Synthesis of New derivatives of 2,3,6,7-tetra substituted –N-(3-chloroquinoxalin-2-yl) acridin-9-amine and their anti-bacterial, anti-cancer activity

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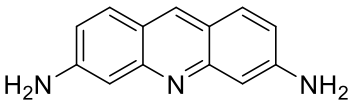
Abstract: The new derivatives of 2,3,6,7-tetra substituted-N-(3-chloroquinoxalin-2-yl)acridin-9-amine (**6a-l**) have been synthesized, and most of the derivatives were promisingly active towards anti bacterial, anti cancer strains as compared with ampicilin as positive controls due to the presence of quinoxaline and acridine heterocyclic reaction systems. All the new derivatives were prepared from 2-chloro-4,5-disubstituted benzoic acid (**2a-l**) condensed with 3,4-disubstited aniline (**1a-l**) in the presence of potassium carbonate, copper powder in isopropyl alcohol yields 2-((3,4-di substituted phenyl)amino)-4,5-disubstituted benzoic acid **(3a-l)**. Reacting **3a-l** with phosphorus oxy chloride, ammonium carbonate in the presence of phenol yields 2,3,6,7-tetra substituted acridin-9-amine **(4a-l).** Finally 2,3-dichloroquinoxaline (**5**) reacts with 2,3,6,7-tetra substituted acridin-9-amine (**4a-l**) to form N-(3-chloroquinoxalin-2-yl)-2,3,6,7-tetra substituted acridin-9-amines (**6a-l**). The structures of the resulted compounds (**6a-l**) were identified and confirmed by IR, ^{1}H-NMR, Mass spectral data and elemental analysis. All the synthesized derivatives were screened for their antimicrobial and anticancer activity.

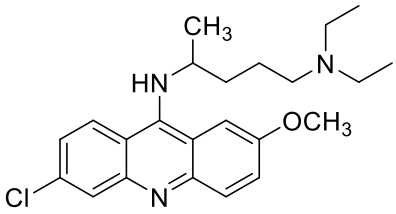
Key words: 2-chloro-4,5-disubstituted benzoic acid(2a-l), 3,4-disubstituted aniline(1a-l), 2,3-dichloro quinoxaline(5), N-(3-chloroquinoxalin-2-yl)-2.3,6,7-tetra substituted acridine-9-amines (6a-l), anti bacterial activity, anti cancer activity.

I. INTRODUCTION:

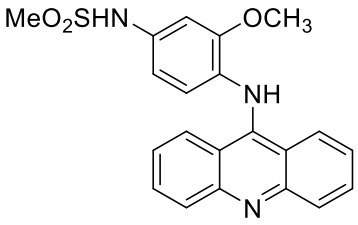
Acridine was first developed as dyes and during the early 20th century and its pharmacological properties were evaluated. There are numerous biologically active fused heterocyclic rings. First time isolation of acridine was dine in 1870, from high boiling fraction of coal tar by Carl grabe and Heinrich caro in germany, the trypanocidal activity of 10-methyl-3,6- diaminoacridinium chloride was reported in 1912 by Ehrich and Benda[1]. Acridines are of interest in many pharmaceutical areas, since they exhibit a variety of biological properties such as anti inflammatory[2], anti malarial[3], anti microbial[4], and anti cancer[5] agents etc. Some of the drugs containing this heterocyclic are Porflavine[6], Mepacrine[7], Amsacrine[8], Euflavine (Acriflavine)[9], Ethacridine[10], Acridine carboxamide (DACA)[11] etc.



Proflavine

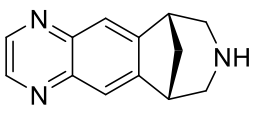


Mepacrine

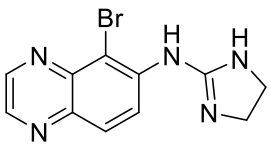


Amsacrine

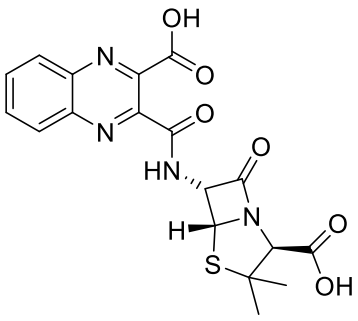
Quinoxaline are very important compounds due to their wide spectrum of biological activities such as antimicrobial[12], antioxidant[13], anticancer[14, 15], antihypertensive[16], anti-HIV[17], anticonvulsant[18], antitumor[19], and antiviral activities[20]. Quinoxaline derivatives are used as dyes, pharmaceuticals and antibiotics such as vareniciline[21], brimonidine[22], quinacilin[23], carbadox[24], ehchinomycin[25] etc.



Varenicline



Brimonidine



Quinacillin

Materials and Methods:

Scheme:

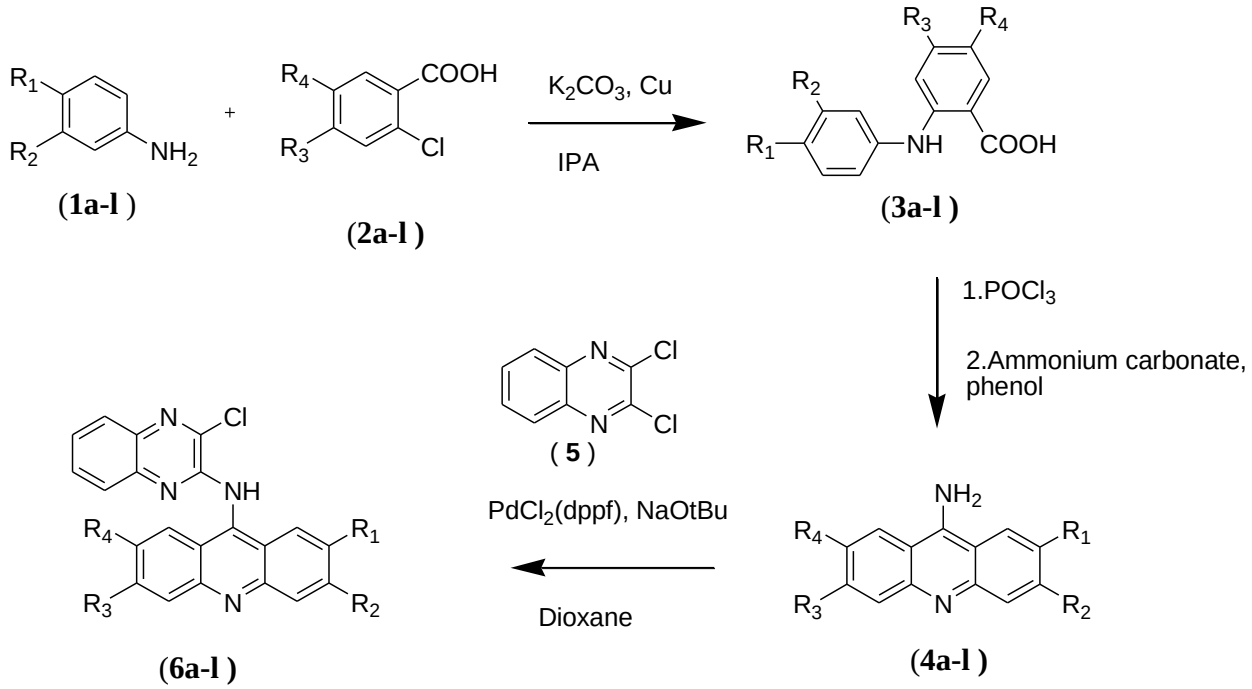


Table-1

Compound	R_1	R_2	R_3	R_4
6a	-OH	-NO2	-C6H5	-CH3
6b	-CH3	-CH3	-C6H5	-CH3
6c	--CH3	-NO2	-C6H5	-CH3
6d	-OCH3	-NO2	-C6H5	-CH3
6e	-OH	-NO2	-CH3	-CH3
6f	-CH3	-CH3	-CH3	-CH3
6g	-CH3	-NO2	-CH3	-CH3
6h	-OCH3	-NO2	-CH3	-CH3
6i	-OH	-NO2	-CF3	-CH3
6j	-CH3	-CH3	-CF3	-CH3
6k	-CH3	-NO2	-CF3	-CH3
6l	-OCH3	-NO2	-CF3	-CH3

GENERAL

Instrumentation :

We purchased solvents and chemicals from commercial sources (Sigma-Aldrich, USA; Merck, Germany; and Mallinckrodt, USA). Silica gel 60 (Merck, Germany) was used to column chromatography. The compounds' purity was tested using TLC-silica gel 60 GF254 (Merck, Germany), while their melting points were measured using the StuartTM melting point apparatus (Stuart Scientific, UK) and were uncorrected. All compounds were purified by flash chromatography on silica gel(partical size 100-200 mesh) and characterized by spectral studies. The IR spectra were recorded on Shimadzu FTIR model 8010 spectrophotometer and are given in cm^{-1} in KBr. The ^{1}HNMR & ^{13}CNMR spectra were recorded on Bruker AM-400 MHz NMR spectrometer in $CDCl_3$ & DMSO-d_6. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal standard. Mass spectra analyses performed with an Agilent-6400 series equipped with an electrospray ionization source.

General procedure for the preparation of 2-((3,4-disubstited phenyl) amino)-4,5-disubstituted benzoic acid 3(a-l):
Add 3,4-disustituted aniline (**1a-l**, 1 equiv), 2-chloro-4,5-disustituted benzoic acid (**2a-l**, 1.0 equiv), copper powder (0.5 mol), potassium carbonate (5 equiv) and isopropyl alcohol (20 ml) in a RBF. RM heated to reflux temperature for 8-10 hours. After completion of reaction solvent removed by distillation and the mixture added water (20 ml), pH is adjusted with hydrochloric acid (pH =2). Stir the reaction mass for 1 hour at 25-30°C, filter reaction mass and wash with water (5 ml). The product is purified by using acetone-water.Yield: 55-62%.

General procedure for the preparation of 9-amino-2,3,6,7-tetrasubstituted acridine 4(a-l) :

Charge 2-((3,4-disubstitutedphenyl)amino)-4,5-disustitutedbenzoicacid 3(a-l) (**1 equiv**) and phosphorus oxy chloride (**1 equiv**) in round bottom flask. The mixture was slowly heat to 85-90 for 30 minutes on a water bath. The flask was heat to 140-145^{0}C for 1 hour. After completion of reaction Phosphorus oxy chloride was removed by distillation, the residue after cooling quenched into Ice and add ammonia solution for pH adjusted (pH is 7.0). Add dichloromethane (50 ml) & stir for 1 hour. Separate organic layer and aq layer. Aq layer is extracted with dichloromethane (30 ml). Combined organic layers and the solvent were removed by distillation. The resultant solid and phenol (5 equiv) in RBF.RM heat to 70^{0}C slowly and added ammonium carbonate (1.5 equiv) at 70^{0}C**.** The RM temperatures raised to 120^{0}C and maintain the mixture for 2 hours,. The mixture is cooled and filter the solid washed with H_2O (33 ml). Product is purified in H_2O.

Yield: 39-55%

General procedure for the preparation of N-(3-chloronaphthalen-2-yl)-2,3,6,7-tetrasubstituted anthracen-9-amine 6(a-l) :

Charge 1,4-Dioxane (30 ml), 9-amino-2,3,6,7-tetrasubstituted acridine 5(a-l) (1 equiv), 2,3-dichloroquinoxaline, PdCl2(dppf) (0.1 equiv) in a RBF at room temperature. RM heated to 100^{0}C. Stir the RM for 24 hours. After completion of reaction filter RM on Celite bed and take filtrate and add H_2O (40 ml), ethyl acetate (20 ml). Stir the RM for 10 minutes. Separate organic layer and aq layer. Aq layer extracted with ethyl acetate (20 ml). Combined organic layers and the solvent were removed by distillation. The resultant product is purified by column chromatography (Hexane : Ethyl acetate 7:3), Yield: 37-50%.

Physical and Spectral Data of The Synthesized Compounds:

3a: 5-((4-hydroxy-3-nitrophenyl)amino)-2-methyl-[1, 1'-biphenyl]-4-carboxylic acid.

Yellow solid, Yield: 58%, M.P: 178-180^{0}C, ^{1}H-NMR: 2.6(3H,s,-CH_3), 7.22-7.25(1H,t,-Ar-CH), 7.35-7.42(6H,m,-Ar-H), 7.65(1H,s,-Ar-CH), 8.02(1H,s,-Ar-CH-),12.30(1H,s,-NH), 13.21(1H,s,-COOH), 14.29(1H,s,-OH), ^{13}C-NMR : 18.9, 111.5, 113.2, 117.4, 120.5, 126.8, 127.2, 127.6, 127.8, 129.0, 129.0, 131.1, 131.8, 132.2, 135.4, 139.6, 140.1, 142.7, 157.7, 169.5, FAB Mass : m/z 365.11(M^+), CHN Analysis: Found: C(66.14%), H(3.98%), N(7.56%), Calc: C(65.93%), H(4.43%), N(7.69%).

3b: 5-((3,4-dimethylphenyl)amino)-2-methyl-[1,1'-biphenyl]-4-carboxylic acid.

