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Synthesis of New pyrazoline – phenoxazine Derivatives

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Abstract

Phenoxazine prepared by the reaction of o-aminophenol with Zinc chloride in the presence of phosphoric acid. This work comprises the synthesis of new phenoxazine derivatives containing heterocyclic moieties. These heterocyclic compounds were synthesized in three groups. The first group is made up of 3-(oxoalk-en-1-yl)phenoxazine derivatives (3a-3g) obtained from the reaction of 10-acetyl-phenoxazine with different aromatic aldehyde in the presence of sodium hydroxide. The other two groups involve compounds produced from the reaction of (3a-3g) with hydrazine hydrate in acetic acid to get 10-(pyrazolin-3-yl)phenoxazine derivatives (4a-4g) and hydroxyl amine hydrochloride in the presence of ethanosodium hydroxide to afford 10-(1-phenyl pyrazolin-3-yl)phenoxazine derivatives (5a-5g). All these compounds of two groups above are substituted in position (5) in pyrazoline ring with different aryl groups according to aromatic aldehyde used in the preparation of the first group.

Keywords: phenoxazine, oxoalken, pyrazolin.

تحضير مشتقات جديدة للبايرازولين فينوكسازين

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الخلاصة

تم تحضير الفينوكسازين من تفاعل اورثوامينوفينول مع كلوريد الزنك بوجود حامض الفسفوريك. تضمن البحث تحضير مشتقات جديدة من الفينوكسازين التي تحتوي على حلقات غير متجانسة. وقد صنفت جميع هذه المركبات المحضرة الى ثلاث مجاميع تحتوي كلا منها على سبعة مركبات. المجموعة الاولى هي مشتقات ل3-(اوكسي الكين-1-يل)فينوكسازين ل(3a-3g) والمحضرة من تفاعل 10-استيل فينوكسازين مع مختلف المركبات العطرية الالديهايدية وبوجود هيدروكسيد الصوديوم. اما مركبات المجموعتين الثانية والثالثة فقد تم تحضيرها عن طريق مفاعلة مركبات المجموعة الاولى (3a-3g) مع كل من الهيدرازين بوجود حامض الخليك للحصول على مشتقات 3-(1-اسيتيل بايرازولين-3-يل) للفينوكسازين (4a-4g)، ومع هيدروكسيل امين هيدروكلورايد بوجود ايثانوصوديوم هيدروكسايد لتعطي مشتقات 3-(1-فنيل بايرازولين-3-يل)فينوكسازين (5a-5g). جميع مركبات المجموعتين اعلاه معوضة في الموقع(5) في حلقة البايرازولين بمجاميع اريل وحسب المركبات العطرية الالدهايدية المستخدمة في تحضير مركبات المجموعة الاولى.

Introduction:

Hetrocyclic compounds are cyclic compounds in which the ring atom are carbon and some other element nitrogen, oxygen and sulfur are by far the most common but other atoms such as boron phosphours, or silicon compound also are members of hetrocyclic ring. Phenoxazine was made first by Bernthsen [1] in 1887, and though known for many years has not had a systematic study made of its chemistry. Oxazine dyes, which are derivatives of phenoxazine, are widely used as biological stains [2]. They have been studied for staining brain tumors and as tuberculostatic agent. In general in the

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reaction of phenoxazine related directly to these dyes [3,4]. Numbering of phenoxazine nucleus follows only two systems, (a) and (b): Figure-1.

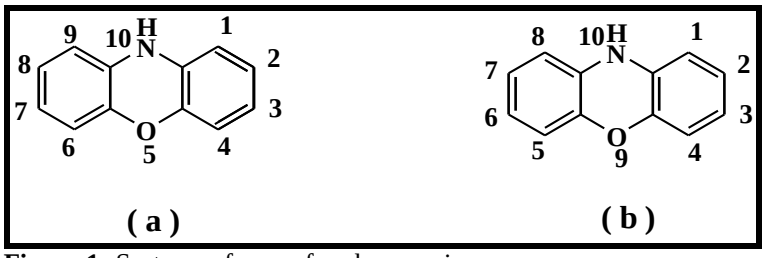


Figure 1- Systems of name for phenoxazine

The heterocyclic oxygen atom of the phenoxazine nucleus places certain restriction on the aromaticity of this ring system, which appears to be somewhat less aromatic than the phenothiazine system for instance. The aromatic model show that the phenoxazine nucleus is slightly folded along its short axis i.e., the axis passing through the two central hetero atoms [5]. The dipole moment of phenoxazine which was found to be 1.93 D (benzene) is also consistent with the non planarity of molecule. Now the proton or the substituent at the nitrogen atom may be placed either between or out of the planes of the two latral ring. Thus two geometrical configurations can be analogy to phenothiazine may be called *H*-extra (I) and *H*-antra (II) configuration Figure-2.

