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Synthesis, Spectral Characterization and Biological Studies of 2-(4-Methoxynaphthalen-1-Yl)-1-(4-Methoxyphenyl)-1H-Phenanthro[9,10-D] Imidazole

Periyasamy Ramanathan*

PG and Research Department of Chemistry, Thanthai Hans Roever College (Autonomous), Bharathidasan University, Perambalur, Tamil Nadu, India

***Corresponding author:** Ramanathan P, Thanthai Hans Roever College (Autonomous), Bharathidasan University, Perambalur, Tamil Nadu, India, Tel: +91-7904500575; E-mail: ramanathanp2010@gmail.com

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Abstract

Synthesised 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro [9,10-d] imidazole has been characterized by ^{1}H, ^{13}C NMR and FT-IR spectral analysis and also biological studies were carried out. The imidazole nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance. The imidazole ring is ionizable aromatic compound, it improves pharmacokinetic characteristics of imidazole molecules and thus used as a medicine to optimize solubility and bioavailability parameters. There are several methods used for the synthesis of imidazole containing compounds and also their various structure reactions offer enormous scope in the field of medicinal chemistry. The imidazole possesses extensive biological activities such as antimicrobial and anticancer activities.

Keywords: Imidazole; ^{1}H, ^{13}C NMR; FT-IR; Antimicrobial; Anticancer activities

Introduction

Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents. Mostly researchers have maintained their interest in sulphur and nitrogen-containing heterocyclic compounds through decades of historical development of organic synthesis but heterocycles with other heteroatoms such as oxygen, phosphorus and selenium also appear [1-4]. There are widespread therapeutic uses of synthetic heterocycles such as antibacterial, antimycobacterial, trypanocidal, anti-HIV activity, genotoxic, herbicidal, analgesic, antiinflammatory, muscle relaxants, antileishmanial agents, anticonvulsant, anticancer, antimalarial, antifungal and lipid peroxidation inhibitor, antitubercular, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents [5-10].

Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20- HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [11-19]. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters [20-22]. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases.

Vijesh et al. carried out the *in vitro* antibacterial activity of newly synthesized compound. *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhimorium*. *Clostridium profingens* and *Pseudomonas aeruginosa* were used to investigate the activity. The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains [23].

Experimental

Materials and methods

R3Phenanthrene-9,10-dione, 4-methoxynaphthaldehyde, 4-methoxy aniline and ammonium acetate were purchased from Sigma Aldrich. A mixture of phenanthrene-9,10-dione (1 mmol), aldehyde (1 mmol), aryl amine (1 mmol), ammonium acetate (1 mmol) and BF_3 (1 mol%) kept under stirring at 80°C for 2 hrs. The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was cooled, dissolved in ether and filtered. The product was purified by column chromatography with benzene: ethyl acetate (9:1) as the eluent (Scheme 1).

Spectral measurements

The FT-IR spectrum of the synthesized compounds was measured in the 4000-400 cm^{-1} region using on SPECTRUM RX I spectrophotometer (Perkin Elmer). The 1 H NMR spectra of imidazole were recorded at room temperature with a Bruker 400 NMR spectrometer at 400 MHz. Proton decoupled ^{13}C NMR spectra of imidazole was obtained at room temperature using a Bruker 400 NMR spectrometer for imidazole.

Antimicrobial studies

Antibacterial studies: The following Gram-positive and Gram-negative strains have been used for the study. 1. *Escherichia coli*; 2. *Salmonella typhi*; 3. *Pseudomonas aeruginosa*; 4. *Staphylococcus aureus*.

Nutrient agar plates were prepared under steriled conditions and incubated overnight to detect contamination. About 0.2 mL of working

stock culture was transferred into separate nutrient agar plates and spreaded thoroughly using a glass spreader. Whatmann No. 1 discs (6 mm in diameter) were impregnated in the test compounds dissolved in DMSO (200 µg/mL) for about half an hour. Commercially available drug disc (Ciprofloxacin 10 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size in DMSO solvent. The discs were placed on the inoculated agar plates and incubated at 37 ± 1°C for about 18-24 hours. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism [24,25].

Antifungal studies: The following fungal strains were used for the study.

1. *Candida albicans*; 2. *Aspergillus niger*; 3. *Mucor*; 4. *Rhizopus sp*.

