chemistry proceedings

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Design, Synthesis, Molecular Docking and Biological Evaluation of Some Novel 1,2,3,4-Tetrahydropyrimidine-2-(1H)-ones (DHPMs) Analogues: Antibacterial, Antifungal and Antioxidant Activity †

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† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

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. Antibacterial activity was evaluated against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa*, with several compounds exhibiting significant activity comparable or superior to standard drugs. Antioxidant screening identified promising radical scavenging activity among selected derivatives. Antifungal studies further confirmed broad-spectrum efficacy. In addition, 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.

Keywords: tetrahydropyrimidine carboxamide derivatives; 6-Methyl-4-(4-morpholinophenyl)-N-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (DPPH); antibacterial activity; antifungal activity; antioxidant activity; molecular coupling

Academic Editor(s): Name

Published: date

Citation: Gaidhane, N.S.; Magar, B.K.; Shinde, D.W.; Sangshetti, J.N. Design, Synthesis, Molecular Docking and Biological Evaluation of Some Novel 1,2,3,4-Tetrahydropyrimidine-2-(1H)-ones (DHPMs) Analogues: Antibacterial, Antifungal and Antioxidant Activity. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

1. Introduction

Multicomponent one-pot reactions have emerged as efficient strategies for construct-ing com- plex molecules from simple, readily available starting materials. These methods are highly valued in organic synthesis due to their numerous benefits, including structural diversity, simple reaction pathways, cost-effectiveness, easy accessibility of reagents and

catalysts, reduced reaction time, and eco-friendly nature[1–3]. Pyrimidine-based compounds have played a crucial role in the pharmaceutical industry due to their wide range of biological activities, including antitumor, antihypertensive, antimicrobial, antiviral, antioxidant, antitubercular, and anti-inflammatory effects. Several clinically approved drugs contain a pyrimidine core, high- lighting its therapeutic significance [17–21]. Examples include 5-fluorouracil, cytarabine, floxuridine, stavudine, zidovudine, and etravirine, each showing various pharmacological application.

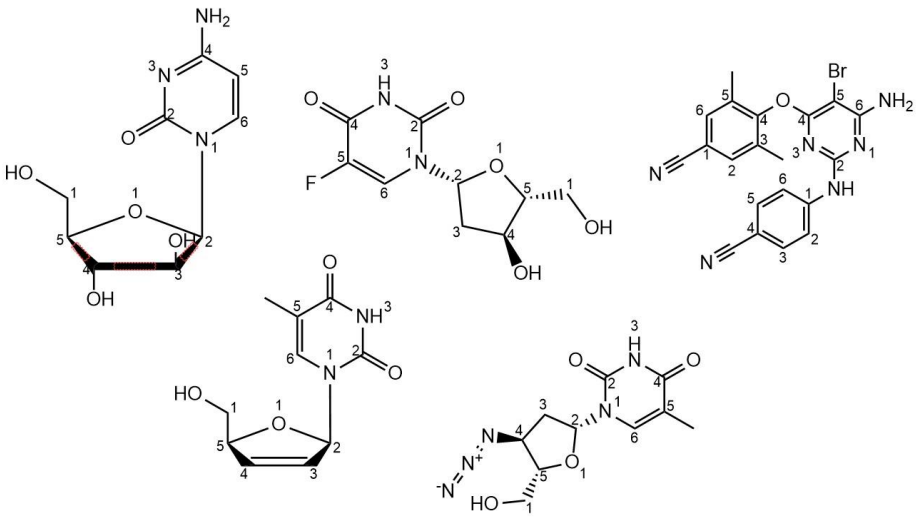


Figure 1. Structures of currently marketed drugs having Pyrimidine nucleus.

PyRx, an open source docking software, was employed to determine the most suitable protein targets for the designed compounds [4–6]. It allows high-throughput screening of multiple compound libraries, starting from job setup to submission and result evaluation. With its user-friendly interface, PyRx serves as a valuable platform for computer-assisted drug design and incorporates the Autodock Vina docking engine through its docking wizard. The results can be visually examined using the embedded Python Molecular Viewer (ePMV), while all data are systematically stored in a database [7–9].

In the present study, our objective is to identify cell-specific compounds that exhibit enhanced biological activity without inducing toxic effects. To achieve this, we designed a series of pyrimidine derivatives, among which a subset of compounds were successfully synthesized and evaluated for their biological potential [10–13].

