Heterocyclic Letters
Vol. 7| No.3|745-762|May-July| 2017
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

AN EFFICIENT IODOBENZENE DIACETATE (IBD) CATALYZED TETRAZOLO[1,5-*a*] QUINOLINE INCORPORATED 1,3,4-OXADIAZOLE NUCLEUS: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

Nirav H. Sapariya*, Beena K. Vaghasiya, Rahul P. Thummar, Ronak D. Kamani, Kirit H. Patel and Dipak K. Raval

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar- 388 120, Gujarat, India
**Corresponding author. Tel.: +91-02692-226856 - Ext. - 211; Fax: +91-02692 236475.*
E-mail: nir.sapariya@gmail.com, dipanalka@yahoo.com

Abstract
A facile, convenient and high yielding library of 7-substituted tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole nucleus was reported by the cyclization of the corresponding schiff base derivatives. Variously substituted schiff base derivatives *i.e.* (**5a-l**) and (**5m-r**) were obtained by the reaction of various tetrazolo[1,5-*a*]quinoline-4-carbaldehyde with substituted benzohydrazide as well as nicotinohydrazide/isonicotinohydrazide respectively. The targeted substituted 1,3,4-oxadiazole derivatives (**6a-r**) were obtained by cyclization with different cyclising reagents among which iodobenzenediacetate was found to be an extremely good catalyst. The structures of the targeted compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. All the resultant compounds were evaluated for their *in vitro* antibacterial activity against a panel of pathogenic strains of bacteria and fungi, *in vitro* antioxidant activity by the ferric-reducing antioxidant power method, *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain and for their *in vitro* antimalarial activity against *Plasmodium falciparum*. Many candidates of this new class revealed noticeable activities against first line drugs.

Keywords: Tetrazolo[1,5-*a*]quinoline clubbed 1,3,4-oxadiazole nucleus; antimicrobial activity; iodobenzenediacetate (IBD)

1. Introduction

Heterocyclic compounds are the scaffolds on which pharmacophores are arranged to provide potent and selective drugs[I]. This is especially true for five-membered ring heterocyclic compounds. 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been used as "privileged" scaffolds to produce substances of interest in broaden therapeutic area.[II-VIII] Tuberculosis has become a serious global health problem as it is one of the leading causes of death amongst infectious diseases. About one-third of the world's population is infected by

*Mycobacterium tuber*culosis every year and more than 2 million deaths are reported[IX]. The World Health Organization has declared TB to be a 'global emergency' and a recent estimation by WHO showed that within the next 20 years around 30 million people will be infected by *M. tuberculosis*. [X, XI] and new forms of tuberculosis like multidrug resistant tuberculosis (MDR TB) and extensively drug resistant tuberculosis (XDR TB) are found to be emerging as new challenge for medicinal chemists[XII].

Malaria remains a significant worldwide health problem, with serious social and economic consequences in affected countries. Malaria is also a critical diseases in public health around the world. It is caused by five different types of protozoan of the genus *Plasmodiu*m, but *Plasmodium falciparum* is responsible for most of the critical cases[XIII]. Amongst them, to reduce the variety of resistant parasites, the WHO has suggested the combined formulation of artemisinins with traditional antimalarial drugs such as lumefantrine, amodiaquine and mefloquine, and ACT (Artemisinin Combination Therapy) is currently approved in multiple countries [XIV, XV]. Pharmaceutical chemists are in focussing on creation of library of new analogues of existing drugs or new chemical entities with hope to obtain the agents with potential antitubercular activity as well as antimalarial activity with reduced toxicity and treatment duration.

Quinolines represent an essential group of heterocyclic compounds as they are pivotal skeletons in many biologically active natural products as well as various pharmacologically interesting compounds [XVI-XIX]. Azole class of compounds are gaining importance because of their key property liphophilicity that influence the ability of the drug to reach the target by transmembrane diffusion [XX]. Quinoline incorporated 1,3,4-Oxadiazoles have exhibited wide range of biological activities such as antibacterial [XXI, XXII], antitubercular [XXIII, XXIV], antitumor [XXV, XXVI], antifungal [XXVII, XXVIII], anti-inflammatory [XXIX, XXX], antimalarial [XXXI-XXXIV] activities and are key component of antibiotic furamizole [XXXV] as well as antiretroviral raltegravil [XXXVI].

We thought worthwhile to design and synthesize new hybrid substituted tetrazolo[1,5-*a*]quinoline clubbed 1,3,4-oxadiazoles with substituted phenyl and pyridyl ring systems in a single molecular framework with a hope to obtain the new molecules with enhanced antimycobacterial activity.