Sabouraud's dextrose agar (SDA) medium was used for the growth of fungi and testing was done in Sabouraud's dextrose broth (SDB) medium.

The subculture and the viable count were carried out by the same procedure as done in antibacterial studies except the temperature which sound be maintained at 28 ± 1°C for about 72 hours. Similarly, for disc diffusion method, the petri dishes were incubated at 28 ± 1°C for about 72 hours. The same concentration of the test compound, solvent (DMSO) and Amphotericin B (standard) prepared previously were used for the antifungal studies.

In vitro anticancer activities

In vitro anticancer [26-35] activity was determined using a standard MTT assay with protocol appropriate for the individual test system (Abdel-Hafez). In brief, exponentially growing cells were plated in 96-well plates (104 cells/well in 100 µL of medium) and incubated for 24 hrs. Test compounds were prepared prior to the experiment by dissolving in 0.1% DMSO and were diluted with the medium. The cells were then exposed to different concentrations of the drugs (1-100 µm) at a volume of 100 µL/well. Cells in the control wells received the same volume of medium containing 0.1% DMSO. After 24 hrs, the medium was removed, and the cell cultures were incubated with 100 µL MTT reagent (1 mg/mL) for 4 hrs at 37°C. The formazan crystals produced by the viable cells were solubilized by the addition of 100 µL DMSO. The suspension was placed on micro-vibrator for 5 min and the absorbance was recorded at 540 nm by the ELISA reader. The experiment was performed in triplicate. The percentage of anticancer activity was calculated using the formula.

Results and Discussion

IR spectroscopy

Infrared (IR) radiation refers the part of electromagnetic spectrum between the visible and microwave region. Greater practical use to the field of organic chemistry is the limited portion between 4,000 and 400 cm-1. Absorption bands in the spectrum result from energy changes due to molecular vibration of the stretching and bending modes of a bond. Though this absorption is quantized, vibrational spectra appear as bands rather than a line because a single vibrational energy change is accompanying by a number of rotational energy changes. Band positions in infrared spectra are presented either as wavenumber (γ) or wavelength (λ).

Even a very simple organic molecule can give extremely complex infrared spectrum. The organic chemist takes advantage of this complexity when he matched the spectrum of an unknown compound against that of an authentic sample. A peak-by-peak correlation is an excellent evidence for identity. It is unlikely that any two compounds except enantiomers give the same infrared spectrum.

In the present study, IR spectra are utilized in conjugation with other spectral data to determine the molecular structure.

FT-IR spectrum analysis

The FT-IR spectrum of the synthesized compounds was measured in the 4000-400 cm^{-1} region using on SPECTRUM RX I spectrophotometer (Perkin Elmer). The FT-IR spectrum shown in Figure 1, the peaks at 2837 to 3063 cm^{-1} attributed due to C-H stretching vibration of aromatic and aliphatic groups. Absorption band at 1583 cm^{-1} are characteristic for C=N stretching vibration. A band at 1513 cm^{-1} can be easily assigned to C=C stretching mode of phenyl rings. The bands observed at 1456 cm^{-1} were characteristic for the skeletal stretching modes of the unsaturated C-C bonds.

^{1}H and ^{13}C NMR analysis of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole

^{1}H NMR signals are assigned based on their positions multiplicity, integral values and comparison with that of prepared compound signals. ^{1}H and ^{13}C NMR spectra of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole is displayed in Figure 2a.

In general, the aromatic protons are absorbed in the higher frequency region around at 7 ppm due to their magnetic anisotropic effect. In 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole the signals observed in the region of 6.65-8.63 ppm with an expected integral value. Therefore, these signals are unambiguously assigned to aromatic protons. The methoxy proton signals are observed in the region of 3.71, 3.90 ppm as a singlet.

^{13}C NMR spectrum of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole is displayed in Figure 2b. In general, the aromatic carbons could be readily distinguished from the other carbons due to their characteristic absorption around 120 ppm. The ipso carbons are absorbed in the higher frequency region compared to the aromatic carbons. In 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole the signal appeared in the region 101.87-159.16 ppm is due to the aromatic carbons. Methoxy carbon signal is appeared at 54.47, 54.60 ppm.

