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DESIGN, SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL THIAZOLE AND QUINOLINE CONTAINING SCHIFF BASES AND EVALUATION OF THEIR *IN-VITRO* ANTI-INFLAMMATORY AND ANTIMICROBIAL ACTIVITY

Prashant K. Vibhute[a], Arvind K. Aghao[a], Satish B. Jadhav[b], Bhaskar S. Dawane[c]*

[a]Department of Chemistry, Balbhim Arts, Science & Commerce College, Beed, 431122, Maharashtra, India.
[b]R. B. Attal College, Georai,432127,Maharashtra, India
[c]School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded, 431605, Maharashtra, India.
Email Id: vibhutep16@gmail.com

ABSTRACT:
A novel and eco-friendly series of quinoline based Schiff bases **(6a-f)** in PEG-400hasbeensynthesized.Itcontainingtwo pharmacologically active nucleus i.e.8-hydroxyquinoline and 4-substituted phenylthiazole. The targeted compounds were obtained in good yield by reacting 2-amino-4-substitutedphenylthiazole**(5a-f)** with 8-hydroxyquinoline-2-carbaldehyde **(4)** which was obtained by oxidative product of 8-hydroxy-2-methyl quinoline **(3).**The molecular structures of the synthesized compounds were confirmed by physicochemical properties and spectral characteristics (IR, NMR, elemental analysis and Mass spectra). The synthesized compounds were screened for the*in-vitro* anti-inflammatory and antimicrobial activity.Thiazole quinoline Schiff base can be a promising molecule in developing area of antimicrobial agents for modern pharmacologists and chemists.

KEYWORDS:8-hydroxy-2-methyl quinoline, 8-hydroxyquinoline-2-carbaldehyde, 2-amino-4-phenylthiazole, Schiff bases, *in-vitro* anti-inflammatory, antimicrobial activity.

INTRODUCTION:

Nitrogen and sulphur containingheterocyclic compounds represent a common architectural device in the field of drugs and pharmaceuticals, which make them important synthetic targets and always drawn the attention of medicinal chemist over the last two decades[i-ii].Analysis of database reveals that 75% of the drugs approved by FAD containan unique small nitrogen containing heterocycles.Sulfur is the fifth most prevalent element in overall drugs[iii].The8-hydroxyquinoline and 4-phenylthiazole derivatives are the most extensively investigated heterocycles containing nitrogen, sulfur heteroatoms.

Quinoline derivatives is an important class of nitrogen heterocycles,present as an important scaffold in number of natural and synthetic compounds which exhibits antibacterial[iv], antifungal[v],antimycobacterial[vi],anticonvulsant[vii], anti-inflammatory[viii], antimalarial[ix-x],anticancer[xi-xii], anti-toxoplasmosis[xiii]activities (figure 1).

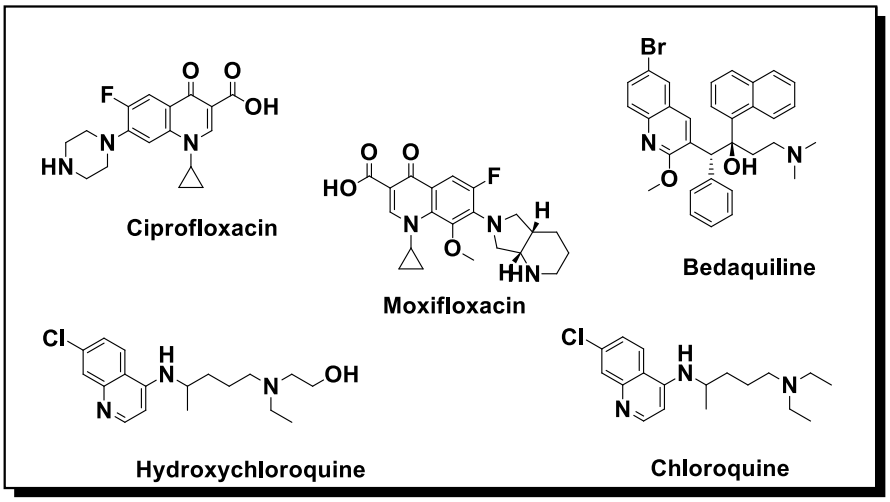


Fig. 1. Some Quinoline based important drugs

Theheterocyclethiazole or 1,3-thiazole nucleus is an anotherframework, which extraordinary impact on field of medicine. Therefore chemist and pharmacologist have great interest in synthetic and medicinal perspective[xiv], also owing to their wide range of biological properties such as anti-inflammatory[xv], antibacterial[xvi], antifungal[xvii], antitubercular[xviii] and antitumor[xix] activities etc (figure 2).

