

■ Organic & Supramolecular Chemistry

Antimicrobial, Antioxidant and Antiproliferative Activities of Novel Quinolones

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The compound (2) formed by esterification of dimethyl morpholine (1) was converted to acetohydrazide (3). Subsequently Schiff bases (4a–d) and carboxy(thio)amide derivatives (5a–e) were synthesized. Then 1,2,4-triazole (6a–e), thia(oxa)zolidine (7c,e) and thia(oxa)zol (8c,e) derivatives were obtained by ring closure from carboxy(thio)amides. Mannich bases, which are containing quinolone were synthesized from 1,2,4-triazoles. The structures of newly synthesized compounds were illuminated by spectroscopic methods. Their antimicrobial (MIC

method), antioxidant (DPPH, FRAP, and CUPRAC methods), and anticancer activities (MTT method) were examined. Results showed that most of the compounds exhibited good antimicrobial (<0.03–31.25 µg/mL with MIC values) and antioxidant activities (IC₅₀ = 0.001–0.004 with DPPH values). Also, some of the compounds have been found to have antiproliferative effects on the prostate (PC-3), liver (Hep3B), and breast (MCF-7) human cancer cells, and also these compounds did not have a cytotoxic effect on a normal cell.

Introduction

Cancer is the secondary reason of death after cardiovascular illnesses and remains a great health issue worldwide.^[1] Infections with specific bacteria, viruses, and parasites have been known as risk agents for different kinds of cancer in humans.^[2] Infection is the infestation of body organisms and produced by illness agents which can be formed in a little piece and effuse to the entire body.^[3] The bacterial infection is one of the most widespread infections both in society and in hospitals, and it creates for a primary reason for sickly and death rates in all world.^[4,5] Antibiotics are very important for the cure of bacterial infections.^[6,7] But bacteria resistance has occurred to nearly whole antibiotics because of the long-range misuse of antibiotics.^[8–10] To resolve this matter, it is urgent to improve new molecules with high antimicrobial properties.

Hybrid compounds are molecules with two or more structural fields, which have diverse dual activities and biological features. These substances generally possess the

capacity to get over medicine resistance, develop pharmacokinetic structures, and abate toxicity.^[11,12]

Diverse investigators focus significantly on heterocyclic compounds due to their multidirectional structure.^[13] Heterocycle groups, the part of many marketed medicines, is one of the most significant pieces with antimicrobial activity in modern medicine exploration.^[14]

Morpholine is an organic molecule with a six-membered ring in its structure and two heteroatoms such as oxygen and nitrogen and it has been accepted as an important moiety in medical chemistry. Morpholine is an ambidextrous nucleus as it related to a large range of pharmacological activities. Morpholine derivatives are commonly used as antimicrobial, Anti-viral, antidepressant, anticancer, anti-inflammatory, analgesics and HIV-protease inhibitors, etc.^[15–17]

Literature research showed that a lot of molecules containing five-membered rings such as triazoles and thiazoles display substantial biological property. Molecules having 1,2,4-triazole moiety show antibacterial,^[18,19] antifungal,^[18,20] anti-tubercular,^[21] anti-inflammatory^[22,23] activities. The thiazole moiety also exists in different molecules with various pharmacological activities, such as antimicrobial,^[24] anti-inflammatory,^[25] antitumoral.^[26] Recently different novel substances with perfect activity towards both medicine-resistant and medicine-sensitive pathogens have been improved by the hybridization of 1,2,4-triazole with other antimicrobial pharmacophores.

Quinolones are widespread pharmacophores in the antibacterial substances. Fluoroquinolones are noted as one of the most broadly used antibacterial agents for the cure of bacterial illness. Ciprofloxacin is a wide spectrum antibiotic that belongs to the second generation of fluoroquinolone. It has been confirmed for the cure of infections, particularly uretic system infections, acute sinusitis, and chronic microbial prostatitis.^[27–29]

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Thus, the hybridization of quinoline/quinolone with 1,2,4-triazole is inclined to present hopeful anti-bacterial agents.^[30,31]

Schiff bases are the molecules having imine parts ($\text{C}=\text{N}$), which are created by the condensation matters of aldehydes or ketones together with primary amines. This kinds of products are utilized as beginning materials in the reactions of significant medicines.^[32–34]

Literature showed that the Schiff bases have mostly moderate to significant activities towards diverse microbial and fungal strains.^[35,36] Adding 1,2,4-Triazole in the Schiff bases could efficiently develop its biological property, thus the request and share of 1,2,4-triazole Schiff bases molecules in pharmaceutical chemistry is growing.^[37]

The aminomethylation synthesis is most generally utilized for drug development studies and it results in the formation of the so-called Mannich bases. The aminomethylation of aromatic substances by the Mannich reaction is of important significance for the synthesis and modification of biologically active molecules.^[38] Recently Mannich bases have acquired significance because of their practiced in medicinal chemistry. They have been indicated to have analgesic and anti-inflammatory,^[39] antifungal, anticancer, antimicrobial,^[40,41] antitubercular,^[42] activities.