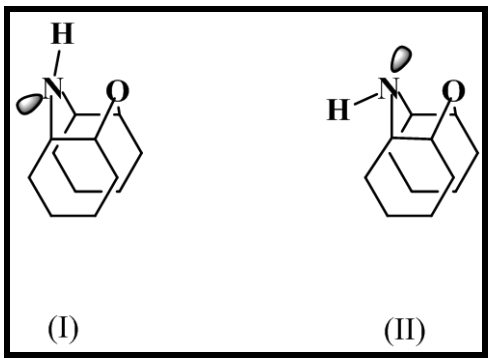


Figure 2- Geometrical configuration for phenoxazine

Experimental:

FT-IR spectra were recorded on (SHIMADZU) FT-IR 8400 S spectrophotometer; solid samples were run in KBr disc, liquid were run as smears. UV spectra were recorded on UV-visible spectrophotometer (SHIMADZU) UV-160 A. ^{1}H-NMR spectra were recorded on Ultra Sheild 300 MH_z with tetramethyl silane as internal standard. Melting points were determined in a (Gallen kamp) melting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus. Thin Layer chromatography (TLC) were performed on pre-coated plastic sheet with o.25 mm Layer of silica-gel F 254. Spots were detected with iodine vapour.

General procedure for Synthesis of phenoxazine and its derivatives:

Phenoxazine (1):

A mixture of (109g, 1mol) of o-aminophenol, (2g) $ZnCl_2$ and 5 ml conc. H_3PO_4 was heated in a sand bath maintained at 270-275 ^{0}C for 4 hr. The reaction mixture was cooled and extracted with cyclohexane in soxhlet extraction apparatus. The solvent was removed and the formed colorless needles crystallized from ethanol m.p. 152-154 ^{o}C, yield (54g,50%) IR: 3405 cm^{-1} (N-H) str.

10-acetyl phenoxazine (2):

A mixture of (40g, o.22mol) of phenoxazine, 140 ml acetic anhydride and 109 ml glacial acetic acid was refluxed for 2 hr. then cooled to room temperature and diluted with 250 ml cold water to give colorless prisms [6] which was recrystallized from ethanol, m.p. 142 ^{0}C, yield (38.36g, 78%) IR: 1669 cm^{-1} (C=O) str.

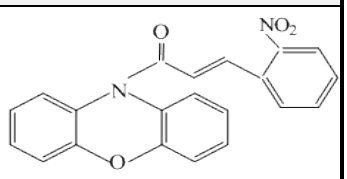
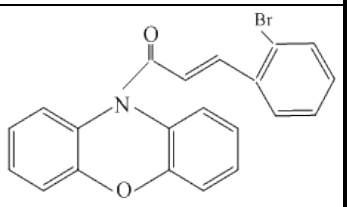
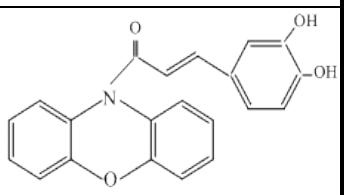
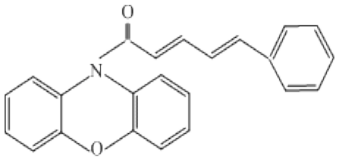
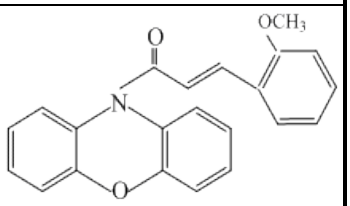
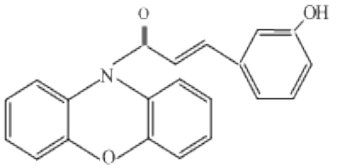
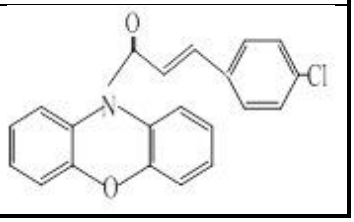
Part one

10-(oxoalken -1-yl) phenoxazine derivatives (3a-3g):

A mixture of (3g, 0.013mol) 2-acetyl phenoxazine and (1.56g, o.o147mol) of appropriate benzaldehyde in (80 ml) of ethanol and (1.5 ml) of (1% NaOH) solution was refluxed for 2hrs. The reaction mixture was poured in cold water [7], the precipitate filtered off and recrystallized from

(ethanol- water) to give (3a-3g). FT-IR spectra of these compounds showed (C=O)str. band at (1670-1685) cm^{-1} and (1608-1600) cm^{-1} aliphatic (C=C) str. Table-1 represent the physical data of compounds (3a-3g).