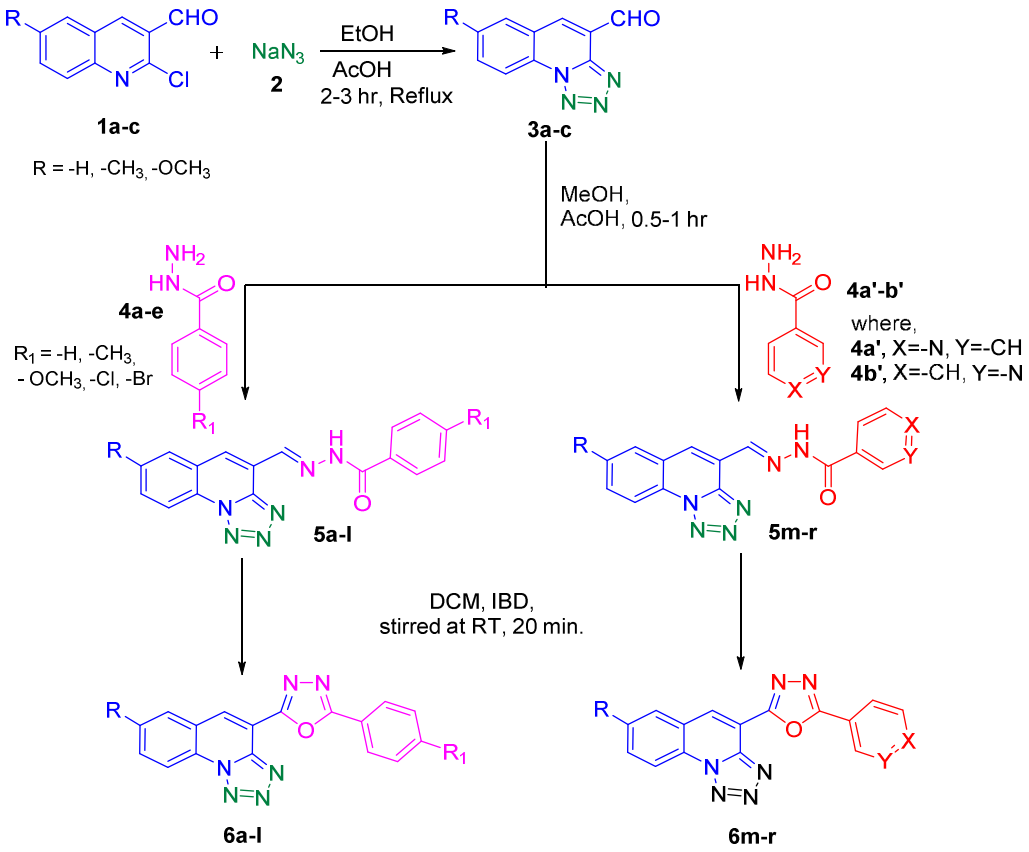
2. Results and discussion

2.1. Chemistry

The synthetic protocol adopted to obtain the targeted quinoline nucleus incorporated 1,3,4-oxadiazole derivatives is depicted in Scheme 1. The starting material 2-chloroquinoline-3-carbaldehydes **1** was prepared according to Vilsmeier-Haack reaction according to a literature procedure [XXXVII]. 7-substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehydes (**3a-c**) were prepared by reacting 7-substituted 2-chloroquinoline-3-carbaldehyde **1** and sodium azide **2** in the presence of catalytic amount of glacial acetic acid and ethanol as a solvent.

Then after 7-substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehydes (**3a-c**) were refluxed with 4-substitutedbenzohydrazide **4a-e** (10 mmol), nicotinohydrazide (**4a'**) and/or isonicotinohydrazide (**4b'**) in the presence of catalytic amount of glacial acetic acid in methanol (40 mL) was refluxed for 1h to give (E)-4-substituted-N'-((7-substitutedtetrazolo[1,5-*a*]quinolin-4-yl)methylene)benzohydrazide (**5a-l**) and (E)-N'-((7-substitutedtetrazolo[1,5-*a*]quinolin-4-yl)methylene)nicotinohydrazide/isonicotinohydrazide (**5m-r**) respectively. The obtained hydrazones *i.e.* **5a-l** and **5m-r**, were then subjected to an oxidative cyclization using iodobenzenediacetate (IBD) in dichloromethane (DCM) by stirring at room temperature for 20 min to afford corresponding 1,3,4-oxadiazoles *i.e.* **6a-l**

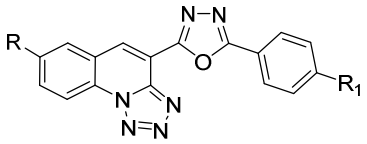
and **6m-r** respectively**.** The cyclization of the resultant schiff base derivatives *i.e.* **5a-l** and **5m-r** was carried out under different cyclizing reagents such as mercuric acetate, lead dioxide, chloramine-T, iodobenzenediacetate and aqueous sodium hydroxide with iodine in aqueous potassium iodide.



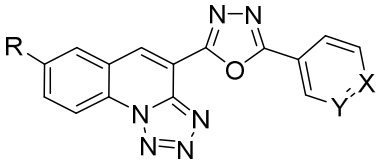
Scheme1. Synthesis of 7-substituted tetrazolo [1,5-*a*]quinoline incorporating 1,3,4-oxadiazole nucleus (**6a-r**).

The choice of substituents introduced in the synthesized compounds **6a-r** is based on the most influential aspect of lipophilicity as it determines solubility, reactivity and formulation of pharmaceuticals as well as metabolism of drugs.

Table 1. Preliminary characterization of all synthesized compounds **6a**-**r**.



6a-l



6m-r

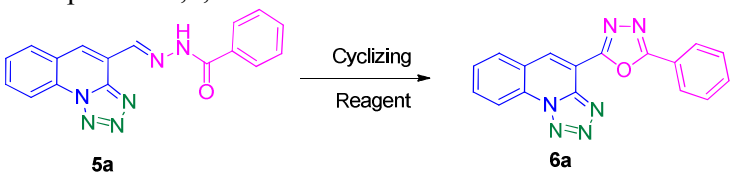
Comp.	R	R_1	Yield[a] (%)
6a	H	H	93
6b	H	CH_3	73
6c	H	OCH_3	81
6d	H	Cl	80
6e	H	Br	86
6f	CH_3	H	83
6g	CH_3	CH_3	79
6h	CH_3	OCH_3	74
6i	CH_3	Cl	89
6j	OCH_3	H	76
6k	OCH_3	CH_3	84
6l	OCH_3	OCH_3	80

Comp.	R	X	Y	Yield[a] (%)
6m	H	N	CH	84
6n	H	CH	N	77
6o	CH_3	N	CH	86
6p	CH_3	CH	N	81
6q	OCH_3	N	CH	85
6r	OCH_3	CH	N	83

[a] Isolated yield

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, mass spectrometry and elemental analysis. The IR spectrum of all the synthesized compounds showed absorption in the range of 1620–1638 cm^{-1} due to C=N stretching. The characteristic C–H stretching of aromatic ring was observed at around 3051–3067 cm^{-1}. Strong absorption bands were observed in the range of 1589–1598 cm^{-1} and 1361–1373 cm^{-1} due to the presence of the C=C stretching as well as CH_3 group respectively. In the ^{1}H NMR spectra of the resultant compounds, the aromatic protons of quinoline and benzene resonate as multiplet around δ 7.45–9.31 ppm. The methyl and methoxy protons of the quinoline and benzene ring appeared near to δ 2.33 ppm and δ 3.91 ppm respectively. ^{13}C NMR spectra of the 1,3,4-oxadiazole ring, C-2 carbon was displayed as a very downfield signal at δ 164.1–165.9 ppm for the reason that it was shrink between one oxygen atom and one nitrogen atoms. The mass spectra of all the compounds showed molecular ion peaks at M+ corresponding to their molecular weights, which confirmed the respective chemical structures.

Scheme 2. Screening of catalysts to optimize reaction condition for the synthesis of tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole **6a**.