The free radicals are responsible for most of the diverse degenerative illnesses that affect humans. These contain diabetes mellitus, inflammatory diseases, mild cognitive impairment, cancer, Alzheimer's disease, Parkinson's disease, and atherosclerosis.^[43] Antioxidants can passive the free radicals before they assault cells and biological materials to cause different illnesses. Antioxidants are broadly researched for their capability to preserve cells and organisms from harm that is induced by oxidative stress. Scholars in many diverse fields

become more concerned novel molecules, either synthesized or get from native resources that could supply active materials to prevent or decrease the effect of oxidative stress on cells.^[44,45]

In this paper, we declared the synthesis of quinolones, Schiff, and Mannich base derivatives containing 1,2,4-triazole and morpholine rings. The newly obtained molecules were evaluated for their antimicrobial, antioxidant, and antiproliferative activities.

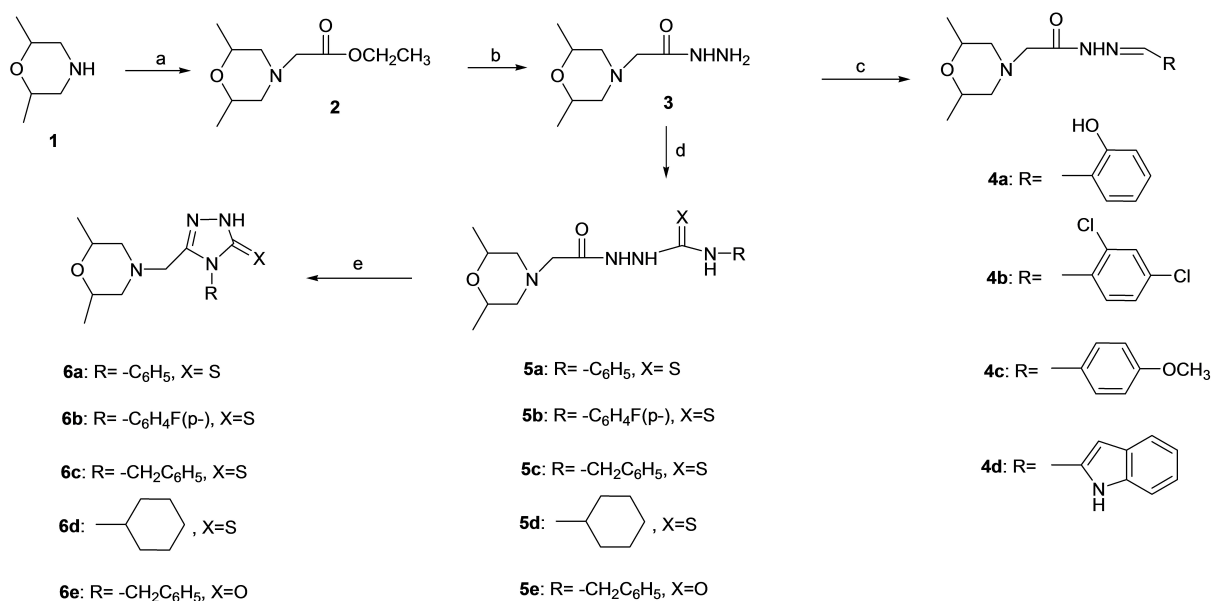
Results

Chemistry

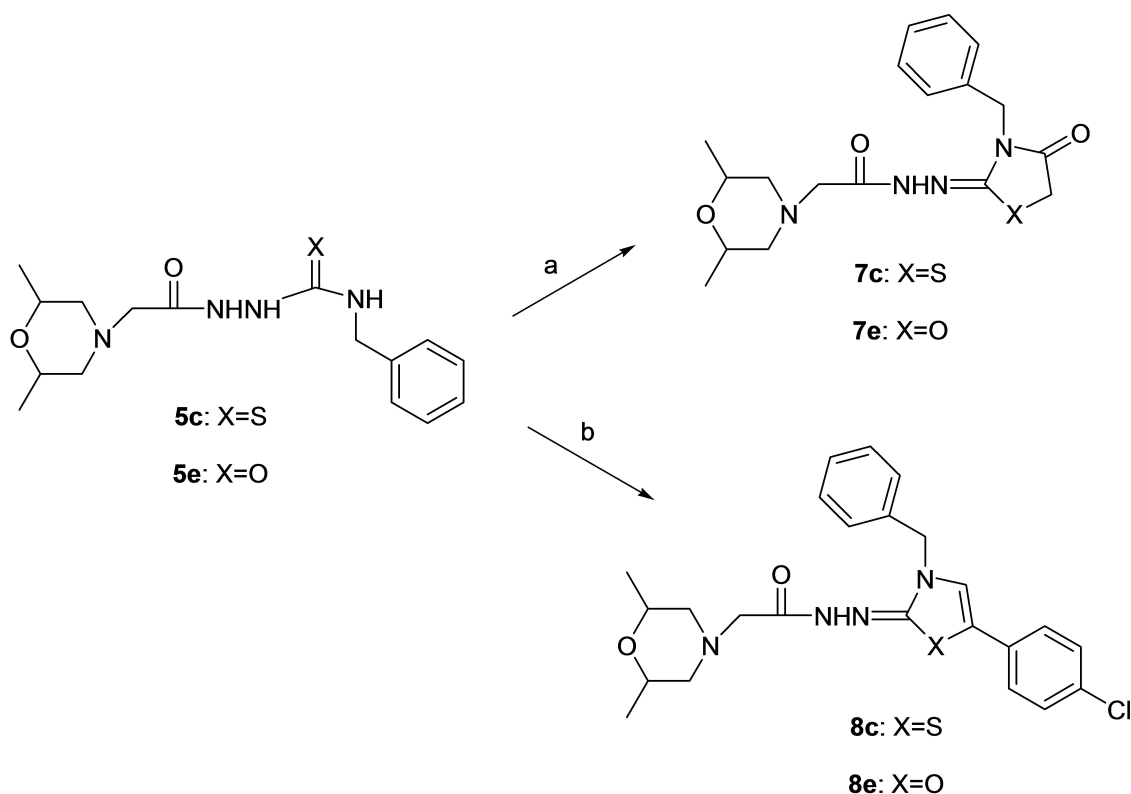
The main goal of this paper was to improve antibacterial hybrid molecules covering different pharmacophore groups. Reactions of target and intermediate molecules were achieved as pictorial in Scheme 