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Original Article

Synthesis and Antimicrobial Evaluation of the Potassium Salts of Benzhydrazine Dithiocarbamates

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Abstract

Background: New antimicrobial agents must be designed and synthesized for treating infectious diseases. In this study, antibacterial and antifungal activities of 6 potassium dithiocarbamates including three newly synthesized products were assessed on 10 bacterial and 3 fungal pathogens.

Methods: To this end, some benzhydrazine derivatives were reacted with carbon disulfide to afford dithiocarbamates, followed by applying diethyl ether and potassium hydroxide as solvent and base. Then, antimicrobial susceptibility tests were used to determine minimum inhibitory concentration, the minimum bactericidal concentration, and minimum fungicidal concentration values.

Results: The chemical structure of all synthesized dithiocarbamates were characterized with ^{1}H-, ^{13}C-NMR (hydrogen-1 and 13-carbon nuclear magnetic resonance) and Fourier-transform infrared spectra. A variety of inhibitory effects was observed by the synthesized salts. Most synthetic dithiocarbamates affected bacterial strains and could efficiently block the proliferation of pathogenic fungi.

Conclusions: In general, prepared dithiocarbamates as potent chelating agents are able to interact with cell wall sulfur-containing compounds and the essential enzymes of microorganisms. In addition, the design of new hydrazine-based ligands and their corresponding complexes in future research can improve therapeutic properties. The evaluation of the cytotoxic effects of synthesized dithiocarbamates can also help their antimicrobial usages. Thus, these sulfur-rich and water-soluble salts are potential agents for combating plant pests.

Keywords: Antibacterial activity, Antifungal effect, Broth microdilution, Potassium dithiocarbamate, Streak plate

Background

The lack of personal and social hygiene has led to the spread of infectious diseases in society (1). In addition, drug-resistant bacterial and fungal pathogenic strains have increasingly spread because of the inappropriate and unnecessary use of antibiotics and antifungal agents (2). As a result, the discovery, design, and synthesis of new antimicrobial compounds have become an inevitable necessity in the field of hygiene and healthcare (3). Dithiocarbamates are biologically active organic compounds containing the -N(C=S)S- moiety, which are usually prepared in the presence of a base from the reaction of amines or their equivalent derivatives with carbon disulfide (4). According to (5), numerous available functional groups in dithiocarbamates have given them diverse therapeutic properties (Figure 1). Thiram is a potent scabicidal drug, which is especially prescribed for the treatment of skin diseases. It is also used as a fungicide in agriculture (6). In addition, dithiocarb as a chelating agent helps to remove toxic metals from body tissues (7). Further, (8) confirmed the inhibitory effects of brassinin derivatives on cancer cell lines, especially human clones (Caco-2). Furthermore, the blocking properties of valine dithiocarbamate zinc(II) complex against breast cancer cells (MCF-7) were more pronounced compared to cisplatin (9). Moreover, the excellent inhibitory effects against two β-carbonic anhydrase enzymes belonging to pathogenic *Mycobacterium tuberculosis* were observed with *N*-mono- and *N*-,*N*-disubstituted dithiocarbamates (10). The varied biological properties of dithiocarbamates encouraged us to synthesize several derivatives of this family via the reaction of different benzhydrazines and carbon disulfide, and their antimicrobial properties were assessed against a wide range of bacterial and fungal pathogens.

Materials and Methods

Chemicals

All chemicals were purchased from Merck Company (Germany). The progress of the reaction was checked by aluminum thin-layer chromatography plates (20 × 20 cm) with silica gel 60 coated with the fluorescent indicator

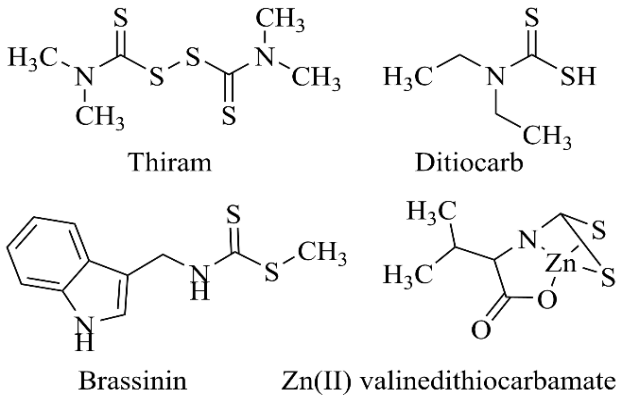


Figure 1. Biologically Active Dithiocarbamate Derivatives (6-9).