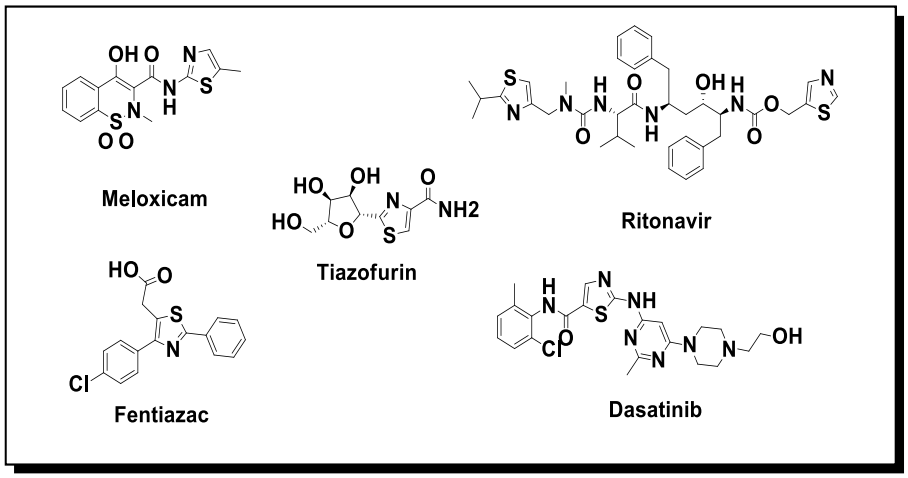


Fig. 2. Some of thiazole skeleton based pharmaceuticals

Quinoline based Schiff bases play an appreciated role in biological and pharmacological systems as well as a versatile tool in many other fields such as inorganic and analytical chemistry. They hold as anti-inflammatory[xx], antibacterial[xxi], antifungal[xxii], anticancer[xxiii], antitubercular[xxiv],diuretic activities[xxv], antiviral[xvi] and so on.

Investigation of literature reveals that when one pharmacological active nitrogen and sulphur containing heterocyclic system is coupled with other biodynamic heterocyclic molecule which enhances pharmacological activity[xxvii]. The chemistry of these linked biheterocycles is an attractive area of research in pharmacological studies, as they have been shown to have improved biological profiles[xxviii]. Literature survey reveals that not much work

has been carried outin the view ofmedicinal and pharmacological activity of fused8-hydroxy quinoline and 4-substituted phenylthiazolecompounds and in continuation of our work on heterocycles compound[xxix-xxx]. It has motivated us to develop newer platforms to synthesis and investigates *in-vitro* anti-inflammatory and antimicrobial activity of the compounds in which8-hydroxy quinoline moiety has been linked with 4-substituted phenylthiazole to afford novel series of Schiff base i.e. (E)-2-(((4-substitutedthiazol-2-yl)imino)methyl)quinolin-8-ol**(6a-f)**.

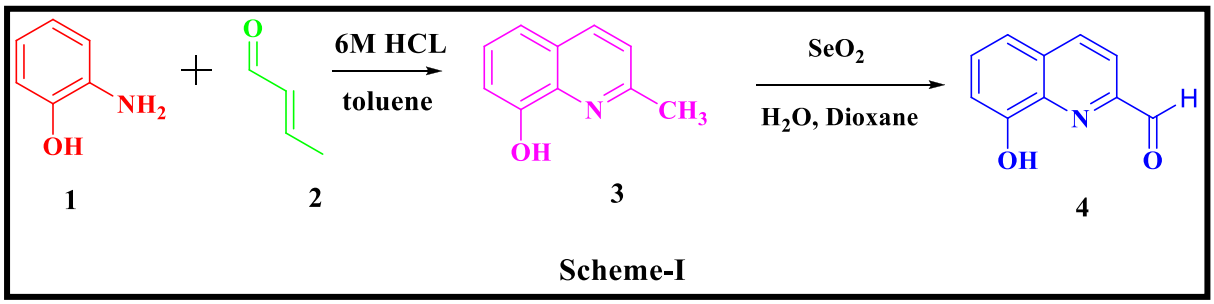
MATERIALS AND METHODS:

Experimental

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded using Perkin–Elmer spectrometer. ^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60F_{254} with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). Physical constants and analytical data of all the compounds reported in this paper.