1, Scheme 2, and Scheme 3. The finishing of the synthesis was observed via the thin-layer chromatography (TLC) process. All product structures were based on the foundation of spectral and physicochemical data.

Antimicrobial Activity

All novel products were tested for their antibacterial activities utilizing the minimal inhibition concentration method (MIC) and the outcomes for active hybrid groups are summarized in Table 1. The antimicrobial activities of compounds (2–9) were tested against 4 bacteria and 3 yeasts. The microorganisms selected for the antimicrobial activity studies are among important plant and human pathogens and biofilm-producing microorganisms and are targeted by many scientists in their



Scheme 1. Reactions and conditions. a: THF, ethyl bromoacetate, room temperature, 11 h; b: absolute ethanol, hydrazine hydrate, reflux for 7 h; c: absolute ethanol, 2-hydroxy phenylaldehyde (for **4a**) or, 2,4 dichloro benzaldehyde (**4b**) or, 4-methoxy phenylaldehyde (for **4c**) or, indole-3-carbaldehyde (for **4d**), reflux for 6 h; d: phenyl- (for **5a**) or 4-fluorophenyl- (**5b**) or, benzyl- (**5c**) or, cyclohexyl isothiosyanate (**5d**) or, benzylisocyanate (for **5e**), in dichloromethane, room temperature for 24 h; e: 2 N NaOH in ethanol/water (1:1), reflux for 4 h.



