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DESIGN, SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL AND ANTIMALARIAL STUDIES OF NOVEL 1,3,4-OXADIAZOLE DERIVATIVES.

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ABSTARCT

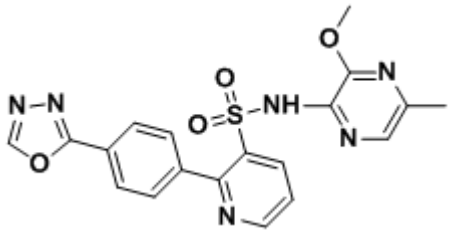
A new series of (3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl) based phenyl aniline derivatives 6(A-L) are synthesized via preparation of hydrazide using hydrazine hydrate followed by formation of 1,3,4 oxadiazole using $POCl_3$.The Final compound was synthesized via buchwald reaction. The final compounds were Analyzed by Spectroscopic Methods such as FT-IR, ^{1}HNMR, LCMS and Mass Spectrometry as well as melting point measurement. All synthesized compounds were screened for antimicrobial activity against staphylococcus aureus, Bacillus megaterium, Escherichia coli & Proteus vulgaris.

KEYWORDS:Methyl-3-bromobenzoate,Quinoxaline-2-carboxylicacid,$POCl_3$,Antimalarial Activity,Antimicrobial Activity.

1. Introduction

1,3,4-Oxadiazole[1] is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. There are three well-known isomers: 1,2,4-oxadiazole[2], 1,2,3-oxadiazole[3] and 1,2,5-oxadiazole[4]. 1,3,4-oxadiazole and 1,2,4-oxadiazole are better famous, and more broadly studied by researchers because of their lots of chief chemical and biological properties.1,3,4-Oxadiazoles are an importantclass of heterocyclic compounds with broad spectrum of biologicaln activities. Substituted 1,3,4-oxadiazoles have shown antibacterial[5], antimycobacterial[6], antifungal[7], anti-inflammatory[8],analgesic[9], anticonvulsant[10] and anticancer[11] properties.1,3,4-Oxadiazole have also concerned importance in medicinal chemistry as surrogates(bioisosteres) for carboxylic acids, esters and carboxamides. The capability of 1,3,4-oxadiazole heterocyclic compounds to go through various chemical reactions examples of compound containing the 1,3,4-oxadiazole unit currently used in clinical medicine is Zibotentan an anticancer agent.

Figure 1. Structure of Zibotentan drug that is in clinical devlopment.



1,3,4-Oxadiazole was first prepared by Ainsworth in 1965 by the thermolysis of ethylformate, formally hydrazine, at atmospheric pressure and is liquid in character. It was first known by the common names such as oxybiazole, diazoxole,biozole. Common names were replaced by the IUPAC name 1,3,4-oxadiazole.

In the present work, we have design synthesis of 2-Quinoxalin-5-phenylaniline 1,3,4 Oxadiazole derivatives from easily accessible starting chemicals. In this work, we explain a synthesis for 3-bromobenzohydrazide **(2)** from methyl 3-bromobenzoate **(1)**. Which was followed incorporated with quinoxaline-2-carboxylic acid Under go cyclization using $POCl_3$ to give 2-(3-bromophenyl)-5-(quinoxalin-2-yl)-1,3,4-oxadiazole. The 1,3,4 Oxadiazole moiety react with diffrent amine **5(A-L)** in buchwald reaction give bioactive moiety **6(A-L)**.

2. Experimental

2.1 Chemicals and Reagents

All reagents were used as obtained from commercial suppliers not including further purification.

2.2 Analyticals Methods

Melting points (mp, °C) of all the synthesized compounds were determined on an Electrothermal equipment by open capillaries technique and are uncorrected. The purity of synthesized compounds was checked using TLC plates (Merck Keiselgel F_{254}) and visualization was attained via UV light. The FT-IR spectrum were recorded on IR affinity-1 FTIR (Shimadzu) spectrometer in KBr and wave numbers (ν_{max}) are reported in cm^{-1} ^1H NMR spectra were scanned on Bruker Avance II NMR spectrometer operating at 400 MHz using DMSO-d_6 and TFA as solvents and tetramethylsilane(TMS) as internal standard. Chemical shift (δ)values are articulated in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on Waters Quadrupole Detector (TDQ).

