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EVALUATION OF ANTIMICROBIAL AND ANTIFUNGAL PROPERTIES OF NEW CHRYSENE-PHENOTHIAZINE DERIVATIVES

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Abstract:
A novel series of Chrysene–Phenothiazine derivatives was synthesized via the Buchwald–Hartwig C–N coupling reaction using 6-Bromochrysene and substituted phenothiazine derivatives. The reaction employed palladium catalysis under inert conditions with appropriate ligands and bases to achieve efficient N-arylation at the phenothiazine nitrogen. This strategy enabled the formation of C–N bonds between the polyaromatic chrysene core and electronically modified phenothiazine units, providing structurally diverse heterocyclic hybrids. All compounds were purified and characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry to confirm the desired molecular architecture. Preliminary antimicrobial and antifungal screening was performed using the agar well diffusion method, indicating that halogenated analogues displayed better activity profiles. Overall, this work demonstrates the utility of Buchwald–Hartwig amination as a robust synthetic route for accessing polycyclic nitrogen-bridged heterocycles with potential bioactivity.

Keywords: 6-Chlorochrysene, Phenothiazine derivatives, C-N coupling, Antimicrobial and Antifungal activity.

Introduction:
Polycyclic aromatic hydrocarbons (PAHs), such as chrysene, have drawn considerable interest in the fields of medicinal and materials chemistry due to their rigid, π-conjugated structures and favorable electronic characteristics. Functionalized chrysene scaffolds have demonstrated significant biological potential, including antimicrobial, anticancer, and anti-inflammatory activities[i-iv]. Likewise, phenothiazine, a tricyclic heterocyclic system containing nitrogen and sulfur atoms, is a well-established pharmacophore known for its wide spectrum of bioactivity, including antipsychotic, antimicrobial, and antioxidant properties[v-ix].
The combination of chrysene and phenothiazine into a single molecular framework is a promising strategy for the development of new hybrid molecules with synergistic and enhanced biological properties. In this study, a novel series of chrysene–phenothiazine derivatives was synthesized via the Buchwald–Hartwig C–N coupling reaction—a robust and widely used

palladium-catalyzed method for carbon–nitrogen bond formation[x-xii]. Substituted phenothiazine derivatives bearing electron-withdrawing groups such as chloro, fluoro, bromo, cyano, and ester were successfully coupled with 6-Bromochrysene under inert reaction conditions.

The aim of this research is to develop a new synthetic route for constructing nitrogen-bridged polyheterocyclic systems, investigate the impact of electronic effects on reactivity and product stability, and explore the preliminary antimicrobial and antifungal potential of the synthesized compounds[xiii-xix]. The novelty of this work lies in the fusion of two pharmacologically important scaffolds using a transition-metal-catalyzed C–N bond formation strategy an underexplored approach for these systems.

The manuscript is structured as follows: the experimental section details the synthetic procedures and spectral characterization; the results and discussion provide insight into reaction outcomes and biological activity profiles; and the conclusion highlights the overall significance and future directions of the study.

Materials and Methods:

All chemicals were purchased commercially and used without prior purification. Reagents and solvents were obtained from Sigma-Aldrich, Merck, or SD Fine Chemicals. All reactions were carried out in oven-dried glassware under an inert nitrogen atmosphere. 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 and ^{13}C NMR spectra were obtained on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO using TMS as the internal reference. Mass spectra were recorded on a ESI-MS system.

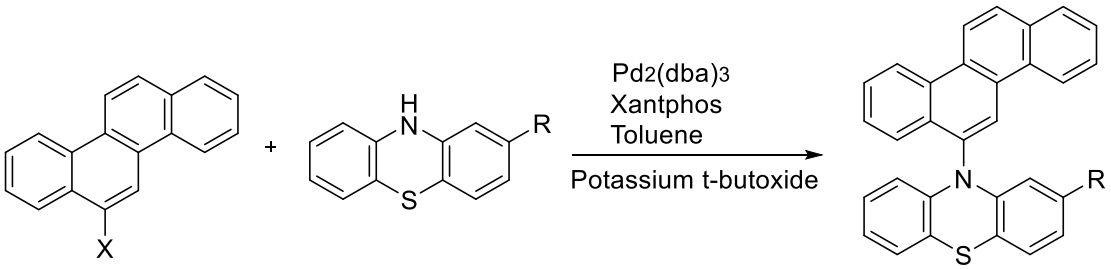
General procedure for Synthesis of Phenothiazine Derivative:

All compounds were prepared using the same procedure. In a dry round-bottom flask, a mixture of 6-Bromochrysene (1mole equivalent), appropriate substituted Phenothiazine derivatives (1.1mole equivalent), bis(dibenzylidene acetone) palladium(0) [$Pd_2(dba)_3$, 0.05mole equivalent], and 4,5-bis(diphenyl phosphino)-9,9-dimethylxanthene (Xantphos, 0.10mole equivalent) was dissolved in anhydrous toluene (10 mL) under a nitrogen atmosphere. Potassium tert-butoxide (2.0mole equivalent) was added as a base, and the reaction mixture was heated at 110 to 130 °C under reflux with stirring for 12-24 hours.

