

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Life Sciences

Research Article.....!!!

Received: 22-04-2016; Revised: 04-05-2016; Accepted: 05-05-2016

SYNTHESIS CHARACTERIZATION OF NOVEL IMIDAZOLE COMPOUNDS AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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Keywords:

Imidazole;
Antimicrobial Activity;
Insertion Chemistry

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ABSTRACT

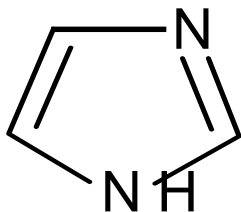
Imidazoles are an important class of heterocycles and include many substances of both biological and chemical interest. Insertion of the imidazole nucleus is an important synthetic strategy in drug discovery. Imidazole drugs have broad applications in many areas of clinical medicine. These are currently used as tools in pharmacological studies. The important therapeutic properties of imidazole related drugs have encouraged the medicinal chemists to synthesize and test a large number of novel molecules. In this investigation, it was of interest to synthesize imidazole by refluxing 9, 10-phenanthraquinone with aryl aldehyde, primary amines and ammonium acetate in the presence of glacial acetic acid and a novel series of imidazole derivatives. The structures of the compounds have been established on the basis of spectral analytical data. All the derivatives have been screened for their antimicrobial activities at the 100µg/ml and 200µg/ml against *Candida albicans*.

INTRODUCTION

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity-the ability to kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative, rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism while still being tolerated by the host[1]. During the past decade, imidazole derivatives have occupied a unique place in the field of medicinal chemistry. They have wide range of biological activities. They are well known analgesics, anti-inflammatory, antiparasitic, anthelmintic, platelet aggregation inhibitors and antiepileptic agents[2-7]. Imidazole can be found in many other drugs such as dacarbazine, metronidazole, cimetidine, flumazenil, thyroliberin, methimazole, pilocarpine and etomidate which are used as antineoplastic antibiotic, antiulcerative, benzodiazepine antagonist, prohormone, antihyperthyroid, muscarinic receptor antagonist and hypnotic agents, respectively[8-11]. In view of such reports the present study was design to evaluate the antimicrobial activity of some 1,2-diphenylethanedione (9,10-Phenanthraquinone).

The arrangement of certain functional groups in 3 dimensional spaces and their electron density recognizes the site of these groups rather the structure of the entire drug molecule that result in an interaction. The presence of heterocyclic ring among drug mean that this moiety of necessity constitute part of the pharmacophore. Molecule with certain structural feature would elucidate a specific biologic response. Very slight changes in structure could cause significant change in biological activity. This structural variation could increase or decrease activity or change an agonist into antagonist.

Imidazole is a planar five-member ring system with N atom in 1 and 3 positions. The systemic name for the compound is 1, 3 dizole, one of the annular N bear a H atom and can be regarded as a pyrrole type. N.

Structure

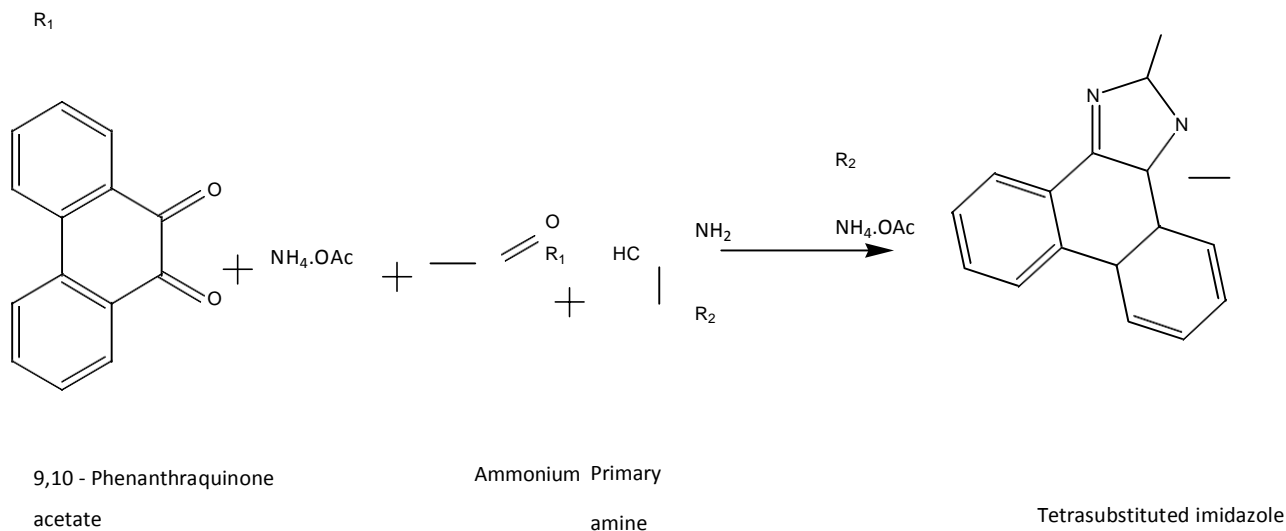
Imidazoles are prepared by combining 1, 2-diphenylethanedione (9,10-Phenanthraquinone) with different aryl aldehyde and these imidazole derivative have a broad spectrum of activity.