F254. Additionally, the Kruss type KSP1N melting point meter (Germany) and UV-2100 RAY Leigh UV-Vis spectrophotometer (China) were used to determine uncorrected melting points and the absorption spectra, respectively. The Fourier-transform infrared (FT-IR) spectra of all synthesized dithiocarbamates were recorded on a Bruker Tensor-27 FT-IR spectrometer (Germany) available in the instrumental analysis laboratory of University of Zabol. Their ^{1}H- and ^{13}C-NMR (400 & 100 MHz) spectra were collected via a Bruker FT-NMR Ultra Shield-400 spectrometer (Germany).

General Process for the Preparation of Dithiocarbamates 3a-f

A mixture containing 10 mmol of hydrazines **1a-f**, 10 mmol of potassium hydroxide (0.56 g), and 25 mL of diethyl ether in a 50-mL round-bottom flask was stirred in an ice-bath. Next, 10 mmol of carbon disulfide (0.76 g) was added dropwise to it for 1 hour under these conditions. The reaction continued for another 3 hours at room temperature. Eventually, the solids were collected, washed with cold ethanol (5 mL) and diethyl ether (5 mL), respectively, and then dried over P_2O_5 in the vacuum desiccator to give potassium salts of dithiocarbamate **3a-f**.

Potassium 2-Phenylhydrazine-1-carbodithioate (3a)

IR *v*: 3413, 1623, 618, 475 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.39 (m, 2H, H-3,5 Ar), 7.09 (m, 2H, H-2,6 Ar), 6.71 (m, 1H, H-4 Ar), 5.29 (s, 2H, 2×NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 228.7 (C=S), 147.6 (C-1 Ar), 129.3 (C-3,5 Ar), 123.0 (C-4 Ar), 113.7 (C-2,6 Ar) ppm.

Potassium 2-(p-Tolyl)hydrazine-1-carbodithioate (3b)

IR *v*: 3413, 1624, 619, 475 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51 (d, *J* = 8.2 Hz, 2H, H-3,5 Ar), 7.22 (d, *J* = 8.2 Hz, 2H, H-2,6 Ar), 5.12 (s, 2H, 2×NH), 2.31 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 230.3 (C=S), 144.8 (C-1 Ar), 137.6 (C-4 Ar), 129.2 (C-3,5 Ar), 125.9 (C-2,6 Ar), 21.1 (CH_3) ppm.

Potassium 2-(4-Fluorophenyl)hydrazine-1-carbodithioate (3c) (New Compound)

IR *v*: 3413, 1624, 618, 475 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.25 (d, *J* = 8.0 Hz, 2H, H-2,6 Ar), 6.94 (d, *J* = 8.0 Hz, 2H, H-3,5 Ar), 4.90 (s, 2H, 2×NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 229.8 (C=S), 144.4 (C-4 Ar), 136.0 (C-1 Ar), 116.3 (C-3,5 Ar), 115.1 (C-2,6 Ar) ppm.

Potassium 2-(4-Chlorophenyl)hydrazine-1-carbodithioate (3d) (New Compound)

IR *v*: 3413, 1624, 619, 475 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 8.4 Hz, 2H, H-3,5 Ar), 7.50 (d, *J* = 8.4 Hz, 2H, H-2,6 Ar), 4.17 (s, 2H, 2×NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 225.4 (C=S), 132.2 (C-1 Ar), 128.8 (C-3,5 Ar), 127.8 (C-2,6 Ar), 122.1 (C-4 Ar) ppm.

