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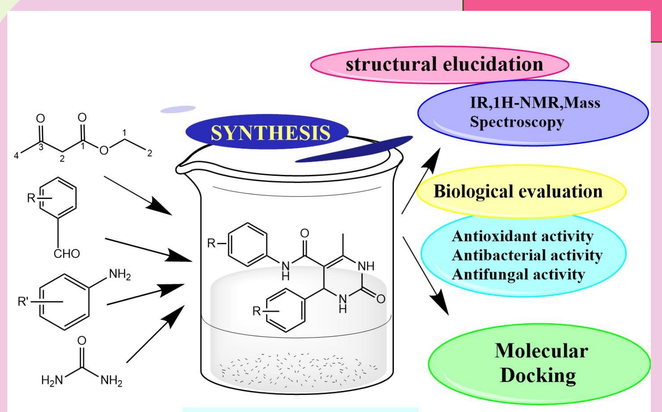
MDPI

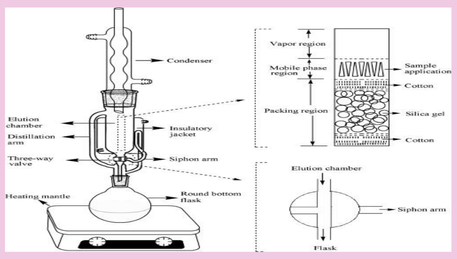
DESIGN, SYNTHESIS OF SOME NOVEL (DHPMS) ANALOGUES AS MULTIFUNCTIONAL THERAPEUTICS: MOLECULAR DOCKING, AND BIOEVALUATION"

INTRODUCTION

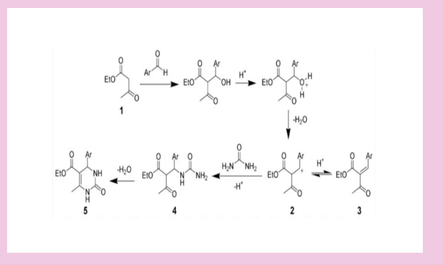
- AN EFFICIENT AND ENVIRONMENTALLY BENIGN MULTICOMPONENT REACTION (MCR) STRATEGY WAS EMPLOYED FOR THE SYNTHESIS OF 5-CARBOXAMIDE-SUBSTITUTED 1,2,3,4-TETRAHYDROPYRIMIDINE-2(1H)-ONES (DHPMS).
- THE SYNTHESIZED DERIVATIVES WERE CHARACTERIZED USING IR, MASS SPECTROMETRY, ^{1}H NMR, AND ^{13}C NMR TECHNIQUES.
- THEIR BIOLOGICAL POTENTIAL WAS ASSESSED THROUGH IN VITRO ANTIOXIDANT, ANTIBACTERIAL, AND ANTIFUNGAL ASSAYS.
- MOLECULAR DOCKING WAS PERFORMED AGAINST SELECTED PROTEIN TARGETS TO ELUCIDATE BINDING MODES AND RECEPTOR–LIGAND INTERACTIONS. DOCKING RESULTS REVEALED STABLE HYDROGEN BONDING AND π–π STACKING INTERACTIONS, WHICH CORRELATE WELL WITH THE EXPERIMENTAL FINDINGS.
- OVERALL, THE SYNTHESIZED DHPM DERIVATIVES, PARTICULARLY THOSE BEARING HETEROARYL SUBSTITUTIONS, DEMONSTRATED STRONG PHARMACOLOGICAL POTENTIAL AND REPRESENT PROMISING SCAFFOLDS FOR FUTURE DRUG DEVELOPMENT AND STRUCTURE–ACTIVITY RELATIONSHIP (SAR) INVESTIGATIONS.