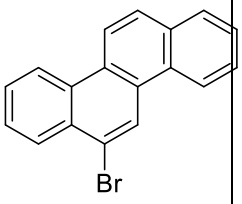
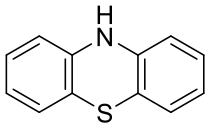
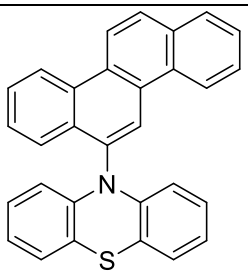
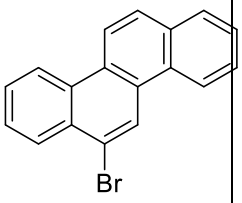
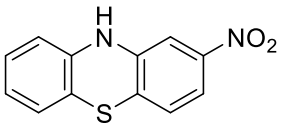
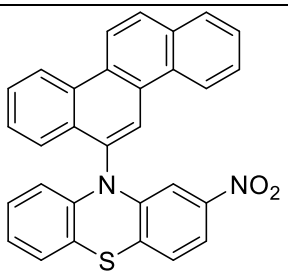
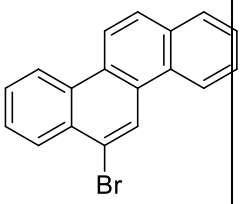
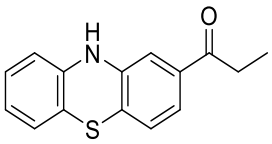
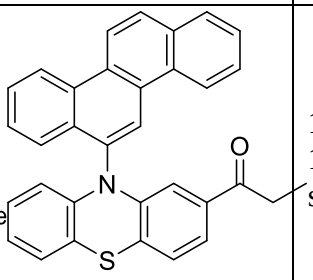
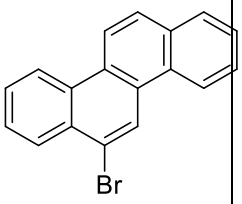
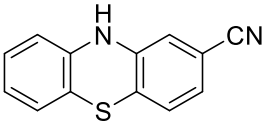
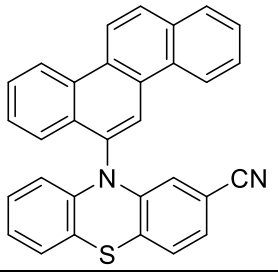
The progress of the reaction was monitored by thin-layer chromatography (TLC). On TLC four to five spot observed. Upon completion, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was filtered to remove any solids and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using a hexane:ethyl acetate (9:1) mixture as eluent to afford the target chrysene–phenothiazine derivatives in moderate to good yield.

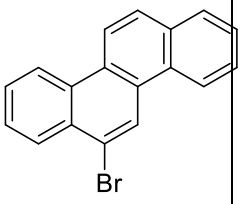
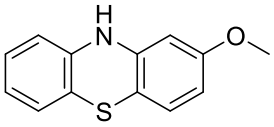
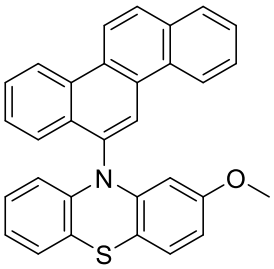
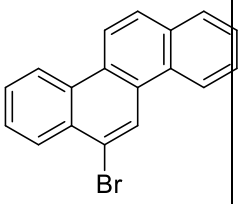
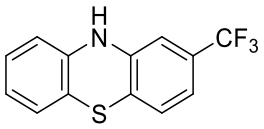
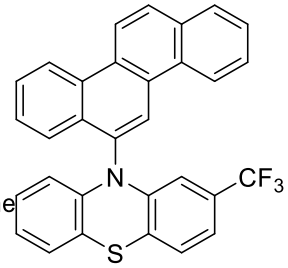
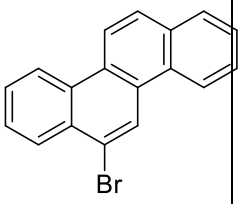
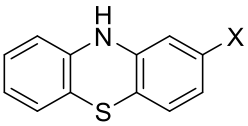
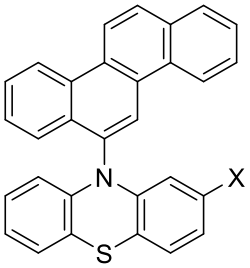
All final compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry to confirm their structures and purity.

Reaction Scheme



Where X= F,Cl, Br, I
R = H, CF3, CN, -CH3 , -COCH2CH3, NO2, X

Sr. No.	Bromo Chrysene	Phenothiazine derivatives	Product	Time	Isolated Yield
1		 Phenothiazine		12-14hrs	52%
2		 2-Nitro Phenothiazine		15-17hrs	56%
3		 1-Phenothiazine-2-yl-propan-1-one		12-14hrs	49%
4		 2-Cyano Phenothiazine		15-16hrs	58%

5		 2-methoxy-phenothiazine		16-18hrs	52%
6		 2-(trifluoromethyl) Phenothiazine		16-18hrs	60%
7				16-18hrs	50-60%

RESULTS AND DISCUSSION

Spectral analysis

The physical and spectral measurements of the synthesized compounds are given below.