Potassium 2-(2,4-Dinitrophenyl)hydrazine-1-carbodithioate (3e)

IR *v*: 3413, 1625, 1324, 620 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.75 (1H, s, H-3 Ar), 8.16 (d, *J* = 10.2 Hz, 1H, H-5 Ar), 7.60 (d, *J* = 9.2 Hz, 1H, H-6 Ar), 5.03 (s, 2H, 2×NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 230.3 (C=S), 149.3 (C-1 Ar), 134.5 (C-4 Ar), 129.8 (C-5 Ar), 128.1 (C-2 Ar), 123.9 (C-3 Ar), 116.0 (C-6 Ar), 55.6 (CH_3) ppm.

Potassium 2-(4-Bromophenyl)hydrazine-1-carbodithioate (3f) (New Compound)

IR *v*: 3413, 1623, 1112, 619, 477 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.72-7.62 (m, 4H, Ar-H), 4.20 (s, 2H, 2×NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 230.3 (C=S), 138.9 (C-1 Ar), 131.8 (C-3,5 Ar), 128.1 (C-2,6 Ar), 120.7 (C-4 Ar) ppm.

Antimicrobial Assay

Microorganisms

Roswell Park Memorial Institute (RPMI) 1640 media (Roswell Park Memorial Institute 1640), Mueller-Hinton broth (MHB), and Mueller-Hinton agar (MHA) were purchased from HiMedia Company (India). Gram-negative and -positive bacterial strains and fungal strains were prepared from the Persian Type Culture Collection. The first group included *Salmonella enterica subsp. enterica* (PTCC 1709), *Klebsiella pneumoniae* (PTCC 1290), *Escherichia coli* (PTCC 1399), *Shigella dysenteriae* (PTCC 1188), *Acinetobacter baumannii* (PTCC 1855), and *Pseudomonas aeruginosa* (PTCC 1310). In addition, the second group of strains encompassed *Streptococcus pyogenes* (PTCC 1447), *Listeria monocytogenes* (PTCC 1297), *Staphylococcus epidermidis* (PTCC 1435), and

Bacillus cereus (PTCC 1665). Finally, fungal strains included yeast *Candida albicans* (PTCC 5027), molds *Fusarium oxysporum* (PTCC 5115), and *Aspergillus fumigatus* (PTCC 5009). Broth microdilution and streak plate methods were applied to evaluate antibacterial and antifungal susceptibility tests (11). In addition, the initial suspensions of bacteria, yeast, and molds were prepared in appropriate broth media with concentrations of 5×10^5, $0.5\text{-}2.5 \times 10^3$, and $0.4\text{-}5 \times 10^4$ CFU.mL^{-1}, respectively. The results were reported as the mean of three independent experiments.

Minimum Inhibitory Concentration Experiment

To this end, 20 µL of each dithiocarbamate was added to twelve wells in a row of a 96-well microliter plate at concentrations of 20480, 10240, 5120, 2560, 1280, 640, 320, 160, 80, 40, 20, and 10 µg.mL^{-1} in distilled water, respectively. Then, 80 µL of RPMI 1640 or MHB, as well as 100 µL of microbial suspensions were added to all wells. Next, the plates were incubated at 37 and 35°C for 20 and 48 hours for bacteria and fungi on an orbital shaker (100 rpm), respectively. Eventually, the minimum inhibitory concentration (MIC) value was the lowest concentration of salts which stopped microbial growth (11).

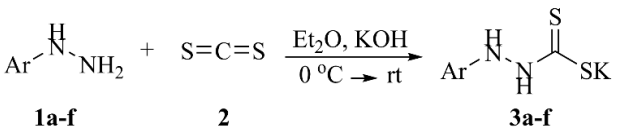
MBC and Minimum Fungicidal Concentration Experiments

The samples of all non-turbid wells in the MIC experiment were re-cultured in RPMI 1640 or MHA agar media plates. Then, the plates were incubated for 24 hours at appropriate temperatures except that 45%-55% relative humidity was supplied for fungi. Finally, the Minimum Fungicidal Concentration (MFC) or MBC value was determined as the lowest concentration of compounds that killed microorganisms (11).