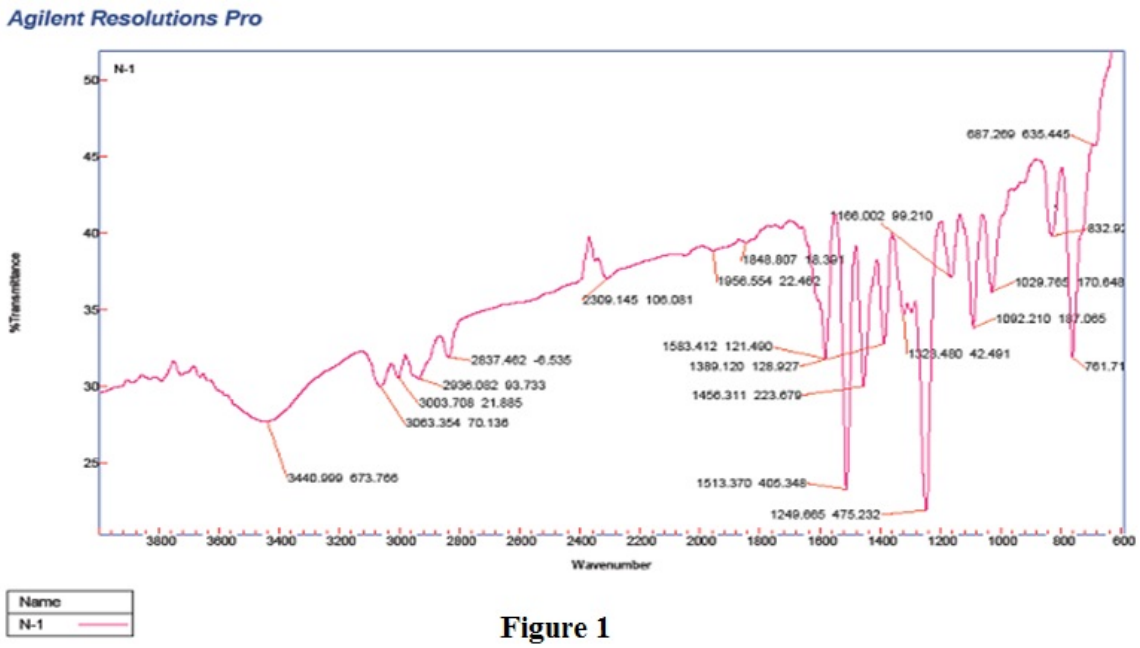

Figure 1

Figure 1: FT-IR Spectrum of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d]imidazole.

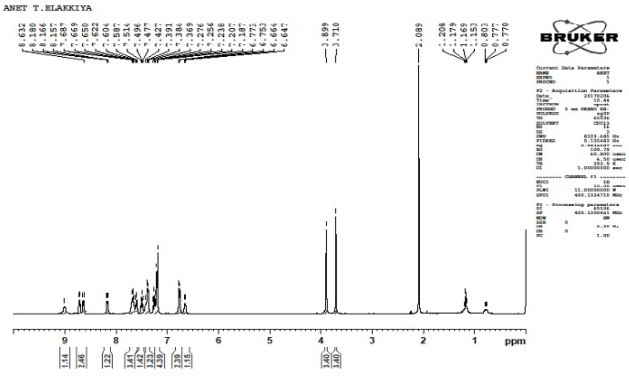

Figure 2a

Figure 2a: ^{1}H NMR spectrum of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole.

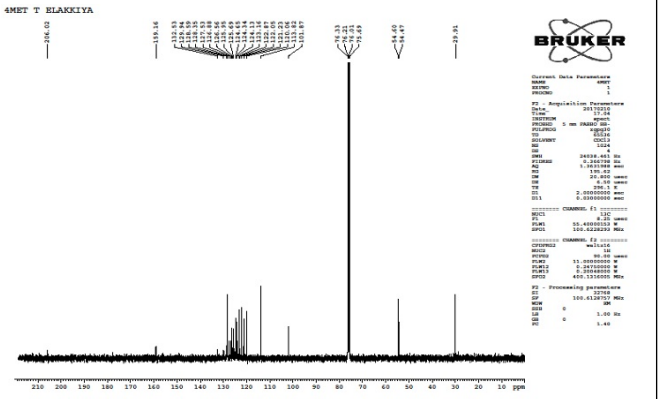

Figure 2b

Figure 2b: ^{13}C NMR spectrum of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d]imidazole.

