 1665 (C=N) and 765 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.7 (1H, d, J = 5.8Hz, CH-Cl of Azetidinone), 5.2 (1H, s, CH-N), 7.6 (1H, s, Ar-OH) and 6.44 (1H, dd, J = 1.8, 8.4 C-NH) p.p.m.; ^{13}C NMR (DMSO-d_6) δ: 173, 162, 131 and 121 p.p.m.; fast atom bombardment mass spectroscopy (FAB-MS) (*m/z*): 507 (M^+, 7%), 508 (M^+ + 1, 6%), 506 (M^+ − 1, 5%), 416 (24%), 311 (22%) 235 (44%), 132 (27%), 106 (100%), and 77 (39%). Anal. Calcd for $C_{29}H_{22}ClN_5O_2$: C, 68.57%; H, 4.37%; N, 13.79%. Found: C, 68.54%; H, 4.37%; N, 13.77%.

3-Choro-4-(4-hydroxyphenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2o)

Yield 62.80%; m.p. 200–202 °C; IR (υ_{max}, /cm, KBr): 3396 (Ar-OH), 3349 (N-H), 2960 (C-H), 1753 (Azetidinone, C=O), 1665 (C=N) and 764 (C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.8 (1H, d, J = 5.8, CH-Cl of Azetidinone), 5.4 (1H, s, CH-N), 4.2 (1H, s, C-NH) and 7.2 (1H, s, Ar-OH) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.26, 162.55, 156.58, 149.34 and 62.43 p.p.m.; FAB-MS (*m/z*): 507 (M^+, 5%), 508 (M^+ + 1, 4%), 506 (M^+−1, 3%), 414 (25%), 311 (22%), 286 (31%), 221 (29%), 193 (30%), 103 (32%), 80 (100%), and 58 (47%). Anal. Calcd for $C_{29}H_{22}ClN_5O_2$: C, 68.57%; H, 4.37%; N, 13.79%. Found: C, 68.54%; H, 4.37%; N, 13.77%.

3-Chloro-4-(4-methoxyphenyl)-1-(2-((E)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2p)

Yield 80.01%; m.p. 268–272 °C; IR (υ_{max}, /cm, KBr): 3347(N-H), 1749(Azetidinone, C=O), 1655 (C=N), 1229(Ar-OCH_3) and 764 (Azetidinone, C-Cl); ^{1}H NMR(DMSO-d_6, 300 MHz) δ: 5.8 (1H, dd, J = 5.7,10.7, CH-Cl of Azetidinone), 5.4 (1H, s, CH-N), 4.2 (1H, s, C-NH) and 3.9 (1H, s, Ar-OCH_3) p.p.m.; ^{13}C (DMSO-d_6) δ: 62.32, 163.22, 157.142 and 63.45 p.p.m.; FAB-MS (*m/z*): 521 (M^+,11%), 522 (M^+ + 1, 7%), 520 (M^+ − 1, 5%), 415 (8%), 340 (7%), 206 (20%), 107 (38%), 80 (100%) and 77 (42%). Anal.Calcd for $C_{30}H_{24}ClN_5O_2$: C 69.03%; H, 4.63%; N, 13.42%. Found: C, 69.03%; H, 4.60%; N, 13.39%.

3-Choro-4-(4-chorophenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2q)

Yield 70.20%; m.p. 180–182 °C; IR (υ_{max}, /cm, KBr): 3339 (N-H), 2889(C-H), 1743 (Azetidinone, C=O), 1655 (C=N), 765 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.4 (1H, dd, J = 5.8, 10.3, CH-Cl of Azetidinone), 4.6 (1H, s, CH-N), and 4.0 (1H, s, C-NH) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.65, 132.67, 117, 132.54 and 63.58 p.p.m.; FAB-MS (*m/z*): 525 ($M^{+\cdot}$ 3%), 526 (M^+ + 1, 5%), 524 (M^+ − 1, 5%), 434 (7%), 311 (26%), 243 (49%), 234 (35%), 191 (37%), 113 (38%), 84 (31%), 80 (100%) and 68 (9%). Anal. Calcd for $C_{29}H_{21}Cl_2N_5O$: C, 66.17%; H, 4.02%; N, 13.28%. Found: C, 66.14%; H, 4.00%, N, 4.00%.

3-Choro-4-(2-chlorophenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2r)

Yield 27.97%; m.p. 220–222 °C; IR (υ_{max}, /cm, KBr): 3348 (N-H), 2995(C-H), 1757 (Azetidinone, C=O), 1658 (C=N), 1338 (C-N) and 747 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.7 (1H, d, J = 5.8, CH-Cl of Azetidinone), 4.9 (1H, dd, J = 1.76,8.34 CH-N) and 4.0 (1H, s, C-NH) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.21, 161.98, 135.33, 132.78 and 62.54 p.p.m.; FAB-MS (*m/z*): 525 (M^+, 8%), 526 (M^+ + 1, 6%), 524 (M^+ − 1, 5%), 448 (19%), 304 (18%), 290 (20%), 144 (42%), 91 (28%), 80 (100%), 90 (16%) and 45 (51%). Anal. Calcd for $C_{29}H_{21}Cl_2N_5O$: C, 66.17%; H, 4.02%; N, 13.28%. Found: C, 66.14%; H, 4.60%; N, 13.30%.