Table 1- Physical properties of compounds (3a-3g)

Comp. No.	Scietific name	m.p ^0C	Yield %	Color of crystal	Chemical structure
3a	10-[3-(2-nitrophenyl) oxoprop-2-en-1-yl] phenoxazine	130-132	88	Brown	
3b	10-[3-(2-Bromophenyl) oxoprop-2-en-1-yl] phenoxazine	131-133	73	Light Brown	
3c	10-[3-(3,4-dihydroxyphenyl) oxoprop-2-en-1-yl] phenoxazine	140-142	91	Light green	
3d	10-[(5-phenyl) oxoprop-2,4- dien-1-yl] phenoxazine	122-124	31	Yellowsh green	
3e	10-[3-(2-methoxyphenyl) oxoprop-2-en-1-yl] phenoxazine	136-138	83	Yellowsh Brown	
3f	10-[3-(3-hydroxyphenyl) oxoprop-2-en-1-yl] phenoxazine	110-112	33	Brown	
3g	10-[3-(4-chlorophenyl) oxoprop-2en-1-yl] phenoxazine	126-128	45	Brown	

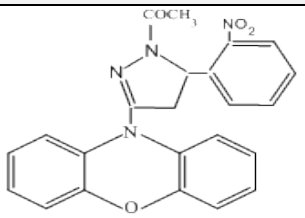
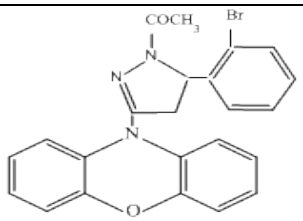
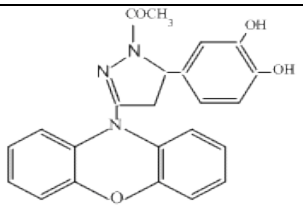
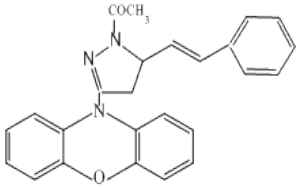
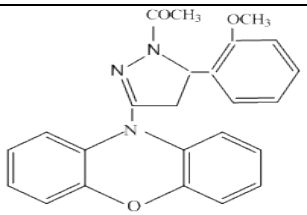
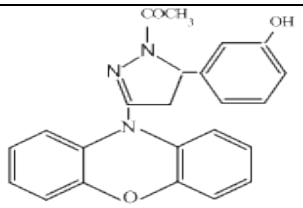
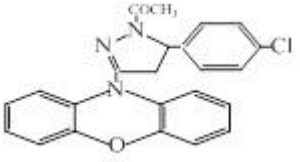
Part two

10-(1-acetyl pyrazolin-3-yl) phenoxazine derivatives (4a-4g):

To asolution of 10-(3-phenyl oxopropen-1-yl) phenoxazine (3a) (0.313g, 0.001mol) in acetic acid (96%, 1ml) hydrazine hydrate (0.4ml, 0.008mol) was added and the mixture was refluxed for 5 hrs [8], the product separated out on cooling was crystallized from (ethanol-water) to give (4a), compounds (4a-4g) were prepared in this manner. FT-IR of these compounds showed absorption band at (1460-

1585) cm^{-1} aromatic (C=C) str., (1597-1612) cm^{-1} (C=N) str. and (1227-1258) cm^{-1} (C-N) str. Table-2 represent the physical data of compounds (4a-4g).

Table 2- Physical properties of compounds (4a-4g)

Comp. No.	Scientific name	m.p. ^0C	Yield %	Color of crystal	Chemistry structure
4a	10-[1-acetyl-5-(2-nitrophenyl)pyrazolin -3-yl]phenoxazine	116-118	73	Light gray	
4b	10-[1-acetyl-5-(2-Bromophenyl)pyrazolin-3-yl]phenoxazine	121-123	44	Light Brown	
4c	10-[acetyl-5-(3,4-dihydroxyphenyl) pyrazolin-3-yl] phenoxazine	112-114	70	Light Brown	
4d	10-[1-acetyl-5-(styrenyl) pyrazolin-3-yl] phenoxazine	147-149	29	Light gray	
4e	10-[1-acetyl-5-(2-methoxyphenyl)pyrazolin-3-yl]phenoxazine	117-119	44	Reddish Brown	
4f	10-[1-acetyl-5-(3-hydroxyphenyl) pyrazolin-3-yl] phenoxazine	140-142	68	Reddish Brown	
4g	10-[1-acetyl-5-(4-chlorophenyl)pyrazolin-3-yl] phenoxazine	131-133	42	Off-white	