5a **6a**

Table 2. The influence of different cyclizing reagents on the model reaction under different conditions

Entry[a]	Catalyst	Solvent	Time[b] (min.)	Yield[c] (%)
1	Conc. H_2SO_4	Acetic acid	50	Trace
2	Chloramine-T	DCM	50	40
3	$Hg(OAc)_2$	Methanol	40	45
4	$Hg(OAc)_2$	DCM	35	50
5	**IBD**	**DCM**	**20**	**93**
6	IBD	Methanol	25	70
7	IBD	Ethanol	45	57
8	Aq. NaOH	Methanol	35	47
9	Aq. NaOH	DCM	40	55
10	Aq. NaOH	Ethanol	43	51

[a] Reaction of schiff base **5a** (1.0 mmol) in the presence of (1.0 mmol) catalyst.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

For the screening of different cyclizing reagents we selected a model reaction between (*E*)-N'-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)benzohydrazide **5a** and different cyclizing reagents (**Scheme 2**). After cyclization, the corresponding benzohydrazide derivatives get converted into the resultant product *i.e.* 7-substituted tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole **6a-r**. The results are summarized in **Table 2**.

2.2. Optimization of synthetic protocol

2.2.1. Screening of catalysts to optimize the reaction conditions for 7-substituted tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole 6a-r.

We began our examination with variously substituted schiff base derivatives. Various schiff base derivatives *i.e.* (*E*)-4-substituted-N'-((7-substitutedtetrazolo [1,5-*a*]quinolin-4-yl) methylene)benzohydrazide (**5a-l**) and (*E*)-N'-((7-substitutedtetrazolo[1,5-*a*]quinolin-4-yl)methylene)nicotinohydrazide/isonicotinohydrazide (**5m-r**) were obtained by the mixing equimolar amounts of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde with the corresponding substituted benzohydrazide / nicotinohydrazide / isonicotinohydrazide in a good to excellent yield in the presence of glacial acetic acid as the catalyst and methanol as a solvent media over a time duration of 0.5-1.0 hr.

To optimize the reaction conditions, a series of experiments were performed with the model reaction of (*E*)-N'-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)benzohydrazide (1.0 mmol) **5a** and different cyclizing reagents (1.0 mmol) (**Scheme 2**) in the various reaction media.

In order to search for the best solvent, the model reaction was performed in three different solvents such as acetic acid, ethanol, methanol and dichloromethane (DCM) for the

synthesis of **6a**. The results are summarized in **Table 2**. For optimization of the reaction conditions, initially the reaction in acetic acid in the presence of concentrated H_2SO_4 as the catalyst afforded the desired product **6a** in a very trace amount (Table 2, entry 1). After further investigation of various catalysts, IBD was found to be more effective than other catalysts such as chloramine-T, mercuric acetate, Aq. NaOH. IBD showed advantages in the DCM reaction media over the other solvents not only in influencing the reaction but also miscibility of iodobenzene diacetate (IBD) in it and easy separation of the targeted compound to yield **6a** (93%) (Table 2, entry 5).

Due to these results, IBD was selected as the cyclizing reagent for the synthesis of tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole, and thus the reaction was carried out in a single step by stirring different schiff bases **5a-r** in the presence of iodobenzenediacetate (IBD) at room temperature in DCM as a solvent to produce the desired 7-substituted tetrazolo [1,5-*a*]quinoline incorporated 1,3,4-oxadiazole (**6a-r**).

2.3. Pharmacology

2.3.1. *In vitro* antimicrobial activity

Table 3. *In vitro* antimicrobial activity (MIC, µg/mL) of compounds **6a-r**.

Compound	*Gram positive bacteria*			*Gram negative bacteria*			*Fungi*	
	S.P. MTCC	B.S. MTCC	C.T. MTCC	E.C. MTCC	S.T. MTCC	V.C. MTCC	C.A. MTCC	A.F. MTCC
	1936	441	449	443	98	3906	227	3008
6a	500	**200**	500	**100**	250	250	>1000	500
6b	**100**	500	**250**	200	500	200	1000	>1000
6c	**100**	**200**	500	250	**200**	200	1000	500
6d	**62.5**	500	1000	250	200	500	**250**	500
6e	500	**250**	500	**100**	250	1000	**500**	**100**
6f	500	500	500	250	**100**	**62.5**	1000	>1000
6g	**100**	**100**	500	500	200	500	1000	1000
6h	250	**200**	**100**	**100**	500	500	500	>1000
6i	200	**100**	**62.5**	500	**100**	**100**	**500**	**100**
6j	500	500	**250**	**100**	200	200	**1000**	1000
6k	**100**	1000	**100**	200	200	**100**	**250**	1000
6l	500	500	**250**	500	500	500	1000	**100**
6m	200	**100**	**100**	**62.5**	**100**	500	1000	1000
6n	500	**62.5**	500	**100**	**200**	500	**250**	1000
6o	**100**	1000	**62.5**	250	**100**	100	**500**	500
6p	500	**200**	500	500	**62.5**	100	1000	**100**
6q	**100**	**200**	**200**	**62.5**	**100**	1000	**250**	500
6r	**62.5**	1000	**100**	500	500	**100**	1000	500
A	100	250	250	100	100	100	n. t.[a]	n. t.
B	10	100	50	10	10	10	n. t.	n. t.
C	50	50	50	50	50	50	n. t.	n. t.
D	25	50	100	25	25	25	n. t.	n. t.
E	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	100	100
F	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	500	100

S.P.: *Streptococcus pneumoniae*, B.S.: *Bacillus subtilis*, C.T.: *Clostridium tetani*, E.C.: *Escherichia coli* S.T.: *Salmonella typhi*, V.C.: *Vibrio cholerae*, C.A.: *Candida albicans*, A.F.: *Aspergillus fumigatus*, MTCC: Microbial Type Culture Collection. A: Ampicillin, B:

Norfloxacin, C: Chloramphenicol, D: Ciprofloxacin, E: Nystatin, F: Griseofulvin, [a] n.t.: not tested.

The *in vitro* antimicrobial screening of targeted compounds **6a-r** at minimal inhibitory concentration (MIC) was carried out using the broth microdilution method according to the National Committee for Clinical Laboratory Standards (NCCLS)[XXXVIII, XXXIX]. The antibacterial activity was tested against three Gram positive (*Streptococcus pneumoniae* MTCC 1936, *Bacillus subtilis* MTCC 441 and *Clostridium tetani* MTCC 449) and three Gram negative (*Escherichia coli* MTCC 443, *Salmonella typhi* MTCC 98, and *Vibrio cholera* MTCC 3906) bacteria using ampicillin, ciprofloxacin, norfloxacin and chloramphenicol as the reference antibacterial drugs.