General procedure for the synthesis of 8-hydroxyquinoline-2-carbaldehyde (4):

8-hydroxy-2-methyl quinoline (3) and 8-hydroxyquinoline-2-carbaldehyde (4) were synthesized according to the reported procedures C. M. Leir*et al.* and S. H. Chan *et al*. respectively(Scheme 1).



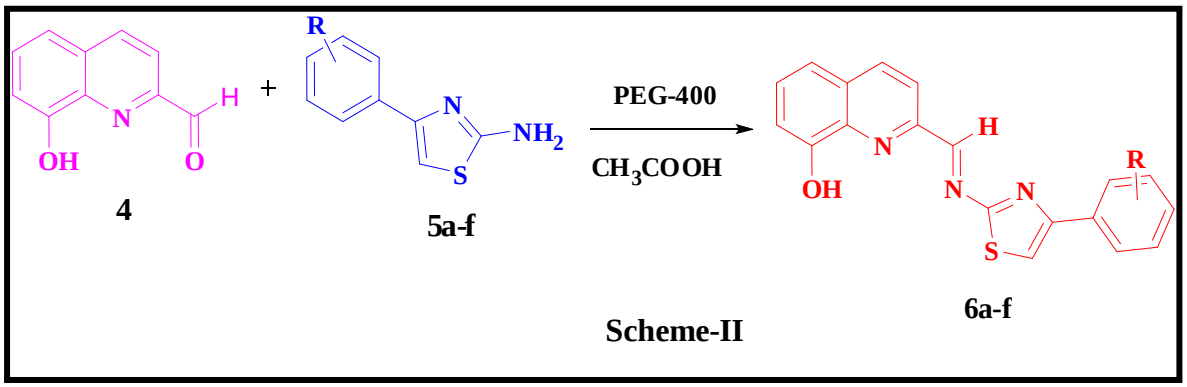
Scheme-I

General procedure for the synthesis of 2-amino-4-sustituted phenylthiazole[xxxi] (5a-f):

Substituted amino phenylthiazole was prepared by mixture of phenacyl bromide (0.01 mol), Thiourea (0.02 mol) was stirred in 5 mL PEG-400 at room temperature for 2-3 h. After completion of reaction (monitored by TLC) mixture was worked up in ice cold water. Product was separated out and PEG-400 was recovered by distillation from aqueous filtrate and reused.Recrystallization with ethanol gave crystal. Percentage yield and physical constants were recorded.

General procedure for the synthesis of Schiff base i.e. 2-(((4-substitutedphenylthiazol-2-yl)imino)methyl)quinolin-8-ol (6a-f):

A mixture of substituted 2-amino-4-phenylthaiazole (0.01 mol) **(5a-f)** and 8-hydroxyquinoline-2-carbaldehyde (0.01 mol) **(4)** was dissolved in PGE 400 (5 mL), catalytic amount of glacial acetic acid (0.5 mL) and refluxed for 2-3 h at 70-75^{0}C. The progress of reaction monitored by TLC. After completion, the reaction mixture was poured into ice water. The precipitate solid was filtered off, dried and recrystallized from ethanol. PGE 400 was recovered by simple distillation without affecting the product. Percentage yield and physical constants were recorded.



Scheme-II

RESULT AND DISCUSSION:

In the present investigation, some novel Schiff bases **6(a-f)** were synthesized which containing 8-hydroxyquinoline and 4-substituted phenylthiazole. The targeted compounds wassynthesized by reacting 8-hydroxyquinoline-2-carbaldehyde **(4)** with2-amino-4-substitutedphenylthiazole **(5a-f)** in PEG-400 in presence of 0.5 mL glacial acetic acid as a catalyst and refluxed in water bath.The entire synthesized compounds are qualitatively analyzed by running T.L.C. and melting point.

The molecular structures of the synthesized compounds were confirmed by physicochemical properties and spectral characteristics (IR, NMR, elemental analysis and Mass spectra).The characteristic IR band at 1635 $Cm^{-1}$for N=CH it indicates formation of Schiff base and the presence of a singlet peak at δ 8.62 ppm it confirms the target molecule is formed i.e. Schiff base**6(a-f)**.Similarly IR stretch at 725 cm^{-1} for C–S indicated the existence of thiazole nucleus within the target molecule which is confirmed from singlet peak at δ 6.62 ppm for thiazole ring.