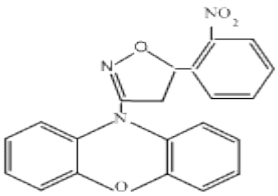
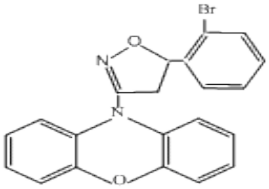
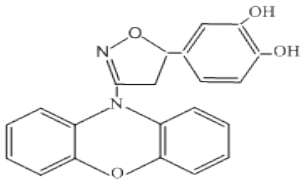
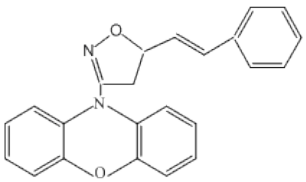
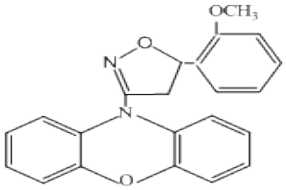
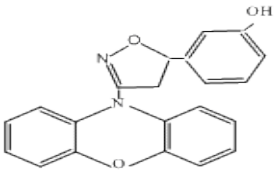
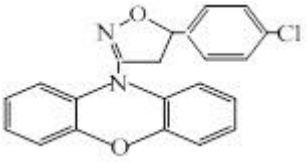
Part Three

10-(isoxazolin-3-yl) phenoxazine derivatives (5a-5g):

Asolution of (0.3g, 0.001mol) of 10-(3-phenyl oxopropen-1-yl) phenoxazine (3a) and (0.07g, 0.001mol) of hydroxyl amine hydrochlorid in ethano sodium hydroxide solution was refluxed for 6 hrs

[9]. The product separated out. This was crystallized from ethanol to give (5a). FT-IR of these compounds showed absorption band at (1588-1595) cm^{-1} (C=C) and (1588-1618) (C=N). Table-3 represents the physical data of compounds (5a-5g).

Table 3- Physical properties of compounds (5a-5g)

Comp. No.	Scientific name	m.p. ^0C	Yield %	Color of crystal	Chemistry structure
5a	10-[5-(2-nitrophenyl) isoxazolin-3-yl] phenoxazine	136-138	93	Gray	
5b	10-[5-(2-Bromophenyl) isoxazolin-3-yl] phenoxazine	96-98	32	Grennsh gray	
5c	10-[5-(3,4-dihydroxy phenyl)isoxazolin-3-yl] phenoxazine	108-110	77	Light Brown	
5d	10-[(5-styrenyl) isoxazolin-3-yl] phenoxazine	127-129	50	Off-white	
5e	10-[5-(2-methoxy phenyl)isoxazolin-3-yl] phenoxazine	139-141	38	Gray	
5f	10-(5-(3-hydroxy phenyl)isoxazoline-3-yl] phenoxazine	146-148	23	Brown	
5g	10-[5-(4-chlorophenyl) isoxazolin-3-yl] phenoxazine	135-137	50	Brown	

