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SYNTHESIS OF POLYCYCLIC CHRYSENE-IMIDAZOLE DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

Alpesh T. Shiyani[*1], Suranjana V. Mayani[*1], Navnath B. Shinde[*2] and Dharmesh G. Shah[*3]

[1*]*Department of Chemistry, Marwadi University, Rajkot-Morbi Road, P.O. Gauridad, Rajkot-360003, India, surajana.mayani@marwadieducation.edu.in; Shiyani_alpesh72@yahoo.com*
[2] *Lewens Labs Pvt. Ltd., Dahej, Dist. Bharuch-392130, India, navnayh1983@gmail.com*
[3] *CadilaHealthcate Ltd., DabhasaUmaraya Road, Padra, Dist. Vadodara-391440, India, dgshah68@gmail.com*

Abstract:
A novel series of chrysene imidazole derivatives were synthesized and evaluated for their antimicrobial properties. For this 6-Chrysenecarboxaldehyde was treated with the Ammonium hydroxide and benzoin product to give imidazole derivative. The structures of the synthesized compounds were confirmed by physio-chemical test and spectral techniques, representative samples were screened for their antimicrobial activity. The antimicrobial activity of the synthesized compounds was assessed against a panel of Gram-positive and Gram-negative bacteria. The study highlights the potential of chrysene imidazole derivatives as novel antimicrobial agents, and provides a foundation for further research into their structure-activity relationships and potential applications in medicinal chemistry.

Keywords: 6-Chrysenecarboxaldehyde, Benzoin, Imidazole derivatives.

Introduction:

Chemical compounds that include heterocyclic nuclei have significant chemotherapeutic properties and serve as an approach for the advancement of new pharmaceuticals. There are numerous heterocyclic compounds widely used in clinical practice for the treatment of infectious disorders. Hence, the significance of drugs containing heterocyclic rings is considerable.[i] Nitrogen-containing heterocyclic rings are common structural components of commercialized drugs. Among these heterocycles,the first synthesis of imidazole was conducted by Heinrich Debus.[ii] The synthesis of imidazole initiated by the combination of glyoxal and formaldehyde in ammonia resulted in the formation of glyoxaline, the end product.[iii] Although yielding quite low quantities, this synthesis is still employed for the production of C-substituted imidazole's[iv]. Imidazole is a five membered heterocyclic ring system characterized by the presence of both aza (-N=) and amine (-NH-) nitrogen atoms in the ring.[v]Imidazole/fused imidazole rings are present in a wide range of bioactive

compounds. Imidazole is a significant nitrogen-based heterocyclic chemical essential for human functions.[vi] Encompassed within the fields of chemical sciences, biological sciences, and materials science, it serves as a catalyst in the synthesis of compounds and the development of novel pharmaceuticals.[vii]The unique properties of such structures, including high polarity and the ability to participate in hydrogen bonding and coordination chemistry, allow them to interact with a wide range of biomolecules, and imidazole-/fused imidazole-containing compounds are reported to have a broad spectrum of biological activities.[viii]

Chrysene derivatives have garnered considerable interest in recent times in light of their wide range of biological actions, encompassing antibacterial, anti-inflammatory, and anticancer features.[ix] The broad-spectrum antibacterial activity of imidazole derivatives renders them a compelling framework for the advancement of novel antimicrobial drugs.[x] The integration of chrysene and imidazole chemical groups has the potential to generate new molecules that exhibit improved biological properties.[xi]

In this study, we aimed to synthesize novel chrysene imidazole derivatives and evaluate their antimicrobial activity against a panel of bacterial and fungal strains. The synthesis of these derivatives was achieved through a multi-step reaction involving the condensation of chrysene-6-carbaldehyde with various imidazole derivatives. These ring systems are key components of structural scaffolds occurring in modern medicinal chemistry, thus forming critical building blocks for new drug design. Compounds containing an imidazole ring display a wide range of pharmacological activities including anticancer, antibacterial, antiviral, antiepileptic, antitubercular, and antifungal activities. Moreover, derivatives of polycyclic imidazole have excellent pharmacological activity.