Spectral data of compounds:

(6a) 2-(((4-phenylthiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 79%, M.P. 258^{0}C. Elemental analysis Cal. for $C_{19}H_{13}N_3OS$; C, 68.86; H, 3.95; N, 12.68; found: C, 68.76; H, 3.85; N, 12.58; IR (KBr pellets Cm^{-1}): 3435 cm-1(OH), 2808(Ar-CH stretch), 1598 (N=CH), 1038 (C-S): ^{1}H NMR (DMSO, 400 MHz);δ11.26, (1H, s, Ar-OH),8.62(s, 1H, N=CH), 8.50-7.90-(m, 5H, Ar-H), 7.80-7.03(m, 5H, Ar-H),6.62 (1H, s, thiazole);Mass (m/z): 331.08 (M+1).

(6b) 2-(((4-(4-chlorophenyl)thiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 82%, M.P. 268^{0}C. Elemental analysis Cal. for $C_{19}H_{12}ClN_3OS$; C, 62.38; H, 3.31; N, 11.49 found C, 62.30; H, 3.25; N, 11.45; IR (KBr pellets Cm^{-1}): 3439 cm-1(OH), 2970(Ar-CH stretch), 1634 (N=CH), 1038 (C-S): ^{1}H NMR (DMSO, 400 MHz); δ11.20 (1H, s, Ar-OH), 8.60 (s, 1H, N=CH), 8.55-7.88-(m, 5H, Ar-H), 7.79-7.00(m, 4H, Ar-H),6.60 (1H, s, thiazole); Mass (m/z): 365.04 (M+1).

(6c) 2-(((4-(4-bromophenyl)thiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 80%, M.P. 260^{0}C. Elemental analysis Cal. for $C_{19}H_{12}BrN_3OS$; C, 55.62; H, 2.95; N, 10.24; found C, 55.60; H, 2.90; N, 10.20;IR (KBr pellets Cm^{-1}): 3382 cm-1(OH), 3060(Ar-CH stretch), 1632 (N=CH), 1125 (C-S): ^{1}H NMR (DMSO, 400 MHz); δ 11.18 (1H, s, Ar-OH), 8.55 (s, 1H, N=CH), 8.50-7.90-(m, 5H, Ar-H), 7.80-7.35(m, 4H, Ar-H),6.50 (1H, s, thiazole); Mass (m/z): 310.29 (M+1).

(6d) 2-(((4-(4-flourophenyl)thiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 88%, M.P. 280^{0}C. Elemental analysis Cal. for $C_{19}H_{12}FN_3OS$; C, 65.32; H, 3.46; N, 12.03; found C, 65.30; H, 3.40; N, 12.00; IR (KBr pellets Cm^{-1}): 3382 cm-1(OH), 3075(Ar-CH stretch), 1640 (N=CH), 1130 (C-S): ^{1}H NMR (DMSO, 400 MHz); δ11.35 (1H, s, Ar-OH), 8.62 (s, 1H, N=CH), 8.51-7.85-(m, 5H, Ar-H), 7.80-7.20(m, 4H, Ar-H),6.62 (1H, s, thiazole); Mass (m/z): 349.38 (M+1).

(6e) 2-(((4-(p-tolyl)thiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 77%, M.P. 310^{0}C. Elemental analysis Cal. for $C_{20}H_{15}N_3OS$; C, 69.54; H, 4.38; N, 12.17; found C, 69.50; H, 4.35; N, 12.12; IR (KBr pellets Cm^{-1}): 3390 cm-1(OH), 3080(Ar-CH stretch), 1640 (N=CH), 1135 (C-S): ^{1}H NMR (DMSO, 400 MHz); δ 11.22 (1H, s, Ar-OH), 8.63 (s, 1H, N=CH), 8.50-7.87-(m, 5H, Ar-H), 7.75-7.10(m, 4H, Ar-H), 6.66 (1H, s, thiazole), 3.30 (s, 3H, -CH_3); Mass (m/z): 345.42 (M+1).