10-(chrysen-6-yl)-10H-phenothiazine (1):
Yield=52%
IR (cm-1): 1320 (C-N stretching), 700 (C-S bending).
^{1}H NMR (DMSO-d6, δ/ ppm): 6.5 to 8.5ppm (m, 18H, Ar-H)
^{13}CNMR(DMSO-d6,δ/ppm): Phenothiazine C-N (142ppm), Chrysene C-N (139ppm), Phenothiazine C-S (121ppm), 25Aromatic carbon (116-133ppm)
LCMS;m/z: 426.7

10-(chrysen-6-yl)-2-nitro-10H-phenothiazine (2):
Yield=56%
IR (cm-1): 1280 (C-N stretching), 695 (C-S bending), 1545 (N-O, NO_2 stretching)
^{1}H NMR (DMSO-d6, δ/ ppm): 6.5 to 8.5ppm (m, 18H, Ar-H)
^{13}CNMR(DMSO-d6,δ/ppm): Phenothiazine C-N (142 & 144ppm), Chrysene C-N (139ppm), Phenothiazine C-S (121 & 127ppm), Nitro C-N (147.7ppm), 24 Aromatic carbon (116-133ppm)
LCMS;m/z: 472.1

1-(10-(chrysen-6-yl)-10H-phenothiazin-2-yl)propan-1-one (3):
Yield=49%

IR (cm-1): 1275 (C-N stretching), 700 (C-S bending), 1690 (C=O stretching)
^{1}H NMR (DMSO-d6, δ/ ppm): 1.25 (t, 3H, CH_3), 3.5 (q, 2H, CH_2), 6.5 – 9.00 (m, 21H, Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm): -C=O (197ppm), -CH_2 (11ppm), -CH_3 (33ppm), Phenothiazine C-N (143ppm), Chrysene C-N (139ppm), Phenothiazine C-S (122 & 127ppm), 25 Aromatic carbon (116-133ppm)
LCMS;m/z: 482.8

10-(chrysen-6-yl)-10H-phenothiazine-2-carbonitrile (4):
Yield=58%
IR (cm-1): 2220 (-CN stretching), 700 (C-S bending), 1420 (C-N stretching).
^{1}H NMR (DMSO-d6, δ/ ppm): 6.9 – 8.8 (m, 18H, Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm): -CN (118ppm), Phenothiazine C-N (144ppm), Chrysene C-N (139ppm), Phenothiazine C-S (122 & 127ppm), 25 Aromatic carbon (110-133ppm)
LCMS;m/z: 451.8

10-(chrysen-6-yl)-2-methoxy-10H-phenothiazine (5):
Yield=52%
IR (cm-1): 2860 (O-CH_3 stretching), 1230 (C-O bending), 685 (C-S bending).
^{1}H NMR (DMSO-d6, δ/ ppm): 3.75 (s, 3H, CH_3), 7.05 – 9.10 (m, 18H, Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm): -C-O (160ppm), -CH_3 (56ppm), Phenothiazine C-N (143ppm), Chrysene C-N (139ppm), Phenothiazine C-S (119 & 121ppm), 24 Aromatic carbon (116-133ppm)
LCMS;m/z: 456.3

10-(chrysen-6-yl)-2-(trifluoromethyl)-10H-phenothiazine (6):
Yield=60%
IR (cm-1): 1315 (CF_3 stretching), 1410 (C-N stretching), 685 (C-S bending).
^{1}H NMR (DMSO-d6, δ/ ppm): 6.90 – 8.90 (m, 18H, Ar-H).
^{13}CNMR(DMSO-d6,δ/ppm): -C-F (130ppm), Phenothiazine C-N (143ppm), Chrysene C-N (139ppm), Phenothiazine C-S (121 & 125ppm), 25 Aromatic carbon (116-133ppm)
LCMS;m/z: 494.6

Antimicrobial and Antifungal activities

All the newly synthesized compounds were evaluated for their antimicrobial activity against gram-negative bacteria, E. coli and P. Putide and gram-positive bacteria, B. Subtilis and S. lactis and antifungal activity against Fungi, A. niger and P. Sp. and Yeast C. Albicans 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 and Antifungal activities of some newly synthesized compounds.**

Compounds	Inhibition Zone(mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
1	20	16	18	20	19	10	9
2	17	15	19	20	18	10	8
3	17	16	17	21	19	11	8
4	21	18	16	18	21	12	12

5	20	17	16	19	19	10	9
6	19	16	15	17	18	11	9
DMSO	0	0	0	0	0	0	0
Ampicilin®	24	20	19	22	24	14	14

E.coli.=Escherichiacoli; P.Putide=Pseudomonas Putide; B.Subtilis=Bacillus Subtilis; S. lactis = Sterptococcus lactis; A. niger= Aspergillus niger; P.Sp.= Penicillium Sp; C. Albicans= Candida Albicans

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.

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