Results and Discussion

Potassium dithiocarbamates **3a-f** were generated via the reaction of benzhydrazines **1a-f** and carbon disulfide (**2**). In addition, potassium hydroxide and diethyl ether were used as base and solvent, respectively (Scheme 1). The synthetic data are reported in Table 1. The chemical structure of synthesized dithiocarbamates was characterized by spectral data (Figure 2).

In vitro blocking potential of all synthesized dithiocarbamates was assessed on some important pathogenic bacteria and fungi including four gram-positive and 6 Gram-negative bacterial strains, 2 molds and one yeast. Further, ampicillin and clotrimazole were used as control drugs. As shown in Table 2, a wide variety of activities was obtained with dithiocarbamates that had substituted or unsubstituted phenyl. All dithiocarbamates except for salts **3c** and **3d** inhibited the tested bacteria and no blocking effects on *Escherichia coli* and *Klebsiella pneumoniae* strains were observed with derivatives **3c** and **3d**. On the other hand, good inhibitory effects against gram-negative *Shigella flexneri* and *Listeria monocytogenes*, as well as gram-positive *Bacillus cereus* and *Staphylococcus aureus* strains were observed with the potassium salts of morpholine dithiocarbamate, along with its Cu(II) and Ni(II) complexes. More precisely, complexation decreased antibacterial activities (15). Furthermore, the disk diffusion method was applied to determine the blocking properties of potassium 3-dithiocarboxy-3-aza-5- aminopentanoate on nine hospital bacteria (16). Pyrrolidine dithiocarbamates are potent chelating agents and ionophores that easily enter into the cell (17). Moreover, the antibacterial effects of their Zn(II) complexes are usually higher compared to Cu(II) equivalents.



Scheme 1. Representative Strategy for the Synthesis of Potassium Dithiocarbamates **3a-f .**

The *in vitro* blocking effects of synthetic salts were investigated on three pathogenic fungi (Table 3). Based on the results, all synthesized dithiocarbamates affected *Candida albicans* and *Fusarium oxysporum* strains. No inhibitory activity against *Aspergillus fumigatus* was observed with dithiocarbamates **3b** and **3d**. Additionally, the antifungal activity of some synthesized Pt(II), Pd(II), and Ni(II) dithiocarbamate complexes was studied against *Penicillium citrinum*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus parasiticus*. They were more efficient at blocking fungi than nystatin (18). Some nontoxic dirutheniumpentadithiocarbamate complexes were synthesized to treat invasive fungal infections. In other words, their MIC values were very similar to those of fluconazole (19). It was proposed that dithiocarbamates act as nonspecific and multisite antifungal agents (20). They further inactivate cellular thiol enzymes and disrupt the energy supply process of fungal cells.

Conclusions

In general, dithiocarbamates are multi-functionalized compounds with a variety of biological properties and thus their synthesis is important. This study evaluated the antibacterial and antifungal effects of 6 synthesized potassium dithiocarbamates (three new salts) on pathogenic bacteria and fungi. These dithiocarbamates showed relatively acceptable antibacterial effects against Gram-negative *S. enterica* and *S. dysenteriae*, as well as Gram-positive *S. epidermidis* and *L. monocytogenes*. In addition, good to excellent antifungal activities were observed with dithiocarbamates. More precisely, they are potent chelating ligands and complexation may improve