2. Material and Methods

Chemistry

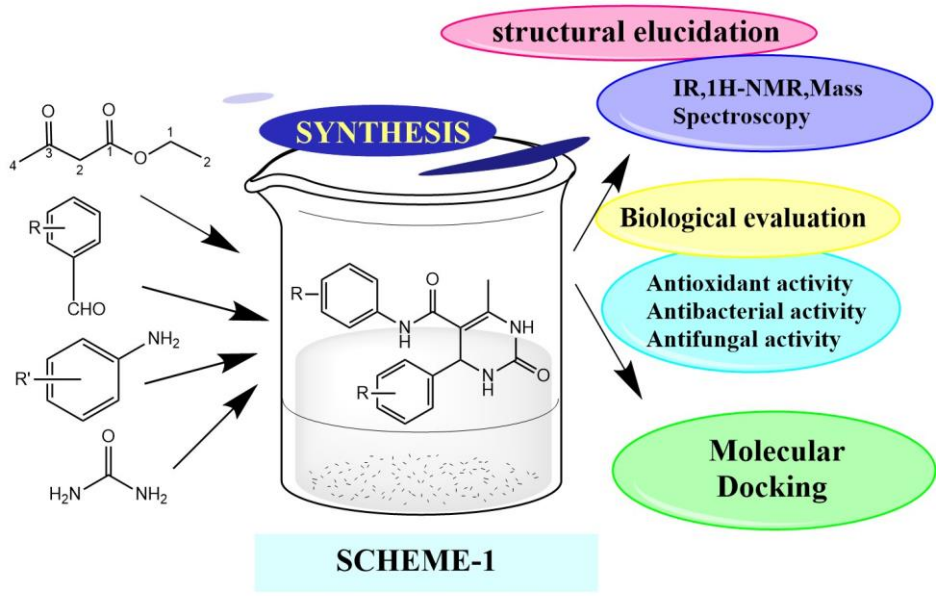
Our initial focus was directed toward readily available derivatives to evaluate their catalytic efficiency in the multicomponent reaction. These compounds were chosen based on their accessibility, non-toxic nature, and environmentally benign characteristics, aligning with the principles of green chemistry.

All solvents and reagents used in this study were of analytical grade and obtained from commercial suppliers without any further purification. The progress of the reactions and the purity of the synthesized compounds were monitored using thin layer chromatography (TLC), with visualization under UV light. Melting points were determined using an open capillary tube apparatus and are reported uncorrected. Elemental analyses were carried out using a standard elemental analyzer. Infrared (IR) spectra were recorded on an FT/IR 6000 Fourier transform infrared spectrometer (Japan) using the KBr pellet

method, and the results are reported in wavenumbers (ν, cm^{-1}). ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts for ^{13}C NMR spectra are expressed in parts per million (δ, ppm) downfield from TMS. The observed splitting patterns are denoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Mass spectra (MS) were obtained using a GC–MS spectrometer.

General procedure for synthesis of 6-methyl-4-(4-morpholinophenyl)-N-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

In this study, a series of pyrimidine derivatives (NG I–VIII) was synthesized for the evaluation of their biological activities. The synthesis was carried out by one-pot synthesis of a substituted benzaldehyde, urea, substituted aniline, and ethyl acetoacetate in a round bottom flask in the presence of a catalytic amount of hydrochloric acid, and solvent methanol and DMF, as illustrated in Scheme 1.



Scheme 1. Caption.

6-methyl-4-(4-morpholinophenyl)-N-(4-nitrophenyl)-2-oxo1,2,3,4tetrahydropyrimidine-5-carboxamide.

1310–1250 cm^{-1} (C–N stretching amide), 3400–3200 cm^{-1} (N–H stretching amide), 3148 cm^{-1} (Aromatic C–H stretching), 1670 cm^{-1} (C=O stretching amide carbonyl), 1520 cm^{-1} (N=O stretching (NO_2), 1580 cm^{-1} (C=C, aromatic ring), 780–710 cm^{-1} (C–H). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.26 (s, 3H), 3.15–3.73 (t, 2H, J = 6–8 Hz), 6.65–6.71 (d, Ar–H, J = 7–8 Hz), 7.56 (s, NH), 9.09 (s, NH), 9.53 (s, NH), 7.82–8.17 (d, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 66.3 (CH_2), 150.2 (C–NH), 147.6 (Ar–C), 146.2 (=CH_2), 53.8 (CH), 171.3 (C=O–NH), 17.5 (CH_3), 112.7 (Ar–C), 126.3 (CH).MS (LCMS, m/z): 437.17 (100.0%), 438.17 (23.8%), 439.18 (2.7%). Anal. Calcd for $C_{22}H_{23}N_5O_5$ (437.46): C, 60.40; H, 5.30; N, 16.01; O, 18.2. Found: C, 60.40; H, 5.30; N, 16.01; O, 18.2.

6-methyl-4-(4-morpholinophenyl)-N-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1334 (C-N), 1643 (NH–C=O), 1670 (C=O), 3150 (Ar–H), 3220 (NH), 1532 (NO_2).^{1}H NMR (DMSO-d_6, δ, ppm): 2.22 (s, 3H), 3.18–3.75 (t, 2H, J = 6–8 Hz), 6.64–6.72 (d, Ar–H, J = 7–8 Hz), 7.55 (s, NH), 9.12 (s, NH), 9.50 (s, NH), 7.82–8.17 (d, Ar–H).MS (LCMS, m/z): 437.17 (100.0%), 438.17 (23.8%), 439.18 (2.7%). Anal. Calcd for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30; N, 16.01; O, 18.2. Found: C, 60.40; H, 5.30; N, 16.01; O, 18.2.

