Synthesis characterization and evaluation of Novel Heterocyclic Imidazole derivatives

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ABSTRACT

Some new 2-substituted aryl-4-fluoro phenyl-5-(2-Chloropyridinyl)-1H-imidazole derivatives have been synthesized by the reaction of 2-(2-chloropyridin-4-yl)-1-(4-fluorophenyl) ethanone [obtained by the reaction of ethyl -4- fluoro benzoate with 2-chloro-4-methylpyridine] with selenium dioxide in dioxane followed by cyclisation with substituted aryl(or hetero aryl)aldehyde in presence of acetic acid and ammonium acetate. All the synthesized compound were characterized by elemental analysis, ^{1}H NMR and LCMS and also screened for their in- vitro antimicrobial activity against two gram positive (Streptococcus pyogenes and Staphylococcus aureus) and two gram negative bacteria (Pseudomonas aeruginosa and Escherichia coli) along with antifungal and antimalarial activity.

Keywords: Imidazoles, antimicrobial and antimalarial activity.

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INTRODUCTION

Imidazole is a planar five-membered heterocyclic ring, highly polar and ionisable aromatic compound. The physiological and pharmacological significance of imidazole and its derivatives has interested many investigators since imidazole compounds were first discovered. This five-membered ring is a component of many important natural products, such as purine and nucleic acid [1-3].The imidazole scaffold is an important heterocyclic nucleus due to its wide spectrum of applications in the field of biology, chemistry as well as in pharmaceutical products. It is found in a large number of pharmacologically active compounds such as Omeprazole [4].Cimetidine and lansoprazole [5, 6]. The substituted imidazole derivatives have been reported to have a wide range of applications in diverse therapeutic areas including anti-inflammatory, antiviral, antibacterial, anti-allergic, and antitumor [7-10]. Imidazoles and their salts in particular comprise a boundless and emerging field. The polar imidazole ring, which contains two nitrogens separated with a methylene, hydrogen bonds through the amino hydrogen as the donor and the imino nitrogen as the acceptor [11]. The importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of new substituted imidazoles derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity.

MATERIALS AND METHODS

2.1 General Procedures:

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and mass of the synthesized compounds was checked. ^{1}H NMR spectral was recorded in CDCl3 /DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively.

2.2 Chemistry:

We have prepared the novel imidazoles in four steps. Using ester compound with active methyl group and formed ethanone. Oxidize with SeO_2 formed ethane-1, 2-dione.Cyclise with substituted aldehyde with intermediate ethane- 1, 2-dione and formed new imidazoles. The clear procedure for the preparation of desired imidazoles was given below.

3. Preparation of new substituted imidazoles

3.1.General procedure for the *Synthesis of ethyl -4- fluoro benzoate*

To the stirred solution of compound 4-fluorobenzoic acid (13 gm.1mmole) in T.H.F, (250 ml) .Added thionyl chloride solution (25 ml) at ^{0}C of reaction mass .Heated the reaction mass at 80 ^{0}C for 6 hr. Evaporated the reaction mass under reduced pressure under nitrogen atmosphere. Maintain 0^{0}C of residue and added ethanol (25 ml) and stirred at R.T. Progress of reaction mass was monitored through Thin layer chromatography (T.L.C). Reaction mass was evaporated under reduced pressure. Further this diluted with water and extracted with three times ethyl acetate (500 ml).Ethyl acetate layer was dried over anhydrous sod sulphate. Filtered and evaporated under reduced pressure. Product (Viscous liquid) 13.5 gm. (Yield: 86.5%) was obtained and characterized by its NMR spectroscopy.

^{1}HNMR: (400MHz, $CDCl_3$): δ 8.04-8.07 (m, 2H), 7.08-7.12 (m, 2H), 4.368 (q, *J* = 7.2 Hz, 2H), 1.399 (t, *J* = 7.2Hz,3H).