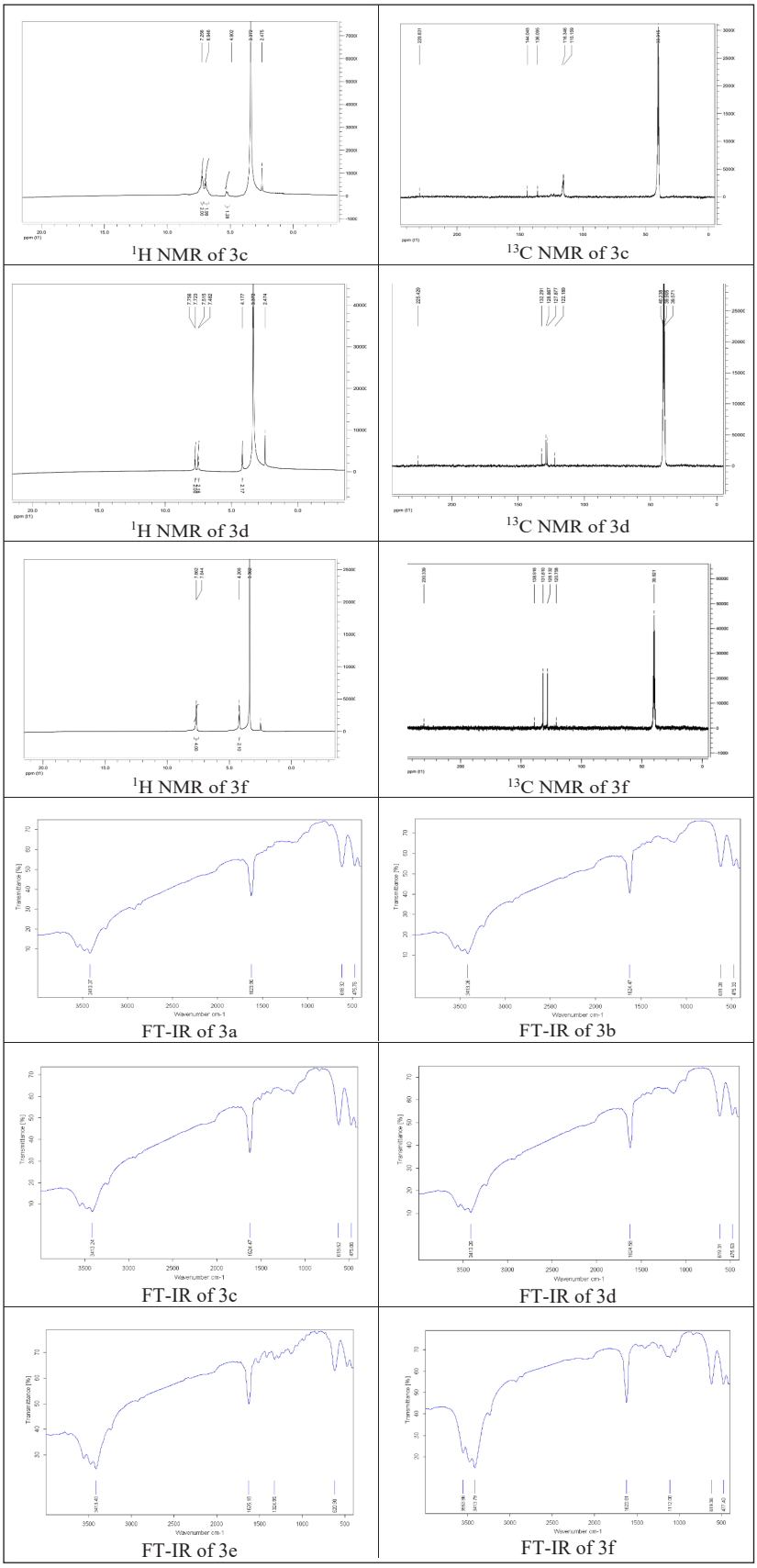
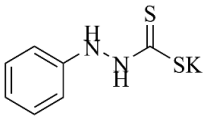
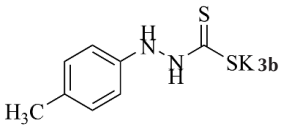
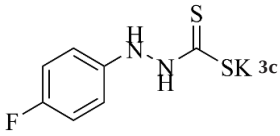
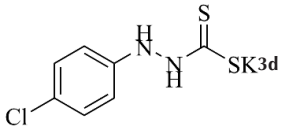
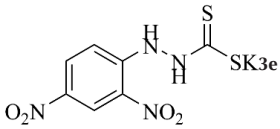
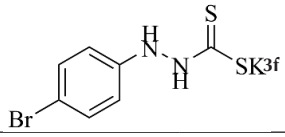


Figure 2. Selected Spectral Graphs of Dithiocarbamic Acid Potassium Salts **3a-f**.