2.3 General experimental procedure for synthesis of 1,3,4 Oxa diazol derivatives

2.3.1 Procedure of synthesis of 3-bromobenzohydrazide(2)

To a stirred solution of Inter-1 in methanol, Hydrazine hydrate (50% solution in water) was added at Room temp. Then heated the RM at 65°C for 12hr.Then cool the RM at RT. The product Formation was checked by TLC.(60% ethyl acetate in Hexane).solvent was evaporated under reduced pressure and the crude compound was triturated with diethyl ether to get solid product.

2.3.2 Synthesis of 2-(3-bromophenyl)-5-(quinoxalin-2-yl)-1,3,4-oxadiazole(4)

To a stirred solution of Inter-2 in toluene inter-3 was added and cooled the RM at 0°C.$POCl_3$ was added drop wise to the RM. Then heated the RM at 110°C for 4 hr. The product formation was checked by TLC (50% Ethyl acetate in Hexane).The RM was cooled at RT and poured slowly in crushed ice and extracted with ethyl acetate. The organic layer dried over Na_2SO_4 an evaporated under reduced pressure to give crude compound. The crude compound was purified by column chromatography and product was eluted at 29% ethyl acetate in hexane to give inter-4.

2.3.3 Synthesis of compound 6(A-L) via Buchwald reaction.

To a stirred solution of inter-4 in Dioxane,Inter-**5(A-L)** and NaotBu was added and the reaction mass was degassed with argon gas for 20 min. $Pd_2(dba)_3$ and xantphos was added to the reaction mixture and again the Reaction mass was degassed with argon for 15 min. Then heated the RM at 120°C for 5hr..The product formation was checked by TLC. The RM was diluted in water and product was extracted with ethyl acetate. The organic layer dried over Na_2SO_4 an evaporated under reduced pressure to give crude compound. The crude compound was purified by column chromatography and product was eluted at 16% ethyl acetate in hexane.

2.4 Characterization of compounds.

1. 2-(3-bromophenyl)-5-(quinoxalin-2-yl)-1,3,4-oxadiazole(4),

Yield:-82%,white solid,m.p:-170-174°C.^{1}HNMR(400MHZ,TFA) 9.64(s,1H),8.29-8.26(d,1H,12Hz),8.15-8.13(d,1H,8Hz), 8.01-7.96(m,3H,J=20Hz),7.83-7.81(d,1H,J=8Hz), 7.48-7.50(d,1H,J=8Hz), 7.16-7.12(t,1H,J=16Hz). m/z:-352$(M+H)^{+}$**.**

2. 3-chloro-4-fluoro-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6A, Yield:-78%,off white solid,m.p:-195-199°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.71(s,1H),8.35(s,1H),8.32-8.30(d,1H,J=10Hz).8.28-8.25(m,1H,J=9.7Hz),8.05-8.03(m,1H,J=9.6Hz), 7.81(s,1H),7.55-7.53(d,1H,J=7.8Hz),7.48-7.44(t,1H,J=15.6Hz),7.29-7.27(d,1H,J=8.3Hz),6.98-6.95(d,1H,J=8.8Hz),6.835-6.824(d.1H,J=2.1Hz),6.77-6.76(d,1H,J=2Hz)6.72-6.71(d,1H,J=2.1Hz).m/z:-417$(M+H)^{+}$**.**

3. 3,4-dimethoxy-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6B,

Yield:-81%,light brown solid,m.p:-185-189°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.7(s,1H),8.38(s,1H),8.31-8.29(d,1H,J=10Hz).8.27-8.24(m,1H,J=9.6Hz),8.05-8.03(m,1H,J=9.6Hz), 7.77(s,1H),7.54-7.52(d,1H,J=7.6Hz),7.48-7.44(t,1H,J=15.6Hz),7.25(S,1H,J=8Hz),6.98-6.95(d,1H,J=8.8Hz),6.837-6.826(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.746(d,1H,J=2.4Hz),3.67(s,6H). m/z:-426$(M+H)^{+}$**.**