N-(4-chlorophenyl)-6-methyl-4-(4-morpholinophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1332 (CN), 1650 (NH–C=O), 1665 (C=O), 3152 (Ar–H), 3218 (NH), 700 (C–Cl), 1000–1200 (C–O–C).^{1}H NMR (DMSO-d_6, δ, ppm): 2.26 (s, 3H), 3.15–3.73 (t, 2H, J = 6–8 Hz), 6.65–6.71 (d, Ar–H, J = 7–8 Hz), 7.56 (s, NH), 9.09 (s, NH), 9.53 (s, NH), 7.91–8.53 (d, Ar–H).MS (LCMS, m/z): 426.15 (100.0%), 428.14 (32.0%), 427.15 (23.8%), 429.15 (7.6%). Anal. Calcd for $C_{21}H_{21}ClN_4O_3$: C, 61.90; H, 5.43; Cl, 8.30; N, 13.12; O, 11.24. Found: C, 61.90; H, 5.43; Cl, 8.30; N, 13.12; O, 11.24.

N-(4-bromophenyl)-6-methyl-4-(4-morpholinophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1320 (CN), 1635 (NH–C=O), 1650 (C=O), 3140 (Ar–H), 3236 (NH), 600 (C–Br), 1100 (C–O–C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.25 (s, 3H), 3.15–3.73 (t, 2H, J = 6–8 Hz), 6.65–6.71 (d, Ar–H, J = 7–8 Hz), 7.58 (s, NH), 9.10 (s, NH), 9.55 (s, NH), 7.52–7.66 (d, Ar–H). MS (LCMS, m/z): 470.10 (100.0%), 472.09 (97.3%), 473.10 (23.1%). Anal. Calcd for $C_{21}H_{21}BrN_4O_3$: C, 56.06; H, 4.92; Br, 16.95; N, 11.89; O, 10.18. Found: C, 56.06; H, 4.92; Br, 16.95; N, 11.89; O, 10.18.

N-(2,4-dinitrophenyl)-6-methyl-4-(4-morpholinophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1310 (CN), 1624 (NH–C=O), 1640 (C=O), 3120 (Ar–H), 3210 (NH), 1550 (NO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.24 (s, 3H), 3.18–3.75 (t, 2H, J = 6–8 Hz), 6.64–6.71 (d, Ar–H, J = 7–8 Hz), 7.54 (s, NH), 9.09 (s, NH), 10.53 (s, NH), 6.96–7.70 (d, Ar–H). MS (LCMS, m/z): 482.15 (100.0%), 483.16 (23.8%), 484.16 (2.7%). Anal. Calcd for $C_{21}H_{20}N_6O_7$: C, 54.77; H, 4.60; N, 17.42; O, 23.21. Found: C, 54.77; H, 4.60; N, 17.42; O, 23.21.

N-(4-methoxyphenyl)-6-methyl-4-(4-morpholinophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1314 (CN), 1630 (NH–C=O), 1652 (C=O), 3145 (Ar–H), 3250 (NH), 1045 (C–O–C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.00 (s, 3H), 3.18–3.75 (t, 2H, J = 6–8 Hz), 6.64–6.72 (d, Ar–H, J = 7–8 Hz), 7.55 (s, NH), 9.12 (s, NH), 9.50 (s, NH), 7.82–8.17 (d, Ar–H), 3.81 (s, 3H, OCH_3).MS (LCMS, m/z): 422.20 (100.0%), 423.20 (24.9%), 424.20 (2.7%). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 65.39; H, 6.20; N, 13.26; O, 15.15. Found: C, 65.39; H, 6.20; N, 13.26; O, 15.15.

6-methyl-4-(4-morpholinophenyl)-2-oxo-N-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

IR (KBr, cm^{-1}): 1324 (CN), 1645 (NH–C=O), 1665 (C=O), 3115 (Ar–H), 3225 (NH), 1065 (C-O-C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.21 (s, 3H), 3.15–3.75 (t, 2H, J = 6–8 Hz), 6.63–6.75 (d, Ar–H, J = 7–8 Hz), 7.56 (s, NH), 9.18 (s, NH), 9.45 (s, NH), 7.84–8.17 (d, Ar–H).MS (LCMS, m/z): 406.20 (100.0%), 407.20 (24.9%), 408.21 (2.7%). Anal. Calcd for $C_{22}H_{24}N_4O_3$: C, 67.96; H, 6.45; N, 13.78; O, 11.81. Found: C, 67.96; H, 6.45; N, 13.78; O, 11.81.

4-(6-methyl-4-(4-morpholinophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido) benzenesulfonic acid.