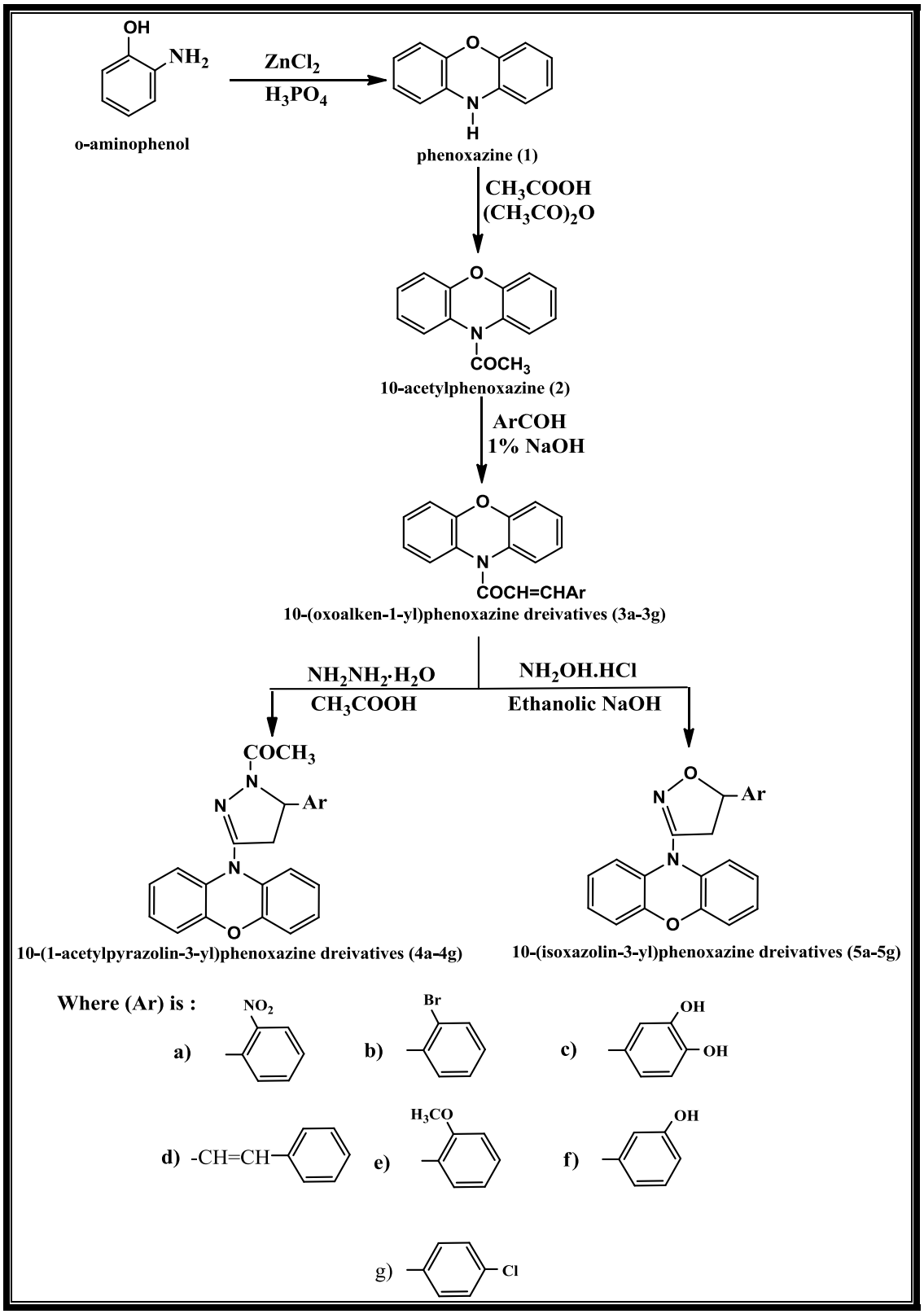
Result and Discussion:

Phenoxazine prepared by the reaction of o-aminophenol with Zinc chloride in presence of phosphoric acid showed scheme -1. Phenoxazine (1) showed strong stretching band at 3342 cm^{-1} (N-H), strong stretching bands at 1570 cm^{-1} and 1596 cm^{-1} assigned to phenoxazine ring.The ^{1}H-NMR spectrum showed signal at δ (6.7-7) ppm signals to aromatic protons and signal at δ (8.2) ppm a ssignal to (N-H) shown in Figure-3.

The phenoxazine (1) was then converted to 10-acetylphenoxazine (2) using acetic anhydride and glycial acetic acid. IR spectrum of 10-acetylphenoxazine (2) showed the disappearance of (N-H) band at 3342 cm^{-1} and showed a stretching band at 1670 cm^{-1} (C=O). The IR spectrum also showed a band at 3075 cm^{-1} (C-H) aromatic and 1590 cm^{-1} (C=C). Compound (2) reacted with numarous aromatic aldehydes in ethanolic NaOH solution as a catalyst to a afford (3a-3g). The IR spectra of compounds (3a-3g) showed bands at (1660-1680) cm^{-1}(C=O)str. and (1577-1612) cm^{-1} (C=C) as showed in Table-4. The last step, compound (3a) reacted with hydrazine hydrate in acetic acid and hydroxyl amine hydrochloride in ethanosodiumhydroxide to give compounds (4a-4g) and compounds (5a-5g). IR spectrum of compounds (4a-4g) showed absorption band at (3015-3058) cm^{-1} aromatic (C-H) str, (2923-2997) cm^{-1} aliphatic (C-H)str, (1648-1670) cm^{-1} (C=O) str, (1595-1630) cm^{-1} (C=N) str, and (1500-1591) cm^{-1} aromatic (C=C) str. as showed in Table-5. IR spectrum of compounds (5a-5g) showed absorption band at (3010-3062) cm^{-1} aromatic (C-H) str, (2923-2990) cm^{-1} aliphatic (C-H) str. Strong bands at (1618-1629) cm^{-1} (C=N) str, (1585-1591) cm^{-1} (C=C) str. as showed in Table-6. FT-IR spectrum of compound (5b) shown in Figure-4.