4. 3-chloro-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6C,

Yield:-76%,white solid,m.p:-192-195°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.76(s,1H),8.38(s,1H),8.31-8.29(d,1H,J=10Hz).8.27-8.24(m,1H,J=9.6Hz),8.05-8.03(m,1H,J=9.6Hz), 7.77(s,1H),7.54-7.52(d,1H,J=7.6Hz),7.48-7.44(t,1H,J=15.6Hz),7.25(s,1H),6.98-6.95(d,1H,J=8.8Hz),6.837-6.832(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.746(d,1H,J=2.4Hz)6.73-6.71(t,1H,J=7.6Hz). m/z:-400$(M+H)^{+}$**.**

5. 3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(p-tolyl)aniline 6D,

Yield:-82%,Dark yellow solid,m.p:-196°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.72(s,1H),8.36(s,1H),8.31-8.29(d,1H,J=10Hz).8.27-8.24(m,1H,J=9.6Hz),8.05-8.03(t,1H,J=9.6Hz), 7.77-7.75(d,1H,J=9.2Hz),7.54-7.52(d,1H,J=7.6Hz),7.48-7.44(t,1H,J=15.6Hz),7.25(s,1H),6.98-6.95(d,1H,J=8.8Hz),6.837-6.823(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.746(d,1H,J=2.4Hz)6.73-6.71(d,1H,J=7.4Hz),2.28(s,3H).m/z:-380$(M+H)^{+}$**.**

6. 3-methoxy-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6E,

Yield:-81%,Dark brown solid,m.p:-200-204°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.78(s,1H),8.36(s,1H),8.31-8.29(d,1H,J=10Hz).8.25-8.22(m,1H,J=9.6Hz),8.07-8.05(m,1H,J=9.6Hz), 7.75(s,1H),7.54-7.52(d,1H,J=7.6Hz),7.48-7.44(t,1H,J=15.6Hz),7.25(s,1H),6.98-6.95(d,1H,J=8.8Hz),6.838-6.823(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.746(d,1H,J=2.4Hz)6.71-6.73(t,1H,J=7.6Hz),3.83(s,3H). m/z:-396$(M+H)^{+}$**.**

7. 2,4-dimethoxy-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6F,

Yield:-74%,brown solid,m.p:-205-209°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.72(s,1H),8.38(s,1H),8.33-8.31(d,1H,J=10Hz).8.29-8.25(m,1H,J=9.7Hz),8.04-8.02(m,1H,J=9.5Hz), 7.77(s,1H),7.58-7.56(d,1H,J=7.5Hz),7.48-7.44(t,1H,J=15.6Hz),7.26(s,1H),6.98-6.95(d,1H,J=8.8Hz),6.837-6.832(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.71-6.742(d,1H,J=2.4Hz),3.73(s,6H) m/z:-426$(M+H)^{+}$**.**

8.N-(4-chlorophenyl)-3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)aniline 6G,

yield:-80%,ple yellow solid,m.p:-192-197°C,

^{1}HNMR(400MHZ, $DMSOd_6$),9.78(s,1H),8.35(s,1H),8.33-8.31(d,1H,J=10.2Hz).8.25-8.22(m,1H,J=9.5Hz),8.10-8.07(t,1H,J=9.8Hz), 7.80-7.78(d,1H,J=9.4Hz),7.60-7.58(d,1H,J=7.9Hz),7.48-7.44(t,1H,J=15.6Hz),7.29(s,1H),6.99-6.96(d,1H,J=8.8Hz),6.837-6.825(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.73-6.71(d,1H,J=2.3Hz)6.69-6.67(d,1H,J=7.3Hz).m/z:-380$(M+H)^+$**.**

9. 3N-(4-methoxyphenyl)-3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)aniline 6H,