3.2.General procedure for the Synthesis of *2-(2-chloropyridin-4-yl)-1-(4-fluorophenyl) ethanone* –

To the stirred solution of compound 2-chloro-4-methylpyridine (6.5 gm, 50.95 m.mole) in 300 ml T.H.F and added Lithium hexamethyldisilazane (2.0 M) solution (38.2 ml,76.42 m.mole) in reaction mass under nitrogen atmosphere. Maintained 0 ^{0}C of reaction mass for 1 hr. Added synthesized compound of *ethyl -4- fluoro benzoate* (8.5 gm, 50.95 mmole) and stirred at R.T for 6 hr. Progress of reaction mass was monitored through thin layer chromatography (T.L.C). Reaction mass was diluted with saturated solution of ammonium chloride and extracted with three times ethyl acetate (300 ml).Total ethyl acetate layer was dried over anhydrous sod sulphate. Filtered and evaporated under reduced pressure. Product (Yellow solid) 9.7 gm. (Yield: 76.3%) was obtained and characterized by its NMR spectroscopy.

^{1}HNMR: (400MHz, $CDCl_3$): δ 8.357 (s, *J* = 5.2Hz, 1H), 8.00-8.04 (m, 2H), 7.12-7.26 (m, 4H), 4.26 (s, 2H).

3.3.General procedure for the Synthesis of *1-(2-chloropyridin-4-yl)-2-(4-fluorophenyl) ethane -1, 2-dione* –

To the stirred solution of synthesized compound 2-(2-chloropyridin-4-yl)-1-(4-fluorophenyl) ethanone (9.7 gm, 38.85 m.mole) in 15 dioxane solution, 150 ml and added selenium di oxide (9.4 gm, 93.24 m,mole) at 0 ^{0}C of reaction mass. Refluxed the reaction mass for 5 hr. Progress of reaction mass was monitored through thin layer chromatography (T.L.C). Reaction mass was filtered through celite bed. Filtrated solution diluted with water and extracted with three times ethyl acetate (300 ml).Total ethyl acetate layer was dried over anhydrous sod sulphate. Filtered and evaporated under reduced

pressure. Product (Yellow solid) 9.5 gm. (Yield: 93.1%) was obtained and characterized by its NMR spectroscopy.
^{1}HNMR: (400MHz, $CDCl_3$): δ 8.645 (d, *J* = 5.2Hz, 1H), 8.02-8.04 (m, 2H), 7.82 (s, 1H), 7.71-7.72 (m, 1H), 7.21-7.26 (m, 2H).

***3.4.*General procedure for the Synthesis of substituted *imidazoles* derivative-**

To the stirred solution of synthesized compound 1-(2-chloropyridin-4-yl)-2-(4-fluorophenyl) ethane - 1, 2- dione (0.973 m.mole) in 5.0 ml acetic acid, added substituted aldehyde (0.97m,mole) at 0 ^{0}C of reaction mass. Furthur this added ammonium acetate (2.91 m.mole). Refluxed the reaction mass for 5 hr. Progress of reaction mass was monitored through thin later chromatography (T.L.C). Reaction mass was diluted with water and basify with saturated solution of sod bicarbonate and maintain the pH about 8.0. Extracted the aquous layer with three times ethyl acetate (30 ml).Total ethyl acetate layer was dried over anhydrous sod sulphate. Filtered and evaporated under reduced pressure. Crude compound was obtained and purify by using column silica and characterized by its NMR spectroscopy and by mass spectroscopy... Same procedure was followed for the compound H1 (a), H1 (b), H1(c) H1 (j).

Spectral data of Imidazoles :

2 -Chloro-4-(2-(2, 6-difluorophenyl)-4-(4-fluorophenyl)-1H imidazol-5-yl) pyridine. H1 (a)

^{1}HNMR: (400MHz, DMSO-d6): δ 13.25 (bs, 1H), 8.33 (d, *J* = 5.2Hz, 1H), 7.56-7.65 (m, 4H), 7.23-7.40 (m, 5H). LCMS: 386.05 (M^+), 388.03 (M+2). Purity: 95.84 %, Anal. cacld. For $C_{20}H_{11}C_lF_3N_3$: C, 62.27; H, 2.87; N, 10.89.

2- Chloro-4-(4-(4-fluorophenyl)-2-phenyl-1H-imidazol-5-yl) pyridine. H1 (b) –

^{1}HNMR: (400MHz, DMSO-d6): δ 13.10 (bs, 1H), 8.28 (s, 1H), 8.08 (d, *J* = 7.2Hz, 2H), 7.58-7.61 (m, 3H), 7.48-
7.52 (m, 2H), 7.40-7.44 (m, 4H).LCMS; 350.04 (M^+), 352.02 (M+2).Purity; 99.97%, Anal. cacld. For $C_{20}H_{13}C_lFN_3$:
C, 68.67; H, 3.75; N, 12.01.