Methodology

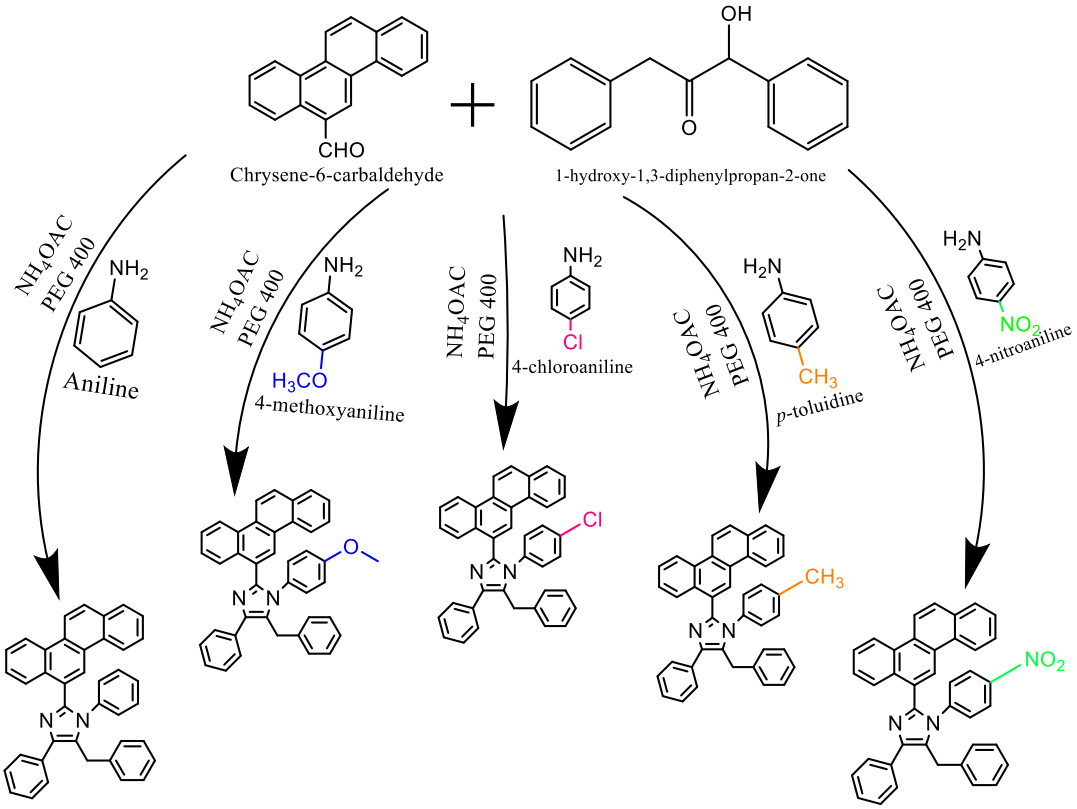
The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δppm).

C, H, N elimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General procedure for Synthesis of Chrysene Imidazole Derivative:

All compounds were prepared using the same procedure. A mixture of compound, different aromatic amine (1mole equivalent), 6-Chrysenecarboxaldehyde (1.0mole equivalent), Benzoin product (1 mole equivalent), ammonium acetate (1mole equivalent) and PEG 400 was refluxed for 5-6hrs, Progress of the reaction mass was monitored by TLC. Upon completion reaction mass was quenched in water and extracted in organic solvents (Dichloromethane, Toluene, hexane and Ethyl acetate etc). Organic layer was separated, concentrated to get Product.

Reaction Scheme



Results and Discussion:

In the present study, a series of 6-Chrysene carboxaldehyde and different aromatic amine with Benzoin product and ammonium acetate to give imidazole derivative were designed and synthesized, it involves one step, the compound 1 to 5 were synthesized in high yields. The representative compounds were evaluated for antimicrobial activity, which showed promising activity. The structure of all the synthesized compounds were characterized on the basis of the chemical and spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and elemental analysis techniques.