Scheme 2. Reactions and conditions. a: absolute ethanol, sodium acetate, ethyl bromoacetate, reflux for 8 h; b: absolute ethanol, sodium acetate, 4-chlorophenyl bromide, reflux for 8 h.

recent studies. Table 1 shows the MIC ranges of compounds (2–9) by broth microdilution for isolates. At the tested concentrations, both compounds 2–9 did not show an important antifungal activity ($< 250 \mu\text{g/mL}$). Among the synthesized compounds, compounds 2–8 displayed low-moderate activity concerning test microorganisms ($31.25\text{--}8000 \mu\text{g/mL}$).

Mannich bases, **9b**, **9c**, **9d**, **9f**, **9g**, **9h**, and **9i** ($< 0.03 \mu\text{g/mL}$) strong antibacterial activities against *Bacillus subtilis* NRRLB-4378 than compound **9e** ($0.24 \mu\text{g/mL}$). And also compounds **9b–i**, ($0.06\text{--}3.9 \mu\text{g/mL}$) exhibited excellent antibacterial activities against *Staphylococcus aureus* ATCC 6538, *Salmonella typhimurium* ATCC 13311, and *Escherichia coli* ATCC 8739. These antimicrobial reports are somewhat in agreement with some previous results of obtained Mannich bases.^[46,47]

Antioxidant Activity

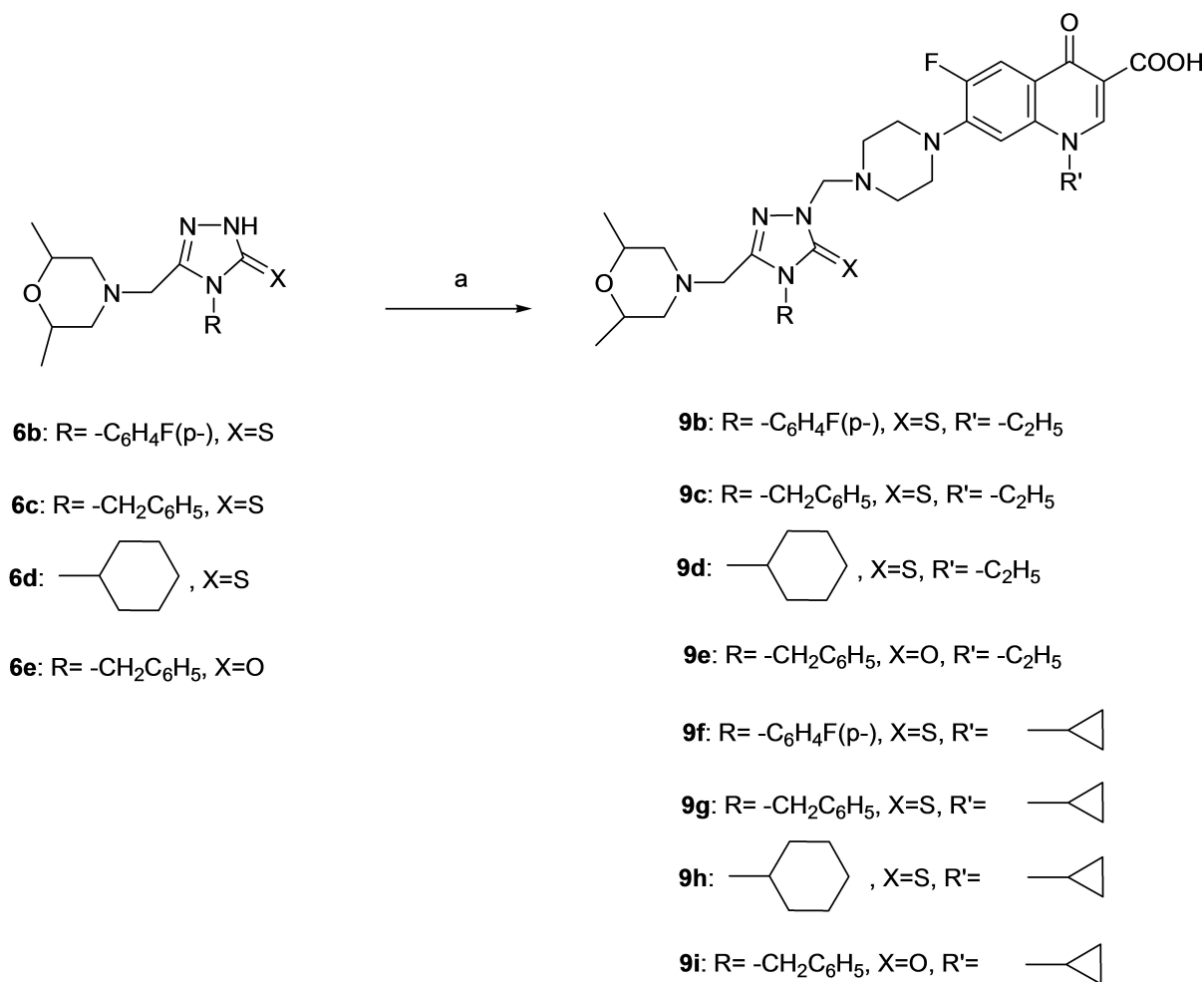
The newly synthesized analogs were evaluated for their antioxidant capacity by FRAP, CUPRAC, and DPPH techniques (Table 2 and Figure 1). When the antioxidant studies of the synthesized molecules were investigated, it was found that the Carbothioamid derivatives **5a–c** and Mannich base derivatives **9b**, **9d**, **9f**, **9g**, and **9h** exhibited showed better activity. The conclusions stated that the presence of quinolone and carbothioamid groups may contribute to the antioxidant activity. These conclusions also confirmed the result of the antioxidant activities of some acquired Mannich bases.^[48]