IR (KBr, cm^{-1}): 1334 (CN), 1643 (NH–C=O), 1670 (C=O), 3150 (Ar–H), 3220 (NH), 1025 (C–S). ^1H NMR (DMSO-d_6, δ, ppm): 2.26 (s, 3H), 3.15–3.73 (t, 2H, J = 6–8 Hz), 6.65–6.70 (d, Ar–H, J = 7–8 Hz), 7.58 (s, NH), 9.05 (s, NH), 9.53 (s, NH), 7.54–7.74 (d, Ar–H), 8.50 (s, SH).MS (LCMS, m/z): 472.14 (100.0%), 473.15 (23.8%), 474.14 (4.5%). Anal. Calcd for $C_{22}H_{23}N_4O_5S$: C, 55.92; H, 5.12; N, 11.86; O, 20.32; S, 6.78. Found: C, 55.92; H, 5.12; N, 11.86 S, 6.78.

3. Results and Discussion

There remains a continued interest in advancing this reaction through the use of novel reagents that offer improved efficiency, simplified operational protocols, milder reaction conditions, and enhanced product yields. Additionally, the incorporation of potential biological activity further underscores the significance of such developments.

Table 1. Physical data of compounds NG I–NG VIII.

Compound	R	M.P. (°C)	Yield (%)
NG I	4–NO_2	160–165	78
NG II	2–NO_2	180–185	76
NG III	4–Cl	220–250	90
NG IV	4–Br	175–180	82
NG V	2,4–NO_2	178–182	79
NG VI	4–OCH_3	182–185	71
NG VII	4–CH_3	183–185	76
NG VIII	4–SO_3H	200–220	82

A series of tetrahydropyrimidine derivatives was synthesized via a one-pot procedure as depicted in Scheme 1. This approach resulted in significantly higher yields compared to the conventional reflux method. The synthesized compounds exhibited high purity, with impurities effectively removed by simple recrystallization. Furthermore, the method demonstrated a notable reduction in reaction time.

4. Biological Evaluation

4.1. Antioxidant Activity

Reactive oxygen species (ROS) and free radicals contribute significantly to oxidative stress, which is implicated in various chronic diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases. Antioxidants are agents capable of neutralizing ROS, thus playing a vital role in disease prevention and health promotion.

In this study, a series of synthetic compounds NG I to NG VII were evaluated for their antioxidant activity using a standard IC_{50} (half maximal inhibitory concentration) assay, with butylated hydroxytoluene (BHT) serving as a reference antioxidant. The antioxidant activity was measured using a standard in vitro free radical scavenging assay (e.g., DPPH or ABTS assay), which quantifies the ability of compounds to inhibit 50% of free radical activity. The IC_{50} value represents the concentration (in μM or μg/mL) at which the compound exhibits 50% radical scavenging effect. Lower IC_{50} values indicate stronger antioxidant potential.

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

NG I (41.05 ± 0.16) and NG VII (41.23 ± 0.44) demonstrated the most promising antioxidant activity among the NG series, though still significantly less potent than BHT.

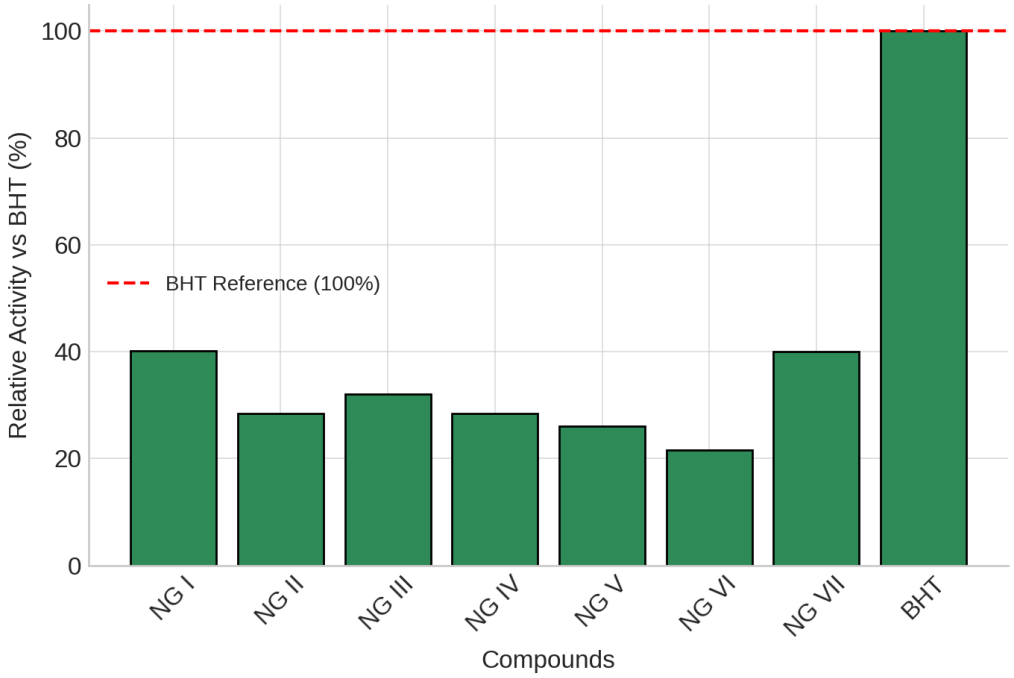


Figure 3. Relative antioxidant activity compared to BHT.