5-benzyl-2-(chrysen-6-yl)-1,4-diphenyl-1H-imidazole (1):

Yield=72%

Anal. Calcd for $C_{40}H_{28}N_2$: C, 89.6; H, 5.0; N, 5.4. Found C, 89.7; H, 5.10; N, 5.2.

IR (cm-1): 1420 (C-N stretching), 1035 (N-H bending).

^{1}H NMR (DMSO-d6, δ/ ppm): 3.75 (d, 2H, CH_2), 7.20 – 8.95 (m,36H,Ar-H).

^{13}CNMR(DMSO-d6,δ/ppm): 29.6 (-CH_2), 146.8 (Ar-C-N), 122-150 (Ar-C).

LCMS;m/z:536

5-benzyl-2-(chrysen-6-yl)-1-(4-methoxyphenyl)-4-phenyl-1H-imidazole (2):

Yield=66%

Anal. Calcd for $C_{41}H_{30}N_2O$: C, 86.90; H, 5.32; N, 4.92; O, 2.86. Found C, 86.90; H, 5.30; N, 4.92; O, 2.88.

IR (cm-1): 1420 (C-N stretching), 1035 (N-H bending), 1130 (C-O-C stretching),

^{1}H NMR (DMSO-d6, δ/ ppm): 3.81 (s, 3H,O-CH3), 3.75 (d, 2H, CH_2), 6.96– 9.10 (m, 36H,Ar-H),

^{13}CNMR(DMSO-d6,δ/ppm):29.9 (-CH_2), 55.7 (-CH_3), 159 (Ar-C-O), 146.3 (Ar-C-N),

122-150 (Ar-C).
LCMS;m/z:566

5-benzyl-1-(4-chlorophenyl)-2-(chrysen-6-yl)-4-phenyl-1H-imidazole (3):
Yield=79%
Anal. Calcd for $C_{40}H_{27}N_2Cl$: C, 84.10; H, 4.70; N, 4.90; Cl, 6.30. Found C, 84.15; H, 4.69; N, 4.90; Cl, 6.26.
IR (cm-1): 1420 (C-N stretching), 1035 (N-H bending), 1615 (CH=N stretching), 740 (C-Cl strong)
^{1}H NMR (DMSO-d6, δ/ ppm): 3.75 (d, 2H, CH_2), 7.05 – 9.10 (m, 38H,Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm):29.5 (-CH_2), 132.9 (Ar-C-Cl),146.5 (Ar-C-N), 122-150 (Ar-C).
LCMS;m/z:570

5-benzyl-2-(chrysen-6-yl)-4-phenyl-1-(p-tolyl)-1H-imidazole (4):
Yield=78%
Anal. Calcd for $C_{41}H_{30}N_2$: C, 89.50; H, 5.30; N, 5.20. Found C, 89.45; H, 5.30; N, 5.25.
IR (cm-1): 1420 (C-N stretching), 1035 (N-H bending).
^{1}H NMR (DMSO-d6, δ/ ppm): 2.34 (s, 3H, CH_3), 3.75 (d, 2H, CH_2), 7.05 – 9.10 (m, 36H,Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm):21.3 (-CH_3), 29.6 (-CH_2), 147.2 (Ar-C-N), 122-150 (Ar-C).
LCMS;m/z:550

5-benzyl-2-(chrysen-6-yl)-1-(4-nitrophenyl)-4-phenyl-1H-imidazole (5):
Yield=89%
Anal. Calcd for $C_{40}H_{27}N_3O_3$: C, 82.65; H, 4.70; N, 7.20; O, 5.45. Found C, 82.60; H, 4.75; N, 7.20; O, 5.45.
IR (cm-1): 1420 (C-N stretching), 1035 (N-H bending), 1360, 1545 (N-O, NO_2 stretching)
^{1}H NMR (DMSO-d6, δ/ ppm): 3.72 (d, 2H, CH_2), 7.05 – 9.10 (m, 38H,Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm):29.6 (-CH_2), 147.2 (Ar-C-N), 146.4 (Ar-C-NO2), 122-150 (Ar-C).
LCMS;m/z:582

Antimicrobial activities
All the newly synthesized compounds were evaluated for their antimicrobial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheria using disc diffusion method. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in **TABLE I**.