MATERIALS AND METHODS

The chemicals and reagents used in this were of AR and LR grade. They were procured from Spectro Chem, Hi-Media, Merck, Sigma Aldrich and Ranbaxy.

EXPERIMENTATION**Synthesis of imidazole**

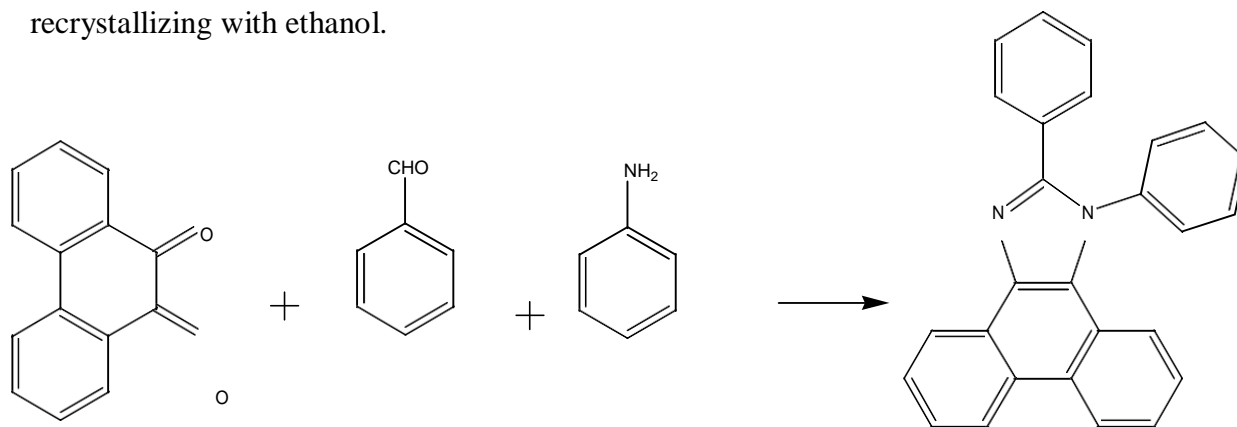
In this scheme, the synthesis of imidazole is carried out by refluxing 9, 10-phenanthraquinone with aryl aldehyde, primary amines and ammonium acetate in the presence of glacial acetic acid in round bottom flask for 3 hrs. The completion of reaction was checked out by TLC. The mixture was poured in ice cold water and neutralized with ammonium hydroxide. The precipitate was filtered and washed with water and purified by recrystallizing with ethanol. Note down the % yield and melting point.



Synthesis of imidazole derivatives

(I) Synthesis of 1,2-diphenyl-1H-phenanthro[9,10-d]imidazole

9, 10-phenanthraquinone (0.001 mole, 208.2 mg.) was refluxed with benzaldehyde (0.001 mole, 106 mg.), aniline (0.001 mole, 93 mg.) and ammonium acetate (0.001 mole, 77mg.) in glacial acetic acid (50 ml.) in round bottom flask for 3 hrs. After refluxing, the mixture was cooled to room temperature and was added to 200ml of ice water and neutralized with ammonium hydroxide. The precipitate was filtered and washed with water and solid was purified by recrystallizing with ethanol.