(6f) (((4-(4-methoxyphenyl)thiazol-2-yl)imino)methyl)quinolin-8-ol

Yield: 75%, M.P. 285^{0}C. Elemental analysis Cal. for $C_{20}H_{15}N_3O_2S$; C, 66.46; H, 4.18; N, 11.63; found C, 66.40; H, 4.15; N, 11.60;IR (KBr pellets Cm^{-1}): 3454 cm-1(OH), 3075(Ar-CH stretch), 1645 (N=CH), 1125 (C-S): ^{1}H NMR (DMSO, 400 MHz); δ 11.25 (1H, s, Ar-OH), 8.65 (s, 1H, N=CH), 8.52-7.90-(m, 5H, Ar-H), 7.85-7.08(m, 4H, Ar-H), 6.62 (1H, s, thiazole), 3.90(s, 3H, OCH_3).; Mass (m/z): 361.42 (M+1).

Biological activity:

In-vitro anti-inflammatory activity[xxxii-xxxiii]

The standard drug and synthesized compounds **6(a-f)** were dissolve in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentration of drugs was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at 27±1^{0}C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60±1 ^{0}C in water bath for 10 min. After cooling, the turbidity was measured at 660nm (UV-Visible Shimadzu Spectrophotometer). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The ibuprofen was used as standard drug. Results are tabulated in **Table no. 1**

$$\% \text{ of inhibition } = \left(\frac{Vt}{Vc} - 1 \right) X\ 100$$

Where, Vt = Mean absorbance value of test group.

Vc = Mean absorbance value of control group

TABLE 1 ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS**6a-f.**

Sr. No.	Compounds	Mean absorbance value ± SEM	Inhibition of denaturation (in %)
1	**Control**	0.0845	-
2	**Ibuprofen**	0.161 ± 0.007	90.53
3	**6a**	0.104 ± 0.003	23.07
4	**6b**	0.141 ± 0.002	66.86
5	**6c**	0.135 ± 0.002	59.76
6	**6d**	0.133 ± 0.006	57.39
7	**6e**	0.102 ± 0.002	20.71
8	**6f**	0.110 ± 0.003	30.17

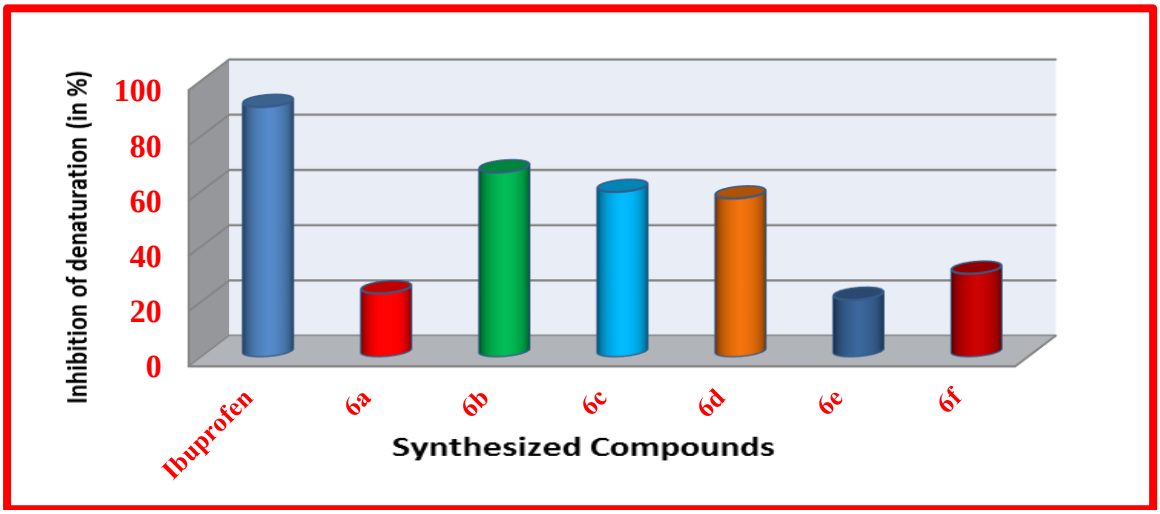


Fig. 1 Anti-inflammatory activity of the synthesized compounds

Antimicrobial activity

The newly synthesized Schiff bases i.e.(E)-2-(((4-substitutedthiazol-2-yl)imino) methyl)quinolin-8-ol derivatives **6(a-f)** were screened for their antibacterial activity against *E.coli, Salmonella typhi, Staphylococcusaureus* and *Bacillus subtilis* by disc diffusion method[xxxiv-xxxv] using penicillin as standard and antifungal activity against *Aspergillus niger, Aspergillus flavus,penicilliumchrysogenum, Fusariummoneliforme,* by poison plate method[xxxvi] using Griseofulvin as reference standard and DMSO as control solvent. From antibacterial screening results it indicates that some of the compounds shows significant antibacterial property and some of the compounds are moderately activity. The data of antifungal activity revealed that some novel Schiff bases of 8-hydroxyquinoline-2-carbaldehyde **(4)** and 2-amino-4-substituted phenylthiazole**(5a-h)** derivatives possess promising and some compounds show no antifungal activity. The results are shown in **Table 2 and 3** respectively.