3-Choro-4-(4-methylphenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2s)

Yield 58.33%; m.p. 176–178 °C; IR (υ_{max}, /cm, KBr): 3341 (N-H), 2965 (C-H), 2850, 2917 (Ar-CH_3); 1749 (Azetidinone, C=O), 1655 (C=N), 1439 (C-N) and 749 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.5 (1H, d, J = 5.7, CH-Cl of Azetidinone), 4.6 (1H, s,

CH-N), 3.9 (1H, s, C-NH) and 2.3 (3H, s, (Ar-CH_3) p.p.m.; ^{13}C (DMSO-d_6) δ: 164.11, 165.52, 134.73 and 63.16 p.p.m.; FAB-MS (*m/z*): 505 (M^+, 5%), 506 (M^+ + 1, 4%), 504 (M^+ − 1, 7%), 428 (17%), 325 (27%), 235 (36%), 191 (37%), 132 (34%), 106 (100%) and 77(33%). Anal. Calcd for $C_{30}H_{24}ClN_5O$: C, 71.21%; H, 4.78%; N, 13.84%. Found: C, 71.20%; H, 4.75%; N, 13.81%.

3-Choro-4-(4-(dimethylamino)phenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2t)

Yield 11.48%; m.p. 190–192 °C; IR (υ_{max}, /cm, KBr): 3348 (N-H),2967(C-H), 1437(C-N), 1753 (Azetidinone, C=O), 1655 (C=N), 1290 (N-$(CH_3)_2$) and 765 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.3 (1H, s, CH-Cl of Azetidinone), 5.2 (1H, dd, J = 1.7,8.34, CH-N), 4.0 (1H, s, C-NH) and 2.9 (6H, s, N-$(CH_3)_2$) p.p.m.; ^{13}C (DMSO-d_6) δ: 164.22, 162.34, 147.64, 135.56 and 40.3 p.p.m.; FAB-MS (*m/z*): 534 (M^+, 9%), 535 (M + 1, 7%), 533 (M^+ − 1, 7%), 313 (16%), 222 (18%), 180 (28%), 132 (25%), 106 (100%), 103 (23%) and 77(42%). Anal. Calcd for $C_{31}H_{27}ClN_6O$: C, 69.59%; H, 5.06%; N, 15.70%. Found: C, 69.55%; H, 5.06%; N, 15.70%.

3-Choro-4-(3-nitrophenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2u)

Yield 45.03%; m.p. 212–214 °C; IR (υ_{max}, /cm, KBr):3347 (N-H), 1748 (Azetidinone, C=O), 1658 (C=N), 1557 (C-NO_2) and 764 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.7 (1H, d, J = 5.8, CH-Cl of Azetidinone), 5.2 (1H, s, CH-N) and 3.8 (1H, s, C-NH) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.01, 162.06, 162.06, 148.23, 135.31 and 62.74 p.p.m.; FAB-MS (*m/z*): 536 (M^+, 7%), 537 (M^+ + 1, 6%), 535 (M^+ − 1, 4%), 430 (8%), 310 (16%), 289 (12%), 225 (14%), 221 (18%), 144 (48%), 85(31%), 80 (100%) and 48(47%). Anal. Calcd for $C_{29}H_{21}ClN_6O_3$: C, 64.87%; H, 3.94%; N, 15.65%. Found: C, 64.84%; H, 3.91%; N, 14.51%.

3-Choro-4-(furan-3-yl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2v)

Yield 61.75%; m.p. 258–262 °C; IR (υ_{max}, /cm, KBr): 3349 (N-H), 2991(C-H), 1758 (Azetidinone, C=O), 1665 (C=N), and 765 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.7 (1H, dd, J = 1.53, 8.23, CH-Cl of Azetidinone), 5.1 (1H, d, J = 3.8, CH-N) and 4.0 (1H, s, C-NH) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.04, 142.01, 129.26 and 62.87 p.p.m.; FAB-MS (*m/z*): 481 (M^+, 5%), 482 (M^+ + 1, 5%), 480 (M^+ − 1, 3%), 414 (12%), 311 (7%), 221 (17%), 185 (23%), 170 (10%), 106 (100%) and 91(39%). Anal. Calcd for $C_{27}H_{20}ClN_5O_2$: C, 67.29%; H, 4.18%; N, 14.53%. Found: C, 67.30%; H, 4.15%; N, 14.51%.

3-Choro-4-(4-hydroxy-3-methoxyphenyl)-1-(2-((E)-((E)-3(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)azetidin-2-one (2w)

Yield 47.68%; m.p. 182–186 °C; IR (υ_{max}, /cm, KBr): 3389 (Ar-OH), 3348 (N-H), 1743 (Azetidinone, C=O), 1665 (C=N), 1229 (Ar-OCH_3) and 765 (Azetidinone, C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.8 (1H, s, CH-Cl of Azetidinone), 5.2 (1H, s, CH-N), 4.0 (1H, d, J = 1 .8, C-NH), 4.9 (1H, s, Ar-OH) and 3.7 (3H, s, OCH_3) p.p.m.; ^{13}C (DMSO-d_6) δ: 143.7, 150.2, 143.43, 63.79 and 56.21 p.p.m.; FAB-MS (*m/z*): 537 (M^+, 4%), 538 (M^+ +1, 4%), 536 (M^+ − 1, 3%), 431 (8%), 311 (6%), 221 (17%), 123 (30%), 80 (100%) and 90 (32%). Anal. Calcd for $C_{30}H_{24}ClN_5O_3$: C, 66.97%; H, 4.53%; N, 13.00%. Found: C, 66.97%; H, 4.53%; N, 13.00%.