Yield:-78%,dark yellow solid,m.p:-190-194°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.69(s,1H),8.29(s,1H),8.40-8.38(d,1H,J=10.5Hz).8.30-8.27(m,1H,J=9.7Hz),8.15-8.12(t,1H,J=9.7Hz), 7.85-7.83(d,1H,J=9.6Hz),7.60-7.58(d,1H,J=7.9Hz),7.48-7.44(t,1H,J=15.6Hz),7.29(s,1H),6.97-6.94(d,1H,J=8.8Hz),6.836-6.827(d.1H,J=2Hz),6.79-6.78(d,1H,J=2Hz)6.77-6.76(d,1H,J=2.4Hz)6.68-6.69(d,1H,J=7.6Hz),3.79(s,3H) m/z:-396$(M+H)^+$**.**

10. 3-methyl-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6I,

Yield:-75%, light yellow solid,m.p:-198-202°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.73(s,1H),8.42(s,1H),8.40-8.38(d,1H,J=10.2Hz).8.27-8.24(m,1H,J=9.7Hz),8.10-8.08(m,1H,J=9.8Hz), 7.80(s,1H),7.55-7.53(d,1H,J=7.6Hz),7.50-7.46(t,1H,J=15.9Hz),7.28(s,1H),6.97-6.95(d,1H,J=8.8Hz),6.838-6.833(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.74(d,1H,J=2.4Hz)6.71-6.73(t,1H,J=7.6Hz).2.34(s,3H)m/z:-380$(M+H)^+$**.**

11.3,5-dimethoxy-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6J,

Yield:-81%,Brown solid,m.p:-196-200°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.74(s,1H),8.34(s,1H),8.32-8.30(d,1H,J=10.1Hz).8.28-8.24(m,1H,J=9.5Hz),8.04-8.02(m,1H,J=9.5Hz),7.77(s,1H),7.60-7.58(d,1H,J=7.7Hz),7.50-7.46(t,1H,J=15.5Hz),7.26(s,1H),6.98-6.95(d,1H,J=8.8Hz),6.86(s,1H,J=2Hz),6.81(s,1H)6.72-6.752(d,1H,J=2.4Hz),3.75(s,6H) m/z:-426$(M+H)^+$**.**

12. 4-fluoro-3-methyl-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6K,

Yield:-76%,brown solid,m.p:-203-208°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.73(s,1H),8.34(s,1H),8.31-8.29(d,1H,J=10Hz).8.27-8.24(m,1H,J=9.6Hz),8.07-8.05(m,1H,J=9.7Hz), 7.81(s,1H),7.56-7.54(d,1H,J=7.6.1Hz),7.48-7.44(t,1H,J=15.6Hz),7.36(S,1H),6.94-6.91(d,1H,J=8.8Hz),6.837-6.826(d.1H,J=2Hz),6.79-6.78 (d,1H,J=2Hz)6.74-6.73 (d,1H,J=2.4Hz),2.9(s,3H). m/z:-398$(M+H)^+$**.**