2 -Chloro-4-(2-(2, 4, 6-trifluorophenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl) pyridine. H1 (c) –

^{1}HNMR: (400MHz, DMSO-d6): δ 13.26 (bs, 1H), 8.28 (d, *J* = 5.2Hz, 1H), 7.55-7.60 (m, 2H), 7.23-7.47(m, 6H).LCMS; 404.3(M^+), 406.2(M+2).Purity; 98.3%Anal. cacld. For $C_{20}H_{10}C_lF_4N_3$: C, 59.49; H, 2.50; N, 10.41.

4 - (5-(2-Chloropyridin-4-yl)-4-(4-fluorophenyl)-1H-imidazol-2-yl) benzonitrile. H1 (d) –

^{1}HNMR: (400MHz, DMSO-d6): δ 13.24 (bs, 1H), 8.24-8.38 (m, 3H), 7.98 (d, *J* = 8.0Hz, 2H), 7.58-7.65 (m, 3H),
7.39-7.44 (m, 3H).LCMS; 375.3 (M^+), Purity; 95.9% Anal. cacld. For $C_{21}H_{12}C_lFN_4$: C, 67.30; H, 3.23; N, 14.95.

2 -Chloro-4-(4-(4-fluorophenyl)-2-(thiophen-3-yl)-1H-imidazol-5-yl) pyridine. H1 (e) –

^{1}HNMR: (400MHz, DMSO-d6): δ 12.93 (bs, 1H), 8.30 (d, *J* = 5.2Hz, 1H), 8.07-8.11 (m, 1H), 7.62-7.69 (m, 2H),
7.55-7.61 (m, 3H), 7.25-7.40 (m, 3H).LCMS; 355.98 (M^+), Purity: 99.5% Anal. cacld. For $C_{18}H_{11}C_lFN_3S$: C, 60.76;
H, 3.12; N, 11.81.

2- Chloro-4-(4-(4-fluorophenyl)-2-(4-methoxyphenyl) - 1H-imidazol-5-yl) pyridine. H1 (f) –

^{1}HNMR: (400MHz, DMSO-d6): δ 12.90 (bs, 1H), 8.27 (s, 1H), 8.01 (d, *J* = 8.8Hz, 2H), 7.57-7.60 (m, 3H), 7.38-
7.39 (m, 3H), 7.06 (d, *J* = 8.4Hz, 2H).3.82 (s, 3H).LCMS; 380.04(M^+), 382.03(M+2).Purity;98.1%Anal. cacld.

For $C_{21}H_{15}C_lFN_3O$: C, 66.41; H, 3.98; N, 11.06.

4- (2-(2, 4-bis (trifluoromethyl) phenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl)-2 chloropyridine. H1 (g) –
^{1}HNMR: (400MHz, DMSO-d6): δ 13.35 (bs, 1H), 8.12-8.39 (m, 4H), 7.63 (d, *J* = 5.2Hz, 2H), 7.53 (s, 1H), 7.22-
7.43 (m, 3H).LCMS; 486.24(M^+), 488.23(M+2).Purity; 99.89%Anal. cacld. For $C_{22}H_{11}C_lF_7N_3$: C, 54.39; H, 2.28; N,
8.65

2- Chloro-4-(2-(2-fluoro-5-(trifluoromethyl) phenyl)-4-(4 fluorophenyl)-1H-imidazol-5-yl) pyridine. H1 (h) –
^{1}HNMR: (400MHz, DMSO-d6): δ 13.15 (bs, 1H), 8.38 (d, *J* = 5.6Hz, 1H), 8.28-8.31 (m, 1H), 7.89 (s, 1H), 7.55-
7.68 (m, 4H), 7.23-7.42 (m, 3H).LCMS; 435.99 (M^+).Purity; 99.89% Anal. cacld. For $C_{21}H_{11}C_lF_5N_3$: C, 57.88; H,
2.54; N, 9.64.

2- Chloro-4-(2-(2, 4-difluorophenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl) pyridine. H1 (i) –
^{1}HNMR: (400MHz, DMSO-d6): δ 12.95 (bs, 1H), 8.28 (s, 1H), 8.01-8.07 (m, 1H), 7.54-7.59 (m, 3H), 7.51 (m, 1H),
7.38-7.39 (m, 3H), 7.25-7.29 (m, 1H).LCMS; 386.15(M^+), 388.14 (M+2) Purity; 98.45%.Anal. cacld. For $C_{20}H_{11}C_lF_3N_3$: C, 62.27; H, 2.87; N, 10.89.