Conclusion:

Phenoxazine derivatives are an important type of nitrogen and oxygen containing heterocyclic compounds which have attracted considersion of medicinal chemist due to antimicrobial activites for this purpose new phenoxazine derivatives were synthesizedl. More than 10 derivatives were prepared and characterized by spectroscopic methods namely FT-IR and ^{1}H-NMR.



Scheme 1- Preparation of new Hetrocyclic compounds.

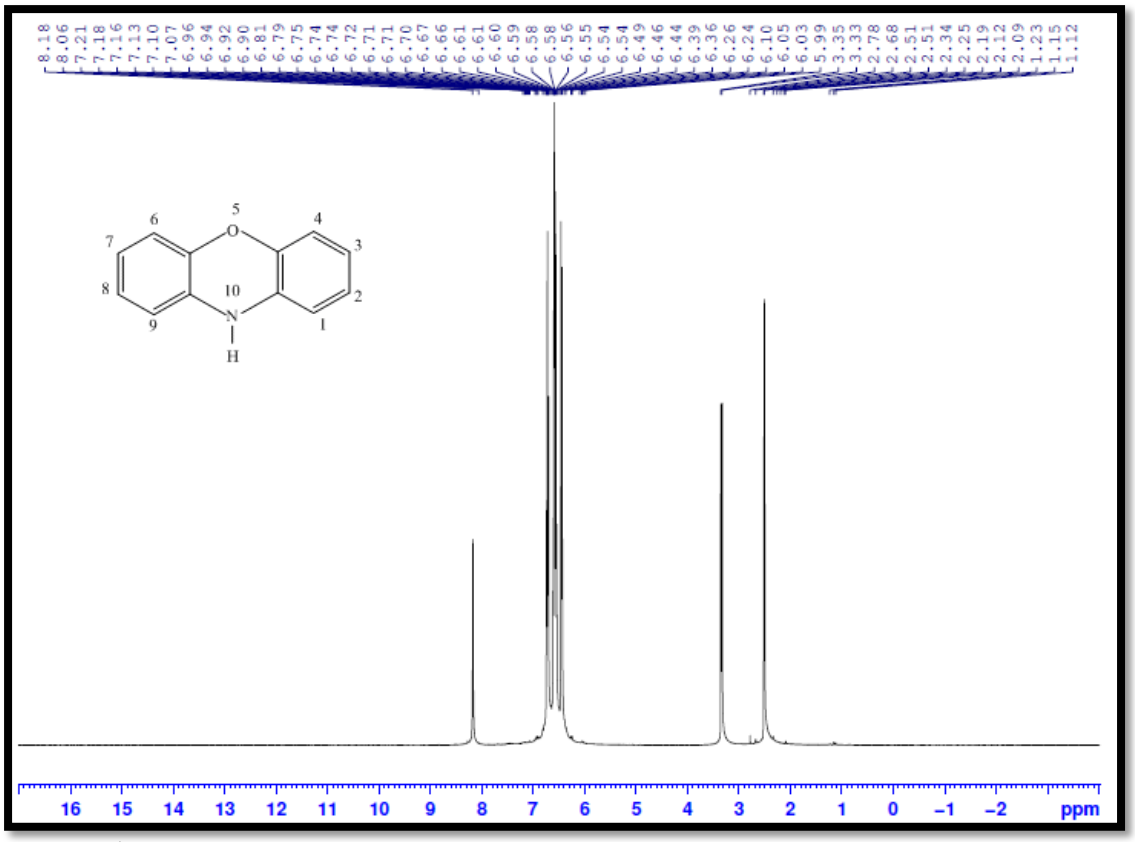


Figure 3- ^{1}H-NMR spectrum of compound (1)

