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PHENANTHRENE: A VERSATILE MOLECULE; A REVIEW

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ABSTRACT

Phenanthrene is a nucleus of the poly aromatic hydrocarbon family consisting of three fused benzene rings. They are of great importance in the field of medicine. They are mainly synthesized through Bardhan-Sengupta synthesis, Haworth synthesis and Pschorr synthesis of phenanthrene. Presently, many naturally existing drugs such as morphine, codeine halofantrine, among others bear the phenanthrene nucleus. Synthetic derivatives including dextromethorphan and other drugs also possess this nucleus. Phenanthrene derivates have many distinct therapeutic benefits including analgesic, antitussive, antimalarial, cytotoxic, and anti-constipation. This study was performed to highlight the various pharmacological uses of phenanthrene derivatives by reviewing experiments performed on its derivatives.

Keywords: Phenanthrene, cytotoxic, Bardhan-Sengupta synthesis, Haworth synthesis, pharmacological activities

INTRODUCTION

Phenanthrene is a poly-aromatic hydrocarbon (PAH) consisting of three fused benzene rings. It is the simplest non-linear polycyclic aromatic hydrocarbon and is derived from two words i.e. "phenyl" and "anthracene" which are further derived from the Latin words "phenos" and "anthrax" indicating "benzene" and "coal" respectively. (National Center for Biotechnology Information, 2020)

Phenanthrene exists as a colorless crystalline solid with mildly aromatic odor and is the chief constituent of coal and coal tar (5%). Phenanthrene is an isomer of anthracene; however, is more stable as compared to it. (Gutman & Stanković, 2007)The parent nucleus phenanthrene does not possess any therapeutic use, however; the various derivatives of phenanthrene have been reported to exhibit different pharmacological activities. Some pharmacological applications of phenanthrene derivatives include analgesic, antitussive, antimalarial, cytotoxic and anti-constipation. It has been further reported that phenanthrene is being used as a precursor for synthesis of steroidal drugs. Various opioid drugs and their derivatives also contain phenanthrene as the basic nucleus and is pharmacologically a potent class of analgesic drugs. (de Azeredo Sirlene Oliveira & Figueroa-Villar, 2015)

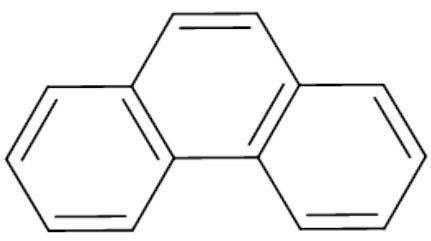


Figure 1: Basic nucleus of phenanthrene

MATERIALS AND METHODS

Methods Of Synthesis

There are mainly three methods used to synthesize Phenanthrene. They are:

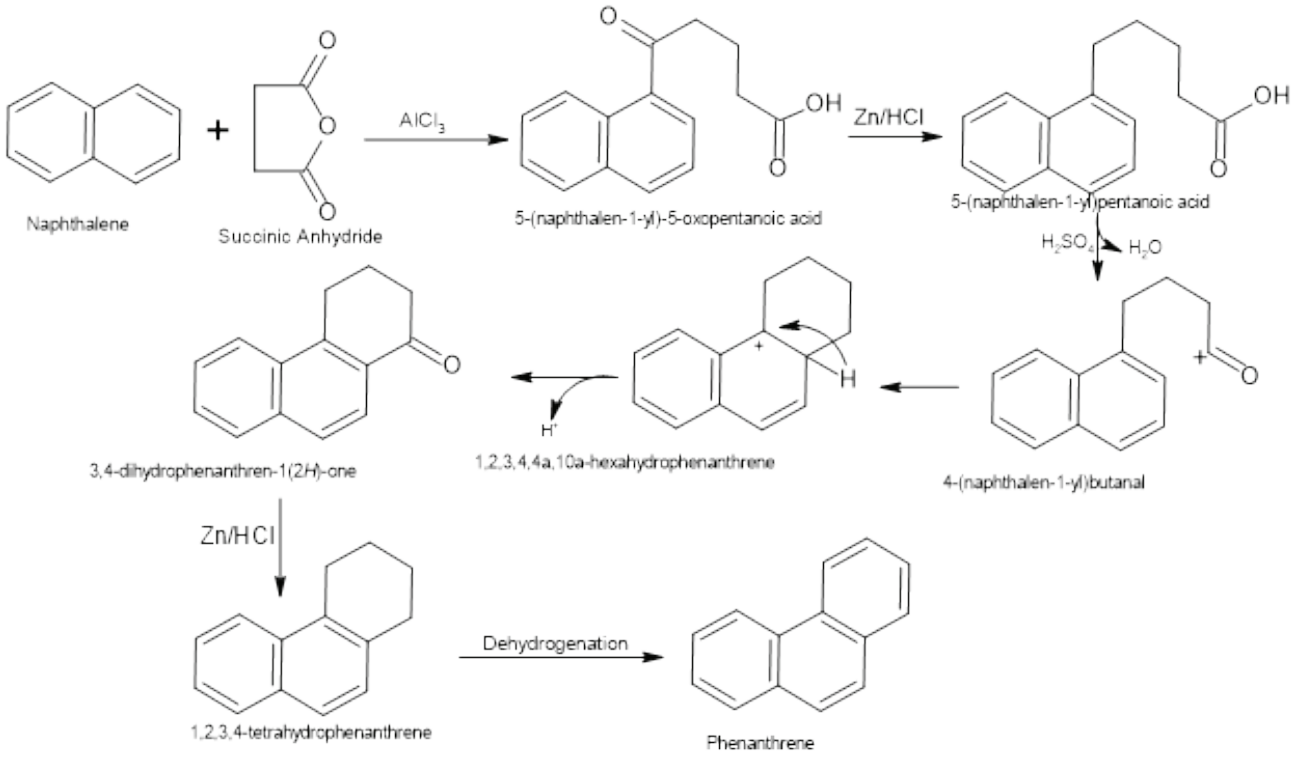
1. Haworth phenanthrene synthesis
2. Bardhan-Sengupta synthesis of phenanthrene
3. Pschorr synthesis of phenanthrene