TABLE 2-ANTIBACTERIAL SCREENING RESULTS OF THE COMPOUNDS**6a-f.**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		E. coli	***Salmonella typhi***	***Staphylococcus aureus***	***Bacillus subtilis***
1	**6a**	10	08	14	18
2	**6b**	17	18	22	24
3	**6c**	18	20	20	27
4	**6d**	15	17	18	20
5	**6e**	09	11	16	14
6	**6f**	11	13	14	17
7	**DMSO**	-ve	-ve	-ve	-ve
8	**Penicillin**	22	25	35	38
-ve no antibacterial activity					

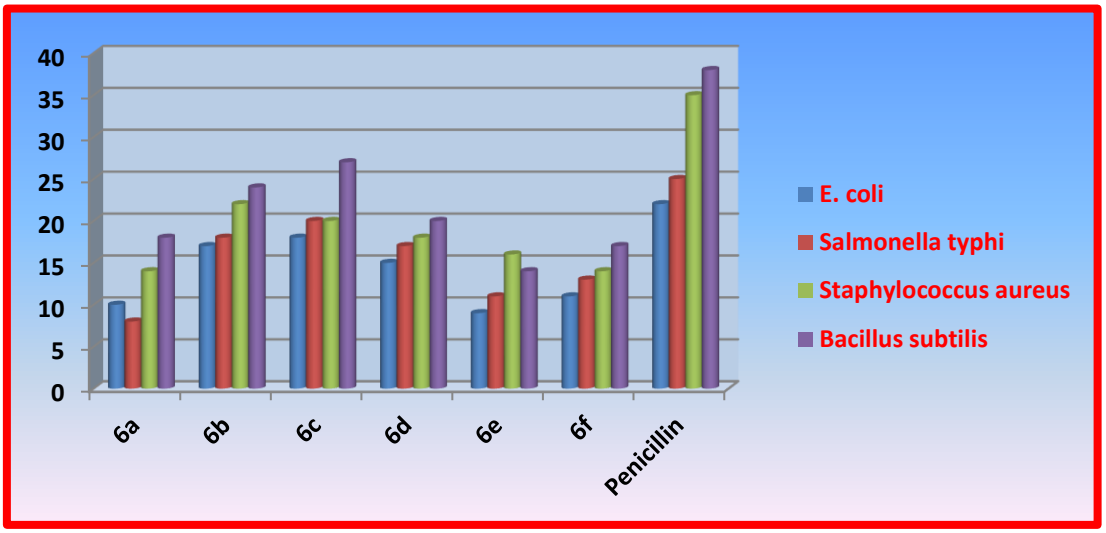


Fig-2 Flow Chart for Antibacterial Screening

TABLE 3-ANTIFUNGAL SCREENING RESULTS OF THE COMPOUNDS **6a-f.**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		Asp. Niger	***Asp. Flavus***	***Pen. chrysogenum***	***Fusarium Moneliforme***
1	**6a**	-ve	-ve	-ve	-ve
2	**6b**	-ve	-ve	-ve	-ve
3	**6c**	-ve	-ve	-ve	-ve
4	**6d**	-ve	-ve	-ve	-ve
5	**6e**	-ve	RG	+ve	+ve
6	**6f**	RG	-ve	-ve	RG
7	**DMSO**	+ve	+ve	+ve	+ve
8	**Griseofulvin**	-ve	-ve	-ve	-ve
-ve -No growth Antifungal activity present , +ve -Growth Antifungal activity absent RG -Reduced growth					

CONCLUSION:

In the present work, all of the synthesized compounds were subjected to *In-vitro* anti-inflammatory, antibacterial and antifungal activities. From *In-vitro* anti-inflammatory, antimicrobial results it can be conclude that tested compounds **6b, 6c and 6d** were possess promising to moderately activity. From the above results it suggest that Schiff bases of 8-hydroxyquinoline and 4-substituted phenylthiazole can be considered as a promising lead motif for modern pharmacologist and chemist who is working under this area for developing as good antimicrobial agents.

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