Among the synthesized compounds, the compound **9f** has the best activity according to the FRAP assay with a value of $1.126 \pm 0.037 \mu\text{mol FeSO}_4 \cdot 7\text{H}_2\text{O/g}$. And also compounds **5d**, **5e**, **6d**, **7c**, and **8e** displayed good-moderate activity. For CUPRAC assays the compound **5a** has the most activity with the value $9.42 \pm 0.13 \text{ mmol TEAC/g}$. Accordingly results of the Cuprac method, good activity was also observed for **5d** and **6a–d** products compared to other compounds. Carbothioamid derivatives **5a–c** showed higher activities with IC_{50} values 0.004 , 0.001 and 0.003 mg/mL , respectively in DPPH method than standard Trolox ($\text{IC}_{50} = 0.005$). Thus they have also more reducing properties. Also, 1,2,4-triazoles **6a–e**, thiazol(idine) derivatives **7c**, **8c**, and mannich bases **9b**, **9d**, **9g**, **9h** displayed good-moderate activity for DPPH assay.

Antiproliferative Activity

The newly synthesized molecules were investigated for their antiproliferative activity by the MTT method^[49] and only the values of the compounds that show good activity are shown in the table (Table 3). Compounds were screened against 8 different human cancer cell lines. The anticancer screening results at $10 \mu\text{M}$ concentration are summarized in Table 3 for Mannich bases **9c**, **9e**, **9g**, **9h**, and **9i** with good activity.

Mannich base derivatives, **9c**, **9e**, **9g**, **9h**, and **9i** displayed severe antiproliferative activity against prostate cancer, PC-3 (46.09% , 55.34% , 47.14% , 56.16% , and 48.79% , respectively)



Scheme 3. Reactions and conditions. a: dimethyl formamide, norfloxacin (for **9b–e**) or ciprofloxacin (for **9f–i**), room temperature, 24 h.

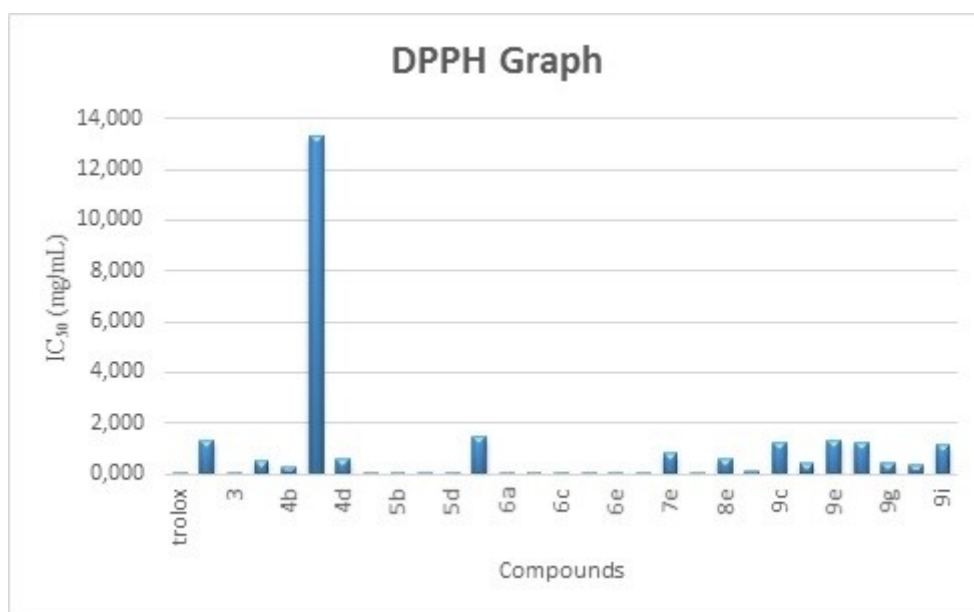


Figure 1. DPPH[•] Activity Result Graph.