Table 1. The Chemical Structure of Dithiocarbamic Acid Potassium Salts **3a-f**

Entry	Product	R	Yield (%)	M. P. (°C)	
				Found	Lit. (Ref.)
1	 **3a**	C_6H_5	91	131-132 (decomp.)	144-145 (decomp.) (12)
2	 **3b**	4-H_3C-C_6H_4	86	210-212	- (13)
3	 **3c**	4-F-C_6H_4	80	289-291	-
4	 **3d**	4-Cl-C_6H_4	83	295-296	-
5	 **3e**	2,4-$(O_2N)_2$-C_6H_3	93	190-191	- (14)
6	 **3f**	4-Br-C_6H_4	89	200-202	-

Note. Melting points of salts 3b and 3e were not reported in the literature.

Table 2. Antibacterial Properties of Dithiocarbamates **3a-f**

Bacterial Strains		Salts						Antibiotic Ampicillin
		3a	3b	3c	3d	3e	3f	
1855	MIC	1024	512	256	512	64	512	64
	MBC	2048	1024	256	512	128	1024	128
1399	MIC	1024	32	>2048	>2048	2048	1024	32
	MBC	2048	64	>2048	>2048	2048	2048	64
1709	MIC	64	128	32	64	256	32	8
	MBC	64	128	32	64	512	32	16
1310	MIC	1	2	32	1024	2048	64	1024
	MBC	2	2	32	1024	2048	64	2048
1290	MIC	128	64	>2048	>2048	2	64	32
	MBC	256	128	>2048	>2048	4	128	64
1188	MIC	512	256	1	1	1	128	256
	MBC	512	256	2	1	2	128	256
1435	MIC	2	2	1	1024	2	2	0.25
	MBC	4	2	1	1024	4	2	2
1447	MIC	128	32	512	512	32	128	4
	MBC	128	32	1024	512	32	128	8
1665	MIC	2048	1024	16	256	2048	2048	32
	MBC	2048	1024	32	256	2048	2048	64
1297	MIC	2	64	2	32	256	256	8
	MBC	2	128	4	32	256	256	16

Note. MIC (μg.mL^{-1}): Minimum inhibitory concentration; MBC (μg.mL^{-1}): Minimum bactericidal concentration.

Table 3. Antifungal Properties of Dithiocarbamates **3a-f**

Fungal Strains		Salts						Antifungal
		3a	3b	3c	3d	3e	3f	Clotrimazole
5027	MIC	512	1	512	128	512	128	256
	MFC	512	2	512	128	512	256	512
5009	MIC	512	>2048	128	>2048	1024	512	32
	MFC	512	>2048	128	>2048	2048	512	32
5115	MIC	64	2	256	16	64	2048	256
	MFC	64	4	256	32	128	2048	512

Note. MIC (μg.mL^{-1}): Minimum inhibitory concentration; MFC (μg.mL^{-1}); Minimum Fungicidal Concentration.

their antimicrobial properties. Eventually, these water-soluble salts can be applied as pesticides and plant growth-promoting agents although their toxic effects must be studied in future studies.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgement

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Ethical Statement

The disclaimer implies that ethical principles have been considered in relation to the proposed work and no ethical issues have been found to be applied to this research proposal.

Authors' Contribution

Hamid Beyzaei: Supervision, writing original draft, writing-reviewing, and editing; Sedigheh Esmaeilzadeh Bahabadi: Data analysis; Shahla Najafi: Investigation; Fahime Heidari Sadegh: Methodology.

Funding/Support

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