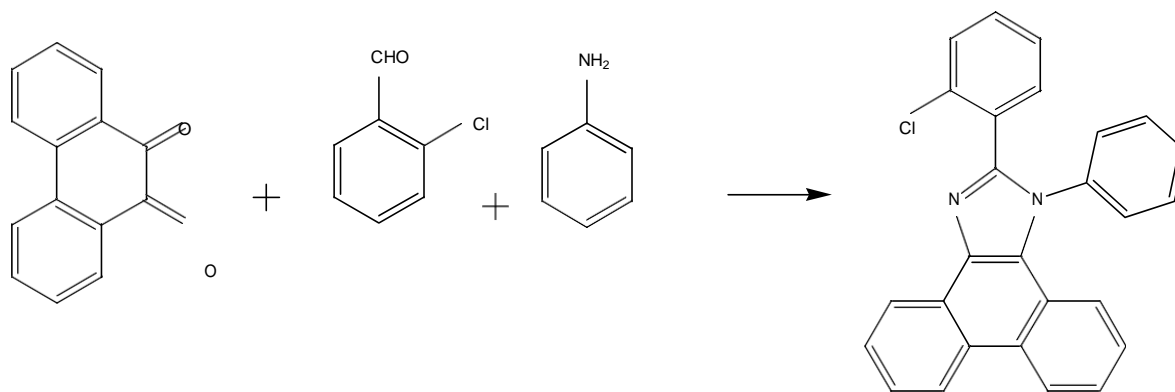


9,10 – Phenanthraquinone Benzaldehyde Aniline 1,2 - Diphenyl - 1H - Phenanthro (9,10) imidazole

The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3429.98, C=N(1519.98), C=C(1545.49) and C-H aromatic (799.85). The NMR spectrum of the compound showed peaks as δ 7.22 (5H, s, Ar-H), δ 7.85(5H, d, J=8.1, Ar-H) δ 8.9(8H, s, phenantherene). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(II) Synthesis of 2-(2-chlorophenyl)-1-phenyl-1H-phenanthro[9,10-d]imidazole

9, 10-phenanthraquinone (0.001mole, 208.2mg) was refluxed with 2-chlorobenzaldehyde (0.001mole, 140 mg), aniline (0.001mole, 93 mg.), ammonium acetate (0.001 mole, 77mg) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.



9,10 - Phenanthraquinone

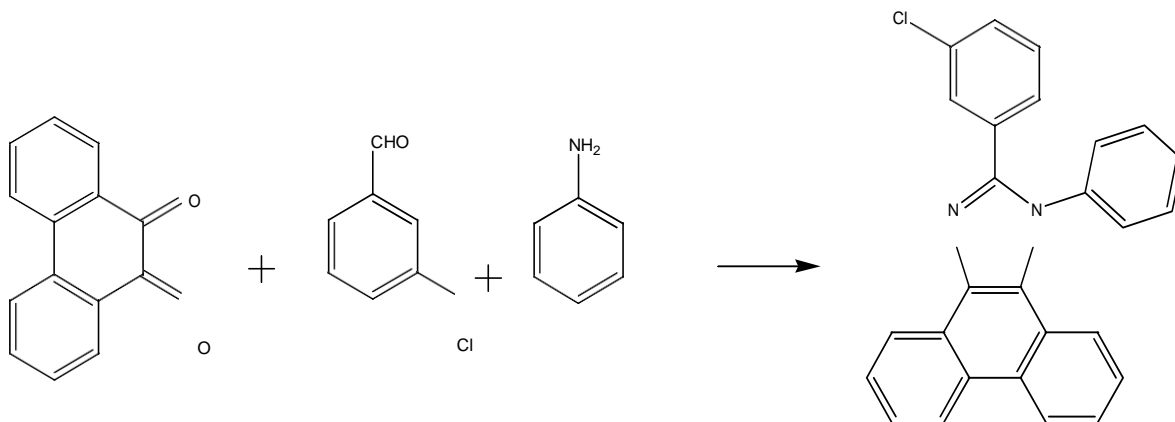
2- Chlorobenzaldehyde Aniline

2 - (2 - Chlorophenyl) - 1 - Phenyl - 1H - Phenanthro (9,10) imidazole

The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3447.40, C=N(1513.29), C=C(1559.83) and C-H aromatic (798.42). The NMR spectrum of the compound showed peaks as δ 7.1 (4H, s, Ar-H), δ 7.8 (5H, d, J=8.5, Ar-H) δ 8.98(8H, s, phenanthrene). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(III) Synthesis of 2-(3-chlorophenyl)-1-H-phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with 3-chlorobenzaldehyde(0.001 mole, 140 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (0.001 mole, 77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.