2-(2-Hydroxyphenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3n)

Yield 82%; m.p. 250–252 °C; IR (υ_{max}, /cm, KBr): 3367 (Ar-OH), 2993 (C-H), 1660 (C=O), 1451 (C=N) and 613 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.5 (2H, s, NH), 3.5 (2H, s, CH_2), 6.0 (1H, s, CH) and 7.5(Ar-OH) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.02, 143.45,131.4, 119 and 110.6 p.p.m.; FAB-MS (*m/z*): 505 (M^+ 6%), 506 (M^+ + 1 3%), 504 (M^+ − 1 5%), 465(19%), 441 (18%), 367 (26%), 192 (25%), 132 (27%) and 91 (100%). Anal. Calcd for $C_{29}H_{23}N_5O_2S$: C, 68.89%; H, 4.59%; N, 13.85%. Found: C, 68.86%; H, 4.56%; N, 13.88%.

2-(4-Hydroxyphenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3o)

Yield 69%; m.p. 238–240 °C; IR (υ_{max}, /cm, KBr): 3349(N-H), 2885(C-H), 1614 (C=O), 1505(C=N) and 663 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.3 (2H, s, NH), 3.7 (2H, s, CH_2), 6.1 (1H, s, CH) and 7.7 (Ar-OH) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.03, 156.4, 112.6, 133.4, 119. p.p.m.; FAB-MS (*m/z*): 505 (M^+, 9%), 506 (M^+ +1, 5%), 504 (M^+ − 1, 7%), 412(16%), 312 (15%), 221(18%), 192 (15%), 132 (13%) and 91 (100%). Anal. Calcd for $C_{29}H_{23}N_5O_2S$: C, 68.89%; H, 4.59%; N, 13.85%. Found: C, 68.87; H, 4.57; N, 13.88.

2-(2-Methoxyphenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3p)

Yield 74%; m.p. 244–246 °C; IR (υ_{max}, /cm, KBr): 3365(N-H), 2992(C-H), 1613 (C=O), 1518(C=N), 1278(Ar-OCH_3) and 720(C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.2 (2H, s, NH), 3.4 (2H, s, CH_2), 5.4 (1H, s, CH) and 4.8 (1H, s, OCH_3) p.p.m.; ^{13}C (DMSO-d_6) δ: 163.87, 150.6, 133.4, 130.3 and 119 p.p.m.; FAB-MS (*m/z*): 519(M^+, 3%), 520 (M^++ 1, 5%), 518 (M^+ − 1, 7%), 412 (31%) 288 (22%),130 (100%) 91 (36%) and 106 (29%). Anal. Calcd for $C_{30}H_{25}N_5O_2S$: C, 69.34%; H, 4.85%; N, 13.48%. Found: C, 69.31%; H, 4.77%; N, 13.35%.

2-(4-Chlorophenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3q)

Yield 71%; m.p. 251–253 °C; IR (υ_{max}, /cm, KBr):3369 (N-H), 2993 (C-H), 1613 (C=O), 1459 (C=N) and 612 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.3 (2H, s, NH), 3.4 (2H, s, CH_2) and 5.8 (1H, s, CH) p.p.m.; ^{13}C (DMSO-d_6) δ: 164.32, 133.4, 131.56, 130.3 and 119 p.p.m.; FAB-MS (*m/z*): 523 (M^+, 8%), 524 (M^+ + 1, 5%), 522

($M^+ - 1$, 7%), 412 (29%), 311 (50%), 211 (31%),106 (100%) and 91(49%). Anal. Calcd for $C_{29}H_{22}ClN_5OS$: C, 66.47%; H, 4.23%; N, 13.36%. Found: C, 66.49%; H, 4.25%; N, 13.39%.

2-(2-Chlorophenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3r)

Yield 88%; m.p. 234–236 °C; IR (υ_{max}, /cm, KBr): 3355 (N-H), 2995 (C-H), 1614 (C=O), 1507 (C=N) and 662 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.3 (2H, s, NH), 3.8 (2H, s, CH_2), and 5.6 (1H, s, CH) p.p.m.; ^{13}C (DMSO-d_6) δ: 136.45, 136.4, 123.3 and 117 p.p.m.; FAB-MS (*m/z*): 523 ($M^{+\cdot}$ 7%), 524 (M^+ +1, 13%), 522 ($M^+ - 1$, 11%), 488 (17%), 312 (19%) 106 (16%) and 91(100%) Anal. Calcd for $C_{29}H_{22}ClN_5OS$: C, 66.47%; H, 4.26%; N, 13.36%. Found: C, 66.51; H, 4.26; N, 13.39.