The antifungal activity was screened against two fungal species (*Candida albicans* MTCC 227 and *Aspergillus fumigatus* MTCC 3008) where nystatin and griseofulvin were used as the reference antifungal agents. The strains employed for the activity screening were obtained from the Institute of Microbial Technology, Chandigarh (MTCC – Micro Type Culture Collection). Mueller Hinton broth was used as the nutrient medium to grow and dilute the drug suspension for the test. The results of the antimicrobial screening are shown in **Table 3**.

Upon investigation of Antibacterial activity data (Table 3), revealed that all the compounds **6a-r** showed moderate to very good inhibitory activity. It has been observed that against *S. pneumonia*, compounds **6d** and **6r** were found to be more potent *i.e*. MIC, 62.5 µg/mL as compared to ampicillin *i.e*. 100 µg/mL. Compound **6n** was found to possess excellent potency i.e. 62.5 µg/mL as compared to ampicillin i.e. 250 µg/mL as well as norfloxacin i.e. 100 µg/mL.

Compounds **6g**, **6i** and **6m** were found to be more potent against *B. subtilis* i.e. 100 µg/mL as compared to ampicillin. Compounds **6a**, **6c**, **6h**, **6p** and **6q** were found to be more effective (MIC = 200 µg/mL) against *B. subtilis* as compared to ampicillin. Compound **6e** was found equipotent as that of ampicillin against *B. subtilis*. Against *S. pneumonia* compounds **6b**, **6c**, **6g**, **6k** and **6q** showed comparable activity to that of ampicillin. Against *C. tetani,* compounds **6i** and **6o** were found to be more potent *i.e*. MIC, 62.5 µg/mL as compared to ampicillin *i.e*. 100 µg/mL. Against *C. tetani*, compounds **6b**, **6j** and **6l** displayed same influence as that of ampicillin.

In case of gram negative bacteria, it has been observed that against *E. Coli*, compounds **6m** and **6q** were found to possess excellent potency *i.e*. MIC 62.5 µg/mL as compared to ampicillin *i.e*. 100 µg/mL and compound **6p** was found to be more potent *i.e*. MIC 62.5 µg/mL against *S. Typhi* as compared to ampicillin. Against *E. Coli*, compounds **6a**, **6e, 6h, 6j** and **6n** were equipotent to that of ampicillin *i.e*. MIC, 100 µg/mL. In case of *S. Typhi,* compounds **6f**, **6i, 6m, 6o** and **6q** were found to be equipotent to that of ampicillin *i.e*. 100 µg/mL. Against *V. Cholerae*, compound **6f** was found to have maximum potency i.e. 62.5 µg/mL as compared to ampicillin i.e. 100 µg/mL. Compounds **6i**, **6k** and **6r** were found equipotent to that of ampicillin i.e. 100 µg/mL. Remaining other compounds are moderate or less active against all gram positive and gram negative bacteria.

The result of antifungal study (Table 3) of the synthesized 1,3,4-Oxadiazole derivatives revealed that all the compounds have excellent activity against *A. Fumigates*. The antifungal screening data from Table **2** revealed that against *C. albicans*, compound **6d**, **6k**, **6n** and **6q** i.e. 250 µg/mL, were found to be foremost active as compared to griseofulvin. Also against *C. albicans* compounds **6e, 6h, 6i** and **6o** showed comparatively similar potency to that of griseofulvin. Compounds **6e, 6i**, **6l** and **6p** exhibited comparable potency i.e. 100 µg/mL against *A. fumigates*. From the above results, we concluded that compound **6q** exhibit very good potency to become new member of antimicrobial agent.

2.3.2. *In vitro* antimalarial activity

All the compounds (**6a-r**) were screened for their *in vitro* antimalarial activity against the *P. falciparum* strain using chloroquine and quinine as the reference compounds. All experiments were performed in duplicate and the results of the antimalarial screening are expressed as the drug concentration resulting in 50% inhibition (IC_{50}) of parasite growth and are listed in **Table 4**.

Table 4. *In vitro* antimalarial activity of compounds **6a-r.**

Compound	IC_{50} (µg/mL)	Compound	IC_{50} (µg/mL)
6a	**0.083**	6k	0.82
6b	**0.064**	6l	1.89
6c	1.55	**6m**	**0.082**
6d	**0.032**	6n	0.85
6e	0.41	6o	1.32
6f	0.78	**6p**	**0.034**
6g	1.53	**6q**	**0.073**
6h	**0.061**	6r	0.37
6i	0.58	**Chloroquine**	0.020
6j	0.51	**Quinine**	0.268

As shown in **Table 4**, the compounds **6a**, **6b**, **6d**, **6h**, **6m**, **6p** and **6q** were found to have IC_{50} in the range of 0.032-0.083 against *P. falciparum* strain. These compounds displayed superior activity against *P. falciparum* strain as compared to quinine IC_{50} 0.268. Moreover compounds **6d** and **6p** were found to possess moderate activity i.e. IC_{50} 0.032 and 0.034 respectively aligned with chloroquine. Remaining all other compounds were found to be less active against *P. falciparum* strain against chloroquine and quinine as the standard drugs.

2.3.3. *In vitro* antituberculosis activity

The encouraging results from the antibacterial activity screening provoked us to carry out preliminary screening of the title compounds for their *in vitro* antituberculosis activity.

Table 5. *In vitro* antituberculosis activity (% inhibition) of compounds **6a-r** against *M. tuberculosis* H37Rv (at concentration 250 and 100 µg/mL).

Compound	% Inhibition		Compound	% Inhibition	
	250 µg/mL	100 µg/mL		250 µg/mL	100 µg/mL
6a	65	31	6k	78	49
6b	79	54	6l	83	67
6c	35	12	**6m**	**94**	69
6d	**92**	79	**6n**	**84**	80
6e	64	43	6o	81	55
6f	48	23	6p	65	45
6g	53	29	**6q**	**98**	**96**
6h	**95**	**94**	6r	67	44
6i	87	81	**Rifampicin**	98	98
6j	71	51	**Isoniazid**	99	99

Primary screening of targeted compounds **6a-r** were performed at 250 µg/mL against the *Mycobacterium tuberculosis* H37Rv strain using Lowenstein–Jensen medium as described

by Rattan[XL, XLI].The acquired results are presented in Table 5 in the form of % inhibition. Rifampicin and isoniazid were used as the reference drugs. From these results the five compounds (**6d**, **6h**, **6m**, **6n** and **6q**) that exhibited the highest % inhibition were screened again to get their MIC values (**Table 5**).