4.2. Antibacterial Activity

Antibacterial activity was determined against Gram-positive (*S. aureus*, *S. pyogenes*) and Gram-negative (*E. coli*, *P. aeruginosa*) strains. The results are presented in Table 2. Compounds NG III, NG VII, and NG VIII displayed strong inhibitory activity with significantly reduced CFU/mL compared to controls.

Table 2. Antibacterial activity of DHPM derivatives (CFU/mL).

Compound	*S. aureus*	*S. pyogenes*	*E. coli*	*P. aeruginosa*
NG I	4.2×10^6	5.6×10^6	7.8×10^7	9.1×10^7
NG II	2.1×10^5	3.4×10^5	5.6×10^6	8.3×10^6
NG III	3.2×10^3	4.7×10^3	6.2×10^4	1.2×10^5
NG IV	7.5×10^7	8.1×10^7	9.2×10^7	9.7×10^7
NG V	2.8×10^6	3.1×10^6	5.0×10^7	6.4×10^7
NG VI	8.4×10^4	1.2×10^5	2.5×10^6	3.8×10^6
NG VII	4.3×10^3	6.7×10^3	1.3×10^5	2.7×10^5
NG VIII	1.1×10^3	2.0×10^3	4.5×10^4	6.9×10^4

The antibacterial efficacy of the NG series was evaluated against two Gram-positive strains (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). The colony-forming unit (CFU/mL) values are summarized in Figure 2. Since the data span several orders of magnitude, results were $\log_{10}$-transformed for clarity. Activity against Gram-Positive Bacteria NG VIII (1.1×10^3

CFU/mL for *S. aureus*, 2.0 × 10^3 for *S. pyogenes*) demonstrated the strongest inhibitory effect, followed closely by NG III and NG VII. NG II and NG VI displayed moderate activity, while NG I and NG V were weaker. NG IV (7.5 × 10^7–8.1 × 10^7 CFU/mL) was the least effective, indicating poor inhibition of Gram-positive strains.

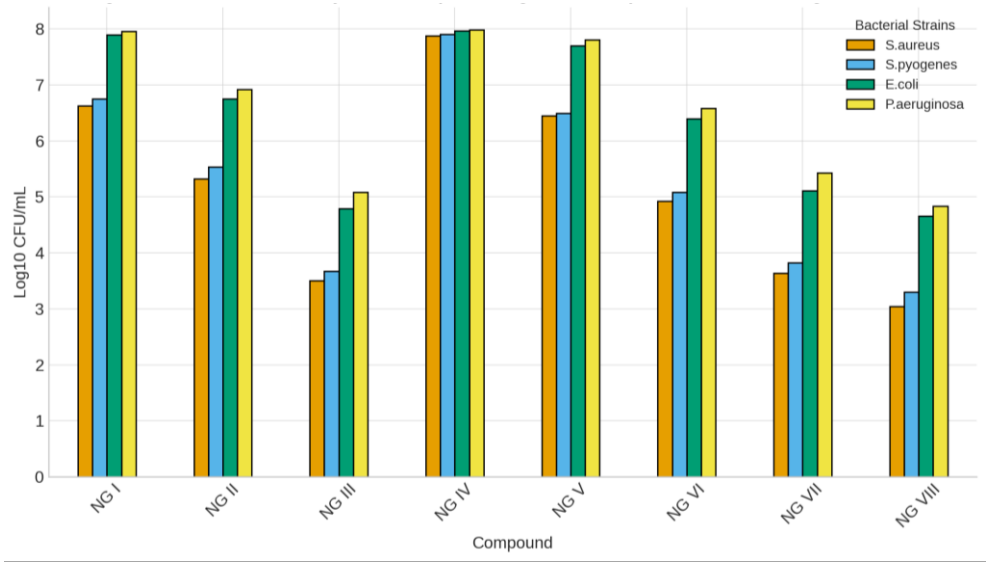


Figure 4. Antibacterial activity of NG compounds against Gram-positive and Gram-negative bacteria.

Activity against Gram-Negative Bacteria A similar trend was observed against Gram- negative strains. NG VIII again showed the best inhibition (4.5 × 10^4 CFU/mL for *E. coli* and 6.9 × 10^4 for *P. aeruginosa*), followed by NG III and NG VII, which also reduced bacterial counts effectively. NG VI demonstrated intermediate activity, while NG I and NG V were weaker inhibitors. NG IV was again the least active, with CFU counts approaching untreated levels (9.2 × 10^7–9.7 × 10^7 CFU/mL).

Trend Analysis Potency ranking across both Gram-positive and Gram-negative strains was generally:

NG VIII > NG III ≈ NG VII > NG VI > NG II > NG V ≈ NG I ≫ NG IV.

The enhanced activity of NG VIII suggests that structural modifications present in this derivative significantly improve antibacterial efficacy, likely through stronger interactions with bacterial cell walls or interference with metabolic pathways. By contrast, NG IV consistently showed poor inhibition, indicating structural features unfavorable for antibacterial activity.