2-Chloro-4-(2-(2-fluoro-4-(tri fluoro methyl) phenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl) pyridine H1 (j) –
^{1}HNMR: (400MHz, DMSO-d6): δ 13.15 (bs, 1H), 8.25-8.38 (m, 2H), 7.91 (d, *J*= 10.4Hz, 1H), 7.75 (d, *J* = 7.6Hz,
1H), 7.55-7.63 (m, 3H), 7.23-7.42 (m, 3H).LCMS; 436.3 (M^+), Purity; 98.3%Anal. cacld. For $C_{21}H_{11}C_lF_5N_3$: C, 57.88; H, 2.54; N, 9.64.

5-Antimicrobial studies-

5.1- Antibacterial and antifungal studies-

Antibacterial and antifungal activity of newly synthesized compounds H1 (a), H1 (b), H1(c) H1 (j) were determined by 'Broth Dilution Method'. Main advantage of the 'Broth Dilution Method 'for MIC determination lies in the fact that it can readily be converted to determine the MIC as well. All the synthesized compounds were tested against two gram positive bacteria (Staphylococcus aureus, Streptococcus Pyogenes) and two gram negative bacteria (Escherichia coli, Pseudomonas aeruginosa)

1. Serial dilutions were prepared in primary and secondary screening.
2. The control tube containing no antibiotic is immediately sub cultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight. The tubes are then incubated overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.
4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
5. The amount of growth from the control tube before incubation [which represents the original inoculum] is compared. [12-16].

6- Antimalarial studies-

All the synthesized compounds were screened for antimalarial activity in the Microcare laboratory & TRC, Surat, Gujarat. In vitro antimalarial assay was carried out in 96 well mi crol i t e r p l a t e s according

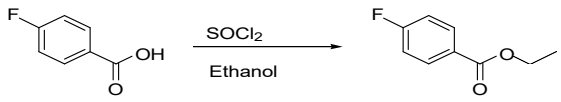
to the micro assay protocol of Rieckmann and co-workers with minor modifications. The culture of P.Falciparum strain medium RPMI1640 supplemented with 25 mm HEPES. 1% D-glucose,0.23%sodium bicarbonate and 10% heat 1% inactivated human serum. The asynchronous parasites of P. falciparum were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µ l of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformally maintained with 50% RBCs (O^+). A stock solution of 5mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µ l volume were added to the test wells so as to obtain final concentrations (at fivef old dilutions) ranging between 0.4 µ g/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37^{o}C in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Chloroquine was used as the reference drug. [17-22].

RESULTS AND DISCUSSION

7.1. **Chemistry**

In this present investigation a novel series of substituted Imidazoles compounds were synthesized as per Schemes (1– 2). Scheme 1 illustrates the pathway used for the synthesis of *Ethyl -4- fluoro benzoate* which was used as an intermediate in scheme 2. Scheme 2 illustrates the pathway used for the synthesis of *2-(2-chloropyridin-4-yl)-1-(4- fluorophenyl) ethanone,* Synthesis of *1-(2-chloropyridin-4-yl)-2-(4-fluorophenyl) ethane -1, 2- dione* and synthesis of novel active imidazoles derivatives.

SCHEME:1-*Synthesisofethyl-4-fluorobenzoate*



(1)