Off white solid, Yield: 54 %, M.P: 200-202^{0}C, ^{1}H-NMR: 2.20(3H,s,-CH3), 2.22(3H,s,-CH_3), 2.58(3H,s,-CH_3), 7.10-7.12(1H,d,-Ar-H), 7.24-7.26(1H,d,-Ar-H), 7.39-7.48(7H,m,-Ar-H), 8.12(1H,s,-Ar-H), 12.28(1H,s,-NH), 13.12(1H,s,-COOH), ^{13}C-NMR: 18.8, 18.89, 18.9, 111.7, 117.3, 118.5, 120.2, 126.0, 126.4, 127.3, 127.6, 127.7, 129.1, 129.1, 129.9, 131.7, 136.2, 137.5, 138.5, 139.4, 140.1, 169.5, FAB Mass: m/z 332.42(M^+), CHN Analysis: Found: C(79.66%), H(6.30%), N(4.34%), Calc: C(79.73%), H(6.39%), N(4.23%).

3c.: 2-methyl-5-((4-methyl-3-nitrophenyl)amino)-[1,1'-biphenyl]-4-carboxylic acid.

Yellow solid, Yield: 59%, M.P: 147-148^{0}C, ^{1}H-NMR: 2.51(3H,s,-CH_3), 2.55(3H,s,-CH_3), 7.39-7.67(6H,m,-Ar-H), 7.68-7.71(2H,t,-Ar-H), 8.14(1H,s,-Ar-H), 8.15(1H,s,-Ar-H), ^{13}C-NMR: 18.4, 18.8, 111.9, 112.0, 117.5, 122.4, 126.8, 127.7, 127.8, 127.8, 129.3, 129.3, 129.3, 130.6, 131.5, 136.2, 137.8, 139.9, 140.8, 150.6, 169.5, FAB Mass : m/z 363.13(M^+), CHN Analysis: Found: C(69.83%), H(4.93%), N(7.64%), Calc: C(69.60%), H(5.01%), N(7.73%),

3d: 5-((4-methoxy-3-nitrophenyl)amino)-2methyl-[1,1'-biphenyl]-4-carboxylic acid.

Yellow solid, Yield: 52%, M.P: 159-161^{0}C, ^{1}H-NMR: 2.57(3H,s,-CH_3), 4.02(3H,s,-OCH_3), 7.19-7.21(1H,d,-Ar-H), 7.38-7.46(6H,m,-Ar-H), 7.94(1H,s,-Ar-H), 8.12(1H,s,-Ar-H), 8.14(1H,s,-Ar-H), 12.27(1H,s,-NH), 13.11(1H,s,-COOH), ^{13}C-NMR: δ18.9, 54.9, 111.5, 113.1, 116.2, 117.4, 126.3, 127.5, 127.8, 127.8, 129.3, 129.3, 130.5, 131.8, 132.2, 136.8, 137.8, 139.5, 140.4, 142.9, 169.5, FAB Mass: m/z 379.12(M^+), CHN Analysis: Found: C(66.67%), H(4.81%), N(7.40%), Calc: C(66.66%), H(4.80%), N(7.40%).

3e: 2-((4-hydroxy-3-nitrophenyl)amino)-4,5-dimethylbenzoic acid.

Yellow solid, Yield: 60%, M.P: 124-127^{0}C, ^{1}H-NMR: 2.22(3H,s,-CH_3), 2.33(3H,s,-CH_3), 7.05-7.07(1H,d,-Ar-H), 7.43(1H,s,-Ar-H), 7.79-7.81(1H,d,-Ar-H), 7.91(1H,s,-Ar-H), 7.96(1H,s,-Ar-H), 12.23(1H,s,-NH), 13.14(1H,s,-COOH), 14.38(1H,s,-OH), ^{13}C-NMR : δ 18.8, 18.8, 109.8, 113.7, 118.5, 120.8, 126.5, 131.2, 131.5, 132.3, 135.4, 140.2, 141.4, 142.5, 169.5, FAB Mass: m/z 302.29(M^+), CHN Analysis: Found: C(58.57%), H(4.60%), N(9.53%), Calc: C(59.60%), H(4.67%), N(9.27%).

3f: 2-((3,4-dimethylphenyl)amino)-4,5-dimethylbenzoic acid.

Off-white solid, Yield: 52%, M.P: 158-160^{0}C, ^{1}H-NMR: 2.18-2.21(9H,t,-CH_3), 2.32(3H,s,-CH_3),7.10-7.12(1H,d,-At-H), 7.24-7.26(1H,d,-Ar-H), 7.42(1H,s.-Ar-H), 7.48(1H,s,-Ar-H), 7.88(1H,s,-Ar-H), 12.28(1H,s,-NH), 13.13(1H,s,-COOH), ^{13}C-NMR : 18.8, 109.7, 118.8, 118.9, 120.5, 126.1, 126.4, 129.9, 131.4, 136.3, 138.4, 140.5, 141.6, 169.5, FAB Mass: m/z 270.14(M^+), CHN Analysis: Found: C(74.93%), H(7.85%), N(4.91%), Calc: C(75.81%), H(7.11%), N(5.20%).

3g: 4,5-dimethyl-2-((4-methyl-3-nitrophenyl)amino)benzoic acid.

Yellow solid, Yield: 55%, M.P: 146149^{0}C, ^{1}H-NMR: 2.21(3H,s,-CH_3), 2.31(3H,s,-CH_3), 2.50(3H,s,-CH_3), 7.41-7.43(1H,d,-At-H), 7.66-7.72(2H,m,-Ar-H), 7.90(1H,s.-Ar-H), 8.13(1H,s,-Ar-H), 12.27(1H,s,-NH), 13.11(1H,s,-COOH), ^{13}C-NMR: δ18.8, 109.7, 111.5, 118.3, 122.7, 126.1, 129.5, 130.1, 131.4, 136.9, 140.3, 141.4, 150.4, 169.5, FAB Mass: m/z 301.31(M^+), CHN Analysis: Found: C(63.38%), H(5.35%), N(9.32%), Calc: C(63.39%), H(5.37%), N(9.33%).

3h: 2-((4-methoxy-3-nitrophenyl)amino)-4,5-dimethylbenzoic acid.

Yellow solid, Yield: 53%, M.P: 129^{0}C, ^{1}H-NMR: 2.23(3H,s,-CH_3), 2.34(3H,s,-CH_3), 4.04(3H,s,-CH_3), 7.21-7.23(1H,d,-At-H), 7.34-7.36(1H,d,-Ar-H), 7.91-7.95(2H,m,-Ar-H), 8.13(1H,s,-Ar-H), 12.29(1H,s,-NH), 13.14(1H,s,-COOH), ^{13}C-NMR: δ18.8, 54.7, 109.8, 116.3, 113.2, 118.5, 126.3, 130.5, 131.8, 132.5, 136.6, 141.4, 142.6, 169.5, FAB Mass: m/z 317.11(M^+), CHN Analysis: Found: C(60.53%), H(4.99%), N(9.12%), Calc: C(60.76%), H(5.10%), N(8.86%).