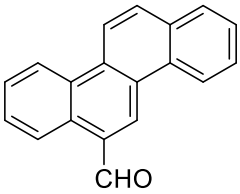
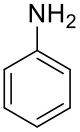
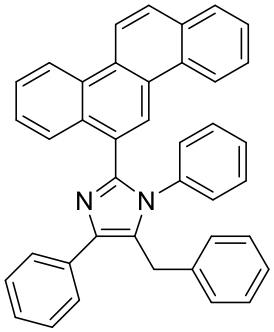
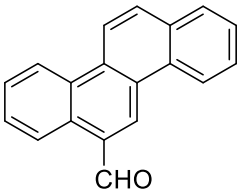
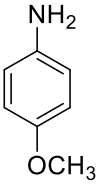
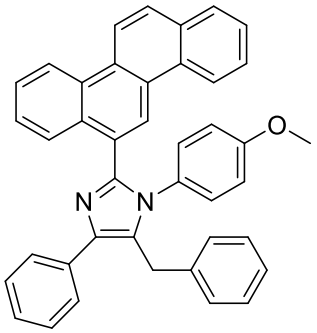
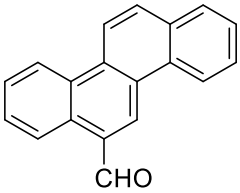
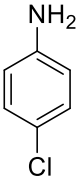
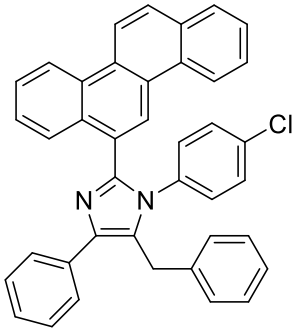
Table-I. **Antimicrobial activities of some newly synthesized compounds.**

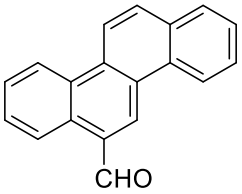
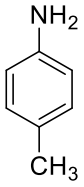
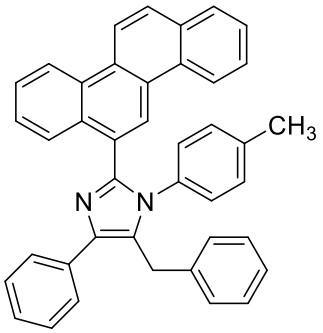
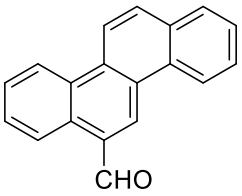
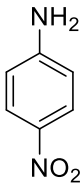
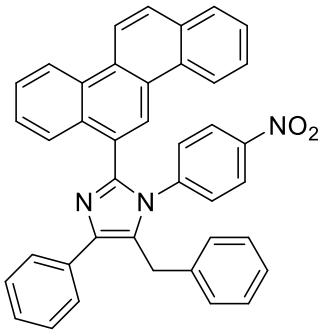
Compds	Inhibition Zone(mm)			
	Gram-negative		Gram-positive	
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*
1	16	15	19	22
2	18	15	18	20
3	16	15	20	18

4	19	20	20	22
5	15	14	19	18
DMSO	0	0	0	0
Ampicilin®	22	21	20	22

E.coli.=Escherichiacoli;P.Putide=PseudomonasPutide;B.Subtilis=Bacillus Subtilis; S. lactis = Sterptococcuslactis.

The sensitivity of microorganisms to the tested compounds is identified in the following manner*;
Highly Sensitive = Inhibition zone:15-20 mm
Moderately Sensitive=Inhibitionzone:10-15mm
Slightly Sensitive = Inhibition zone: 5-10 mm
Not Sensitive=Inhibitionzone:0 mm
*Each result represents the average of triplicate readings.

Sr. No.	Aldehyde	Amine	Product	Time	Isolated Yield
1				1-2hrs	72%
2				3-4hrs	66%
3				2-3hrs	79%

4				5-6hrs	78%
5				3-4hrs	89%

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