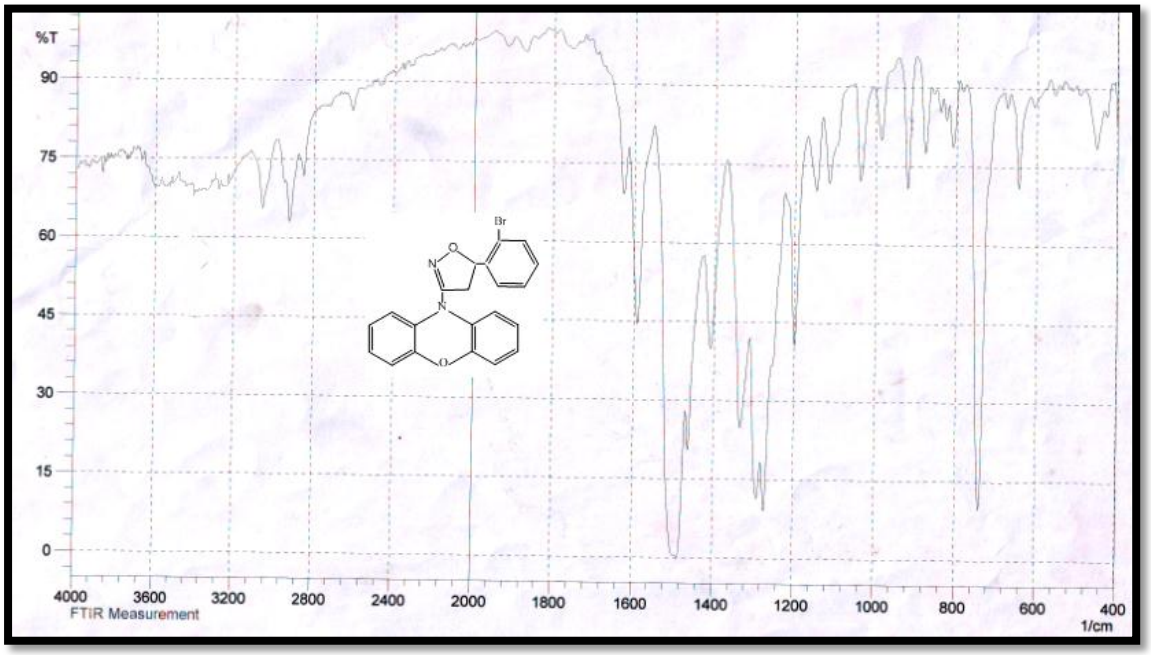


Figure 4- FT-IR spectrum for compound [5b]

Table 4- Infrared spectra of compounds (3a-3g)

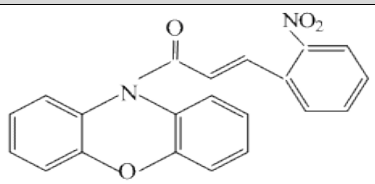
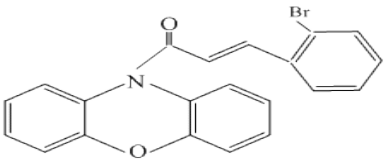
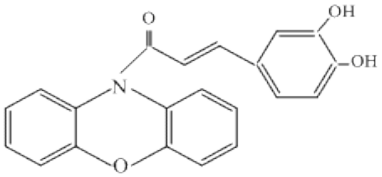
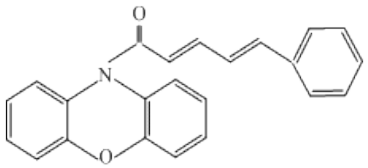
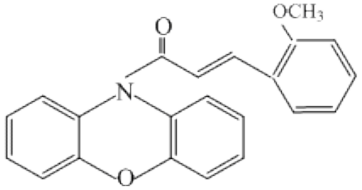
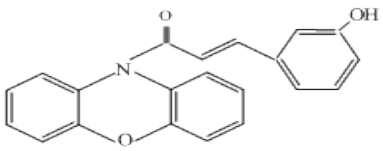
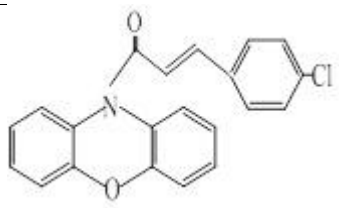
Com. No.	Structure	υ C-H Aromatic	υ C-H Aliphatic	υ C=C cm^{-1}	υ C=O cm^{-1}	Other bands cm^{-1}
3a		**3072 m**	**2989 w**	**1612 s**	**1670 s**	**NO_2 1577, 1367**
3b		**3070 m**	**3010 m**	**1577 s**	**1670 s**	**C-Br 634 s**
3c		**3072 w**	**3006 m**	**1577 s**	**1670 s**	**O-H 3500 b**
3d		**3070 m**	**3923 m**	**1577 s**	**1668 s**	**-**
3e		**3070 w**	**2969 w**	**1612 s**	**1670 s**	**C-O-C 1116-1099**
3f		**3043 m**	**2869 m**	**1585 s**	**1660 s**	**O-H 3505 b**
3g		**3072 m**	**3020 m**	**1590 s**	**1680 s**	**C-Cl 1000 s**

Table 5- Infrared spectra of compounds (4a-4g)