Antituberculosis screening of all the newly synthesized compounds **6a-r** were conducted at two concentrations i.e. 250 µg/mL and 100 µg/mL against tuberculosis H37Rv strain. The bioassay results obtained for the efficacy of all the synthesized analogues against *Mycobacterium tuberculosis* H37Rv is listed in **Table 5**.

The outcome of the result revealed that, compounds **6d** and **6m** were found to possess excellent activity (i.e. 92% and 94% at 250 mg/mL) against *M. tuberculosis* H37Rv. At the commencement of this study in the preliminary screening, compound **6h** displayed better activity and showed 95% inhibition at 250 µg/mL concentration and 94% inhibition at 100 µg/mL concentration as well as compound **6q** showed better activity and showed 98% inhibition at 250 µg/mL concentration and 96% inhibition at 100 µg/mL concentration. While compounds **6i** and **6n** are moderately active against *M. tuberculosis* H37Rv. All other compounds showed poor inhibition of M. tuberculosis growth. From the above results, it can be concluded that, compound **6q** may become new potent member of antitubercular agents in future.

2.3.4. *In vitro* antioxidant activity

The antioxidant activity of the entire series was investigated by using ascorbic acid as the standard antioxidant compound and results are listed in Table 6. Ferric reducing antioxidant power (FRAP) was measured by a modified method[XLII]. The antioxidant potentials of the compounds were estimated as their power to reduce the TPTZ–Fe(III) complex to the TPTZ–Fe(II) complex. The absorbance of the intense blue coloured [Fe(II)–TPTZ] complex was measured at 593 nm.

Table 6. *In vitro* antioxidant activity of compounds **6a-r.**

Comp.	OD (593 nm)	FRAP value[a]	Comp.	OD (593 nm)	FRAP value[a]
6a	0.314	203.20	6k	1.163	259.73
6b	1.689	257.18	6l	1.103	220.24
6c	1.993	79.13	**6m**	**2.413**	**497.43**
6d	**2.503**	**493.50**	6n	1.701	344.82
6e	1.823	332.13	**6o**	**2.273**	**458.23**
6f	1.783	219.81	**6p**	**2.418**	**440.02**
6g	1.953	387.11	6q	1.288	355.68
6h	**2.487**	**495.12**	**6r**	**2.295**	**481.91**
6i	1.804	367.19	A.A.	2.501	
6j	1.273	362.38			

A.A. = ascorbic acid, concentration of compounds used = 200 mg/mL, concentration of standard (A.A.) = 176 mg/mL. [a]A.A. mmol per 100 g of the sample. FRAP = ferric reducing antioxidant power

The standard deviation value is shown in terms of ±SD (≤0.75). All the newly synthesized compounds are screened for their antioxidant activity in three sets (n = 3). The results are expressed as ascorbic equivalents (mmol per 100 g of the compound) in table 6.

Upon the antioxidant assay, synthesized compounds **6d**, **6h**, **6m**, **6o**, **6p** and **6r** gave ferric reducing antioxidant power (FRAP) value ranging from 440.02 to 497.43 mmol per 100 g of compounds. This indicates that these compounds are good antioxidants. Compound **6c** showed poor antioxidant power while the remaining other compounds showed moderate

antioxidant activity (Table 6).

2.4. Structure-activity relationship (SAR)

The structure–activity relationship study (Fig. 1) revealed that various substituents like electron donating and electron withdrawing groups in quinoline and benzene were diversely responsible for a broad range of antimicrobial, antituberculosis, antimalarial and antioxidant activities. In the benzene ring electron donating group like $–CH_3$ and $–OCH_3$ exhibited decrease in the antibacterial activities, whereas the similar group showed increased activity in case of antimalarial, antituberculosis as well as in antioxidant activities. Also compounds having electron withdrawing group in benzene ring showed excellent antibacterial activity against *S. Pneumoniae*. On the other side, quinoline ring containing $–CH_3$ showed very good antimalarial, antioxidant, antituberculosis activity as well as showed best antibacterial activity against all 3 gram positive bacteria. In 1,3,4-oxadiazole nucleus, the ring containing nitrogen at 3rd or 4th position showed excellent antimalarial, antitubercular, antifungal, antioxidant as well as antibacterial activities.

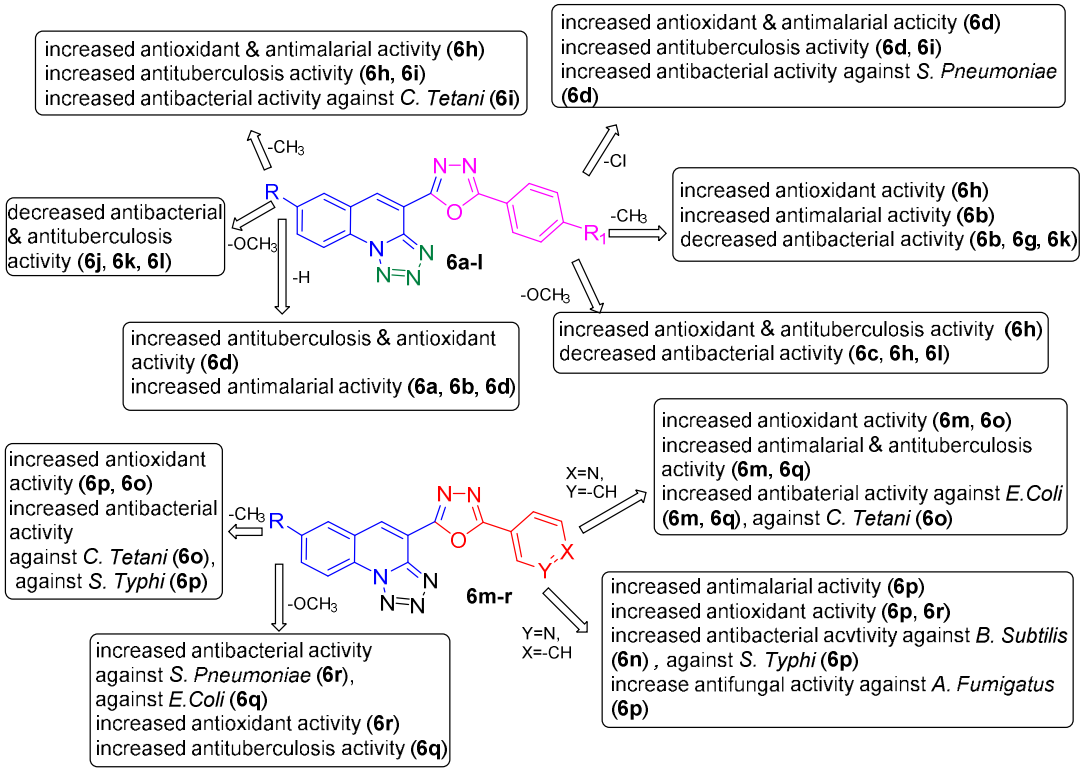


Fig.1. Structure–activity relationship for antimicrobial, antituberculosis, antimalarial and antioxidant activity of the synthesized compound **6a-r**.