SCHEME:2-*SynthesisofnovelImidazolederivatives*

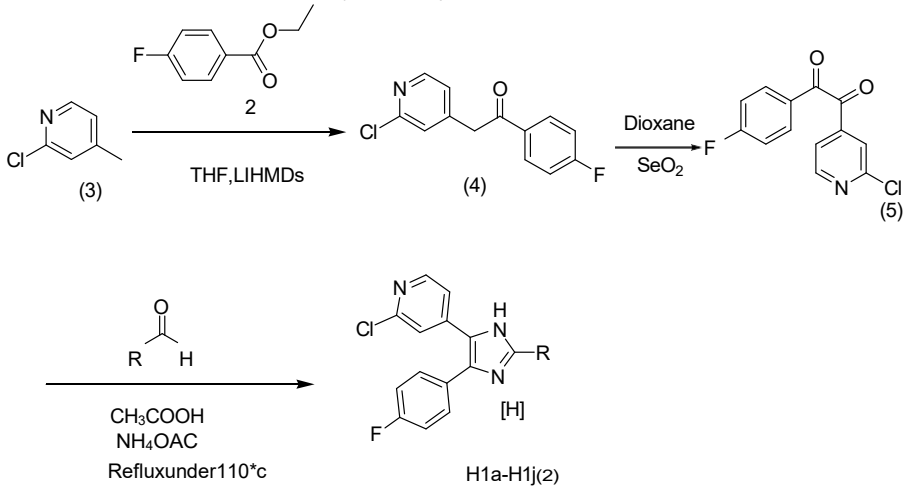


Table-1 List of synthesized compound

Compound	R	M.P	Yield
H 1(a)	2,6-difluoro phenyl	(**228–229 0^0C)**	**85.2%**
H1(b)	Phenyl	**(295–296 0^0C)**	**85.9%**
H1(c)	2,4,6-trifluoro phenyl	**(238–239 0^0C)**	**87.1%**
H1(d)	4-Cyano phenyl	(**225–226 0^0C)**	**83.1%**
H1(e)	3-Thiophene	(**283–284 0^0C)**	**87.5%**
H1(f)	4-methoxy phenyl	(**240–241 0^0C)**	**80.5%**
H1(g)	2,4-Bis(trifluoro methyl)phenyl	(**239–240 0^0C)**	**82.9%**
H1(h)	2-F,5-CF3 phenyl	(**239–240 0^0C)**	**82.9%**
H1(i)	2,4-difluoro phenyl	(**213–214 0^0C)**	**82.2%**
H1(j)	2-F,4-CF3 phenyl	**(241 -242 0^0C)**	**83.3%**

Antibacterial activity (In Minimum inhibitory concentration)

The antibacterial activity of all the synthesized compounds were tested in-vitro against pathogenic *E. coli* MTCC 443**,** *P.aeruginosa* MTCC 1688*, S.aureus* MTCC96 and *S.pyogenus* MTCC 442 and the results were compared with standard drugs (Ampicillin and Chloramphenicol). In case of *S.aureus* MTCC96 compounds H1(e), H 1(a), H1(c)and H1(h), exhibit good activity while H1(b), H1(d), H1(i) and H1(j) show moderate activity. In case of *S.pyogenus* MTCC 442 compounds H1(c) exhibit higher activity while H 1(a), H1 (e), H1 (h) and H1 (j) shows moderate activity. In case of E. coli MTCC 443 Compound H 1(a), H1 (b), H1 (f) and H1 (i)) shows higher activity and H1 (e), H1 (g) and H1 (j) shows moderate activity while rest of the compounds possess less activity. In case of *P.aeruginosa* MTCC 1688 compounds H1 (b), H1 (g) and H1 (h) and shows good activity while H1 (f), H1 (i) and H1 (j) shows moderate activity while rest of the compounds possess less activity. The results are given in **Table-2**

Compound	*E.COLI MTCC 443*	*P.AERUGINOSA MTCC 1688*	*S.AUREUS MTCC96*	*S.PYOGENUS MTCC 442*
H 1(a)	200	200	100	200
H1(b)	200	100	250	500
H1(c)	500	250	100	125
H1(d)	500	500	250	250
H1(e)	250	500	62.5	200
H1(f)	200	125	200	500
H1(g)	250	100	200	250
H1(h)	250	100	125	200
H1(i)	200	250	200	250
H1(j)	250	250	250	200
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50

Antifungal activity:

The antifungal activity of all the synthesized compounds were tested in-vitro against fungi *C.Albicans, A,Niger* and *A.Clavatus* and the results were compared with standard drugs (Nystatin and Greseofulvin. The results are given in Table-3.

Compound	*C.Albicans MTCC 1323*	*A.Niger MTCC 227*	*A.Clavatus MTCC 282*
H 1(a)	1000	500	1000
H1(b)	500	250	500
H1(c)	>1000	>1000	>1000
H1(d)	1000	500	500
H1(e)	1000	>1000	>1000
H1(f)	500	500	500
H1(g)	500	500	1000
H1(h)	1000	1000	1000
H1(i)	1000	1000	1000
H1(j)	1000	1000	>1000
Nystatin	100	100	100
Greseofulvin	500	100	100

Antimalarial activity:

Similarly for antimalarial all the newly synthesized compounds were screened for antimalarial activity and the results were compared with standard drugs Quinine. The results are given in Table-4.