Haworth synthesis of phenanthrene

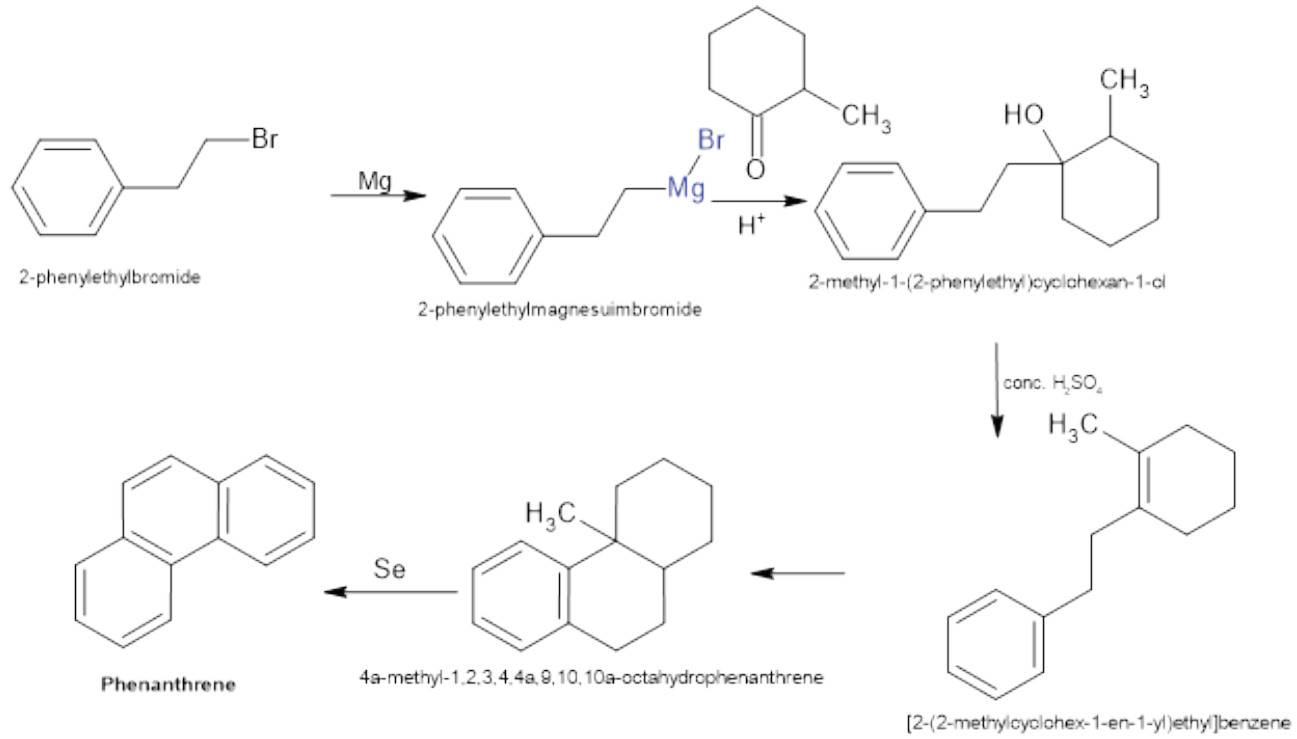
The synthesis of phenanthrene from naphthalene and succinic anhydride is known as Haworth synthesis of phenanthrene. In this, naphthalene undergoes Friedel craft acylation with succinic anhydride. The resulting intermediate then undergoes clemmensen reduction or wolfkishner's reduction, yielding phenanthrene. ("Haworth Synthesis," 2010)

Bardhan-Sengupta synthesis of phenanthrene

Bardhan-Sengupta Synthesis is another method for synthesizing phenanthrenes. It involves the use of 2-phenylethylbromide as a precursor. In the presence of magnesium, it gets converted to a grignard's reagent called 2-phenylethylmagnesiumbromide. The grignard's reagent formed then gets converted to 2-methyl-1-(2-phenylethyl)cyclohexan-1-ol in acidic medium in the presence of 2-methylcyclohexanone. The intermediate formed underdoes condensation reaction in the presence of H_2SO_4 to yield [2-(2-methylcyclohex-1-en-1-yl) ethyl]benzene. A cyclization step then occurs, yielding 4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene,



Scheme 1: Haworth synthesis of phenanthrene



Scheme 2: Bardhan-Sengupta synthesis of phenanthrene

which then undergoes reduction by Selenium (Se) to produce phenanthrene. (Chakraborty & Saha, 2015)

Pschorr synthesis of phenanthrene

Pschorr reaction or pschorr synthesis is another method used in the synthesis of phenanthrenes. In this, *o*-nitrobenzaldehyde and phenylacetic acid are used as precursors. A chemical reaction occurs between the two precursors, causing the formation of (2E)-3-(2-nitrophenyl)-2-phenylprop-2-enoic acid**.** Its nitro group gets converted to an azo group by diazotization reaction, yielding 2-[(E)-2-carboxy-2-phenylethenyl]benzene-1-diazonium. Then, cyclization reaction occurs to produce 4b,8a-dihydrophenanthrene-9-carboxylic acid**,** which on reduction in the presence of copper, gets converted to phenanthrene-9-carboxylic acid. (DeTar, 2004)

Pharmacological activities of phenanthrene and its derivatives

As discussed earlier, phenanthrene derivatives possess various biological activities including analgesic, cytotoxic, antimalarial, antimicrobial, antioxidant, and

anti-inflammatory. Few of these have been discussed below.