3i: 2-((4-hydroxy-3-nitrophenyl)amino)-5-methyl-4-(trifluoromethyl)benzoic acid.

Yellow solid, Yield: 58%, M.P: 152^{0}C, ^{1}H-NMR: 2.29(3H,s,-CH_3), 7.03-7.05(1H,d,-Ar-H), 7.72-7.77(2H,t,-Ar-H), 7.88(1H,s,-Ar-H), 7.95(1H,s,-Ar-H), 12.27(1H,s,-NH), 13.11(1H,s,-COOH), ^{13}C-NMR: δ 18.8, 113.5, 114.9, 116.1, 120.6, 122.7, 123.5, 131.8, 131.4, 132.7, 133.8, 135.9, 140.4, 142.5, 169.5, FAB Mass: m/z 357.06(M^+), CHN Analysis: Found: C(49.94%), H(3.26%), N(7.95%), Calc: C(50.57%), H(3.11%), N(7.86%).

3j: 2-((3,4-dimethylphenyl)amino)-5-methyl-4-(trifluoromethyl)benzoic acid.

Off-white solid, Yield: 54%, M.P: 144^{0}C, ^{1}H-NMR: 2.20-2.21(6H,d,-CH_3), 2.27(3H,s,-CH_3),7.12-7.14(1H,d,-Ar-H), 7.31-7.33(1H,d,-Ar-H), 7.51(1H,s,-Ar-H), 7.73(1H,s,-Ar-H), 7.89(1H,s,-Ar-H), 12.27(1H,s,-NH), 13.14(1H,s,-COOH), ^{13}C-NMR(δ): 18.8, 114.9, 116.5, 118.8, 120.5, 122.5, 123.6, 126.8, 129.9, 131.5, 133.5, 136.6, 138.2, 140.2,169.5, FAB Mass: m/z 324.11(M^+), CHN Analysis: Found: C(62.93%), H(5.01%), N(4.13%), Calc: C(63.15%), H(4.99%), N(4.33%).

3k: 5-methyl-2-((4-methyl-3-nitrophenyl)amino)-4-(trifluoromethyl)benzoic acid.

Yellow solid, Yield: 59%, M.P: 168-171^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 2.51(3H,s,-CH_3), 7.67-7.72(2H,m,-Ar-H), 7.89(1H,s.-Ar-H), 8.14(1H,s,-Ar-H), 12.28(1H,s,-NH), 13.15(1H,s,-COOH), ^{13}C-NMR(δ): 18.8, 111.2, 114.5, 116.7,122.4, 122.9, 123.1, 129.3, 130.9, 131.4, 133.8, 136.5, 140.4, 150.1, 169.5, FAB Mass: m/z 355.08(M^+), CHN Analysis: Found: C(54.25%), H(3.69%), N(7.90%), Calc: C(54.24%), H(3.70%), N(7.91%).

3l: 2-((4-methoxy-3-nitrophenyl)amino)-5-methyl-4-(trifluoromethyl)benzoic acid

Yellow solid, Yield: 56%, M.P: 181-183^{0}C, ^{1}H-NMR: 2.22(3H,s,-CH_3), 2.32(3H,s,-CH_3), 4.04(3H,s,-CH_3), 7.22-7.24(1H,d,-At-H), 7.44-7.46(1H,d,-Ar-H), 7.91-7.95(2H,m,-Ar-H), 8.13(1H,s,-Ar-H), 12.31(1H,s,-NH), 13.14(1H,s,-COOH), ^{13}C-NMR(δ): 18.8, 54.7, 113.2, 114.5, 116.2, 116.3, 122.5, 123.5, 130.7, 131.8, 132.4, 133.8, 136.4, 140.4, 142.6, 169.5, FAB Mass: m/z 371.08(M^+), CHN Analysis: Found: C(50.89%), H(3.65%), N(8.03%), Calc: C(51.90%), H(3.54%), N(7.57%).

4a: 9-amino-7-methyl-3-nitro-6-phenylanthracen-2-ol

Yield: 46%, M.P: 168-170^{0}C, ^{1}H-NMR: 2.78(3H,s,-CH_3), 5.31(2H,s,-NH_2), 7.37-7.45(5H,m,-Ar-H), 7.81-7.83(2H,d,-Ar-H), 7.94(1H,s,-Ar-H), 8.05(1H,s,-Ar-H), 8.36(1H,s,-Ar-H), 14.42(1H,s,-OH), ^{13}C-NMR(δ): 19.2, 102.6, 118.3, 124.2, 124.4, 125.3, 126.4, 127.4, 127.6, 127.8, 127.9, 129.2, 129.2, 130.6, 133.6, 136.2,136.6, 137.3, 137.8, 144.5, FAB Mass: m/z 345.12(M^+), CHN Analysis: Found: C(72.95%), H(4.78%), N(8.53%), Calc: C(73.24%), H(4.68%), N(8.13%).

4b: 2,3,7-trimethyl-6-phenylanthracen-9-amine.

Yield: 51%, M.P: 142-145^{0}C, ^{1}H-NMR: 2.51(6H,s,-CH_3), 2.73(3H,s,-CH_3), 5.31(2H,s,-NH_2), 7.36-7.44(7H,m,-Ar-H), 7.62(1H,s,-Ar-H), 7.91(1H,s,-Ar-H), 8.05(1H,s,-Ar-H), ^{13}C-NMR(δ): 19.2,19.3, 112.3, 115.5, 116.3, 118.8, 123.7, 124.6, 126.7, 127.5, 127.8, 127.8, 129.2, 129.3, 129.3, 133.4, 135.2, 136.2, 136.4, 137.4, 137.7, FAB Mass: m/z 312.17(M^+), CHN Analysis: Found: C(88.59%), H(7.03%), N(4.24%), Calc: C(88.70%), H(6.80%), N(4.50%).

4c: 2,7-dimethyl-3-nitro-6-phenylanthracen-9-amine.

Yield: 56%, M.P: 155-157^{0}C, ^{1}H-NMR: 2.53(3H,s,-CH_3), 2.78(3H,s,-CH_3), 5.33(2H,s,-NH_2), 7.36-7.44(5H,m,-Ar-H), 7.80(1H,s,-Ar-H), 7.92(1H,s,-Ar-H), 8.06(1H,s,-Ar-H), 8.27(1H,s,-Ar-H), 8.57(1H,s,-Ar-H), ^{13}C-NMR(δ): 18.8, 19.1, 117.4, 118.2, 118.5, 123.2, 124.6, 125.4, 126.4, 126.7, 127.7, 127.8, 127.8, 128.2, 129.3, 129.3, 131.7, 133.4, 136.2, 136.2, 137.7, 138.4, 147.1, FAB Mass: m/z 342.14(M^+), CHN Analysis: Found: C(77.17%), H(5.28%), N(8.19%). Calc: C(77.17%), H(5.30%), N(8.18%).