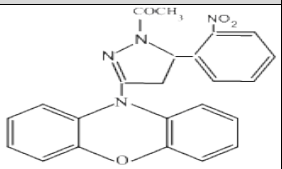
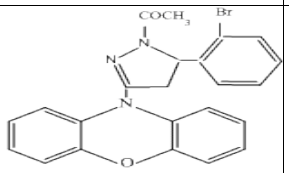
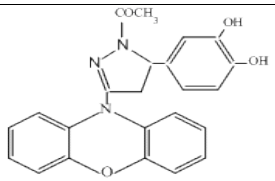
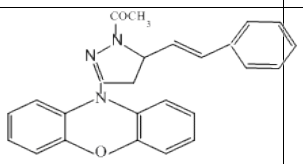
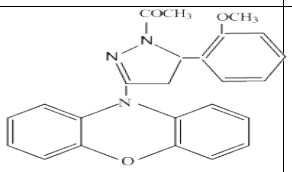
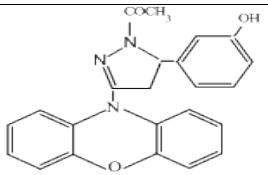
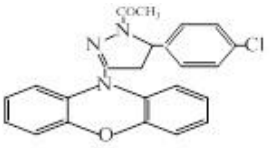
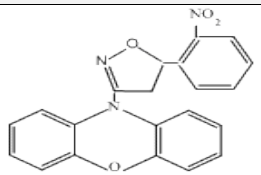
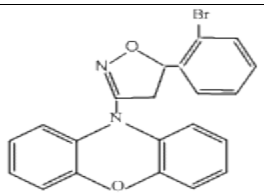
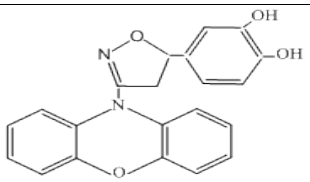
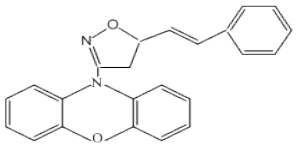
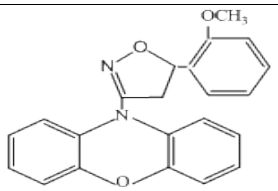
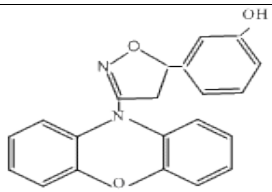
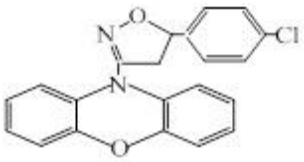
Comp. No.	Structure	υ C-H Aromatic	υ C-H Aliphatic	υ C=C cm^{-1}	υ C=O cm^{-1}	υ C=N cm^{-1}	Other bands cm^{-1}
4a		**3056 w**	**2991 w**	**1500 s**	**1650 s**	**1600 s**	**NO_2 1520, 1303**
4b		**3045 m**	**2940 w**	**1542 s**	**1648 s**	**1595 s**	**C-Br 625 s**
4c		**3050 m**	**2991 w**	**1585 s**	**1666 s**	**1620 s**	**O-H 3500 b**
4d		**3015 m**	**2990 m**	**1585 s**	**1670 s**	**1595 s**	**-**
4e		**3058 m**	**2997 m**	**1558 s**	**1653 s**	**1630 s**	**C-O-C 1116-1029**
4f		**3056 m**	**2923 m**	**1585 s**	**1660 s**	**1595 s**	**O-H 3501 b**
4g		**3040 m**	**2960 m**	**1591 s**	**1670 s**	**1600 s**	**C-Cl 1000 s**

Table 6- Infrared spectra of compounds (5a-5g)

Compd. No.	Structure	υ C-H Aromatic	υ C-H Aliphatic	υ C=C cm^{-1}	υ C=N cm^{-1}	Other bands cm^{-1}
5a		**3058 m**	**2923 w**	**1585 s**	**1627 s**	**NO_2 1500, 1301**
5b		**3060 m**	**2950 m**	**1591 s**	**1623 s**	**C-Br 644 s**
5c		**3066 w**	**2952 w**	**1591 s**	**1629 s**	**O-H 3500 b**
5d		**3010 m**	**2929 m**	**1579 s**	**1622 s**	**-**
5e		**3062 m**	**2950 w**	**1591 s**	**1625 s**	**C-O-C 1147-1099**
5f		**3010 m**	**2929 w**	**1579 s**	**1622 s**	**O-H 3500 b**
5g		**3010 m**	**2990 m**	**1590 s**	**1618 s**	**C-Cl 1000 s**

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