Analgesic activity of phenanthrenes

Eddy N. B. performed an experiment using phenanthrene and four series of its derivatives. The series of phenanthrene derivatives were either substituted on the 2nd, 3rd, or 9th position with either acetyl, carboxylic acid, hydroxyl, or amino functional groups respectively. The drugs used were administered orally in cats. The synthesized derivates were tested for their efficacy as an analgesic in cats. The various parameters such as pain threshold value and latency test were performed to evaluate usefulness of synthesized derivatives. All the synthesized derivatives exhibited analgesic activity, however 3-aminophenanthrene was found to show greatest potency. The compound 2-aminophenanthrene also demonstrated analgesic activity when present in high dose. (EDDY, 1933)

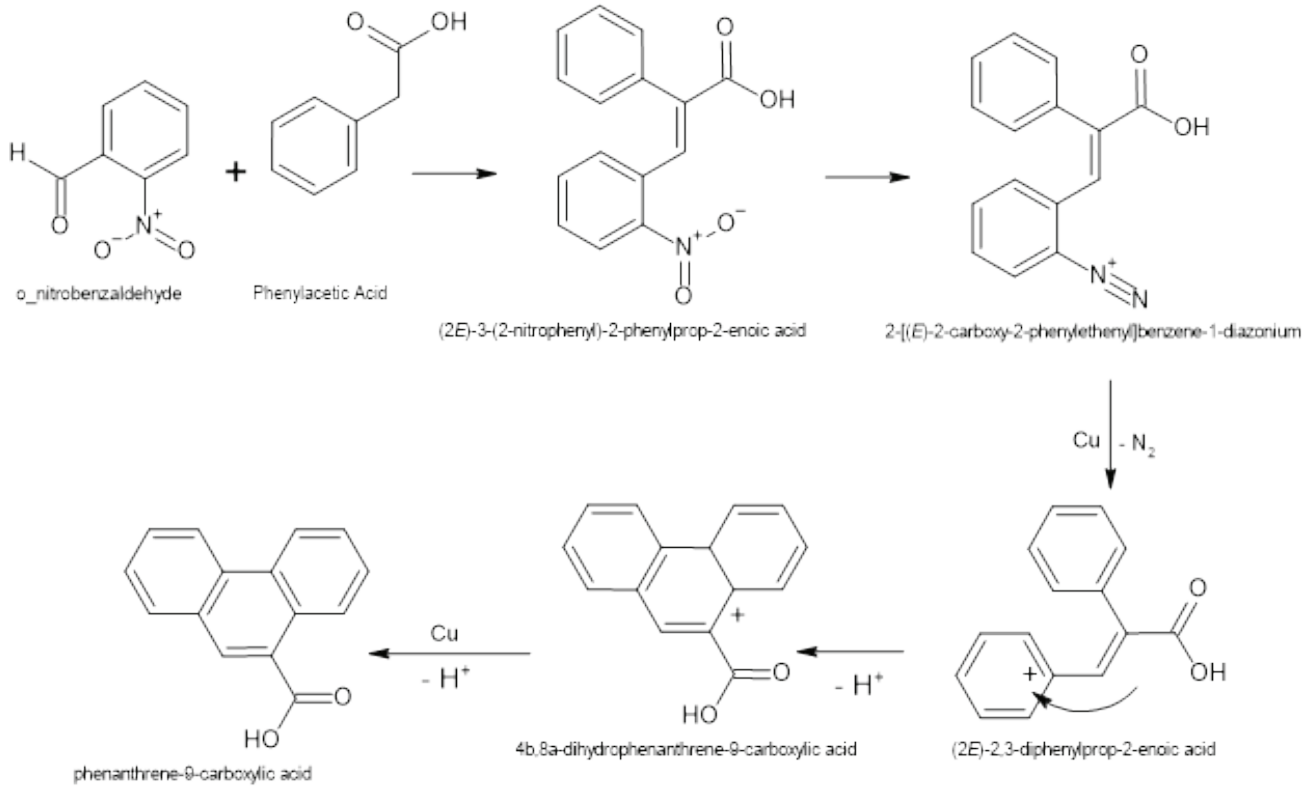
Chen *et al.,* identified six phenanthrene derivatives in 1995 and tested their antiplatelet aggregatory activity. Their activity was carried out using washed rabbit platelet whose aggregation had previously been caused by adenosine 5'-diphosphate, arachidonic acid, collagen, and platelet-activating factor. Out of the compounds tested, it was observed that one completely inhibited platelet aggregation caused by all four factors, two other compounds showed great activity against platelet aggregation caused by arachidonic acid and collagen only, and a different compound was only effective against platelet aggregation caused by collagen. As aspirin was used as the control drug, it may be concluded that the drugs present possess analgesic activity. (Chen *et al.,* 1996)

Cytotoxic Activity

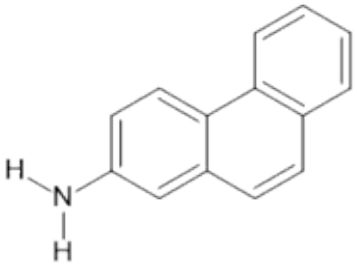
Guédouar *et al.,* also synthesized eight phenanthrene derivatives in 2017 and tested them against human colon cancer and epithelial cell lines. The cytotoxicity of these compounds was determined using the MTT Colorimetric assay method. It was observed that methyl 8-methyl-9,10-dioxo-9,10-dihydrophenanthrene-3-carboxylate was the most potent cytotoxic derivative in that study. Its potency may be attributed to the presence of an ester functional group. (Guédouar *et al.,* 2017)

Bisoli *et al.,* identified five phenanthrene derivatives from the roots and stems of *Combretum laxum* in 2020. The identified compounds were assessed for their cytotoxic activity against five human cancer cell lines. Their antioxidant potency was also checked against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical. These studies were performed in vitro. Upon examination of the compounds, it was observed that 6-Methoxycoelonin showed the greatest activity in terms of cytotoxicity, being selectively higher in non-tumor mammalian cells. However, Callosin displayed the greatest antioxidant activity by scavenging DPPH present in the experiment. (Bisoli *et al.,* 2020)