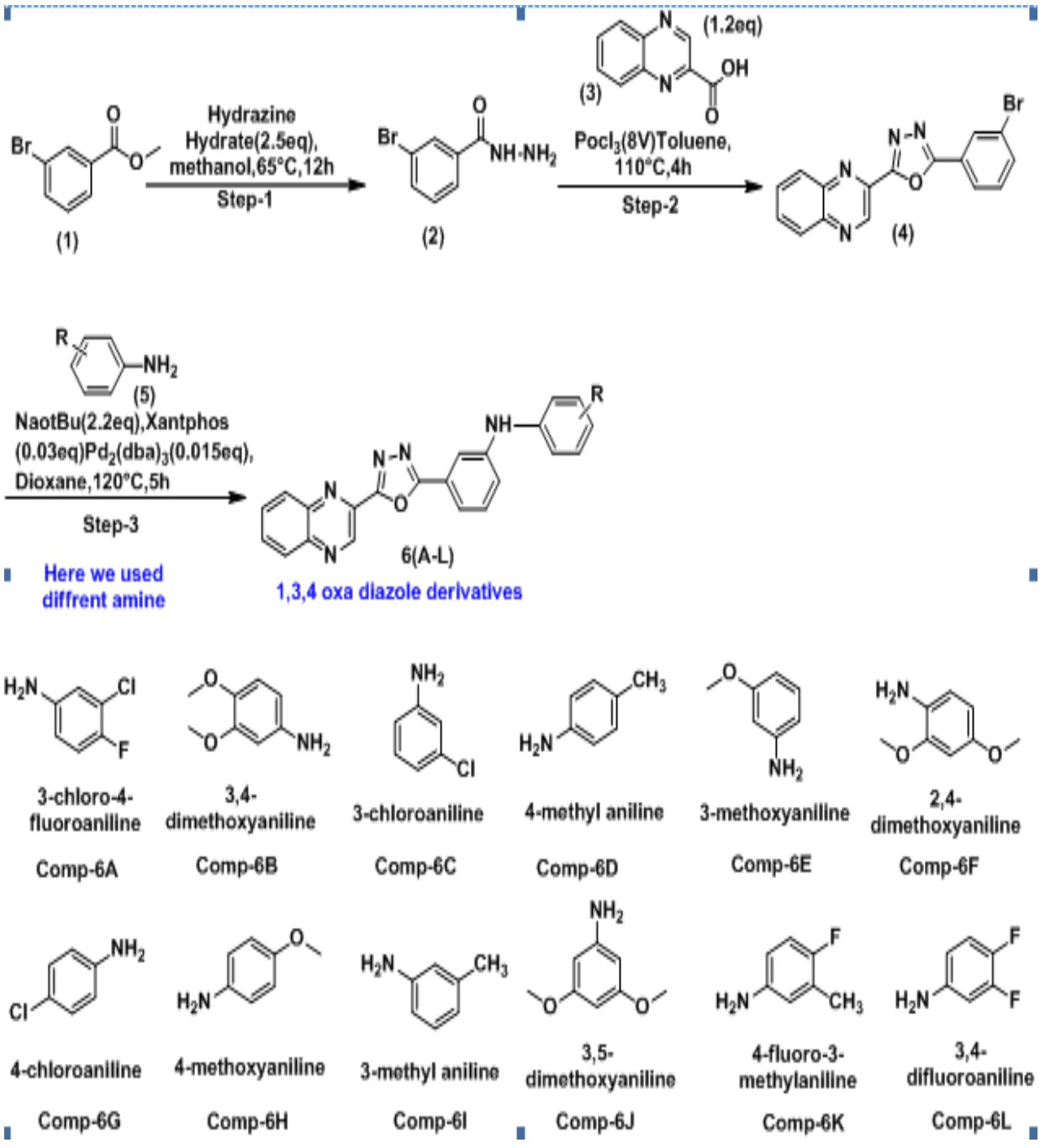
13.3,4-difluoro-N-(3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)aniline 6L,

Yield:-76%,brown solid,m.p:-202-207°C.

^{1}HNMR(400MHZ, $DMSOd_6$),9.76(s,1H),8.38(s,1H),8.31-8.29(d,1H,J=10Hz).8.27-8.24(m,1H,J=9.6Hz),8.05-8.03(m,1H,J=9.6Hz), 7.77(s,1H),7.54-7.52(d,1H,J=7.6Hz),7.48-7.44(t,1H,J=15.6Hz),7.32(S,1H),6.98-6.95(d,1H,J=8.8Hz),6.837-6.826(d.1H,J=2Hz),6.77-6.76(d,1H,J=2Hz)6.75-6.746(d,1H,J=2.4Hz). m/z:-402$(M+H)^+$**.**

3. Result and discussion

3.1 Scheme



3.2 Antimicrobial activity

The antimicrobial action of the recently synthesized compounds 6(A-L) was carried out by both micro dilution method according to National Committee for Clinical Laboratory Standards (NCCLS)[12].Antimicrobial activity was screened against two Gram positive (*Staphylococcus aureus*, *Bacillus megaterium*) and two Gram negative (*Escherichia coli* and *Proteus vulgaris*) bacteria by using ampicillin,gentamycin as the standard antibacterial drugs.