9,10 - Phenanthraquinone

3-Chlorobenzaldehyde Aniline

2 - (3 - Chlorophenyl) - 1 - Phenyl - 1H - Phenanthro (9,10) imidazole

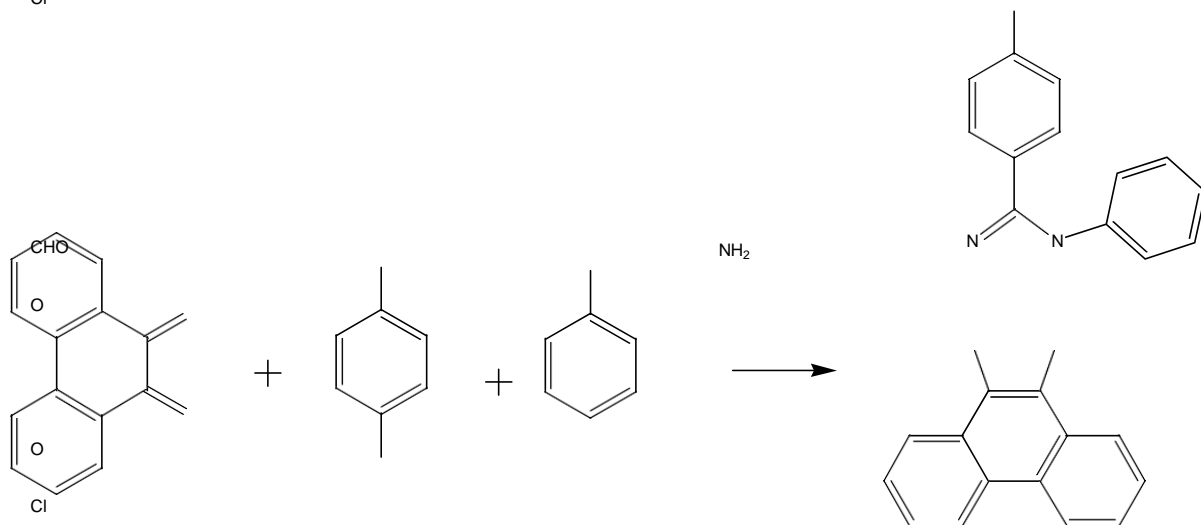
The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3451, C=N (1529.18), C=C(1557.43) and C-H aromatic (799.54). The NMR spectrum of the compound showed peaks as δ 9.3 (8H, d, J=8.1, phenantherene H), δ 7.31 (5H, s, Ar-H) and δ 7.12(4H, s, Ar-H). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(IV) **Synthesis of 2-(4-chlorophenyl) -1-H- phenanthro[9,10-d]imidazole**

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with 4-chlorobenzaldehyde(0.001 mole, 140 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (0.001 mole, 77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs.

After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.

Cl



9,10 - Phenanthraquinone

4 - Chlorobenzaldehyde Aniline

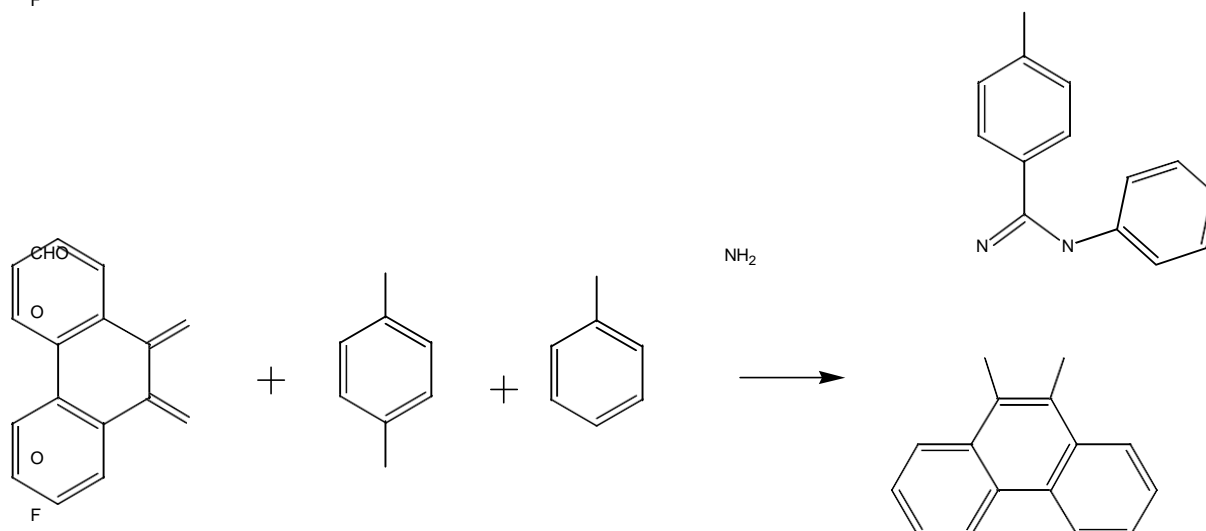
2 - (4 - Chlorophenyl) - 1 - Phenyl - 1H - Phenanthro (9,10) imidazole

The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3487, C=N (1586.53), C=C(1548.54) and C-H aromatic (797.42). The NMR spectrum of the compound showed peaks as δ 8.76 (8H, d, J=7.8, phenanthrene- H), δ 7.95 (5H, s, Ar-H) and δ 7.45(4H, s, Ar-H). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(V) Synthesis of 2-(4-fluorophenyl) -1-H- phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with 4-fluorobenzaldehyde(0.001 mole, 140 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (0.001 mole, 77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.