Table 1. Antimicrobial activity of the compounds ($\mu\text{g/mL}$).

Comp. No.	Minimal Inhibition Concentration Values ($\mu\text{g/mL}$)						
	Sa	Bs	St	Ec	Ca	Cg	Ck
2	4000	2000	125	1000	1000	–	–
3	–	4000	250	1000	2000	–	–
4a	4000	8000	2000	–	–	–	–
4b	–	8000	–	2000	2000	–	–
4c	4000	2000	125	1000	1000	1000	1000
4d	4000	4000	250	4000	1000	2000	1000
5a	–	8000	4000	–	1000	4000	–
5b	8000	8000	–	–	2000	–	4000
5c	2000	1000	1000	2000	1000	2000	1000
5d	8000	–	8000	4000	4000	4000	4000
5e	4000	2000	–	250	8000	–	4000
6a	4000	4000	4000	4000	2000	4000	4000
6b	2000	8000	4000	4000	4000	4000	4000
6c	2000	2000	2000	2000	1000	2000	2000
6d	8000	–	–	500	4000	4000	4000
6e	4000	4000	4000	4000	2000	4000	4000
7c	1000	31.25	4000	31.25	2000	4000	4000
7e	–	2000	–	–	4000	–	4000
8c	–	–	4000	1000	–	–	4000
8e	4000	4000	4000	–	4000	–	–
9b	0.12	< 0.03	15.63	< 0.03	4000	4000	4000
9c	0.49	< 0.03	15.63	0.98	4000	4000	4000
9d	3.9	< 0.03	31.25	0.49	4000	4000	4000
9e	1.95	0.24	15.63	0.98	4000	4000	4000
9f	0.24	< 0.03	1.95	< 0.03	500	4000	2000
9g	0.49	< 0.03	1.95	0.24	–	–	–
9h	1.95	< 0.03	3.9	< 0.03	2000	4000	4000
9i	0.06	< 0.03	0.49	< 0.03	4000	4000	4000
Chlor.	0.0019	0.0019	0.004	0.0156			
Tetra.	0.0009	0.0009	0.0009	0.0019			
Amf. B.					0.25	0.125	0.25
Fluc.					0.125	0.25	0.50

Sa: *S. aureus* ATCC 6538, Bs: *B. subtilis* NRRL B-4378, St: *S. typhimurium* ATCC 13311, Ec: *E. coli* ATCC 8739, Ca: *C. albicans* ATCC 90028, Cg: *C. glabrata* ATCC 2001, Ck: *C. krusei* ATCC 6258, Chlor.: Chloramphenicol, Tetra.: Tetracycline, Amf. B.: Amphotericin B, Fluc.: Fluconazole, (–): no activity of test concentrations.

compared to imatinib mesylate, is a small molecule kinase inhibitor used to treat certain types of cancer. On the other hand, all compounds also have moderate or low antiproliferative activity against liver cancer, Hep3B. Moreover, it was determined that this antiproliferative activity was more effective than etoposide. There are many compounds synthesized as anticancer products in the literature.^[50,51]

Among these compounds, compound **9h** showed the best antiproliferative activity against three cancer cell lines (prostate, liver, and breast cancers). Compound **9h** showed cell growth inhibition 56.16% for prostate adenocarcinoma cell line (PC-3), 41.16% for hepatocellular carcinoma cell line (Hep3B), and 41.72% for breast cancer cell line (MCF-7). The antiproliferative activity studies were examined at the Marmara University, Faculty of Pharmacy, Department of Biochemistry. Also, whether or not compounds caused cytotoxic effects in non-cancerogenic mouse embryonic fibroblast cell line (NIH-3T3) was tested. Compounds showed no cytotoxicity effect on NIH-3T3 cells.