Table-1:*In vitro* antimicrobial activity of polyhydroquinoline derivatives 6(A-L),(MICs, µg/mL).

compound	Gram positive bacteria		Gram negative bacteria	
	Staphylococcus aureus	Bacillus megaterium	Escherichia coli	Proteus vulgaris
6A	8	7	8	6
6B	**14**	**13**	**14**	**15**
6C	9	8	8	6
6D	10	10	7	8
6E	10	11	9	10
6F	**13**	**12**	**14**	**16**
6G	7	6	6	5
6H	9	11	9	10
6I	10	10	7	9
6J	**13**	**13**	**15**	**14**
6K	9	7	8	6
6L	8	6	7	7
Ampicilin	15	14	17	19
Gentamycin	16	15	15	16

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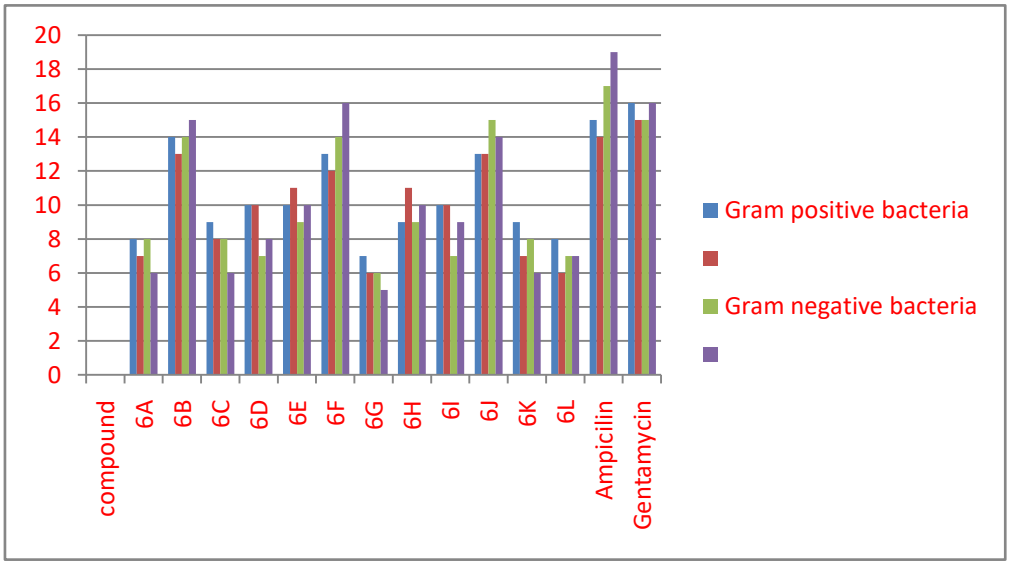

Figure-1:Antibacterial Activities of Compounds 6(A-L)

(I) **Against *Staphylococcus aureus*:**

Maximum activity were found in compounds (**6B,6F,6J)** zone of inhibition-13.0 m.m. and minimum activity were found in compounds (**6A,6G,6L**) zone of inhibition -6.0 m.m.

(II) **Against *Bacillus megaterium*:**

Maximum activity were found in compounds (**6B,6J**) zone of inhibition -12.0 m.m where as minimum activity were found in compound (**6A,,6G,6K,6L**) zone of inhibition -6.0 m.m.

(III) **Against *Escherichia coli*:**

Maximum activity were found in compounds **(6B,6F,6J)** zone of inhibition -14.0 m.m and minimum activity were found in compounds (**6I,6G,6D)** zone of inhibition -5.0 m.m.

(IV) **Against *Proteus vulgaris*:**

Maximum activity were found in compound (**6B,6F)** zone of inhibition -15.0 m.m and minimum activity were found in compounds **(6A,6C,6G,6K)** zone of inhibition -5.0 m.m.