Heatmap Analysis was generated to visualize antibacterial activity ($\log_{10}$ CFU/mL). Blue- green shading indicates lower CFU values (stronger antibacterial effect), while darker colors indicate weaker inhibition. NG VIII, NG III, and NG VII appear as the most active across all bacterial strains, with consistently lower CFU counts. NG IV is highlighted as the least effective, showing the darkest (highest CFU) values across both Gram-positive and Gram- negative bacteria.

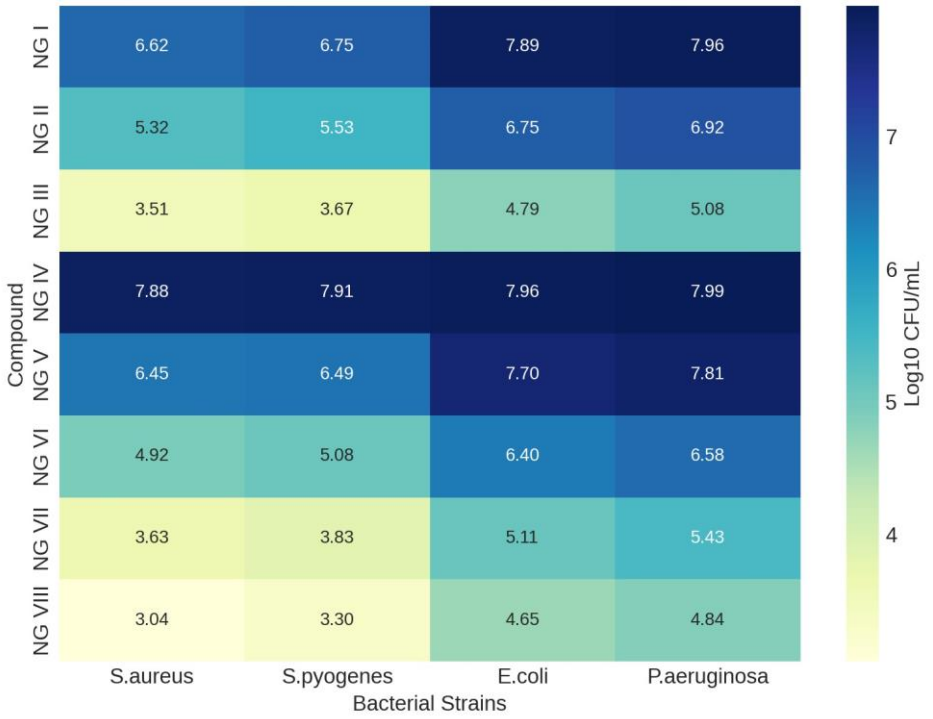


Figure 5. Heatmap of antibacterial activity of NG compounds.

4.3. Antifungal Activity

Antifungal activity against *F. solani*, *P. citrinum*, and *F. oxysporum* was evaluated by growth inhibition on agar plates. The results are summarized in Table 3. NG-2, NG-3, and NG-8 displayed notable inhibition, particularly NG-8 against *F. oxysporum*.

Table 3. Antifungal activity of DHPM derivatives (colony growth in cm).

Fungus	Compound	2.5%	5%	10%
F. solani	NG-2	4.1	3.5	2.5
	NG-3	2.5	2.1	1.7
	NG-8	3.8	3.3	2.2
P. citrinum	NG-2	3.0	2.5	2.0
	NG-3	2.4	2.0	1.9
	NG-8	3.3	2.8	2.5
F. oxysporum	NG-2	3.0	2.2	1.8
	NG-3	2.3	2.1	1.5
	NG-8	4.5	3.6	3.3

The antifungal potential of NG extracts was tested against *Fusarium solani*, *Penicillium citrinum*, and *Fusarium oxysporum* at concentrations of 2.5%, 5%, and 10%. Activity against *F. solani* As shown in Figure 6, NG-3 was the most effective, reducing colony diameter to 1.7 cm at 10%, compared with NG-2 (2.5 cm) and NG-8 (2.2 cm).Activity against *P. citrinum* For *P. citrinum* (Figure 7a, NG-3 again displayed the strongest inhibition (1.9 cm at 10%), followed by NG-8 (2.5 cm) and NG-2 (2.0 cm).Activity against *F. oxysporum* Against *F. oxysporum*(Figure 7b, NG-8 showed superior inhibition, reducing colony diameter to 3.3 cm at 10%, compared with NG-2 (1.8 cm) and NG-3 (1.5 cm). Interestingly, although NG-2 and NG-3 yielded lower colony diameters, NG-8 displayed a more consistent dose-dependent effect, suggesting selective potency.