F



9,10 - Phenanthraquinone

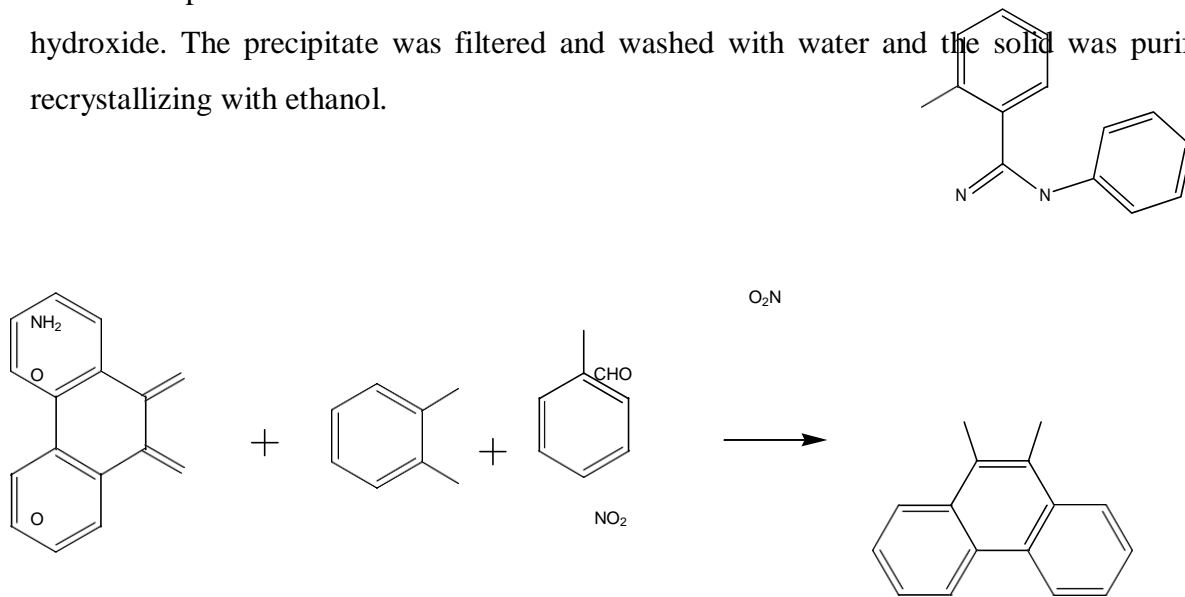
4 - Fluorobenzaldehyde Aniline

2 - (4 - Fluorophenyl) - 1 - Phenyl - 1H - Phenanthro (9,10) imidazole

The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3466, C=N (1538.16), C=C(1544.21) and C-H aromatic (765.87). The NMR spectrum of the compound showed peaks as δ 7.96 (4H, s, Ar-H), δ 8.76 (8H, d, $J=8.3$, phenanthrene- H) and δ 7.85(5H, s, Ar-H). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(VI) Synthesis of 2-(2-nitrophenyl)-1-phenyl-1H-phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with 2-nitrobenzaldehyde(0.001 mole, 152 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.