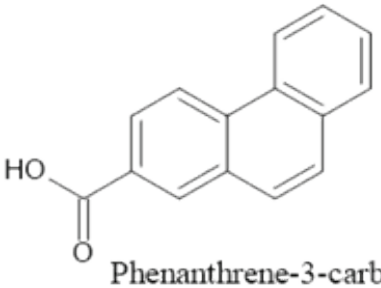
Ma *et al.,* isolated two new phenanthrene



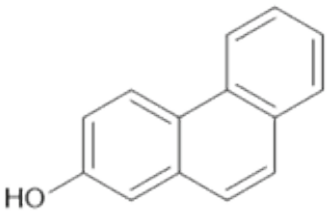
Scheme 3: Pschorr synthesis of phenanthrene



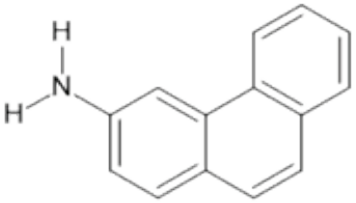
3-aminophenanthrene



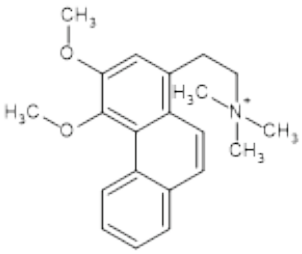
Phenanthrene-3-carboxylic acid



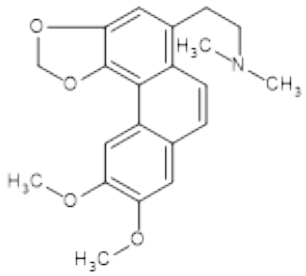
3-hydroxyphenanthrene



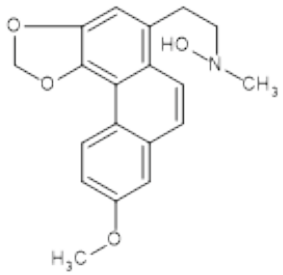
2-aminophenanthrene



2-(3,4-dimethoxyphenanthren-1-yl)-*N,N,N*-trimethylethan-1-aminium



1-(N,N-dimethylethanamin)-6,7-dimethoxy-dioxolano[3,4-a]-phenanthrene



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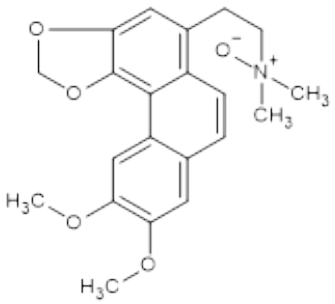
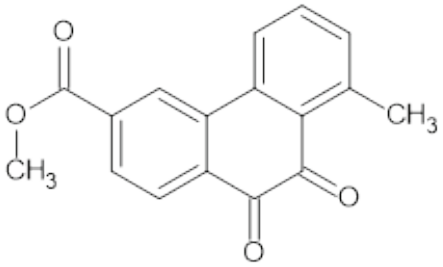
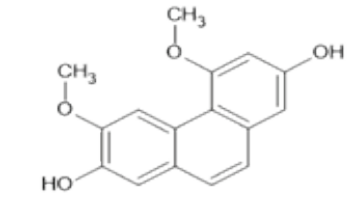


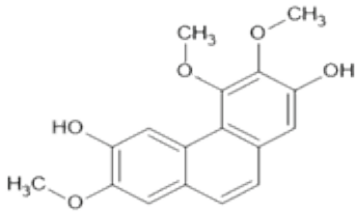
1-(N-oxo-N,N-dimethylethanamin)6,7-dimethoxy-dioxolano[3,4-a]-phenanthrene



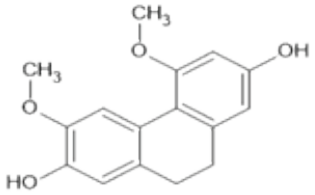
methyl 8-methyl-9,10-dioxo-9,10-dihydrophenanthrene-3-carboxylate



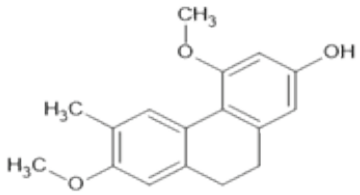
3,5-dimethoxyphenanthrene-2,7-diol



3,4,7-trimethoxyphenanthrene-2,6-diol



3,5-dimethoxy-9,10-dihydrophenanthrene-2,7-diol
6_Methoxycoeloin



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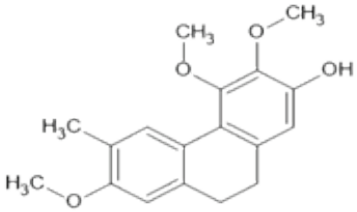
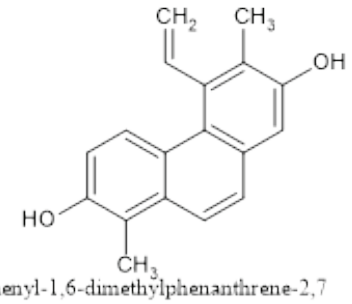
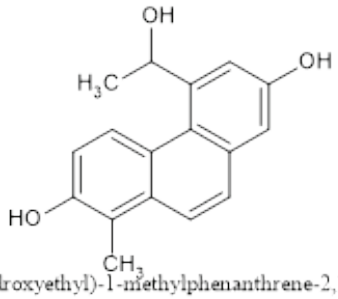


3,4,7-trimethoxy-6-methyl-9,10-dihydrophenanthren-2-ol
Callosin



5-ethenyl-1,6-dimethylphenanthrene-2,7-diol



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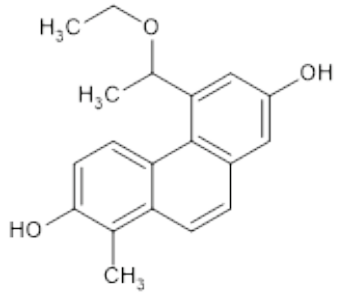