2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole

Yield: 82%, M.p. 273°C., Molecular Formula $C_{33}H_{24}N_2O_2$: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3 H), 3.90 (s, 3 H), 6.65 (d, J=6.8 Hz, 1 H), 6.76 (d, J=8.0 Hz, 2 H), 7.36 (d, J=8.0 Hz, 1 H), 7.89 (d, J=6.8 Hz, 1 H), 8.73 (d, J=8.0 Hz, 1 H), 8.79 (d, J=8.4 Hz, 1 H), 8.88 (d, J=8.0 Hz, 2 H), 7.52 (t, J=11.6 Hz, 1 H), 7.64 (t, J=15.2 Hz, 1 H), 7.58-7.68 (m, 3 H), 7.18-7.36 (m, 4 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 54.47, 54.60, 10187, 113.82, 120.06, 121.23, 122.05, 122.87, 123.16, 124.13, 124.34, 124.65, 125.69, 125.95, 126.56, 126.88, 127.53, 128.35, 128.59, 129.94, 132.53, 159.16. MS: m/z. 480 [M^+].

Antimicrobial studies

The antimicrobial activity of the 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole is examined using disc diffusion method.

The bacterial strains viz., *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and fungal strains viz., *Candida albicans*, *Aspergillus niger*, *Mucor* and *Rhizopus sp.* are used in this study. Dimethyl sulphoxide is used as a control while Streptomycin and Amphotericin B are used as a reference for bactrial and fungal studies respectively.

The antibacterial studies (Figure 3) revealed that the reported 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole against *S. aureus*, *S. typhi* and *E. coli* shows considerable inhibition activity whereas imidazole against *P. aeruginosa* lower inhibition activity against the bacterial strains (Table 1).

The antifungal studies (Figure 4) revealed that the reported 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole against *Candida albicans*, *Aspergillus niger* and *Mucor* exhibit moderate to maximum activity against the reported fungal strains. Whereas, 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole against Rhizopus sp. lower inhibition activity against the fungal strains (Table 2).

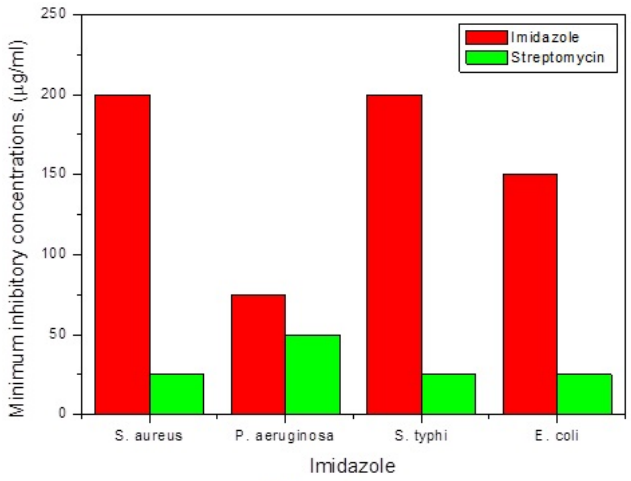

Figure 3

Figure 3: Minimum inhibitory concentration of antibacterial activities of imidazole.

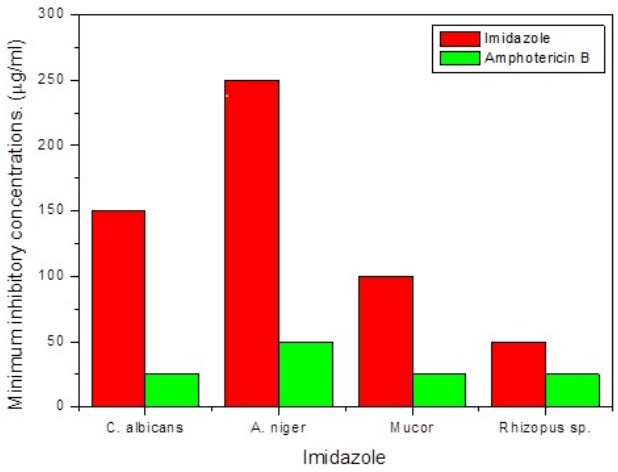

Figure 4

Figure 4: Minimum inhibitory concentration of antifungal activities of imidazole.