9,10 - Phenanthraquinone

2

- Aniline

Nitrobenzaldehyde

2 - (2 - Nitrophenyl) - 1 - Phenyl - 1H - Phenanthro (9,10 - d) imidazole

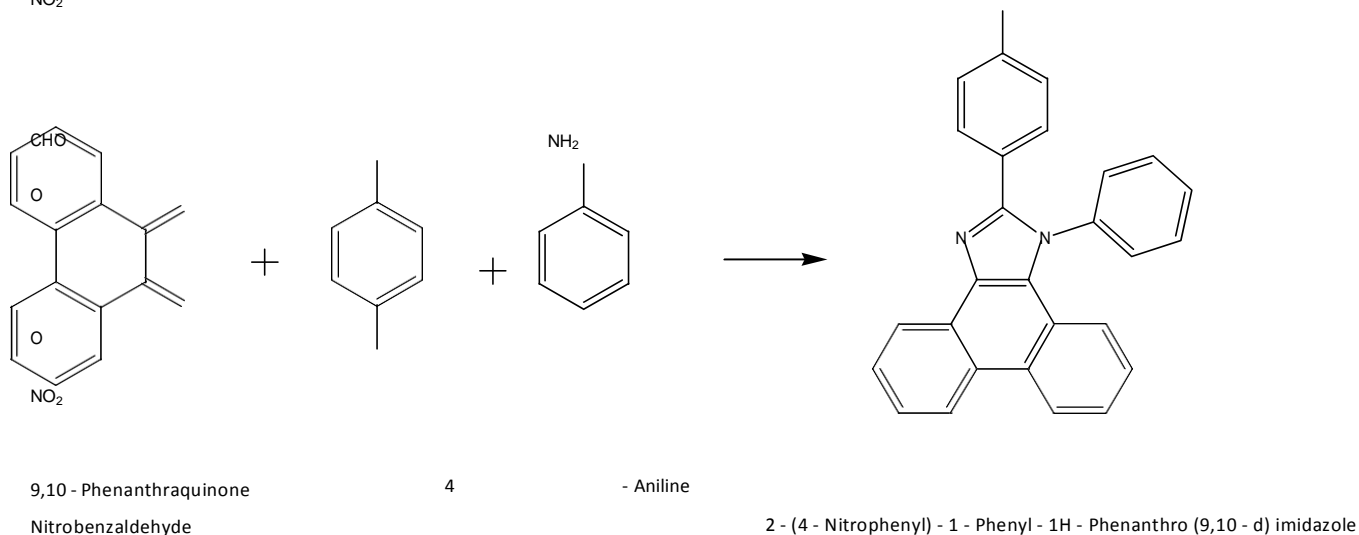
The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3468, C=N (1584.76), C=C(1536.87) and C-H aromatic (757.58). The NMR spectrum of the compound showed peaks as δ 8.93 (8H, t, J=8., phenantherene-H) δ 7.93 (4H, s, Ar-H), and δ 7.98 (5H, s, Ar-H). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(VII) Synthesis of 2-(4-nitrophenyl)-1-phenyl-1H-phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with 4-nitrobenzaldehyde(0.001 mole, 152 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium

hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.

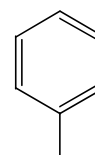
NO₂



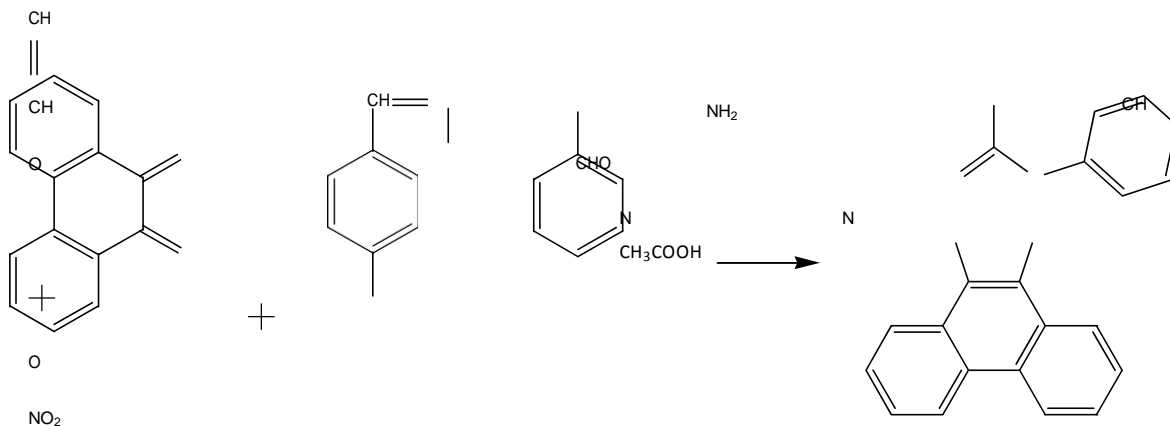
The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3475, C=N (1525.76), C=C(1514.98) and C-H aromatic (797.58). The NMR spectrum of the compound showed peaks as δ 8.29 (8H, t, J=8.6, phenanthrene-H) δ 7.65 (4H, s, Ar-H), and δ 7.65 (5H, s, Ar-H). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(VIII) Synthesis of 1-phenyl-2-(4-styrylphenyl)-1H-phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with cinnamaldehyde (0.001 mole, 132.16 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled



to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol.