3. Conclusion

This study presents the synthesis of 18 new quinoline – oxadiazole hybrids which showed some brilliant biological results. This work helps to corroborate the choice of the quinoline based 1,3,4-oxadiazole scaffold as a useful model for designing new antimicrobial, antitubercular, antimalarial and antioxidant agents. This synthetic approach allows the addition of potent bioactive nuclei in a single scaffold in an easy way. Two leading candidates (**6h** and **6q**) displayed modest antituberculosis activity. Some of the compounds showed brilliant antimalarial activity against *P. falciparum* strains as compared to quinine.

Compound **6q** has emerged as the most promising antimicrobial member of the series, showing better antitubercular, antimalarial as well antioxidant activities. The results indicated that oxadiazoles scaffold which is clubbed with the pyridine ring showed the highest antibacterial, antituberculosis and antimalarial activities.

4. Experimental section

4.1. Chemistry

All the chemicals were purchased from Sigma Aldrich, Spectrochem and Merck – India. Commercial grade solvents were used and were distilled before use. Melting points were determined using a melting point apparatus μThermoCal$_{10}$ (Analab Scientific Pvt. Ltd, India) and are uncorrected. The completion of the reactions was checked by thin-layer chromatography (TLC) on aluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness (Merck) and detection of the components was made by exposure to iodine vapours or UV light. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer Spectrum GX FT-IR 157 spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using the residual solvent signal as an internal standard at 400 MHz. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are in Hz. Mass spectra were recorded on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) at Sardar Patel University (PURSE programme of DST), Vallabh Vidyanagar. The elemental analysis was carried out by using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds were found to be within ±0.4% of the theoretical compositions.

4.2. General procedure for the synthesis of 7-substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (*3a-c*).

2-chloroquinoline-3-carbaldehyde **1** (1 mmol) and sodium azide **2** (2 mmol) in the presence of catalytic amount of acetic acid and ethanol (10 ml) were charged in a 100 mL round bottom flask equipped with a mechanical stirrer and a condenser. The reaction mixture was refluxed at 78 °C for 2-3 hr. The progress of the reaction was monitored by TLC. After the completion of reaction as confirmed by TLC, the separated crude product was filtered, washed thoroughly with ethanol, dried and recrystallized from chloroform to obtain a yellowish-white solid (**3a-c**).

4.3. General procedure for the synthesis of (*E*)-4-substituted-N'-((7-substitutedtetrazolo [1,5-*a*]quinolin-4-yl)methylene)benzohydrazide (*5a-l*).

A mixture of 7-substituted tetrazolo[1,5-a]quinoline-4-carbaldehyde *(3a-c)* (10 mmol), 4-substitutedbenzohydrazide **4a-e** (10 mmol) and catalytic amount of glacial acetic acid in methanol (40 mL) was refluxed for 1 h. After the completion of reaction, the reaction mixture was stirred magnetically for further 10-15 min. After cooling the separated solid mass was collected by filtration, washed well with ethanol (10 mL) dried, and crystallized from hot ethanol (10 mL) to affording compounds (**5a-l**).

4.4. General procedure for the synthesis of (*E*)-N'-((7-substitutedtetrazolo [1,5-a]quinolin-4-yl)methylene)nicotinohydrazide/isonicotinohydrazide (*5m-r*).

A mixture of 7-substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehyde *(3a-c)* (10 mmol), nicotinohydrazide (**4a'**) and/or isonicotinohydrazide (**4b'**) (10 mmol) and catalytic amount of glacial acetic acid in methanol (40 mL) was refluxed for 1 h. After the completion of

reaction, the reaction mixture was stirred magnetically for further 10-15 min. After cooling the separated solid mass was collected by filtration, washed well with ethanol (10 mL) dried, and crystallized from hot ethanol (10 mL) to affording compounds (**5m-r**).

4.5. General procedure for the synthesis of 2-(7-substitutedtetrazolo [1,5-a]quinolin-4-yl)-5-(p-substituted)-1,3,4-oxadiazole (*6a-l*).

A mixture of compound **5a-l** (10 mmol) was dissolved in DCM (20 ml) and continuously stirred. To this solution, $PhI(OAc)_2$ (10 mmol) was added and the mixture was stirred for 15-20 min at room temperature. After the completion of the reaction as monitored by TLC (ethyl acetate: hexane: 3:7), the solvent was evaporated and the residue was washed with diethyl ether, filtered (5 mL), dried and then crystallized from acetone to affording target compounds (**6a-l**).

4.5.1. 2-phenyl-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6a*)

White solid, Yield 93 %; m.p. 213-215 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1623 and 1592 (C=N and C=C); 3052 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57 -8.75 (m, 9H, Ar-H), 9.30 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.7, 126.9, 127.5, 128.4, 128.8, 128.9, 129.3, 130.1, 130.7, 132.9, 135.2, 146.0, 149.2, 164.1; ESI-MS (m/z): 314.31 (M+); Anal. Calcd (%) for $C_{17}H_{10}N_6O$: C, 64.96; H, 3.21; N, 26.74; Found: C, 64.93; H, 3.25; N, 26.77.

4.5.2. 2-(tetrazolo[1,5-*a*]quinolin-4-yl)-5-(p-tolyl)-1,3,4-oxadiazole (*6b*)

Yellowish solid, Yield 73 %; m.p. 207-209 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1622 and 1592 (C=N and C=C); 3053(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, $-CH_3$ of benzene ring), 7.51 -8.74 (m, 8H, Ar-H), 9.27 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.2, 116.7, 126.4, 127.1, 127.7, 128.6, 128.8, 130.3, 131.9, 136.0, 142.5, 146.4, 149.8, 165.6, 165.7; ESI-MS (m/z): 328.34 (M+); Anal. Calcd (%) for $C_{18}H_{12}N_6O$: C, 65.85; H, 3.68; N, 25.60; Found: C, 65.82; H, 3.66; N, 25.64.