2-(4-Methylphenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3s)

Yield 73%; m.p. 252–254 °C; IR (υ_{max}, /cm, KBr): 3339 (N-H), 2887(C-H), 1613 (C=O), 1515 (C=N), 1387 (Ar-CH_3), 615 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.5 (2H, s, NH), 3.7 (2H, s, CH_2) and 2.8 (1H, s, CH_3) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.55,132.8,129.7 and 118.7 p.p.m.; FAB-MS (*m/z*): 503 (M^+, 2%), 504 (M^+ +1 16%), 502 ($M^+ - 1$, 4%), 412 (16%), 397 (15%), 311 (32%), 192 (20%), 158 (17%) and 91(100%). Anal. Calcd for $C_{30}H_{25}N_5OS$: C, 71.55%; H, 5.00%; N, 13.91%. Found: C, 71.57%; H, 5.03%; N, 13.94%.

2-(4-Dimethylaminophenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3t)

Yield 68%; m.p. 228–230 °C; IR (υ_{max}, /cm, KBr):3342 (N-H), 2994 (C-H), 1611 (C=O), 1519 (C=N), 1295 (N-$(CH_3)_2$) and 617(C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.1 (2H, s, NH), 3.7 (2H, s, CH_2), 5.7 (1H, s, CH) and 2.9 (6H, s, N-$(CH_3)_2$) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.44, 133.1, 128.9and 119.6 p.p.m.; FAB-MS (*m/z*): 532 (M^+, 4%), 533 ($M^+ + 1$, 7%), 531 ($M^+ - 1$, 4%), 488 (23%), 312 (36%), 221 (32%), 120 (27%) and 106 (100%). Anal. Calcd for $C_{31}H_{26}N_6OS$: C, 69.9%; H, 5.3%; N, 15.78%. Found, C, 69.96%; H, 5.33%; N, 15.75%.

2-(3-Nitrophenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3u)

Yield 76%; m.p. 270–272 °C; IR (υ_{max}, /cm, KBr): 3361(N-H), 1600 (C=O), 1525 (C=N), 1349 (Ar-NO_2), 688 (C-S); 3361(N-H), 1600 (C=O), 1525 (C=N), 1349 (Ar-NO_2)and 688 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.7 (2H, s, NH), 3.2 (2H, s, CH_2) and 5.6 (1H, s, CH) p.p.m.; ^{13}C (DMSO-d_6) δ: 143.68,133.1, 128.9 and119.6 p.p.m.; FAB-MS (*m/z*): 534 (M^+, 6%), 535 ($M^+ + 1$, 5%), 533 ($M^+ - 1$, 4%), 312 (34%), 299 (16%), 158 (24%) and 91(100%). Anal. Calcd for $C_{29}H_{22}N_6O_3S$: C, 65.15%; H, 4.15%; N, 15.72%. Found: C, 65.12%; H, 4.12%; N, 15.70%.

3-(2-((Z)-((E)-3-(Phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)-2-(tetrahydrofuran-3-yl)thiazolidin-4-one (3v)

Yield 72%; m.p. 245–247°C; IR (υ_{max}, /cm, KBr): 3338 (N-H), 2287 (C-H), 1613 (C=O), 1508 (C=N), 1164 (Ar-CH) and 715 (C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.6 (2H, s, NH), 3.2 (2H, s, CH_2) and 5.8 (1H, s, CH) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.88, 142.54, 132.8, 129.7 and 118.7 p.p.m.; FAB-MS (*m/z*): 479 (M^+, 7%), 480 ($M^+ + 1$, 8%), 478 ($M^+ - 1$, 6%), 311 (38%), 168 (24%), 106 (29%) and 91 (100%). Anal. Calcd for $C_{27}H_{21}N_5O_2S$: C, 67.62; H, 4.41; N, 14.50. Found: C, 67.63; H, 4.40; N, 14.53.

2-(3-Methoxy-4-hydroxyphenyl)-3-(2-((Z)-((E)-3-(phenylimino)-3,4-dihydroquinoxalin-2-(1H)-ylidene)amino)phenyl)thiazolidin-4-one (3w)

Yield 64%; m.p. 278–280°C; IR (υ_{max}, /cm, KBr): 3375 (OH), 3345(N-H), 1610 (C=O), 1515 (C=N), 1387 (Ar-CH_2), 1245 (OCH_3) and 685(C-S); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.0 (2H, s, NH), 2.3 (2H, s, CH_2), 4.6 (1H, s, CH),3.2 (3H, s, Ar-OCH_3) and 5.3(1H, s, Ar-OH) p.p.m.; ^{13}C (DMSO-d_6) δ: 162.56, 150.6, 130.3 and 119 p.p.m.; FAB-MS (*m/z*): 535 (M^+, 6%), 536 ($M^+ + 1$ 2%), 534 ($M^+ - 1$, 6%), 488 (25%), 312 (31%), 123 (24%), 106 (100%), and 91(22%). Anal. Calcd for $C_{30}H_{25}N_5O_3S$: C, 67.27%; H, 4.70%; N, 13.08%. Found: C, 67.24%; H, 4.68%; N, 13.04%.