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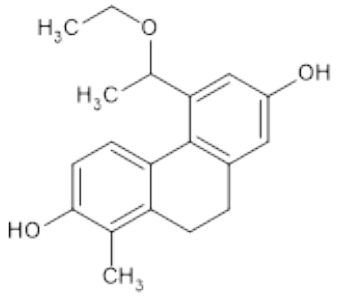

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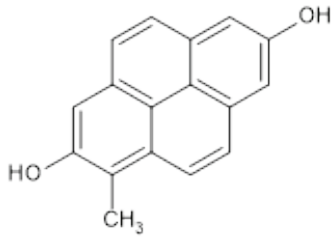
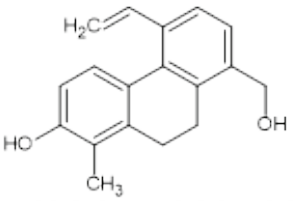


2,7-dihydroxy-1-methylpyrene

derivatives, along with fifteen previously known phenanthrene derivatives from the plant *Juncus effusus*. The new compounds were found to be 8-hydroxymethyl-2-hydroxyl-1-methyl-5-vinyl-9,10-dihydrophenanthrene and 5-(1-methoxyethyl)-1-methyl-phenanthren-2,7-diol. These compounds were then assessed for their cytotoxic activity against five human cancer cell lines using Cell Counting Kit (CCK-8) assay, after which the absorbance of each cell was checked at 450nm using a microplate reader. It was observed that 5-(-1-methoxyethyl)-1-methly-9,10-dihydrophenanthren-2-ol exhibited the greatest cytotoxic activity when used against MCF-7 cell lines, while 2,7-dihydroxy-8-methylphenanthrene-4-carbaldehyde showed the greatest cytotoxic effect against



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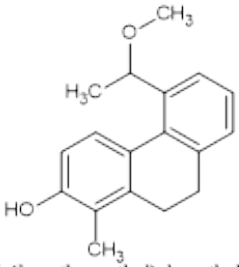

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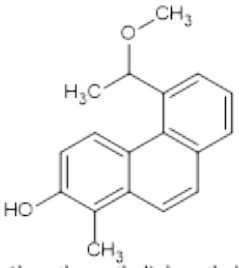

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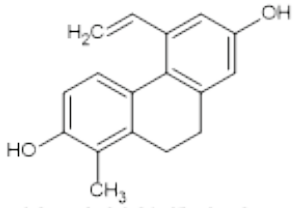

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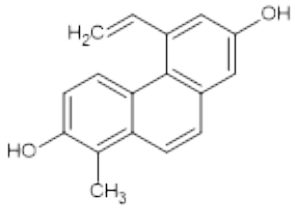
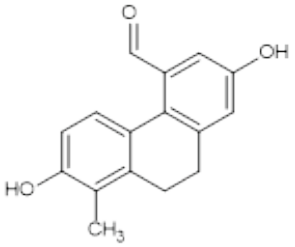
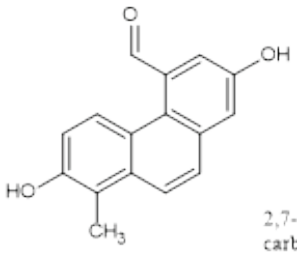


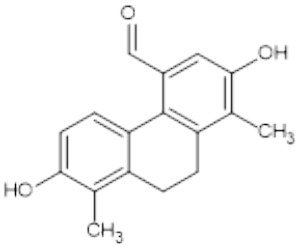
5-ethenyl-1-methylphenanthrene-2,7-diol



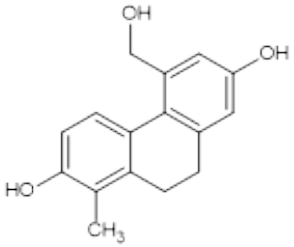
2,7-dihydroxy-8-methyl-9,10-dihydrophenanthrene-4-carbaldehyde



2,7-dihydroxy-8-methylphenanthrene-4-carbaldehyde



2,7-dihydroxy-1,8-dimethyl-9,10-dihydrophenanthrene-4-carbaldehyde



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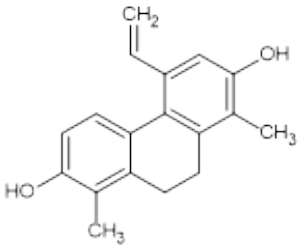

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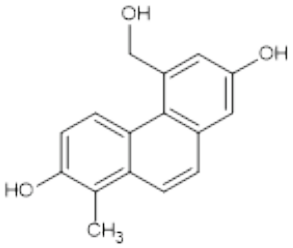

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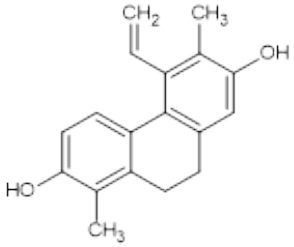
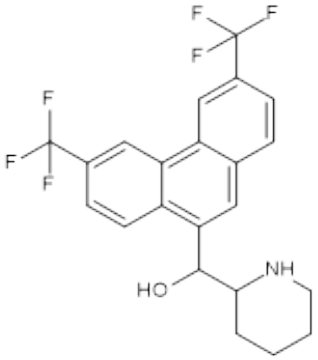
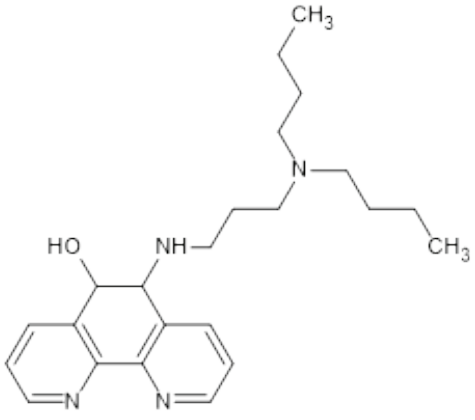