Compound	Mean IC50 (microgram/ml)
H 1(a)	0.54
H1(b)	0.56
H1(c)	0.64
H1(d)	0.94
H1(e)	1.23
H1(f)	1.98
H1(g)	1.05
H1(h)	1.22
H1(i)	1.89
H1(j)	1.13
Quinine	0.268

CONCLUSION

The series of novel substituted imidazole derivatives were synthesized in reasonably good yields. They were characterized by 1H NMR, Liquid chromatography mass spectrometry and elemental analyses. All the newly synthesized compounds were screened for antimicrobial activity. Among the screened samples compound **H1(e))** has showed good anti-bacterial activity at 62.5 microgram/mL concentrations against particular tested microbial strains S.AUREUS MTCC96 as compared to the standard drug. While H1(a) has showed excellent anti-bacterial activity at 100 microgram/mL concentrations against S.AUREUS MTCC96 and 200 microgram/mL concentrations against E.COLI MTCC 443, P.AERUGINOSA MTCC 1688 and S.PYOGENUS MTCC 442 as compared to the standard drug. For antifungal all the newly synthesized compounds were screened for antifungal activity. Among the screened samples compound H1 (b) has showed excellent antifungal activity against the fungus strains of C.ALBICANS MTCC 227, A.NIGER MTCC 282 and A.CLAVATUS MTCC 1323, H1(f) and H1(g) has showed good antifungal activity against the fungus strains of C. ALBICANS MTCC 227, A.NIGER MTCC 282 and A.CLAVATUS MTCC 1323. Similarly for antimalarial all the newly synthesized compounds were screened for antimalarial activity. Among the screened samples compound H1 (a) and H1 (b) showed good antimalarial activity against *Plasmodium falciparum.* While H1(c) and H1 (d) showed moderate antimalarial activity against *Plasmodium falciparum.*

REFERENCES

[1] Mąkosza M. Nucleophilic substitution in nitroarenes: a general corrected mechanism. ChemTexts. 2019;5:10.

[2] Neri JM, Cavalcanti LN, Araújo RM, Menezes FG. 2,3-Dichloroquinoxaline as a versatile building block for heteroaromatic nucleophilic substitution: A review of the last decade. Arab J Chem. 2020;13:721–39.

[3] Ammar YA, Al-Sehemi AG, El-Sharief AMS, El-Gaby MSA. Chemistry of 2,3-Dichloroquinoxalines. Phosphorus Sulfur Silicon Relat Elem. 2009;184:660–98.

[4] Shintre SA, Ramjugernath D, Islam MS, Mopuri R, Mocktar C, Koorbanally NA. Synthesis, in vitro antimicrobial, antioxidant, and antidiabetic activities of thiazolidine–quinoxaline derivatives with amino acid side chains. Med Chem Res. 2017;26:2141–51

[5] Ancizu S, Moreno E, Solano B, Villar R, Burguete A, Torres E, et al. New 3-methylquinoxaline-2-carboxamide 1,4-di-N-oxide derivatives as anti-Mycobacterium tuberculosis agents. Bioorg Med Chem. 2010;18:2713–9.

[6] Ragab A, Abusaif MS, Gohar NA, Aboul-Magd DS, Fayed EA, Ammar YA. Development of new spiro[1,3]dithiine-4,11′-indeno[1,2-b]quinoxaline derivatives as S. aureus Sortase A inhibitors and radiosterilization with molecular modeling simulation. Bioorg Chem. 2023;131:106307.

[7] Ali MM, Ismail MMF, El-Gaby MSA, Zahran MA, Ammar YA. Synthesis and antimicrobial