Anti-mycobacterial activity

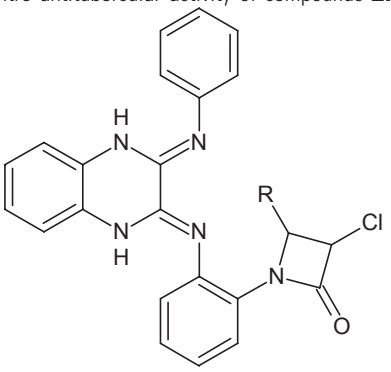
Antitubercular activity was evaluated against *M. tuberculosis* H37 Rv ATCC27294 using Microplate Alamar Blue Assay (27). The test was performed in black, clear-bottomed, 96-well microplates (black view plates; Packard Instrument Company, Meriden, CT, USA) to minimize the background fluorescence. Initial drug dilutions were prepared in dimethylsulfoxide, and subsequent twofold dilutions were performed in 0.1 mL of 7H9GC media in the microplates. 0.1 mL of 2.5×10^6 CFU/mL of *M. 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 (20 mL 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). Minimum inhibitory concentration (MIC) was determined from the colour change.

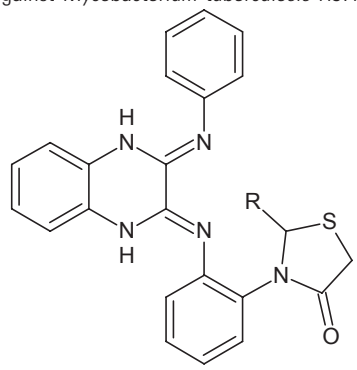
Quantitative structure–activity relationship

The structure of the 20 quinoxalines (Table 1) was drawn, and their minimum energy conformations were determined with MM+ force field using HYPERCHEM version 8 software (Molecular Modelling Tool, Hypercube Inc, Gainesville, FL, USA) (20). The 3D-QSAR studies were performed using VLIFE MOLECULAR DESIGN SUITE 3.5 (VLife Sciences Technologies Pvt. Ltd., Pune, India).

The molecules were aligned on the common fragment, namely quinoxiline. The MIC values in μM were converted to −log (MIC) and

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





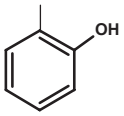
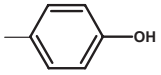
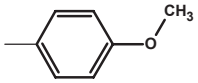
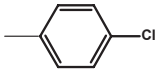
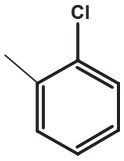
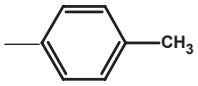
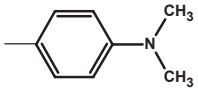
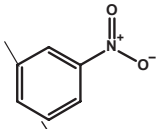
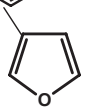
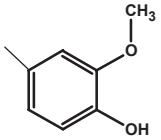
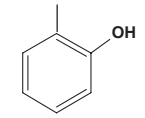
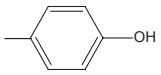
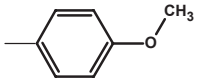
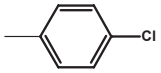
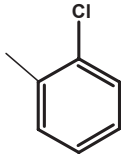
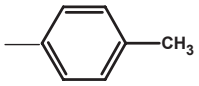
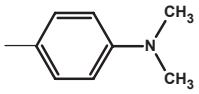
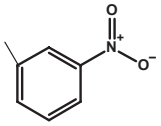
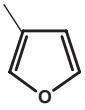
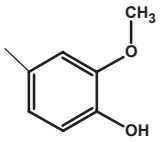
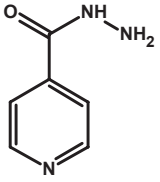
(2n–w) Compounds	R	**(3n–w)** Minimum inhibitory concentration (μg/mL)
2n		50.00
2o		3.00
2p		1.53
2q		1.40
2r		0.89
2s		20.6
2t		0.76
2u		0.97
2v		10.1
2w		11.8

Table 1: (Continued).

Compounds	R	Minimum inhibitory concentration (μg/mL)
3n		13.8
3o		3.70
3p		1.38
3q		1.38
3r		0.76
3s		19.00
3t		0.67
3u		1.77
3v		36.00
3w		35
Isoniazid		0.46

were used as dependant variable in the regression equation. Sixteen molecules were chosen at random in the training set and four molecules in the test set (28). The former was used to generate the model and the later for determining its predictive capability.