5-ethenyl-1,6-dimethyl-9,10-dihydrophenanthrene-2,7-diol



[3,6-bis(trifluoromethyl)phenanthren-9-yl](piperidin-2-yl)methanol



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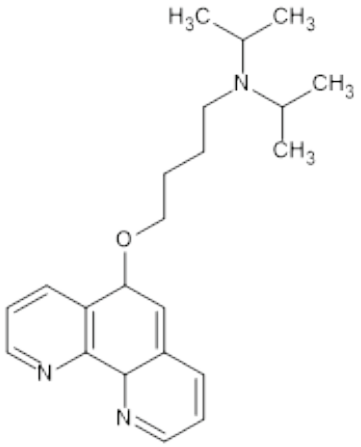
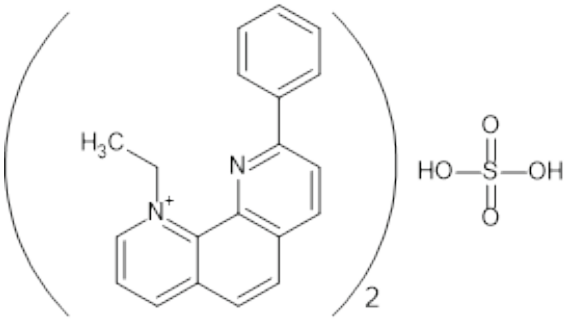


4-(1,10-phenanthroline-5-yloxy)-N,N-dipropylbutan-1-amine



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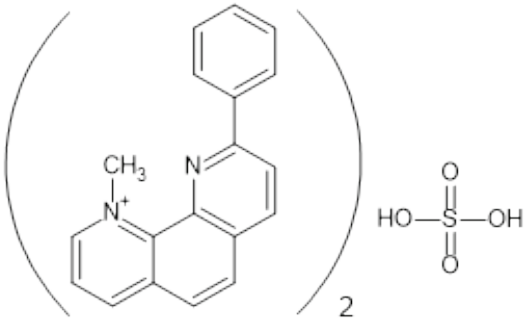

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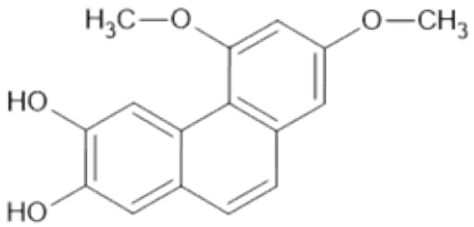
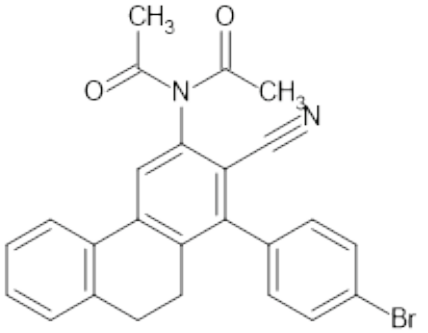
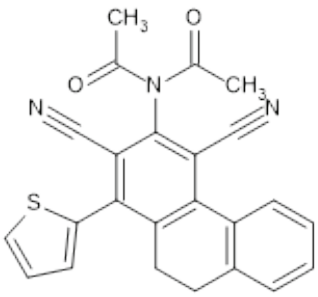


6,7-dihydroxy-2,4-dimethoxyphenanthrene



N-acetyl-*N*-[1-(4-bromophenyl)-2-cyano-9,10-dihydrophenanthren-3-yl]acetamide



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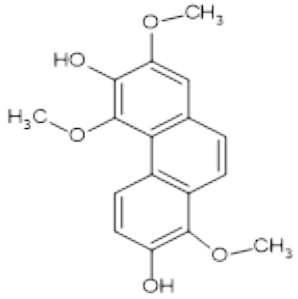
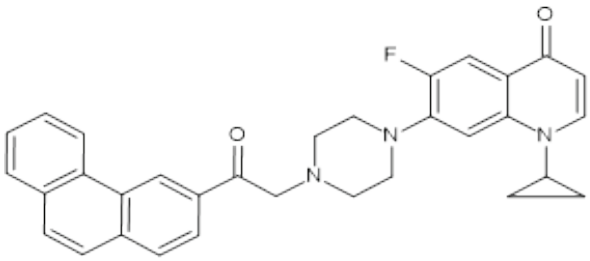
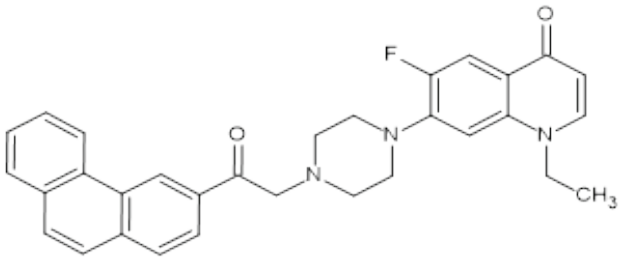


1,5,7-trimethoxyphenanthrene-2,6-diol



6-floro-7-[4-(phenanthrene carbonyl methyl) -piperidine]-1-cyclopropyl-quinoline 4-one



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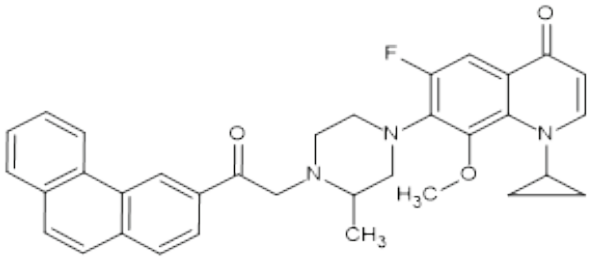