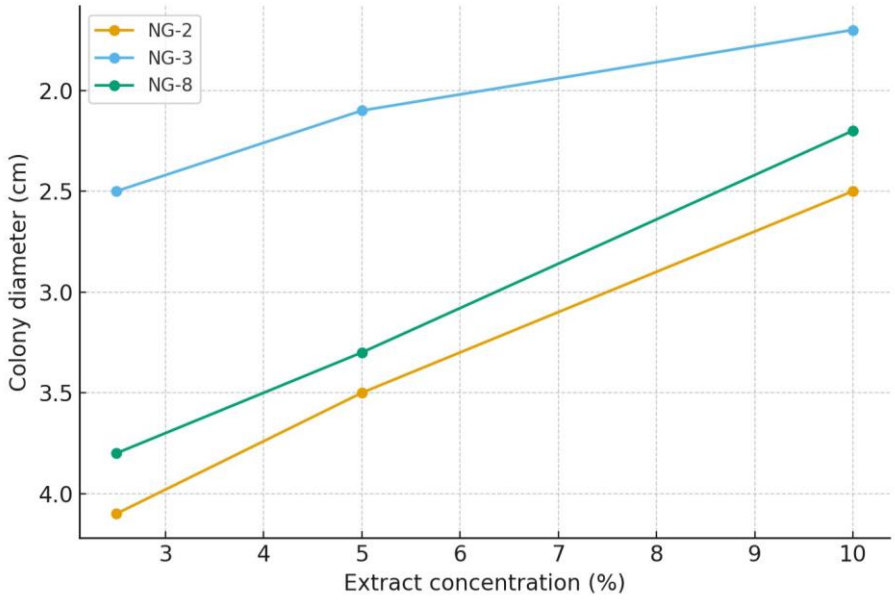
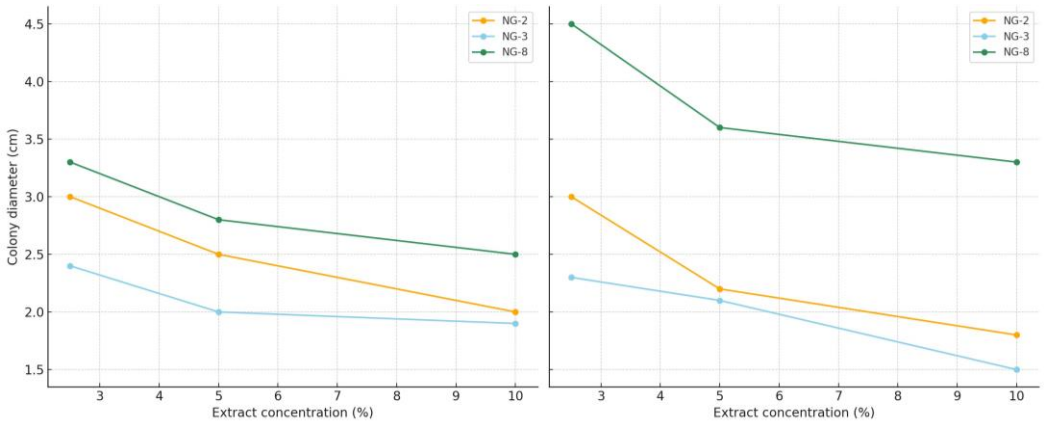


Figure 6. Antifungal activity of NG compounds against *Fusarium solani*.



(**a**) (**b**)

Figure 7. (**a**) Antifungal activity vs. *Penicillium citrinum*; (**b**) Antifungal activity vs. *Fusarium oxysporum*.

4.4. Molecular Docking Studies

Molecular docking investigations were carried out for the synthesized compounds against a panel of six target proteins in order to identify the most suitable target based on binding affinities. To visualize the comparative docking performance, a box plot was constructed representing the distribution of docking scores across all targets. The table illustrates the boxplot analysis, highlighting the interaction profiles of the synthesized compounds with the selected protein targets.

Table 4. Docking results of NG derivatives with selected protein targets, including resolution, binding affinity, and key interacting residues.

PDB ID	Resolution (Å)	Binding Affinity (kcal/mol)	Amino Acid Residues Involved
7M4	2.20	−8.0	Ser16, Gly18, Val17, Ser19, Ser20, Ser21, Ala119, Asp122, Lys120, Lys149, Lys151, Phe81
6WDP	2.50	−6.9	Arg766, Gln725, Tyr890, Cys891, Met801, Leu715, Leu718, Leu763, Val760, Phe778, Trp755, Gly722

1AUN	2.50	−7.9	Asp111, Asp121, Arg114, Arg136, Arg275, Tyr133, Trp110, Trp118, His117, Ala127, Asn130
1A28	2.40	−9.4	Arg48, Leu50, Pro127, Ser220, Ser221, Trp222, Arg211, Gln171, Asp49, Leu183, Val129
1G6E	2.60	−6.4	Asn46, Asn47, Ile86, Ala29, Tyr87, Ser11, Tyr12, Ala27, Val48
8C7M	2.50	−8.0	Glu80, Arg60, Gln78, Ser348, Thr355, Asn346, Trp526, Tyr357

Molecular docking studies revealed binding affinities ranging from –6.4 to –9.4 kcal/mol, indicating moderate to strong interactions of NG derivatives with the selected protein targets. The best affinity was observed for 1A28 (–9.4 kcal/mol), stabilized by multiple hydrogen bonds an dhydrophobic contacts with residues such as Arg48, Ser220, Trp222, and Arg211.Strong interactions were also noted for 7M4S and 8C7M (–8.0 kcal/mol), involving key residues including Ser16, Lys151, Phe81, Glu80, and Trp526. Moderate binding was observed for 1AUN (–7.9, –7.5 kcal/mol) and 6WDP (–6.9, –6.6 kcal/mol), whereas the weakest affinity was recorded for 1G6E (–6.4 kcal/mol) with fewer stabilizing contacts.