A 3D cubic lattice grid in the *x, y* and *z* directions was created (dimension of the box $19.9 \times 20.9 \times 19.5$ Å) to encompass the aligned molecules. The descriptors were calculated using a sp^3 carbon probe atom with a van der Waals radius of 1.52 Å, a charge of +1.0 and a dielectric constant of 1.0 to generate steric, electrostatic and hydrophobic fields at each lattice point (29,30). Three thousand five hundred and thirty descriptors that included all the electrostatic, steric and hydrophobic properties inside this cubic lattice were evaluated for all the twenty quinoxaline molecules. Several literature reports give a description of descriptors that are used in QSAR (31–33). The best set of descriptors from this large pool was short listed using the stepwise forward variable selection method for generating the multiple linear regression equation. The cross-correlation limit of 0.5, q^2 as the selection criteria and autoscaling method were adapted during the selection procedure. Several statistical parameters such as, squared correlation coefficient for the training set (r^2), r^2 PRESS, r^2 BS and r_m^2(test)were evaluated. r_m^2(test) is a modified r^2 and is evaluated for better predictive potential of the model. It is calculated using the formula, $r_m^2(\text{test}) = r_t^2 * (1 - \sqrt{r_t^2 - r_{t0}^2})$, where r_{t0}^2 and r_t^2 are the squared correlation coefficients between the observed and the predicted values of the test set compounds with intercept set to zero and not set to zero, respectively (34). Other statistical parameters that describe the quality of the QSAR which were determined were correlation coefficient of the regression line (between observed versus predicted) with activity passing through the origin (R_0^2), correlation coefficient of regression line (between predicted versus observed) with activity passing through the origin ($R_0'^2$), slope of the regression line (between observed versus predicted) with activity passing through the origin (*k*) and slope of the regression line (between predicted versus observed) with activity passing through the origin (*k'*) (34). *k* and *k'* are expected to be between 0.95 and 1.05. r^2 BS is the bootstrap r^2 that is the average r^2 measured with different sets of test and training sets. r^2 PRESS, also known as r^2_pred = 1 − (PRESS/SD), where SD is the sum of the squared deviations between the activities of the test set and the mean activity of the training set molecules and PRESS, is the squared deviations between predicted and actual activity values for every molecule in the test set. q^2 is the cross-validated r^2 based on leave one out method (also known as internal validation).

Results and Discussion

Synthesis

Scheme 1 outlines the synthetic strategy for compounds **2n–w** and **3n–w**. The preparation of quinoxaline-2,3-dione (**1a**) was carried out as previously reported. Reaction of **1a** with aniline resulted in the formation of 3-((phenylimino)-3,4-dihydroquinoxaline)-one (**1b**). The intermediate *N*-((E)-3-(phenylimino)-3,4-dihydro quinoxalin-2(1H)-ylidene)benzene-1,2-diamine (**1c**) was achieved through reaction between **1b** and *o*-phenylenediamine. The synthesis of Schiff bases (**1n**–**w**) produced good yields (58.00–77.00% of isolated products), with the appropriate aldehyde(s) (**1d–m**) and intermediate *N*-((E)-3-(phenylimino)-3,4-dihydroqunoxalin-2(1H)-ylidene)benzene-1,2-diamine (**1c**), under microwave atmosphere. The cyclization of these intermediates, **1n–w**, with chloroacetyl chloride and thioglycollic acid leads to the formation of products, **2n**–**w** and **3n**–**w**, respectively. During the course of the reaction, the thiazolidinone series, **3n-w**, gave better yields than azetidinone series, **2n–w**. The yields of **2n–w** were in the range of 11.48–80.01%, whereas the yields of thiazolidinones **3n–w** were 64.00–88.00%. All the compounds were characterized by IR, ^{1}H and ^{13}C NMR, MS and elemental analyses.

The IR spectra of the compounds, **2n–w**, showed strong absorption band in the range of 1750–1650/cm characteristic of the β-lactam carbonyl group, which are lower than the reported values (1800/cm) for ketones, aldehydes and other amides. This may be due to the conjugation of unpaired electrons of the ring nitrogen with carbonyl group in the β-lactam of azetidinone resulting in increased single-bond character and lowering of the carbonyl single absorption frequency (35). The absorption peaks because of C-Cl appeared in the range of 749–765/cm in the compounds **2n–w**. The carbonyl stretching vibrations for the thiazolidinones derivatives (**3n–w**) appeared between 1660 and 1600/cm. The absorption bands ranging from 612 to 715/cm indicate the presence of C-S bond in the compounds **3n–w**.

In the proton NMR spectral data, all protons were seen according to the expected chemical shift and integral values. The disappearance of singlet at δ 8.5 p.p.m. indicated the conversion of N=CH proton of the Schiff's base to azetidinone and thiazolidinones. Further, the CH-Cl peak is present in the compounds **2n–w**, in the range of δ 5.3–7.7 p.p.m., demonstrating the formation of 2-azetidinone. CH_2S signal is observed between δ 2.8 and 3.8 p.p.m. for the compounds **3n–w**, which confirms the presence of 4-thiazolidinone. The NH proton of title compounds appeared in the range of δ 3.8–4.7 p.p.m. In addition, the aromatic protons appeared as multiplet peaks within the range δ 6.3–8.9 p.p.m. in all the titled compounds, **2n–w** and **3n–w**. The peaks appearing at δ 7.6, 7.2, 7.5 and 7.7 p.p.m. confirm the presence of OH in compounds **2n**, **2o**, **3n** and **3o**, respectively. Likewise, the appearance of singlets at δ 3.9 and 4.8 p.p.m. in compounds **2p** and **3p** is attributed to methoxy group. The singlets at δ 2.3 and 2.8 p.p.m. in compounds **2s** and **3s** indicated the presence of methyl group. The dimethylamino in compounds **2t** and **3t** was confirmed by singlet produced at δ 2.9 p.p.m. In ^{13}C NMR, the carbon of CH-Cl of azetidinones (**2n–w**) showed a singlet varying between δ 40.3 and 62.3 p.p.m. The aromatic carbons were observed as multiplets in the range of δ 135.31–173.10 p.p.m. Similarly, in thiazolidinone series, the carbon of CH-S showed a singlet at δ 41.6–45.8 p.p.m., and the aromatic multiplets were found at δ 164.32–117.10 p.p.m. The mass spectra showed peaks corresponding to their molecular weights.