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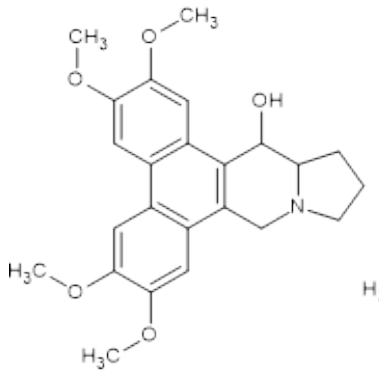
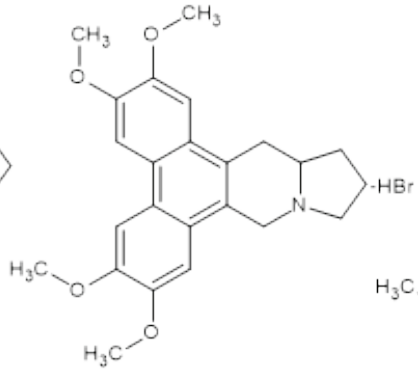
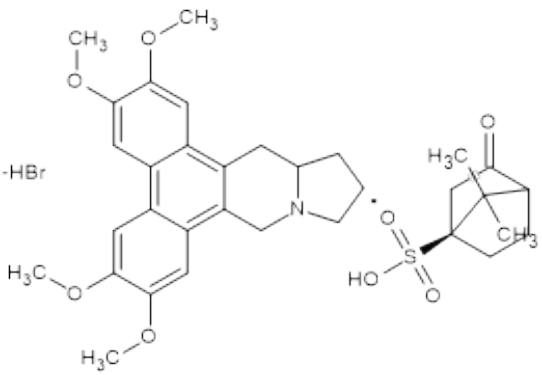


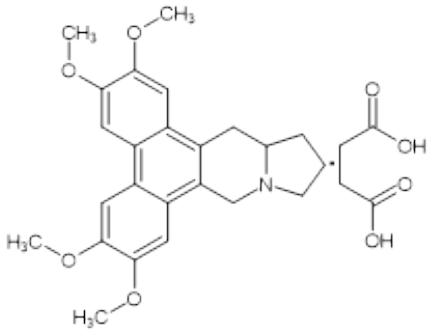
14-hydroxyt ylophorine



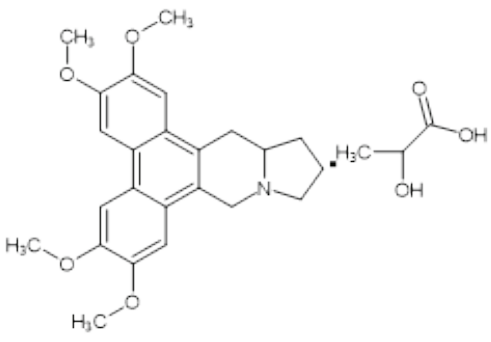
Tylophorine Hydrogen Bromide



Tylophorine camphorsulphonic acid



Tylophorine Succinic acid



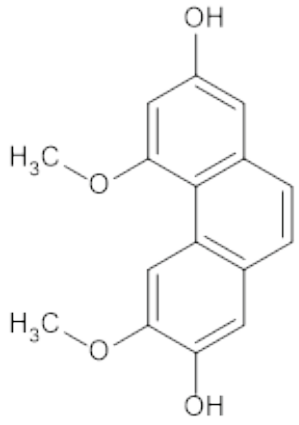
Tylophorine Lactic acid

HepG-2 and Hela cell lines. 2,7-dihydroxy-8-methyl-9,10-dihydrophenanthrene-4-carbaldehyde did not display any cytotoxic activity against the cell samples tested. (Ma *et al.,* 2016)

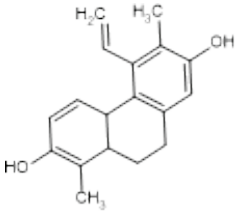
Antimalarial Activity

In 1978, Schmidt *et al.,* examined the activity of 16 phenanthrene derivatives against *Plasmodium falciparum*, a malaria parasite, which had infected owl monkeys. Their activity was compared to a reference drug of know antimalarial activity, 1-(6-bromophenanthren-9-yl)-2-(diheptylamino) ethanol. From the study, (*S*)-[3,6-bis(trifluoromethyl)phenanthren-9-yl]-[(2*R*)-piperidin-2-yl]methanol proved to be the most potent of the drugs used. Its activity is said to be four times that of Chloroquine and fully active against Chloroquine resistant strains of Plasmodium (Schmidt *et al.,* 1978)

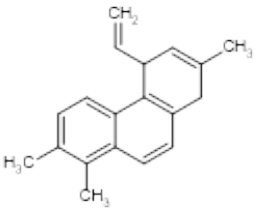
Tahghighi *et al.,* synthesized four phenanthroline



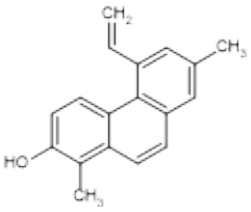
2,7-dihydroxy-4,6-dimethoxy phenanthrene