4.5.3. 2-(4-methoxyphenyl)-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6c*)

White solid, Yield 81 %; m.p. 198-200 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1625 and 1598 (C=N and C=C); 3057(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H, $-OCH_3$ of benzene ring), 7.57 -8.74 (m, 8H, Ar-H), 9.26 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 54.2, 114.3, 115.5, 116.0, 126.8, 127.5, 128.7, 129.0, 129.8, 130.8, 135.6, 146.0, 149.8, 160.3, 165.2; ESI-MS (m/z): 344.33 (M+); Anal. Calcd (%) for $C_{18}H_{12}N_6O_2$: C, 62.79; H, 3.51; N, 24.41; Found: C, 62.77; H, 3.49; N, 24.43.

4.5.4. 2-(4-chlorophenyl)-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6d*)

Yellowish white solid, Yield 80 %; m.p. 196-198 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1638 and 1593 (C=N and C=C); 3055(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 -8.75 (m, 8H, Ar-H), 9.21 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.7, 124.6, 127.3, 128.5, 128.8, 128.9, 129.2, 130.1, 130.7, 134.3, 135.3, 145.8, 149.7, 164.9; ESI-MS (m/z): 348.75 (M+), 350.81 (M+2); Anal. Calcd (%) for $C_{17}H_9ClN_6O$: C, 58.55; H, 2.60; N, 24.10; Found: C, 58.53; H, 2.61; N, 24.14.

4.5.5. 2-(4-bromophenyl)-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6e*)

Yellow solid, Yield 86 %; m.p. 191-193 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1631 and 1598 (C=N and C=C); 3067(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52 -9.18 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.7, 123.3, 125.7, 126.9, 128.1, 128.5, 129.2, 129.8,

130.7, 132.7, 135.6, 145.4, 149.7, 165.9; ESI-MS (m/z): 393.20 (M+), 395.13 (M+2); Anal. Calcd (%) for $C_{17}H_9BrN_6O$: C, 51.93; H, 2.31; N, 21.37; Found: C, 51.91; H, 2.29; N, 21.33.

4.5.6. 2-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-5-phenyl-1,3,4-oxadiazole (*6f*)
White solid, Yield 83 %; m.p. 238-240 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1624 and 1590 (C=N and C=C); 3053(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, -CH_3 of quinoline ring), 7.55 -8.75 (m, 8H, Ar-H), 9.31 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.5, 126.9, 127.1, 128.4, 128.6, 129.5, 131.6, 130.9, 133.6, 134.7, 136.3, 141.8, 149.7, 164.8; ESI-MS (m/z): 328.34 (M+); Anal. Calcd (%) for $C_{18}H_{12}N_6O$: C, 65.85; H, 3.68; N, 25.60; Found: C, 65.83; H, 3.70; N, 25.64.

4.5.7. 2-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-5-(p-tolyl)-1,3,4-oxadiazole (*6g*)
White solid, Yield 79 %; m.p. 197-199 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1627 and 1592 (C=N and C=C); 3056(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, -CH_3 of quinoline ring), 2.67 (s, 3H, -CH_3 of benzene ring), 7.54 -8.64 (m, 7H, Ar-H), 9.19 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4, 21.9, 126.4, 127.5, 127.9, 128.6, 128.9, 130.2, 131.3, 131.9, 134.6, 136.8, 142.8, 144.1, 149.3, 164.9; ESI-MS (m/z): 342.36 (M+); Anal. Calcd (%) for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.55; Found: C, 66.63; H, 4.14; N, 24.53.

4.5.8. 2-(4-methoxyphenyl)-5-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6h*)
Yellowish white, Yield 74 %; m.p. 201-203 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1622 and 1594 (C=N and C=C); 3060(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, -CH_3 of quinoline ring), 3.92 (s, 3H, -OCH_3 of benzene ring), 7.53 -9.22 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.8, 55.9, 114.3, 115.8, 126.7, 128.5, 128.9, 129.4, 130.8, 131.8, 134.6, 136.8, 144.0, 148.6, 160.3, 165.5; ESI-MS (m/z): 358.36 (M+); Anal. Calcd (%) for $C_{19}H_{14}N_6O_2$: C, 63.68; H, 3.94; N, 23.45; Found: C, 63.66; H, 3.96; N, 23.48.

4.5.9. 2-(4-chlorophenyl)-5-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6i*)
White solid, Yield 89 %; m.p. 233-235 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1628 and 1593 (C=N and C=C); 3053(Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, -CH_3 of quinoline ring), 7.55 -9.23 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.7, 124.3, 126.9, 128.4, 128.7, 128.9, 129.8, 130.5, 131.7, 134.6, 135.1, 136.7, 143.8, 148.9, 165.7; ESI-MS (m/z): 362.78 (M+), 364.65 (M+2); Anal. Calcd (%) for $C_{18}H_{11}ClN_6O$: C, 59.59; H, 3.06; N, 23.17; Found: C, 59.60; H, 3.09; N, 23.16.

4.5.10. 2-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-5-phenyl-1,3,4-oxadiazole (*6j*)
White solid, Yield 76 %; m.p. 220-222 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1625 and 1591 (C=N and C=C); 3062 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.90 (s, 3H, -OCH_3 of quinoline ring), 7.56 -8.73 (m, 8H, Ar-H), 9.27 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.4, 103.9, 120.0, 127.5, 127.8, 129.2, 129.5, 130.9, 131.2, 133.6, 133.9, 141.7, 146.8, 157.1, 165.2; ESI-MS (m/z): 344.33 (M+); Anal. Calcd (%) for $C_{18}H_{12}N_6O_2$: C, 62.79; H, 3.51; N, 24.41; Found: C, 62.77; H, 3.49; N, 24.43.

4.5.11. 2-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-5-(p-tolyl)-1,3,4-oxadiazole (*6k*)
Yellowish white, Yield 84 %; m.p. 223-225 °C ; FTIR (KBr, ν_{max}, cm^{-1}): 1623 and 1591 (C=N and C=C); 3067 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, -CH_3 of benzene ring), 3.99 (s, 3H, -OCH_3 of quinoline ring), 7.52 -8.66 (m, 8H, Ar-H), 9.19 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.8, 55.7, 105.9, 122.8, 126.7, 127.6, 129.8,

130.8, 131.2, 131.9, 134.6, 141.5, 142.8, 147.2, 157.8, 164.9; ESI-MS (m/z): 358.36 (M+); Anal. Calcd (%) for $C_{19}H_{14}N_6O_2$: C, 63.68; H, 3.94; N, 23.45; Found: C, 63.71; H, 3.92; N, 23.46.