9,10 - Phenanthraquinone

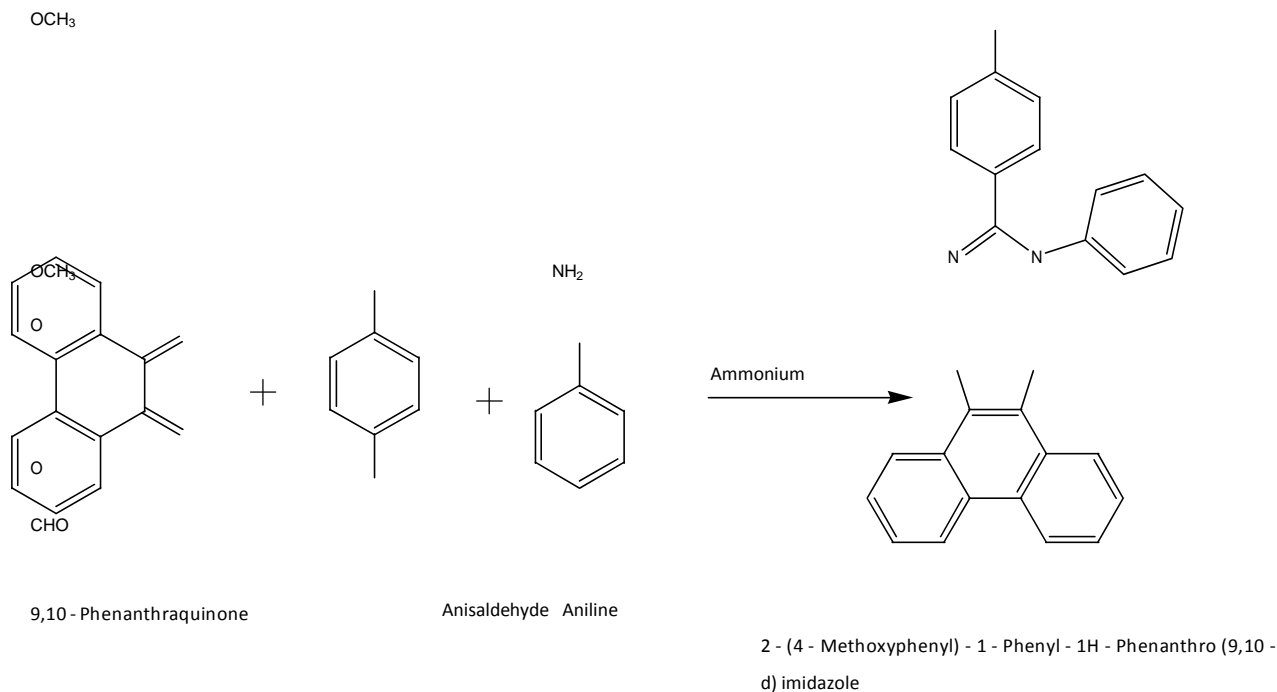
Cinnamaldehyde Aniline

1 - Phenyl - 2 - (4 - Styrylphenyl) - 1H - Phenanthro (9,10 - d) imidazole

The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3451, C=N (1528.76), C=C(1543.76) and C-H aromatic (797.59). The NMR spectrum of the compound showed peaks as δ 6.9(4H, s, Ar-H). δ 7.15 (5H, s, Ar-H), δ 8.79 (8H, d, J=8, phenantherene- H) and δ 3.8(3H,s,CH₃). As the expected structure show absorption in the region, the reaction is deemed to be successful.

(IX) Synthesis of 2-(4-methoxyphenyl)-1H-phenyl-phenanthro[9,10-d]imidazole

9,10-phenanthraquinone (0.001 mole, 208.2mg) was refluxed with anisaldehyde (0.001 mole, 136.15 mg), aniline (0.001 mole, 93 mg.) and ammonium acetate (77mg.) in the presence of glacial acetic acid (50 ml) in round bottom flask for 3 hrs. After refluxing the mixture was cooled to room temperature and was added to 200 ml of ice cooled water and neutralize with ammonium hydroxide. The precipitate was filtered and washed with water and the solid was purified by recrystallizing with ethanol. The IR spectrum of the compound shows stretching of heterocyclic nitrogen containing systems at 3479, C=N (1563.76), C=C(1596.76) and C-H aromatic (748.54).



The NMR spectrum of the compound showed peaks as δ 8.87 (8H, t, J=8.3, A phenantherene- H) δ 7.17(10H, s, Ar-H). δ 7.84 (4H, s,

Ar-H), and δ 6.9(2H,s,-CH=CH-). As the expected structure show absorption in the region, the reaction is deemed to be successful.

Table 1: Physical Properties of the Imidazole Derivatives

Sr. No.	Comp.	R1	R2	m.p. (°C)	% Yield	Rf value
1	I	-C ₆ H ₅	C ₆ H ₅	122	79	0.71
2	II	-2-Cl-C ₆ H ₅	C ₆ H ₅	107	76	0.74
3	III	3-Cl-C ₆ H ₅	C ₆ H ₅	159	68	0.94
4	IV	-4-Cl-C ₆ H ₅	C ₆ H ₅	198	78	0.73
5	V	-4-F-C ₆ H ₅	C ₆ H ₅	247	76	0.88
6	VI	-2-NO ₂ -C ₆ H ₅	C ₆ H ₅	175	63	0.42
7	VII	-4-NO ₂ -C ₆ H ₅	C ₆ H ₅	157	63	0.56
8	VIII	-CH=CH-C ₆ H ₅	C ₆ H ₅	189	73	0.85
9	IX	-4-OCH ₃ -C ₆ H ₅	C ₆ H ₅	164	63	0.63S