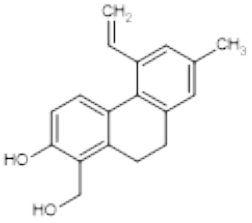
Juncusol



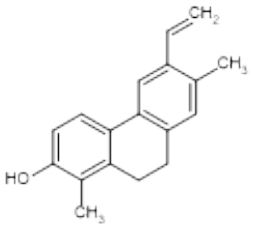
Juncunol



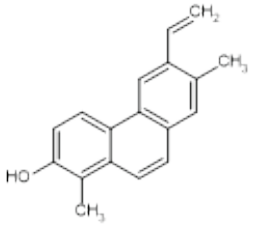
Dehydrojuncunol



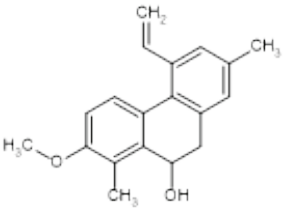
Sylvaticin A



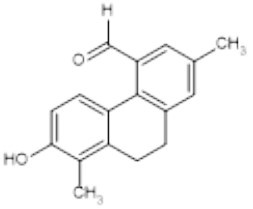
Juncuenin A



Dehydrojuncuenin A



Sylvaticin B



Sylvaticin C

derivatives from 5,6-epoxy-1,10-phenanthroline in 2018. The compounds created were believed to have antimalarial activity due to the possession of an aliphatic side chain bearing a tertiary amine, as present antimalarial compounds possess. The activity of the compounds produced was evaluated using Peter's test, where rats were injected with *Plasmodium berghei*. It was observed that 6-(3-(dibutylamino)propylamino)-5,6-dihydro-1,10-phenanthroline-5-ol and 6-(3-(dibutylamino)propylamino)-5,6-dihydro-1,10-phenanthroline-5-ol showed greatest activity against *Plasmodium berghei* , and thus greatest antimalarial activity, yielding 88.32% and 90.58% respectively. However, the results obtained from 6-(3-(dibutylamino) propylamino)-5,6-dihydro-1,10-phenanthroline-5-ol were obtained upon administration of high doses. (Tahghighi *et al.,* 2018)

Hadanu *et al.,* synthesized two novel phenanthrene derivatives using 8-aminoquinoline as a precursor. The compounds produced were N-methyl-9-phenyl-1,10-phenanthrolinium sulphate and N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate. The synthesized compounds were then assessed for their activity against two strains of chloroquine-resistant *Plasmodium falciparum*; a malaria causing organism. The evaluation was performed in vitro, using a microscopic analysis. Upon analysis, it was observed that (1)-N-ethyl-9-phenyl-1,10-phenanthrolinium sulphate showed greater antimalarial activity against chloroquine-resistant *Plasmodium falciparum* FCR3 strain while (1)-N-methyl-9-phenyl-1,10-phenanthrolinium sulphate showed greater activity against *Plasmodium falciparum* D10 strain (Hadanu *et al.,* 2014)

Antimicrobial activity

Kim *et al.,* isolated and studied three phenanthrene derivatives and two phenanthrequinone derivatives from the plant *Dioscorea batatas* in 2006. The isolated compounds were evaluated for antimicrobial activity, using disk-diffusion assay method. The MIC (Minimum Inhibitory Concentration) and MFC (Minimum Fungicidal Concentration) were the determining parameters of the antimicrobial activity of the drugs. Upon experimentation, 6,7-dihydroxy-2,4-dimethoxyphenanthrene was found to be a potent antimicrobial and antifungal compound. (Kum *et al.,* 2006)

In 2013, Faidallah *et al.,* synthesized 13 phenanthrene derivatives and studied them for antimicrobial and antifungal activities. Their antimicrobial activity was tested against *Staphylococcus aureus* which served as the gram-positive bacteria, and *Escherichia coli*, which served as the gram-negative bacteria. The antifungal activity of these compounds was also determined using *Candida albicans* and *Aspergillus niger*. The method of estimation of activity employed was disc diffusion method and the inhibition zones of each compound was measured. From the synthesized compounds, it was observed that two compounds showed greater activity in terms of antimicrobial and antifungal properties, in comparison with the other compounds synthesized. (Faidallah *et al.,* 2013)

Shamsa *et al.,* synthesized three phenanthrene derivatives from preexisting fluoroquinolones in 2011. The fluoroquinolones used were ciprofloxacin, norfloxacin, and gatifloxacin. The derivatives produced were tested against gram positive and gram-negative bacteria and assessed for their antimicrobial activity by determining the minimum inhibitory concentration (MIC) of the samples. Of the compounds produced, the structure containing ethyl group rather than cyclopropyl ring on first position of piperidine ring showed the greatest activity against both gram positive

and gram-negative bacteria. (Shamsa *et al.,* 2011)

Antioxidant activity

Boudjada *et al.,* isolated seven phenanthrene derivatives out of *Dioscorea communis* in 2018. The structures of the compounds were confirmed using UV, IR, MS, 1D and 2D-NMR techniques. Three of these compounds were evaluated for their antioxidant activity by checking their ability to scavenge DPPH radicals, ABTS cation radical decolorization, cupric reducing antioxidant capacity (CUPRAC), reducing power as well as β-carotene bleaching assays. Of the compounds tested, 1,5,7-trimethoxyphenanthrene-2,6-diol proved to be the most potent in terms of antioxidant activity. Its activity may be attributed to the possession of two hydroxy (-OH) groups. (Boudjada *et al.,* 2019)

Anti-inflammatory activity

In 2019, Lim *et al.,* isolated 2,7-dihydroxy-4,6-dimethoxy phenanthrene from *Dioscorea batatas* which was found to possess anti-inflammatory property. Its anti-inflammatory property was assessed using LPS-stimulated Raw 264.7 macrophage, where it was found to decrease the amount of inflammatory mediators present. (Lim *et al.,* 2019)

Eight phenanthrene derivates were isolated from the shoots of *Luzulu sylvatica* in 2020 by Gainche *et al.,* Their structures were elucidated through HRESIMS, 1D and 2D NMR methods. These compounds were assessed for their anti-inflammatory activity by determining their ability to inhibit ROS production. Upon analysis, it was found that the anti-inflammatory properties of Juncusol, Dehydrojuncunol, and Sylvaticin A were dose dependent. (Gainche *et al.,* 2020)

Wen *et al.,* prepared 34 phenanthrene derivatives from a known Tylophorine drug DCP-3503. The ability of these drugs to induce Foxp3 genes and to hinder production of TNF-α was estimated. Upon evaluation, it was observed that six derivatives enhanced the expression of Foxp3 genes, while eight of these drugs prohibit the formation of TNF-α, thus preventing inflammation. It was observed that increasing water solubility of these drugs caused increased inhibition of TNF-α (Wen *et al.,* 2014).

CONCLUSION

This review demonstrated the significance of the phenanthrene nucleus in the preparation of potent compounds which may be utilized for different pharmacological functions. It proved to be a versatile nucleus since its derivatives has vast uses including antimalarial, cytotoxic, anti-inflammatory and antioxidant. More potent compounds may be synthesized from this nucleus.

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