Cytotoxic activity evaluation by MTT assay

The synthesized compounds subjected for the *in vitro* anticancer effect of spirooxindole in KB cancer cell line. Spirooxindole treatment (24 h incubation) significantly decreased percentage of cell viability in KB cancer cells. This suggested that spirooxindole treatment was able to inhibit the growth of cancer cells during incubation. The response of cytotoxicity of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole with their concentrations are given in Figure 5. These results indicate that 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole and efficient candidate for monitoring changes in the intracellular concentrations under certain biological conditions in order to test its cytotoxicity. We performed MTT assay in KB cancer cells which is treated with same concentrations of compounds for up to 24 h and the imidazole exhibit moderate anticancer activities.

Minimum inhibitory concentrations (µg ml^{-1})	Imidazole	Streptomycin
S. aureus	200	25
P. aeruginosa	75	50
S. typhi	200	25
E. coli	150	25

Table 1: Minimum inhibitory concentration of antibacterial activities of imidazole.

Minimum inhibitory concentrations (µg ml^{-1})	Imidazole	Amphotericin B
C. albicans	150	25
A. niger	250	50

Mucor	100	25
Rhizopus sp.	50	25

Table 2: Minimum inhibitory concentration of antifungal activities of imidazole.

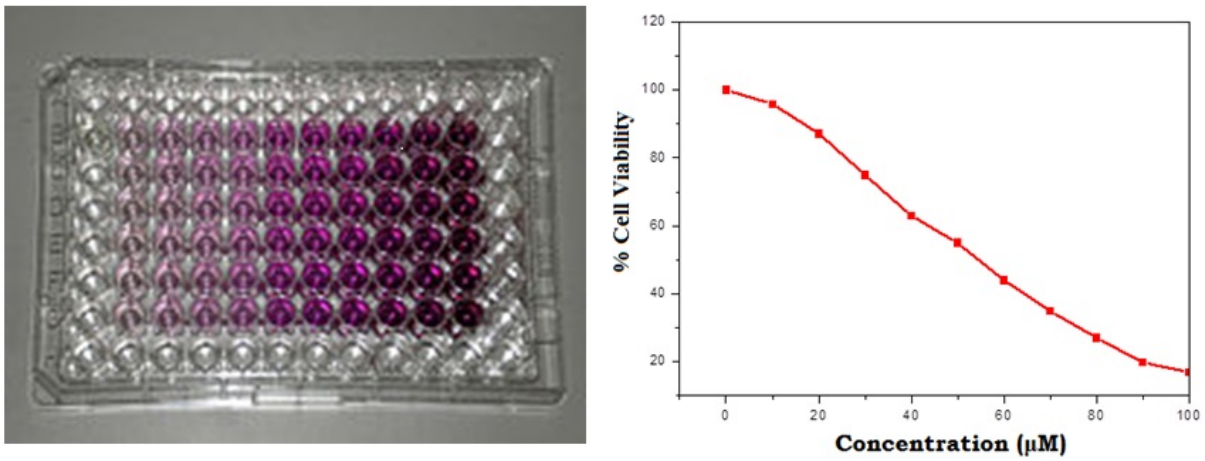

Figure 5

Figure 5: Cytotoxic effect of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxy phenyl)-1H-phenanthro[9,10-d] imidazole on KB cells by MTT assay.

Conclusion

The 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-d] imidazole were characterized by IR and ^{1}H and ^{13}C NMR. Antibacterial studies revealed that the reported imidazole against *E. coli*, *S. typhi* and *S. aureus* shows considerable inhibition activity whereas *P. aeruginosa* lower inhibition activity against the bacterial strains. Antifungal studies revealed that the reported imidazole against *Candida albicans*, *Aspergillus niger* and *Mucor* exhibit moderate to maximum activity against the reported fungal strains whereas against *Rhizopus sp.* lower inhibition activity against the fungal strains. MTT assay in KB cancer cells which is treated with same concentrations of compounds for up to 24 h and the imidazole exhibit moderate anticancer activities.

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