4d: 7-chloro-2-methoxy-3-nitro-6-phenylacridin-9-amine.

Yield: 56%, M.P: 138^{0}C, ^{1}H-NMR: 4.01(3H,s,-OCH_3), 6.34(2H,s,-NH_2), 7.42-7.52(5H,m,-Ar-H), 7.84(1H,s,-Ar-H), 7.95(1H,s,-Ar-H), 8.08(1H,s,-Ar-H), 8.61(1H,s,-Ar-H), ^{13}C-NMR(δ): 54.2, 107.4, 111.2, 114.7, 118.5, 119.2, 121.4, 127.5, 127.6, 127.9, 127.9, 129.3, 129.3, 133.3, 137.9, 138.2, 142.3, 145.2, 145.8, 146.2, 137.8, 159.4, FAB Mass: m/z 359.13(M^+), CHN Analysis: Found: C(73.12%), H(4.89%), N(8.13%), Calc: C(73.73%), H(5.06%), N(7.82%).

4e: 9-amino-6,7-dimethyl-3-nitroanthracen-2-ol.

Yield: 52%, M.P: 179^{0}C, ^{1}H-NMR: 2.48(6H,s,-CH_3), 5.31(2H,s,-NH_2), 7.48(2H,s,-Ar-H), 7.76(1H,s,-Ar-H), 7.81(1H,s,-Ar-H), 8.34(1H,s,-Ar-H), 14.42(1H,s,-OH), ^{13}C-NMR(δ): 19.1, 102.6, 117.4, 117.8, 123.3, 123.6, 123.6, 125.3, 127.7, 129.8, 136.5, 136.7, 136.8, 136.8, 144.7, FAB Mass: m/z 283.10(M^+), CHN Analysis: Found: C(67.81%), H(5.55%), N(10.72%), Calc: C(68.08%), H(5.00%), N(9.92%).

4f: 2,3,6,7-tetramethylanthracen-9-amine.

Yield: 47%, M.P: 180-183^{0}C, ^{1}H-NMR: 2.49(12H,s,-CH_3), 5.32(2H,s,-NH_2), 7.44-7.45(4H,d,-Ar-H), 7.58(1H,s,-Ar-H), ^{13}C-NMR(δ): 19.2, 114.5, 114.7, 115.1, 119.5, 119.7, 123.5, 123.8, 127.6, 129.8, 128.2, 135.7, 136.5, 136.5, 137.3, IR: , FAB Mass: m/z 250.36(M^+), CHN Analysis: Found: C(86.58%), H(7.73%), N(5.84%), Calc: C(86.70%), H(7.68%), N(5.62%).

4g: 2,3,7-trimethyl-6-nitroanthracen-9-amine.

Yield: 52%, M.P: 203-205^{0}C, ^{1}H-NMR: 2.51(6H,s,-CH_3), 2.54(3H,s,--CH_3),5.29(2H,s,-NH_2), 7.41-7.44(2H,d,-Ar-H), 7.72(1H,s,-Ar-H), 8.34(1H,s,-Ar-H), 8.6(1H,s,-Ar-H), ^{13}C-NMR(δ): 18.8, 19.2, 19.2, 115.8, 116.3, 117.6, 122.8, 123.7, 125.1, 126.2, 127.7, 127.8, 131.4, 135.5, 136.4, 137.2. 147.5, FAB Mass: m/z 281.12(M^+), CHN Analysis: Found: C(72.90%), H(5.68%), N(10.14%), Calc: C(72.84%), H(5.75%), N(9.99%).

4h: 2-methoxy-6,7-dimethyl-3-nitroanthracen-9-amine.

Yield: 42%, M.P: 196-198^{0}C, ^{1}H-NMR: 2.48(6H,s,-CH_3), 4.01(3H,s,-CH_3), 5.33(2H,s,-NH_2), 7.48-7.5(2H,d,-Ar-H), 7.76-7.75(2H,s,-Ar-H), 8.42(1H,s,-Ar-H), ^{13}C-NMR(δ): 19.1, 54.7, 98.8, 117.8, 117.9, 123.4, 123.5, 123.5, 125.8, 127.7, 129.5, 136.5, 136.8, 137.3, 137.9. 149.3, FAB Mass: m/z 297.12(M^+), CHN Analysis: Found: C(67.88%), H(5.46%), N(9.45%), Calc : C (68.91%), H (5.44%), N (9.45%).

4i: 9-amino-7-methyl-3-nitro-6-(trifluoromethyl)anthracen-2-ol.

Yield: 54%, M.P: 215-217^{0}C, ^{1}H-NMR: 2.49(3H,s,-CH_3), 5.32(2H,s,-NH_2), 7.80-7.81(2H,d,-Ar-H), 7.90(1H,s,-Ar-H), 8.01(1H,s,-Ar-H), 8.35(1H,s,-Ar-H), 14.43(1H,s,-OH), ^{13}C-NMR(δ): 19.1, 102.6, 119.4, 120.4, 122.9, 123.5, 125.3, 126.4, 126.6, 127.1, 127.4, 128.2, 130.4, 136.8, 137.4, 144.7, FAB Mass: m/z 337.07(M^+), CHN Analysis: Found: C(56.82%), H(3.67%), N(9.01%), Calc: C(57.15%), H(3.30%), N(8.33%).

4j: 2,3,7-trimethyl-6-(trifluoromethyl)anthracen-9-amine.

Yield: 49%, M.P: 162-165^{0}C, ^{1}H-NMR: 2.51(9H,s,-CH_3), 5.34(2H,s,-NH_2), 7.39-7.40(2H,d,-Ar-H), 7.71(1H,s,-Ar-H), 7.81(1H,s,-Ar-H), 8.02(1H,s,-Ar-H), ^{13}C-NMR(δ): 19.2, 113.7, 114.5, 116.1, 116.5, 121.4, 122.5, 123.6, 123.7, 125.6, 127.6, 127.9, 130.6, 130.9, 135.1, 136.4, 137.8, FAB Mass: m/z 304.12(M^+), CHN Analysis: Found: C(71.84%), H(5.24%), N(4.57%), Calc: C(71.28%), H(5.32%), N(4.62%).

4k: 2,7-dimethyl-3-nitro-6-(trifluromethyl)anthracen-9-amine.

Yield: 51%, M.P : 189-191^{0}C, ^{1}H-NMR: 2.31(3H,s,-CH_3), 2.34(3H,s,-CH_3), 6.29(2H,s,-NH_2), 7.71(1H,s,-Ar-H), 7.92(1H,s,-Ar-H), 8.56(1H,s,-Ar-H), 8.72(1H,s,-Ar-H), ^{13}C-NMR(δ): 18.8, 19.2, 110.4, 116.1, 120.7, 122.9, 123.2, 127.5, 128.4, 128.5, 128.9,

130.9, 144.2, 145.6, 151.1, 160.2, FAB Mass: m/z 335.09(M^+), CHN Analysis: Found: C(60.88%), H(4.05%), N(8.57%), Calc: C(61.08%), H(3.92%), N(8.38%).