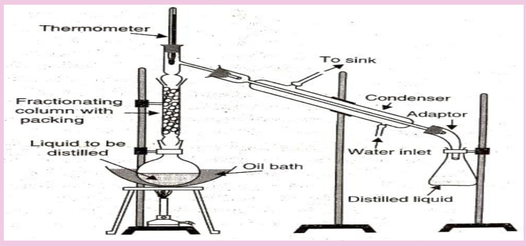
MATERIAL AND METHODS



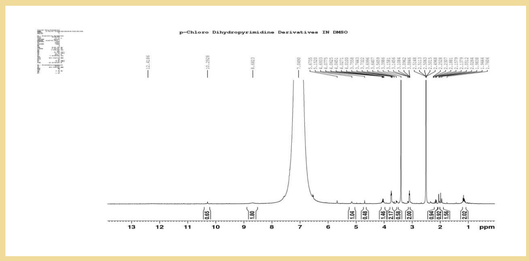


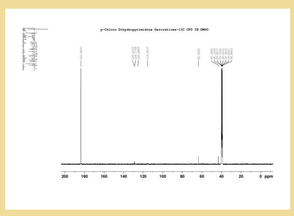
COMPOUNDS	-R	M.P (·C)	% YIELD
NG I	-4NO_2	160-165	78
NG II	-2NO_2	180-185	76
NG III	-4CL	220-250	90
NG IV	-4BR	175-180	82
NG V	-2,4NO_2	178-182	79
NG VI	-4OCH_3	182-185	71
NG VII	-4CH_3	183-185	76
NG VIII	-4SO_3H	200-220	82

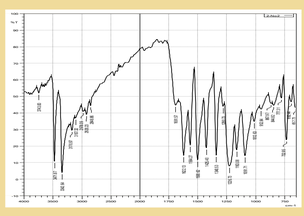




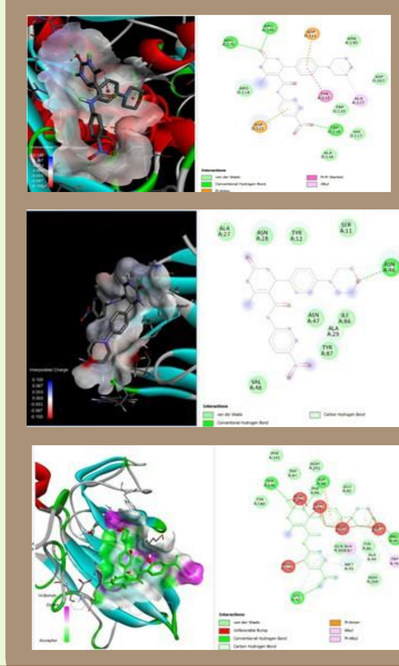
RESULT AND DISCUSSION



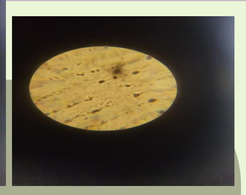




MOLECULAR DOCKING



ANTIBACTERIAL



EVALUATION CRITERIA:-

A.CONTROL (NO ANTIBACTERIAL AGENT):

B.~10^{8} CFU/ML

C.HIGHLY ACTIVE SAMPLES:

D.~10^{2}–10^{3} CFU/ML

E.MODERATELY ACTIVE:

~10^{4}–10^{5} CFU/ML

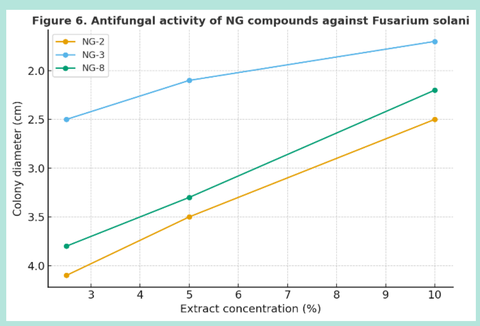
F.LOW ACTIVITY:

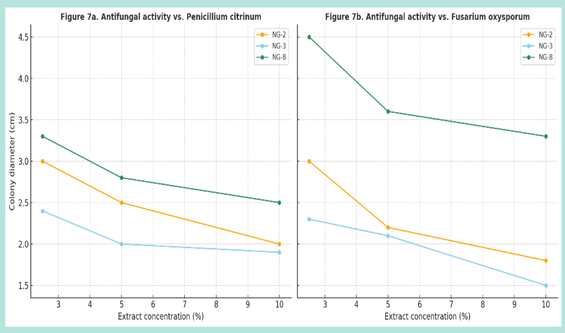
G.~10^{6}–10^{7} CFU/ML

SR. NO.	COMPOUND NAME	ANTIBACTERIAL ACTIVITY (CFU/ML)			
		GRAM +VE BACTERIA		GRAM –VE BACTERIA	
		S.AUREUS	S.PYOGENES	E.COLI	P.AERUGINOSA
1	NG I	1.6×10^{6}	2.2×10^{6}	6.0×10^{7}	7.7×10^{7}
2	NG II	5.3×10^{5}	7.1×10^{5}	2.6×10^{6}	3.5×10^{6}
3	NG III	1.7×10^{4}	2.3×10^{4}	8.0×10^{5}	1.5×10^{6}
4	NG IV	6.3×10^{3}	9.4×10^{3}	2.5×10^{5}	3.7×10^{5}
5	NG V	2.1×10^{3}	3.2×10^{3}	6.9×10^{4}	1.2×10^{5}
6	NG VI	7.8×10^{2}	1.3×10^{3}	3.2×10^{4}	6.4×10^{4}
7	NG VII	3.4×10^{2}	5.9×10^{2}	1.4×10^{4}	2.8×10^{4}
8	NG VIII	1.6×10^{2}	2.8×10^{2}	8.7×10^{3}	1.9×10^{4}

ANTIFUNGAL

THE ANTIFUNGAL POTENTIAL OF NG EXTRACTS WAS TESTED AGAINST *FUSARIUM SOLANI*, *PENICILLIUM CITRINUM*, AND *FUSARIUM OXYSPORUM* AT CONCENTRATIONS OF 2.5%, 5%, AND 10%.FOR *F. SOLANI* (FIGURE 6),



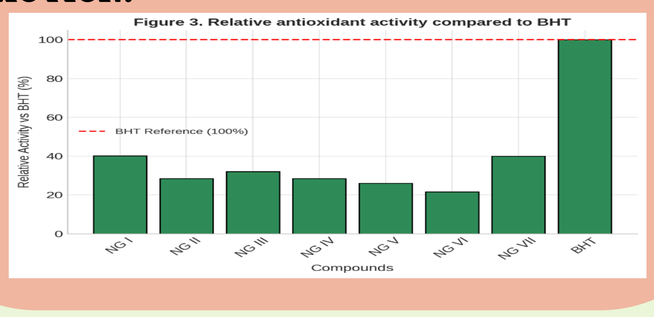


ANTIOXIDANT

REACTIVE OXYGEN SPECIES (ROS) AND FREE RADICALS SIGNIFICANTLY CONTRIBUTE TO OXIDATIVE STRESS, A CONDITION IMPLICATED IN VARIOUS CHRONIC DISEASES, INCLUDING CANCER.

ANTIOXIDANTS ARE AGENTS CAPABLE OF NEUTRALIZING ROS, THUS PLAYING A VITAL ROLE IN DISEASE PREVENTION AND HEALTH PROMOTION.

SR.NO	COMPOUND	IC_{50} (MEAN ± SD)
1	NG I	41.05 ± 0.16
2	NG II	58.05 ± 0.91
3	NG III	51.34 ± 0.11
4	NG IV	58.06 ± 0.25
5	NG V	63.27 ± 0.36
6	NG VI	76.09 ± 0.28
7	NG VII	41.23 ± 0.44
STD.	BHT	16.47 ± 0.35



MOLECULAR DOCKING INVESTIGATIONS WERE CONDUCTED FOR THE SYNTHESIZED COMPOUNDS AGAINST A PANEL OF SIX TARGET PROTEINS TO IDENTIFY THE MOST SUITABLE TARGET BASED ON BINDING AFFINITIES. TARGETS.

PDB ID	RESOLUTION (Å)	BINDING AFFINITY (KCAL/MOL)
7M4	2.20	-8.0
6WDP	2.50	-6.9
1AUN	2.50	-7.9
1A28	2.40	-9.4
1G6E	2.60	-6.4
8C7M	2.50	-8.0

CONCLUSION

AN ECO-FRIENDLY MULTICOMPONENT STRATEGY ENABLED THE SYNTHESIS OF NOVEL DHPM DERIVATIVES WITH CONFIRMED STRUCTURES AND SIGNIFICANT ANTIOXIDANT, ANTIBACTERIAL, AND ANTIFUNGAL ACTIVITIES. COMPOUNDS NG I, NG III, NG VII, AND NG VIII SHOWED THE HIGHEST POTENCY, SUPPORTED BY STRONG MOLECULAR DOCKING INTERACTIONS. THESE DERIVATIVES REPRESENT PROMISING SCAFFOLDS FOR MULTIFUNCTIONAL THERAPEUTIC DEVELOPMENT.

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