Antitubercular activity and structure–activity relationship

The MIC was determined for compounds **2n–w** and **3n–w** against the *M. tuberculosis* strain H37Rv using the micro plate Alamar Blue assay.

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 on the aromatic ring of either 2-azetidinone or 4-thiazolidinone nucleus. The introduction of a hydroxyl, methoxy, chloro, dimethylamino and nitro group on aromatic ring (**2o**, **3o**, **2p**, **3p**, **2q**, **3q, 2t**, **3t**, **2r**, **3r**, **2u** and **3u**) resulted in compounds with an enhanced antitubercular activity (MIC values ranging from 0.67 to 3.70 μg/mL). Amongst them, compounds **2t**, **3t**, **2r**, **3r** and **2u** (MIC values ranging from 0.67 to 0.97 μg/mL) exhibited significant activity when compared with the first-line drug, isonictinyl acid hydrazide (INH) (MIC = 0.47 μg/mL). This antitubercular activity may be attributable to the introduction of electron withdrawing group on the aromatic ring. However, substitution by electron releasing methoxy group also resulted in compounds with moderate antitubercular activity (**2p** and **3p**). It is interesting to note that the introduction of an electron-releasing hydroxyl group in the *p*-position of phenyl ring resulted in moderate activity (**2o** and **3o**), whereas substitution of hydroxyl group in the *o*-position is found to have complete loss of activity (**2n** and **3n**). It has been observed that the replacement of hydroxyl moiety by electron releasing methyl group in the compounds **2s** and **3s** showed mild activity. The compounds with electron withdrawing substituents (chloro, dimethylamino and nitro) were found to be more active than electron releasing methoxy, hydroxyl and methyl moiety. Literature survey reveals that electron withdrawing or donating groups amend the lipophilicity of the test compounds, which in turn alters permeability across the bacterial cell membrane (36). Further, compounds **2v** and **3v** substituted with a five membered furan structure did not show any considerable activity. Similarly, introduction of methoxy and hydroxyl groups in compounds **2w** and **3w** leads to complete activity loss. The obtained results revealed that the nature of the substituent and substitution pattern on the benzene ring may have a considerable impact on the antitubercular activity of the synthesized compounds. The influence of the 2-azetidinone nucleus in compounds **2n–o** and 4-thiazolidinone nucleus in compounds **3n–o** has been studied on the biological activity. The replacement in the core nucleus did not alter the antitubercular activity to a greater extent.

The best 3D-QSAR model developed with the training set (n = 16) and other statistics are given below.

$$-\log(\mathrm{MIC}) = 0.0201 - 0.1857*\mathrm{E\_412} - 2.0065*\mathrm{S\_366}$$

r^2 = 0.81, q^2 = 0.71, r^2 PRESS (r^2_pred = 0.84, F = 27.06, r_m^2 = 0.84, r^2 BS = 0.80, k = 0.906, k'=0.995, R_0^2 = 0.901, $R_0^{2\prime}$ = 0.901. All the statistical parameters are good indicating that the model has good predictive capability.

E_412 and S_366 are the electrostatic and steric descriptors, respectively. 59.8% of the contribution is from the former and the rest from the latter descriptor. The electrostatic descriptor is negatively correlated with activity indicating that electronegative groups would increase activity. The steric descriptor is negatively correlated with activity indicating less bulky groups would enhance activity.

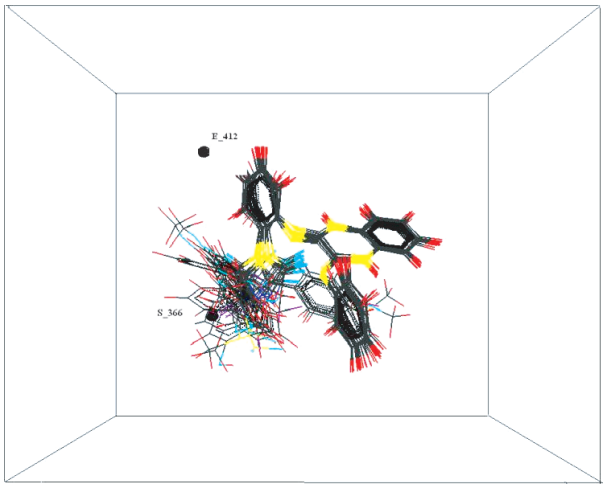


Figure 1: Stereo view of the molecular rectangular field grid around the super-imposed quinoxiline with the location of the electrostatic and steric descriptors used in the three-dimensional quantitative structure–activity relationship (dimensions of the box 19.9*20.9*19.5Å).