4l: 2-methoxy-7-methyl-3-nitro-6-(trifluoromethyl)anthracen-9-amine (4l)

Yield: 53%, M.P: 230-232^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 4.02(3H,s,-OCH_3), 6.36(2H,s,-NH_2), 7.81(1H,s,-Ar-H), 7.84(1H,s,-Ar-H), 7.97(1H,s,-Ar-H), 8.54(1H,s,-Ar-H), ^{13}C-NMR(δ): 19.3, 54.7, 100.4, 112.9, 118.3, 123.2, 126.7, 127.4, 127.9, 128.8, 130.2, 131.6, 138.1, 141.6, 144.8, 148.9, 160.1, FAB Mass: m/z 351.09(M^+), CHN Analysis: Found: C(59.00%), H(3.63%), N(7.94%), Calc: C(58.29%), H(3.74%), N(8.00%).

6a: 9-((3-chloroquinoxalin-2-yl)amino)-7-methyl-3-nitro-6-phenylacridin-2-ol.

Yield: 39%, M.P: 249-251^{0}C, ^{1}H-NMR: 2.58(3H,s,-CH_3), 7.38-7.47(5H,m,-Ar-H), 7.54(2H,s,-NH_2), 7.63-7.69(2H,t,-Ar-H), 7.82-7.85(2H,t,-Ar-H), 8.01(1H,s,-Ar-H), 8.07(1H,s,-Ar-H), 8.20(1H,s,-Ar-H), 8.54(1H,s,-Ar-H), 14.42(1H,s,-OH), ^{13}C-NMR: 19.2, 107.8, 111.2, 112.6, 118.7, 119.8, 120.9, 125.1, 125.6, 126.7, 127.7, 127.9, 127.9, 128.7, 129.3, 129.3, 133.5, 135.4, 135.6, 137.9, 139.2, 140.8, 141.7, 144.4, 145.9, 146.9, 149.2, 162.3, FAB Mass: m/z 508.11(M^+), CHN Analysis: Found: C(65.94%), H(3.62%), N(13.91%), Calc: C(66.21%), H(3.57%), N(13.79%).

6b: N-(3-chloroquinoxalin-2-yl)-2,3,7-trimethyl-6-phenylacridin-9-amine.

Yield: 39%, M.P: 235-237^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 2.47(3H,s –CH_3), 2.54(3H,s,-CH_3), 7.29(1H,s,-Ar-H), 7.36-7.44(5H,m,-Ar-H), 7.53(1H,s,-NH), 7.68-7.72(3H,m,-Ar-H), 7.80-7.84(2H,q,-Ar-H), 8.12(1H,s,-ar-H), 8.21(1H,s,-Ar-H), ^{13}C-NMR: 18.8, 19.1, 119.9, 118.5, 119.4, 120.3, 125.1, 125.5, 126.6, 127.2, 127.5, 127.9, 128.3, 129.4, 129.3, 133.5, 135.4, 135.1, 137.8, 139.1, 140.2, 141.5, 144.6, 145.9, 146.7, 149.2, 162.3, FAB Mass: m/z 475.16(M^+), CHN Analysis: Found: C(75.78%), H(4.97%), N(11.91%), Calc: C(75.86%), H(4.88%), N(11.80%).

6c: N-(3-chloroquinoxalin-2-yl)-2,7-dimethyl-3-nitro-6-phenylacridin-9-amine.

Yield: 51%, M.P:222-225^{0}C, ^{1}H-NMR: 2.34(3H,s,-CH3), 2.57(3H,s,-CH3), 7.38-7.6(5H,m,-Ar-H), 7.57(1H,s,-NH-), 7.67-7.7(2H,t,-Ar-H), 7.80-7.83(2H,t,-Ar-H), 8.07(1H,s,-Ar-H), 8.20(1H,s,-Ar-H), 8.55(1H,s,-Ar-H), 8.77(1H,s,-Ar-H), ^{13}C-NMR: 18.7, 19.1, 107.9, 112.5, 116.1, 119.8, 120.4, 125.6, 125.9, 126.6, 127.6, 127.9, 128.3, 128.9, 129.2, 133.4, 135.2, 135.7, 137.9, 139, 141.6, 144.2, 145.8, 149.1, 151.2, 162.3, FAB Mass: m/z 506.13(M^+), CHN Analysis: Found: C(68.77%), H(4.03%), N(13.90%), Calc: C(68.84%), H(3.98%), N(13.84%).

6d: N-(3-chloroquinoxalin-2-yl)-2-methoxy-7-methyl-3-nitro-6-phenylacridin-9-amine.

Yield: 49%, M.P: 259-261^{0}C, ^{1}H-NMR: 2.52(3H,s,-CH3), 4.02(3H,s,-OCH3), 7.38-7.46(5H,m,-Ar-H), 7.57(1H,s,-NH-), 7.67-7.7(2H,t,-Ar-H), 7.80-7.83(2H,t,-Ar-H), 7.96(1H,s,-Ar-H), 8.07(1H,s,-Ar-H), 8.20(1H,s,-Ar-H), 8.62(1H,s,-Ar-H), ^{13}C-NMR: 19.12, 54.5, 107.7, 107.8, 112.4, 118.2, 119.6, 120.3, 125.2, 125.5, 126.8, 127.5, 127.9, 127.9, 128.8, 129.2, 129.2, 133.5, 135.4, 135.8, 137.7, 138.7, 141.5, 142.5, 144.5, 145.4, 146.2, 149.5, 162.3, FAB Mass: m/z 522.13(M^+), CHN Analysis: Found: C(66.61%), H(3.79%), N(13.98%), Calc: C(66.73%), H(3.86%), N(13.42%).

6e: 9-((3-chloroquinoxalin-2-yl)amino)-6,7-dimethyl-3-nitroacridin-2-ol.

Yield: 52%, M.P: 253-256^{0}C, ^{1}H-NMR: 2.29(3H,s,-CH3), 2.47(3H,s,-CH3), 7.28(1H,s,-Ar-H), 7.57(1H,s,-NH), 7.67-7.7(2H,t,-Ar-H), 7.77-7.80(3H,q,-Ar-H), 8.00(1H,s,-Ar-H), 8.56(1H,s,-Ar-H), 14.43(1H,s,-OH), ^{13}C-NMR: 18.8, 19.1, 106.7, 111.5, 118.6, 118.9, 119.4, 121.3, 125.8, 125.9, 126.4, 128.9, 133.7, 135.2, 135.6, 138.9, 140.5, 141.3, 144, 145.4, 146.8, 148.9, 162.5, FAB Mass: m/z 446.09(M^+), CHN Analysis: Found: C(61.82%), H(3.89%), N(15.83%), Calc: C(61.96%), H(3.62%), N(15.71%).