activities of some novel quinoxalinone derivatives. Molecules. 2000;5:864–73.
[8] Ammar YA, Ismail MMF, El-Gaby MSA, Zahran MA. Some reactions with quinoxaline-2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-d]pyrimidines and pyrrolo [3,4- b]quinoxalines as antimicrobial agents. Indian J Chem – Sect B Org Med Chem. 2002;41:1486–91.
[9] Sakata G, Makino K, Kurasawa Y. Regent progress in the quinoxaline chemistry. Synthes Biol Act Heterocy. 1988;27:2481–515.
[10] Chałupnik P, Szymańska E. Kainate receptor antagonists: Recent advances and therapeutic perspective. Int J Mol Sci. 2023;24:1908.
[11] Shen QK, Gong GH, Li G, Jin M, Cao LH, Quan ZS. Discovery and evaluation of novel synthetic 5-alkyl-4-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoxaline-1-carbox-amide derivatives as anti-inflammatory agents. J Enzyme Inhib Med Chem. 2020;35:85–95.
[12] Xia R, Guo T, Chen M, Su S, He J, Tang X, et al. Synthesis, antiviral and antibacterial activities and action mechanism of penta-1,4-dien-3-one oxime ether derivatives containing a quinoxaline moiety. New J Chem. 2019;43:16461–7.
[13] Ragab A, Elsisi DM, Abu Ali OA, Abusaif MS, Askar AA, Farag AA, et al. Design, synthesis of new novel quinoxalin-2(1H)-one derivatives incorporating hydrazone, hydrazine, and pyrazole moieties as antimicrobial potential with in-silico ADME and molecular docking simulation. Arab J Chem. 2022;15:103497.
[14] Bonilla-Ramírez L, Galiano S, Quiliano M, Aldana I, Pabón A. Primaquine–quinoxaline 1,4-di-N-oxide hybrids with action on the exo-erythrocytic forms of Plasmodium induce their effect by the production of reactive oxygen species. Malar J. 2019;18:201.
[15] Ammar YA, El-Gaby MSA, Zahran MA, Abdel-Salam AA. Some reactions with 6-benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-b]quinoxaline: synthesis of (1,2,4) triazolo[3',2':2,3]thiazolo[4,5-b] quinoxaline and (1,3,4)thiadiazino [5,6-b]quinoxaline derivatives. Phosphorus Sulfur Silicon Relat Elem. 2000;157:87–95.
[16] Ghorab MM, Alsaid MS, El-Gaby MSA, Elaasser MM, Nissan YM. Antimicrobial and anticancer activity of some novel fluorinated thiourea derivatives carrying sulfonamide moieties: Synthesis, biological evaluation and molecular docking. Chem Cent J. 2017;11
[17] Settypalli T, Chunduri VR, Maddineni AK, Begari N, Allagadda R, Kotha P, et al. Design, synthesis, in silico docking studies and biological evaluation of novel quinoxaline-hydrazide hydrazone-1,2,3-triazole hybrids as α-glucosidase inhibitors and antioxidants. New J Chem. 2019;43:15435–52.
[18] Alswah M, Ghiaty A, El-Morsy A, El-Gamal K. Synthesis and Biological Evaluation of Some [1,2,4]Triazolo[4,3-a]quinoxaline derivatives as novel anticonvulsant agents. ISRN Org Chem. 2013;2013:587054.
[19] Hui X, Desrivot J, Bories C, Loiseau PM, Franck X, Hocquemiller R, et al. Synthesis and antiprotozoal activity of some new synthetic substituted quinoxalines. Bioorg Med Chem Lett. 2006;16:815–20.
[20] Hugo WB, Stretton RG. Action of Quinacillin on Staphylococcus aureus. Nature. 1964;202:1217.
[21] Rohde BH, McLaughlin MA, Chiou LY. Existence and role of endogenous ocular melatonin. J Ocul Pharmacol. 1985;1:235–43.
[22] Escobar-Chávez JJ, Merino V, López-Cervantes M, Rodríguez-Cruz IM, Quintanar-Guerrero D, Ganem-Quintanar A. The use of iontophoresis in the administration of nicotine and new non-nicotine drugs through the skin for smoking cessation. Curr Drug Discov Technol. 2009;6:171–85.
[23] Ammar YA, Elhagali GAM, Abusaif MS, Selim MR, Zahran MA, Naser T, et al. Carboxamide appended quinoline moieties as potential anti-proliferative agents, apoptotic inducers and Pim-1 kinase inhibitors. Med Chem Res. 2021;30:1649–68. [24] Ajeet Mishra AK, Kumar A. Recent advances in development of sulfonamide derivatives and their pharmacological effects- a review. Am J Pharmacol Sci. 2015;3:18–24.
[25] Gao H, Yamasaki EF, Chan KK, Shen LL, Snapka RM. Chloroquinoxaline sulfonamide (NSC 339004) is a topoisomerase IIalpha/beta poison. Cancer Res. 2000;60:5937–40.