Human myelogenous leukemia cell line, K562 (ATCC, CCL-243), human Burkitt's lymphoma cell line Raji (ATCC, CCL-86), human lung adenocarcinoma cell line A549 (ATCC, CCL-185), human prostate adenocarcinoma cell line, PC-3 (ATCC, CRL-

1435), human cervical adenocarcinoma cell line, HeLa (ATCC, CCL-2), human breast cancer cell line MCF-7 (ATCC, HTB22), human colon cancer cell line HT-29 (ATCC, HTB-38), human hepatocellular carcinoma cell line, Hep3B (ATCC, HB-8064) and non-cancerogenic mouse embryonic fibroblast cell line NIH-3T3 (ATCC, CRL-1658), bold values represent the cell lines selected for cytotoxic studies.

Discussion

The synthesis of compound (**2**) has been acquired by the reaction of dimethyl morpholine (**1**) with ethyl bromoacetate and after that product (**2**) was transformed to the corresponding hydrazide derivative (**3**). With the introduction of hydrazide function in the molecule, two signals appeared at 4.19 and 8.91 ppm as D_2O exchangeable singlets at the ^1H NMR data of the molecule (**3**).

Schiff bases (**4a–4d**) are obtained by reaction of hydrazide compound (**3**) with various aromatic amines. In the FT IR data of the azomethine function in the Schiff bases, $\text{HC}=\text{N}$ groups are revealed at $1600\text{--}1650\text{ cm}^{-1}$.^[52,53] The view of singlet proton of the azomethine function at 8.24–9.96 ppm in the ^1H NMR data supported the structures of Schiff bases acquired. The

Table 2. Antioxidant Activity Results of Synthesized Compounds.

Compound	FRAP ($\mu\text{mol FeSO}_4 \cdot 7\text{H}_2\text{O/g}$)	CUPRAC (mmol TEAC/g)	DPPH* IC ₅₀ (mg/mL)
2	0.006 ± 0.001	0.63 ± 0.03	1.345
3	0.052 ± 0.009	1.89 ± 0.40	0.025
4a	0.014 ± 0.009	3.66 ± 0.31	0.544
4b	0.001 ± 0.000	3.06 ± 0.01	0.290
4c	0.018 ± 0.003	2.44 ± 0.10	13.329
4d	0.016 ± 0.009	3.11 ± 0.10	0.621
5a	0.055 ± 0.001	9.42 ± 0.13	0.004
5b	0.064 ± 0.002	1.88 ± 0.43	0.001
5c	0.021 ± 0.000	1.02 ± 0.01	0.003
5d	1.020 ± 0.009	5.10 ± 0.09	0.011
5e	1.006 ± 0.030	0.71 ± 0.26	1.481
6a	0.043 ± 0.011	8.57 ± 0.10	0.043
6b	0.022 ± 0.002	6.38 ± 0.94	0.066
6c	0.040 ± 0.010	8.44 ± 0.10	0.032
6d	1.081 ± 0.064	7.23 ± 0.40	0.063
6e	0.041 ± 0.011	8.51 ± 0.10	0.036
7c	1.015 ± 0.029	3.51 ± 0.31	0.080
7e	0.029 ± 0.000	0.43 ± 0.09	0.807
8c	0.119 ± 0.040	0.90 ± 0.01	0.033
8e	1.000 ± 0.007	0.56 ± 0.04	0.613
9b	0.006 ± 0.002	1.31 ± 0.42	0.155
9c	0.042 ± 0.051	1.47 ± 0.31	1.255
9d	0.006 ± 0.001	2.14 ± 0.08	0.411
9e	0.015 ± 0.004	0.71 ± 0.06	1.340
9f	1.126 ± 0.037	2.53 ± 0.21	1.255
9g	0.006 ± 0.000	3.23 ± 0.15	0.442
9h	0.002 ± 0.000	2.44 ± 0.15	0.373
9i	0.041 ± 0.003	1.26 ± 0.08	1.170
Trolox	–	–	0.005

protons of the hydroxyl group in the compound 4a were revealed at 11.85 ppm. Aromatic protons were resonated in the zone 6.82–7.98 ppm. In ¹³C NMR data of novel Schiff bases, the carbon atom (HC=N) was showed between 126.81 and 152.81 ppm. Schiff bases achieved is the [M], [M + 1], [M + 2], and [M + Na] ion signs displayed in the mass data of the molecules.