Anti microbial activity

The sterilized agar medium was poured into petridishes and allowed to solidify for 30 min. On the surface of media fungus was spread with the help of sterilized cotton swab. After 10 min. punching into agar surface a sterile cork bored made cup or cavity and scooping out the punched part of agar. 2 cups were made into each petri dish and into these caps were added the test compound (200µg/ml, 100µg/ml) are well filled with pure solvent DMF and another well was filled with standard antibiotic (voriconazole 200µg/ml,

100µg/ml), against candida albicans organism. The plates were kept in cold for 1 hr and then incubated at 37-38^oc for 24 hrs. The zone of inhibition formed around the cups after overnight incubation was measured and percentage inhibition of the compound evaluated.

RESULTS & DISCUSSION

Synthesis of I- IX compounds was carried out and their physical data is provided in Table 1. The yields were found in between 63- 79%. This technique is a time saving and cost saving method. Purity was also checked by TLC. Considerable antimicrobial activity was shown by compounds I- IX as compare to standard drug. Their results are shown in **Table 2**.

Table 2: Percent zone inhibition at the 100 µg/ml and 200 µg/ml.

S. No.	Compound	Zone of Inhibition (100 µg/ml)	Zone of Inhibition (200 µg/ml)
1	I	15	18
2	II	24	30
3	III	20	28
4	IV	13	17
5	V	17	23
6	VI	18	20
7	VII	17	20
8	VIII	18	21
9	IX	8	12
10	Control	00	00
11	Standard (Voriconazole)	32	43

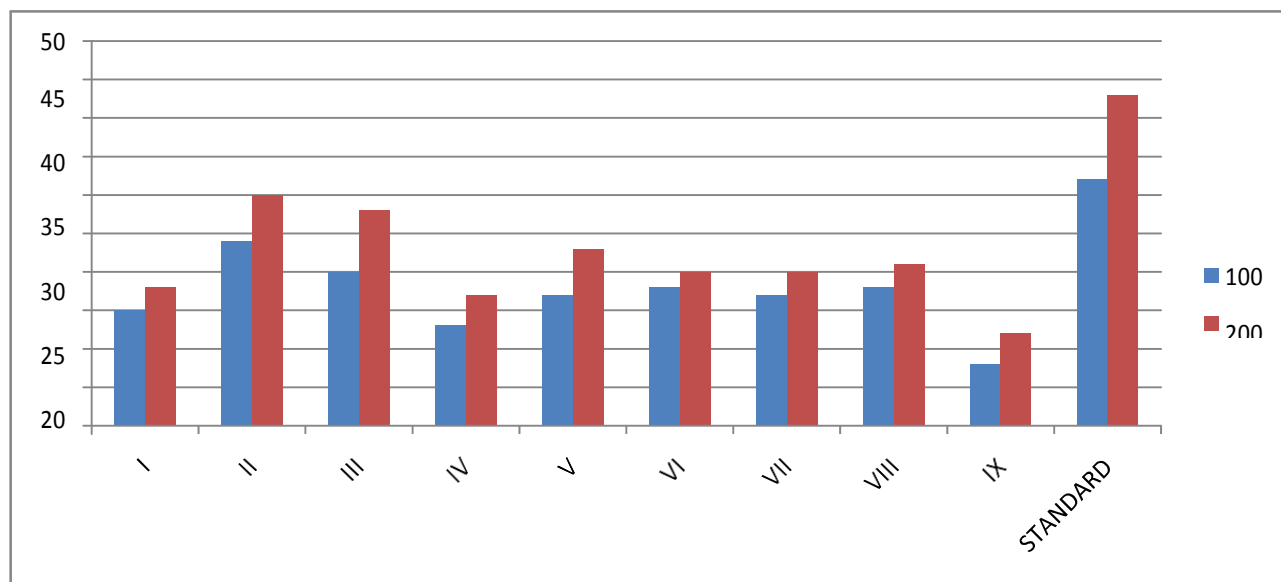


Fig. 1 indicates the Zone of inhibition at the 100 and 200µg/mg conc. of I-IX compound.

The structures of synthesized imidazole derivatives were confirmed from their respective spectral data such as IR, ^1H NMR studies.

The antimicrobial activity of compounds I- IX were tested and it has been found that 200µg/ml dose of every compound has better activity as compare to 100µg/ml. As we consider all all results obtained from antimicrobial activity, we can say that all the compounds active antimicrobial agents.

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