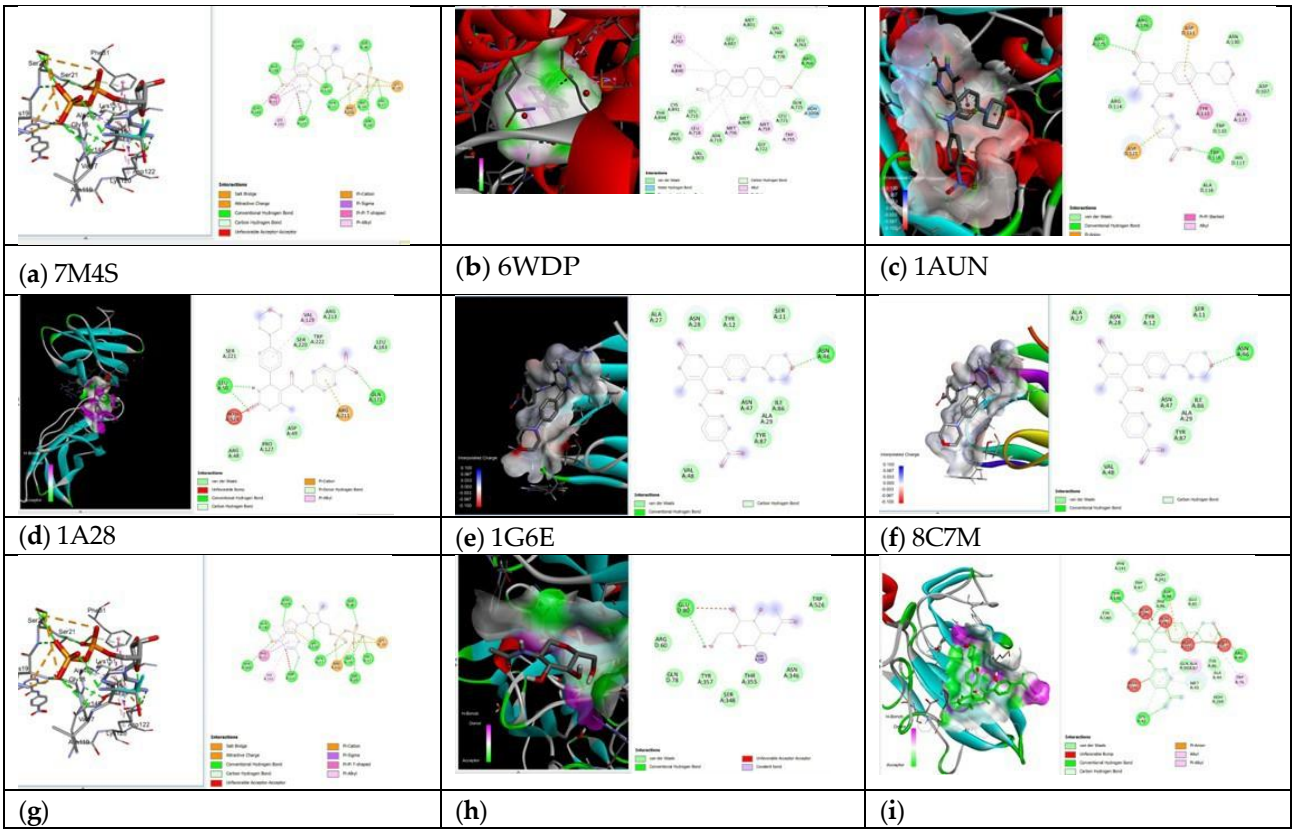


Figure 8. caption.

5. Conclusions

In summary, an eco-friendly multicomponent approach was successfully employed to synthesize a series of novel tetrahydropyrimidines derivatives. The compounds were structurally confirmed and evaluated for antioxidant, antibacterial, and antifungal activities. NG I, NG III, NG VII, and NG VIII demonstrated the most potent antioxidant and antimicrobial activity, comparable with reference standards. Molecular docking revealed strong binding affinities, particularly for protein 1A28 (–9.4 kcal/mol), where hydrogen bonding and hydrophobic interactions with Arg48, Ser220, and Trp222 played crucial

roles. Collectively, both experimental and computational studies highlight these DHPM derivatives as promising scaffolds for the development of multifunctional therapeutic agents. Future investigations will focus on further structural optimization and in vivo validation.

Author Contributions:

Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: The authors gratefully acknowledge the support of respective institutions for providing laboratory facilities and resources essential for this research. We also thank the technical staff for their assistance during the synthesis, characterization, and biological evaluations.

Conflicts of Interest:

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