6f: N-(3-chloroquinoxalin-2-yl)-2,3,6,7-tetramethylacridin-9-amine.

Yield: 47%, M.P: 217-219^{0}C, ^{1}H-NMR: 2.28(6H,s,-CH_3), 2.48(6H,s,-CH_3), 7.29(2H,s,-Ar-H), 7.52(1H,s,-NH-), 7.69-7.81(6H,m,-Ar-H), ^{13}C-NMR:18.7, 19.3, 113.4, 113.5, 122.7, 125.8, 125.9, 126.1, 128.4, 133.3, 135.6, 135.8, 135.9, 139.0, 139.0, 141.5, 146.7, 146.1, 148.2, 162.5, FAB Mass: m/z 413.15(M^+), CHN Analysis: Found: C(72.73%), H(5.15%), N(13.55%), Calc: C(72.72%), H(5.13%), N(13.57%).

6g: N-(3-chloroquinoxalin-2-yl)-2,3,7-trimethyl-6-nitroacridin-9-amine.

Yield: 53%, M.P: 256-258^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 2.37(3H,s,-CH_3), 2.48(3H,s,-CH_3), 7.32(1H,s,-Ar-H), 7.57(1H,s,-NH), 7.69(3H,q,-Ar-H), 7.82(2H,t,-Ar-H), 8.61(1H,s,-Ar-H), 8.73(1H,s,-Ar-H), ^{13}C-NMR: 18.8, 18.9, 19.1, 111.8, 116.2, 121.04, 123.5, 125.3, 125.5, 125.9, 126.5, 127.6, 128.2, 128.9, 133.4, 135.6, 136.2, 139.6, 140.8, 141.7, 149.2, 150.4, 150.8, 162.5, FAB Mass: m/z 444.11(M^+), CHN Analysis: Found: C(64.79%), H(4.09%), N(16.13%), Calc: C(64.94%), H(4.09%), N(15.78%).

6h: N-(3-chloroquinoxalin-2-yl)-2-methoxy-6,7-dimethyl-3-nitroacridin-9-amine.

Yield: 42%, M.P: 252-254^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 2.49(3H,s,-CH_3), 4.03(3H,s,-OCH_3), 7.25(1H,s,-Ar-H), 7.66(2H,t,-Ar-H), 7.77-7.80(3H,q,-Ar-H), 7.93(1H,s,-Ar-H), 8.61(1H,s,-Ar-H), ^{13}C-NMR: 18.8, 19.1, 54.7, 106.9, 107.4, 118.8, 119.3, 125.2, 125.5, 126.6, 128.3, 128.8, 133.1, 135.3, 135.5, 138.8, 141.2, 142.7, 144.2, 145.6, 146.4, 148.1, 162.5, FAB Mass: m/z 460.11(M^+), CHN Analysis: Found: C(62.68%), H(3.95%), N(15.22%), Calc: C(62.68%), H(3.95%), N (15.23%).

6i: 9-((3-chloroquinoxalin-2-yl)amino)-7-methyl-3-nitro-6-(trifluoromethyl)acridin-2-ol.

Yield: 59%, M.P: 212-215^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 7.6(1H,s,-NH), 7.67(2H,t,-Ar-H), 7.82(3H,q,-Ar-H), 8.05(1H,s,-Ar-H), 8.09(1H,s,-Ar-H), 8.59(1H,s,-Ar-H), 14.41(1H,s,-OH), ^{13}C-NMR: 19.2, 110.5, 111.3, 118.4, 120.7, 122.7, 123.5, 125.6, 125.9, 126.3, 127.6, 128.7, 128.9, 130.6, 133.5, 135.3, 140.2, 141.6, 144.1, 145.6, 146.7, 149.4, 162.5, FAB Mass: m/z 500.07(M^+), CHN Analysis: Found: C(55.33%), H(2.58%), N(14.56%), Calc: C(55.27%), H(2.62%), N(14.01%).

6j: N-(3-chloroquinoxalin-2-yl)-2,3,7-trimethyl-6-(trifluoromethyl)acridine-9-amine.

Yield: 51%, M.P: 255-257^{0}C, ^{1}H-NMR: 2.28(6H,s,-CH_3), 2.46(3H,s,-CH_3), 7.31(1H,s,-Ar-H), 7.52(1H,s,-NH), 7.62(3H,q,-Ar-H), 7.84(3H,q,-Ar-H), 8.08(1H,s,-Ar-H), ^{13}C-NMR: 18.8, 110.6, 120.5, 122.5, 123.2, 125.7, 125.4, 125.3, 126.6, 127.8, 128.3, 128.8, 128.9, 130.7, 133.1, 135.2, 136.5, 139.8, 141.6, 144.7, 149.1, 149.4, 162.5, FAB Mass: m/z 467.12(M^+), CHN Analysis: Found: C(64.33%), H(3.86%), N(12.02%), Calc: C(64.31%), H(3.89%), N(12.00%).

6k: N-(3-chloroquinoxalin-2-yl)-2,7-dimethyl-3-nitro-6-(trifluoromethyl)acridine-9-amine.

Yield: 45%, M.P: 247-249^{0}C, ^{1}H-NMR: 2.28(3H,s,-CH_3), 2.36(3H,s,-CH_3), 7.62(1H,s,-NH), 7.67(2H,t,-Ar-H), 7.82(3H,q,-Ar-H), 8.08(1H,s,-Ar-H), 8.52(1H,s,-Ar-H), 8.72(1H,s,-Ar-H), ^{13}C-NMR: 18.8, 19.2, 110.7, 116.3, 120.6, 122.1, 123.8, 125.1, 125.2, 126.7, 127.8, 128.4, 128.8, 128.9, 128.9, 130.8, 133.7, 135.3, 141.5, 144.6, 145.1, 149.8, 151.2, 162.5, FAB Mass: m/z 498.09(M^+), CHN Analysis: Found: C(57.83%), H(3.18%), N(14.45%), Calc: C(57.90%), H(3.04%), N(14.07%).

6l: N-(3-chloroquinoxalin-2-yl)-2-methoxy-7-methyl-3-nitro-6-(trifluoromethyl)acridin-9-amine.