Molecules (5a–e) were performed by the treatment of molecule (3) with phenyl- (for 5a) or 4-fluorophenyl- (for 5b) or benzyl- (for 5c), cyclohexyl isothiocyanate (for 5d) or benzyl isocyanate (for 5e) in ethanolic solution in good yields and molecule structures were approved via FT IR, ¹H NMR, ¹³C NMR, mass data.

The intramolecular cyclization of products (5a–e) at basic media afforded in the transformation of carbox(thio)amide function alter to 5-oxo(mercapto)-1,2,4-triazole derivatives and so molecules 6a–e were synthesized. These compounds (6a–e) were characterized by the presence of a signal at between 13.50–13.89 ppm in the ¹H NMR data as a D₂O exchangeable singlet confirming the existence of a –SH function (6a–d) and 8.30 ppm –NH function (for 6e). The stretching band derived from this group appeared at between 2510–2595 cm⁻¹, and C=O (for 6e) observed at 1667 cm⁻¹ at the FT-IR data of these molecules (Scheme 1).

The synthesis of molecules (7c,e) and (8c,e) was carried out by the treatment of compounds (5c,e) with ethyl bromoacetate and 4-chlorophenacylbromide, respectively, and the structures of these molecules were elucidated by spectroscopic techniques such as ¹H NMR, ¹³C NMR, FT-IR, and EI-MS. Also synthesized molecules confirmed data results consistent with the assigned structures (Scheme 2).

N-Mannich base derivatives have been utilized as potentially helpful prodrug nominees for amines, imides, amides, urea compounds, and hydantoin.^[54] Mannich bases linked 1,2,4-triazole derivatives as containing a significant biological activity that has been reported in the literature.^[54,55] Considering this fact in this paper, the amino alkylation of structures (6b–e) with different amines, such as norfloxacin (9b–e) or ciprofloxacin (9f–i) in an ambience with formaldehyde was performed Mannich synthesis reactions (Scheme 3). No signal symbolizing the presence of the NH band exists on the ¹H NMR and FT-IR spectra of products (9b–i) and in the ¹H NMR and ¹³C NMR spectra of molecules extra signals originated from amine moieties were observed at the concerned chemical ranges. These molecules displayed mass spectral datum records reasonable with their constructions.

Conclusions

This paper statements designed the synthesis of novel molecules containing several bioactive units. Also, antibacterial, antioxidant, and antiproliferative activity of the synthesized molecules were investigated. Among the synthesized compounds, the best activities (antibacterial, antioxidant, and antiproliferative) were found to show compounds 9b–i which are Mannich bases. According to antimicrobial results compounds 9b–i displayed excellent activity on the test micro-

Table 3. Anticancer screening data at 10 μM concentration.

Cell Line	Growth Inhibition (%)						Imatinib mesylate	Etoposid
	9c	9e	9g	9h	9i			
K562	0.95	–5.25	26.74	14.22	12.58	41.35		
Raji	–21.78	–20.61	16.91	23.26	14.91	39.58		
A549	–2.80	24.32	10.68	26.86	28.39	26.1		
PC-3	46.09	55.34	47.14	56.16	48.79	34.52		
HeLa	–16.51	–5.58	–11.59	5.79	–12.69	30.63		
MCF-7	23.58	25.13	31.55	41.72	25.13		–0.4	
HT-29	6.71	4.34	15.68	19.53	–4.48		3.64	
Hep3B	32.54	27.59	38.65	41.16	32.26		6.03	
NIH-3T3	11.77	25.70	21.01	20.13	21.84	–10.21	–2.6	

organisms, *S. aureus*, *B. subtilis*, *S. typhimurium* and *E. coli*. with mic value between <0.03–31.25 mg/mL. In the antioxidant capacity method which is DPPH, CUPRAC, and FRAP, **5a**, **6d**, and **9f** exhibited the best results. Mannich base derivatives **9c**, **9e**, **9g**, **9h**, and **9i** also have antiproliferative activity at rates ranging from 41–56%. Besides compound **9h** was the most potent compound, and has been found anticancer effects on the prostate (PC-3), liver (Hep3B), and breast (MCF-7) human cancer cells, and also this compound did not have a cytotoxic effect on a normal cell.

Supporting Information Summary

You will find the synthetic route, yields, melting points and spectral data, and ¹H NMR and ¹³C NMR spectra in the Supporting Information file of newly synthesized compounds. And also you will see the antimicrobial, antioxidant, and anticancer activity determination methods.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 1, 2, 4-triazole · quinolone · antioxidant · antimicrobial · anticancer activity

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