3.3 Antimalarial activity

All the recently synthesized compounds **6(A-L)** were evaluated for their antimalarial activity against chloroquine and quinine receptive strain of *Plasmodium falciparum*. All experiments were performed in duplicate and a mean value of IC_{50} is mentioned in Table 3. As shown in Table 3, the compounds 6A,6L were found to have IC_{50} in the variety of 0.020 to 0.034 against *P. falciparum* strain. These compounds shown fabulous activity against *P. falciparum* strain as compared to quinine IC_{50} 0.268. In short those group have two halogen group at 3 and 4 position in the phenyl ring are highly active against *P. falciparum* strain. Remaining all other compounds were found to be less active against *P. falciparum* strain against chloroquine and quinine as the standard drugs.

Table 2 : *In vitro* antimalarial activity of compounds 6(A-L)

Compound	IC50 (mg/mL)	Compound	IC50 (mg/mL)
6A	**0.020**	6H	0.057
6B	1.004	6I	1.259
6C	0.036	6J	1.005
6D	1.952	6K	0.258
6E	0.942	**6L**	**0.034**
6F	0.033	Chloroquine	0.020
6G	0.015	Quinine	0.268

The bold characters indicate the higher or equal activity compared to standard drugs

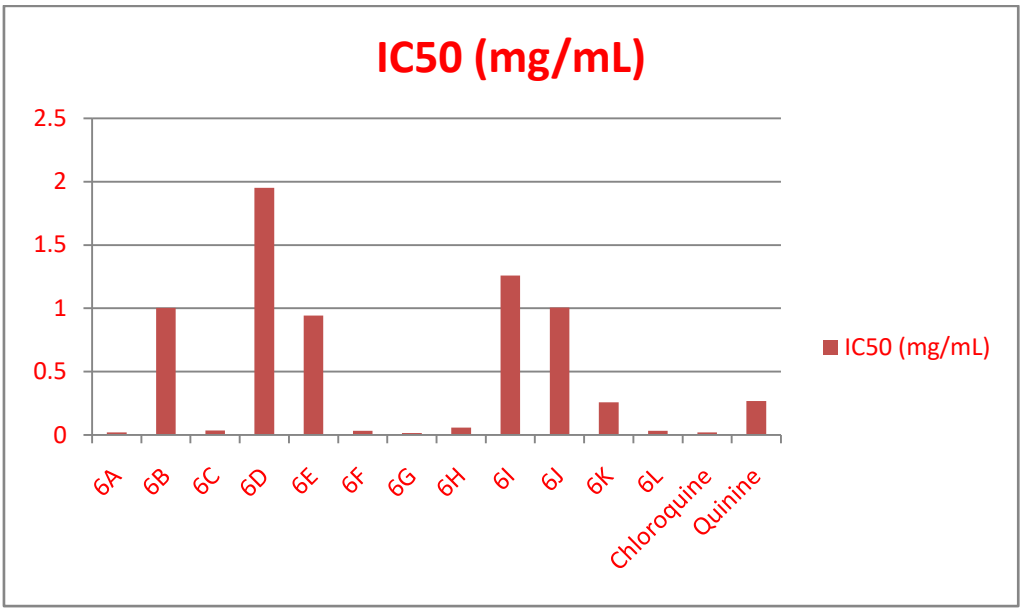

Figure-2:Antimalarial Activities of Compounds 6(A-6L)

4. Conclusion

We planned and synthesized some novel (3-(5-(quinoxalin-2-yl)-1,3,4-oxadiazol-2-yl) based phenyl aniline derivatives and Analyzed their antimicrobial and antimalarial activities. The results showed that 6B,6F and 6J compounds were found to be most active against Ampicilin and gentamycin.Compound bearing methoxy group attached in phenyl ring are active and dimethoxy group is highly active againts Ampicilin and Gentamycin.The compounds 6A and 6L were found to have IC_{50} in the variety of 0.020 to 0.034 against *P. falciparum* strain. These compounds Showed magnificent activity against *P. falciparum* strain as compared to quinine IC_{50} 0.268. In short those moiety posses dihalogen group at 3 and 4 position in the phenyl ring are extremely active against *P. falciparum* strain. Remaining all other compounds were found to be a lesser amount of active against *P. falciparum* strain against chloroquine and quinine as the standard drugs.

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