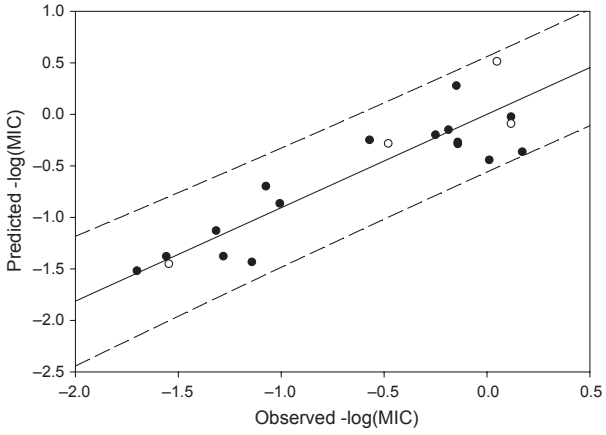


Figure 2: Comparison of observed and predicted activities of the compounds in the training and the test sets (with 95% prediction interval) from template based alignment (closed and open circles = Training and test set compounds respectively).

Figure 1 shows the stereo view of the rectangular field grid around all the molecules, super-imposed (stacked) on the common template, quinoxiline. The location of the electrostatic and steric descriptors selected in the model is also shown in the figure.

Figure 2 shows the comparison of the observed and predicted (from the 3D-QSAR) activities of the compounds in the training and the test set (with the 95% prediction interval) from template-based alignment. All the predictions lie within this prediction band. Similar descriptors have been identified while studying the antiTB activity of thiazolines and thiazolidinones (20).

Table 2: Values of the descriptors selected in the model and comparison of experimental and predicted activities

Compound	E_412	S_366	Experimental activity −log μM	Predicted activity −log μM	Residuals
Training set					
2n	10.0000	−0.1566	−1.6989	−1.5231	−0.1758
2p	5.5800	−0.4293	−0.1847	−0.1549	−0.0298
2q	4.0096	−0.4974	−0.1461	0.2734	−0.4195
2s	5.1682	0.0966	−1.3139	−1.1337	−0.1802
2u	4.2567	−0.1612	0.0132	−0.4471	0.4603
2v	3.9367	0.0793	−1.0043	−0.8702	−0.1341
2w	6.0193	−0.1968	−1.0718	−0.7029	−0.3689
3n	10.0000	−0.1986	−1.1399	−1.4386	0.2987
3o	4.2837	−0.2601	−0.5682	−0.2536	−0.3146
3p	4.3829	−0.2504	−0.1399	−0.2914	0.1515
3q	4.5296	−0.2725	−0.1399	−0.2743	0.1344
3r	3.5086	−0.3005	0.1192	−0.0286	0.1478
3s	9.4975	−0.1799	−1.2788	−1.3829	0.1041
3t	4.8044	−0.2508	0.1739	−0.3690	0.5429
3u	3.2662	−0.1911	−0.2480	−0.2031	−0.0449
3v	9.0376	−0.1368	−1.5560	−1.3839	−0.1721
Test set					
2o	5.8931	−0.3923	−0.4771	−0.2874	−0.1897
2r	3.1354	−0.5337	0.0506	0.5087	−0.4581
2t	5.1974	−0.4236	0.1191	−0.0953	0.2144
3w	10.0000	−0.1898	−1.5440	−1.4563	−0.0877

Table 2 gives the values of the two descriptors, experimental and predicted activities (in −log μM) and the residual error for the twenty compounds.

The antitubercular activity is positively correlated ($r = 0.47$, $p < 0.05$) with AlogP. ALogP is a measure of the hydrophobic – hydrophilic balance of the compounds (37). This indicates that hydrophobic quinoxiline derivatives would exhibit higher antitubercular activity. But this descriptor does not appear in the QSAR because the other two properties (electrostatic and steric) contribute much more to equation. Vincente *et al.* (38) also did not observe lipophilicity in their QSAR while exploring 3-aryl quinoxalines as antiTB compounds. The importance of hydrophobicity on the antiTB activity of chalcones has been reported (22).

Conclusion

Synthesis, spectral characterization, antitubercular activity and 3D-QSAR analysis of a new series of 2-azetidinone and 4-thiazolidinone derivatives of quinoxalines are reported here. The various 2-azetidinone derivatives were synthesized by cycloaddition with chloroacetyl chloride in the presence of triethylamine while the 4-thiazolidinone derivatives of quinoxalines were synthesized by cyclocondensation of substituted arylidene derivatives of quinoxaline-2,3-dione with thioglycollic acid. The *in vitro* antitubercular screening results of the title compounds evidenced that compounds **2t**, **3t**, **2r**, **3r** and **2u** may be considered promising for the development of new antitubercular agents. 3D-QSAR results revealed that electrostatic field regions were found to be important for *M. tuberculosis* inhibitory activity. From the detailed analysis of the results of above studies, it is concluded that antitubercular activity of the synthesized compounds significantly depends on the presence of electronegative group. The results obtained from the 3D-QSAR can be used to predict antitubercular activity of new compounds and also to design novel quinoxaline derivatives with enhanced performance. The current findings can help chemists and pharmacists for further investigations in this field in search of potent antitubercular agents.

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