4.5.12. 2-(4-methoxyphenyl)-5-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6l*)

White solid, Yield 80 %; m.p. 208-210 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1625 and 1593 (C=N and C=C); 3052 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H, -OCH_3 of benzene ring), 3.98 (s, 3H, -OCH_3 of quinoline ring), 7.54 -9.23 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.6, 55.9, 105,8, 114.8, 115.3, 122.7, 129.1, 129.8, 130.7, 131.5, 134.6, 141.8, 147.3, 157.4, 160.7, 165.2; ESI-MS (m/z): 374.36 (M+); Anal. Calcd (%) for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.77; N, 22.45; Found: C, 60.99; H, 3.78; N, 22.43.

4.6. General procedure for the synthesis of 2-(7-substitutedtetrazolo [1,5-*a*]quinolin-4-yl)-5-(pyridin-3/4-yl)-1,3,4-oxadiazole (*6m-r*).

A mixture of compound **5m-r** (10 mmol) was dissolved in DCM (20 ml) and continuously stirred. To this solution, $PhI(OAc)_2$ (10 mmol) was added and the mixture was stirred for 15-20 min at room temperature. After the completion of the reaction as monitored by TLC (ethyl acetate: hexane: 5:5), the solvent was evaporated and the residue was washed with diethyl ether, filtered (5 mL), dried and then crystallized from acetone to affording target compounds (**6m-r**).

4.6.1. 2-(pyridin-4-yl)-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6m*)

Light yellow solid, Yield 84 %; m.p. 201-203 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1622 and 1590 (C=N and C=C); 3052 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 -8.83 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.7, 122.1, 124.3, 128.9, 130.6, 131.0, 132.6, 144.8, 147.7, 150.2, 164.1, 165.5; ESI-MS (m/z): 315.30 (M+); Anal. Calcd (%) for $C_{16}H_9N_7O$: C, 60.95; H, 2.88; N, 31.10; Found: C, 60.92; H, 2.87; N, 31.13.

4.6.2. 2-(pyridin-3-yl)-5-(tetrazolo[1,5-*a*]quinolin-4-yl)-1,3,4-oxadiazole (*6n*)

White solid, Yield 77 %; m.p. 215-217 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1634 and 1589 (C=N and C=C); 3051 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 -8.89 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.7, 122.1, 124.3, 128.9, 130.6, 131.0, 132.6, 144.8, 147.7, 150.2, 164.1, 165.5; ESI-MS (m/z): 315.30 (M+); Anal. Calcd (%) for $C_{16}H_9N_7O$: C, 60.95; H, 2.88; N, 31.10; Found: C, 60.93; H, 2.90; N, 31.14.

4.6.3. 2-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (*6o*)

Yellowish white, Yield 86 %; m.p. 200-202 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1632 and 1590 (C=N and C=C); 3053 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H, -CH_3 of quinoline ring), 7.77 -8.96 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.5, 121.1, 126.9, 127.9, 128.4, 130.7, 131.2, 134.4, 136.9, 143.2, 143.7, 148.6, 149.9, 164.8; ESI-MS (m/z): 329.32 (M+); Anal. Calcd (%) for $C_{17}H_{11}N_7O$: C, 62.00; H, 3.37; N, 29.77; Found: C, 62.04; H, 3.41; N, 29.75.

4.6.4. 2-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (*6p*)

White solid, Yield 81 %; m.p. 216-218 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1628 and 1592(C=N and C=C); 3055 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H, -CH_3 of quinoline ring), 7.75 -8.94 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.8, 124.0, 124.7, 126.8, 128.4, 128.9, 130.8, 131.6, 134.0, 134.8, 136.7, 144.1, 147.3, 148.8, 152.5, 165.6;

ESI-MS (m/z): 329.32 (M+); Anal. Calcd (%) for $C_{17}H_{11}N_7O$: C, 62.00; H, 3.37; N, 29.77; Found: C, 62.03; H, 3.39; N, 29.79.

4.6.5. 2-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (*6q*)
Yellow solid, Yield 85 %; m.p. 197-199 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1622 and 1592(C=N and C=C); 3056 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.90 (s, 3H, -OCH_3 of quinoline ring), 7.45 -8.48 (m, 7H, Ar-H), 8.76 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.7, 105.5, 121.8, 122.9, 130.1, 131.8, 134.6, 141.5, 143.8, 147.7, 150.0, 157.8, 164.9 ; ESI-MS (m/z): 345.32 (M+); Anal. Calcd (%) for $C_{17}H_{11}N_7O_2$: : C, 59.13; H, 3.21; N, 28.39; Found: C, 59.11 H, 3.19; N, 28.42.

4.6.6. 2-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (*6r*)
White solid, Yield 83 %; m.p. 220-222 °C; FTIR (KBr, ν_{max}, cm^{-1}): 1620 and 1592(C=N and C=C); 3053 (Ar, -CH str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H, -OCH_3 of quinoline ring), 7.48 -8.47 (m, 7H, Ar-H), 8.80 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.8, 105.9, 122.7, 124.0, 124.8, 129.7, 130.6, 131.3, 134.3, 134.8, 141.9, 147.7, 148.0, 152.8, 157.4, 164.8 ; ESI-MS (m/z): 345.32 (M+); Anal. Calcd (%) for $C_{17}H_{11}N_7O_2$: C, 59.13; H, 3.21; N, 28.39; Found: C, 59.15; H, 3.23; N, 28.37.

Acknowledgement
We sincerely express our thanks to Head, Department of Chemistry, Sardar Patel University, for providing necessary research facilities. We are also thankful to Dhanji P. Rajani, Microcare Laboratory, Surat for antimicrobial, antituberculosis and antimalarial screening of the compounds reported herein and Sophisticated Instrumentation Centre for Applied Research and Training (SICART), Vallabh Vidyanagar for FT-IR analysis at concessional rate. BKV is thankful to UGC meritorious fellowship and NHS specially thanks the UGC, New Delhi, India for providing financial assistance under the UGC-JRF Scheme and also for mass analysis at PURSE central facility at Sardar Patel university sponsored under PURSE program grant vide sanction letter DO. No. SR/59/Z-23/2010/43 dated 16th March 2011.

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Received on May 18, 2017.