Yield: 49%, M.P: 253-256^{0}C, ^{1}H-NMR: 2.29(3H,s,-CH_3), 4.02(3H,s,-OCH_3), 7.57(1H,s,-NH), 7.67(2H,t,-Ar-H), 7.80(3H,q,-Ar-H), 7.96(1H,s,-Ar-H), 8.09(1H,s,-Ar-H), 8.62(1H,s,-Ar-H), ^{13}C-NMR: 19.2, 54.7, 107.8, 110.4, 118.3, 120.1, 122.5, 123.8, 125.1, 125.4, 126.8, 127.4, 128.5, 128.7, 130.1, 133.2, 135.5, 141.7, 142.2, 144.4, 145.8, 146.2, 149.4, 162.5, FAB Mass: m/z 514.08(M^+), CHN Analysis: Found: C(55.74%), H(3.00%), N(13.99%), Calc: C(56.10%), H(2.94%), N(13.63%).

Results and Discussion:

Chemistry: The chemistry of acridine derivatives and quinoxaline derivatives has been of significant interest because of their synthetic and extensive biological applications in the field of organic chemistry and medicinal chemistry. The reaction scheme for the synthesis of title compounds is depicted in the following scheme. All the new derivatives were prepared from 2-chloro-4,5-disubstituted benzoic acid condensed with 3,4-disubstited aniline in the presence of potassium carbonate, copper powder in isopropyl alcohol yields 2-((3,4-di substituted phenyl)amino)-4,5-disubstituted benzoic acid **(3a-l)**. Reacting 2-((3,4-di substituted phenyl)amino)-4,5-disubstituted benzoic acid **(3a-l)** with phosphorus oxy chloride, ammonium carbonate in the presence of phenol yields 2,3,6,7-tetra substituted acridin-9-amine **(4a-l)**. The coupling of 2,3-dichloroquinoxaline (**5**) with 2,3,6,7-tetra substituted acridin-9-amine (**4a-l**) in the presence of NaOt-Bu, $PdCl_2$(dppf) in dioxane produces final compounds N-(3-chloroquinoxalin-2-yl)-2,3,6,7-tetra substituted acridin-9-amine (**6a-l**). The structures of the resulted compounds were identified and confirmed by ^{1}H-NMR, ^{13}C-NMR, Mass spectral data and elemental analysis.

Bilogical Study:

Antibacterial activity:

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram +ve bacteria screened were Staphylococcus aureus (S.A) and Bacillus Subtilis (B.S). The gram _ve bacteria screened were Escherichia coli (E. Coli) and Pseudomonas Aeruginosa (P.A).

Almost all the compounds showed moderate activity that could be attributed to the presence of Quinoxaline and acridine heterocyclic ring systems with their high potency. The compound **6a-l** shows moderately active with all strains of bacteria

The synthesized compounds were used at the concentration of 250 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and cefaclor 10 µg/disc were used as a standard (Himedia laboratories limited. Mumbai).

Table-2

The antibacterial activity against bacterial strains such as the gram +ve bacteria strains were Staphylococcus Aureus (S.A) and Bacillus Subtilis (B.S). The gram -vet bacteria strains were Escherichia Coli (Ecolab) and Pseudomonas Aeruginosa (P.A).

S.No	Compound	R_1	R_2	R_3	R_4	B.subtilis	S.aureus	P.aeruginosa	E.coli
1	**6a**	-OH	-NO_2	-C_6H_5	-CH_3	12(++)	13(++)	11(++)	12(++)
2	**6b**	-CH_3	-CH_3	-C_6H_5	-CH_3	13(++)	12(++)	12(++)	11(++)
3	**6c**	-CH_3	-NO_2	-C_6H_5	-CH_3	13(++)	13(++)	12(++)	13(++)
4	**6d**	-OCH_3	-NO_2	-C_6H_5	-CH_3	11(++)	12(++)	11(++)	12(++)
5	**6e**	-OH	-NO_2	-CH_3	-CH_3	12(++)	13(++)	12(++)	13(++)
6	**6f**	-CH_3	-CH_3	-CH_3	-CH_3	13(++)	13(++)	12(++)	13(++)
7	**6g**	-CH_3	-NO_2	-CH_3	-CH_3	12(++)	13(++)	10(++)	12(++)
8	**6h**	-OCH_3	-NO_2	-CH_3	-CH_3	10(++)	11(++)	10(++)	11(++)
9	**6i**	-OH	-NO_2	-CF_3	-CH_3	12(++)	12(++)	11(++)	11(++)
10	**6j**	-CH_3	-CH_3	-CF_3	-CH_3	13(++)	14(+++)	13(++)	13(++)
11	**6k**	-CH_3	-NO_2	-CF_3	-CH_3	12(++)	13(++)	12(++)	13(++)
12	**6l**	-OCH_3	-NO_2	-CF_3	-CH_3	11(++)	12(++)	10(++)	11(++)
13	**Ampicillin**					24	26	22	25

Key to symbols: - inactive (inhibition zone < 6 mm); slightly active = + (inhibition zone 7–9 mm); moderately active = + + (inhibition zone 10-13 mm); highly active = + + + (inhibition zone > 14 mm).

Cytotoxic activity:

All the synthesized compounds (**6a-l**) were evaluated for their anticancer activity against two human cancer cell lines including breast cancer (MCF-7) and lung cancer (MDA MB-231) by MTT assay, and these results are summarized in **table-3**. Adriamycin was used as a positive control. All of the tested derivatives displayed good cytotoxic activity *in vitro*. The compounds **6a** and **6l** showed very good activity against two cell lines (**MCF-7 & MDA MB-231**). The compound **6d** showed very good activity against **MCF-7**. The remaining compounds were less active against two cell lines.

Table-3

Compound	IC50 in (µg / ml)	
	MCF-7	MDA MB-231
6a	1.54±1.64	2.76±1.41
6b	-	5.83±2.33
6c	-	4.67±1.42
6d	2.83±0.95	7.03±4.15
6e	4.73±1.86	8.45±3.17
6f	-	-
6g	6.94±2.65	7.53±1.78
6h	5.35±1.26	3.43±1.35
6i	5.68±1.46	8.65±2.21
6j	6.58±1.21	9.75±1.20
6k	4.84±3.15	9.84±3.67
6l	1.83±0.77	2.28±0.45
Adriamycin	3.32±0.21	3.43±0.16

"-" Not active. A Each data represents as mean ±SD values. From two different experiments performed in duplicates. MCF-7: human lung cancer cell line. MDA MB-231: Human lung cancer cell line

Conclusion:

In summary, the synthesis of new derivatives of N-(3-chloroquinoxalin-2-yl)-2,3,6,7-tetra substituted acridin-9-amine (**6a-l**) and their antibacterial and anticancer activities are represented in this study. All of the new acridine derivatives found to posses moderately active against antibacterial Stains and The compounds **6a** and **6l** found to posses active against anticancer cell lines of MCF-7 and MDA MB-231 cell lines. The compound **6d** active against MCF-7 cell line. The results may provide a useful reference for further research on antibacterial and anticancer drugs.

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Conflict of interest:

The authors confirm that this article content has no conflict of interest.

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