INTRODUCTION

In recent years, there has been a significant attempt to develop environmentally sustainable chemical processes that employ more environmentally friendly solvents, catalysts, reagents and chemicals [1]. This approach includes avoiding or minimizing the use of metals in chemical processes because metals can sometimes be toxic and large amounts of such substances can be challenging to dispose of. Due to the challenges in separating them, there is also a risk that they would contaminate the product. Metals are rigorously monitored even at trace concentrations in pharmaceuticals. Therefore, as part of the criteria for a clean environment and industry, a metal-free process is needed.

One of the most effective and important techniques for the combinatorial preparation of structurally varied compounds is the use of multicomponent reactions (MCRs), which can yield a variety of molecules [2]. By merging several reactions into a single synthetic process, as is required by contemporary synthetic design, MCRs can also result in enhancement in molecular complexity [3]. As a result, several workers working in a variety of fields like drug discovery, material science and organic synthesis have given the creation of innovative MCRs using green procedures.

The utilization of significant quantities of volatile and hazardous organic solvents in chemical processes constitute an alarming atmospheric risk due to the huge generation of chemical wastes. Because of their unusual reactivity and environmental acceptability, which cannot be achieved in traditional organic solvents, reactions in water have so gained a lot of attention recently [4]. Dithiocarbamates are valuable substances because of their fascinating chemistry and extensive applications. These substances have demonstrated widespread use as insecticides, fungicides in agriculture, precursors for the synthesis of nanoparticles [5], sulphur vulcanization in the production of rubber [6] and ligands for chelating metals [7]. Due to their potential as helpful synthetic intermediates [8], useful in the synthesis of ionic liquids [9], protecting groups in the synthesis of peptides and linkers in solid-phase chemical synthesis [10], organic dithiocarbamates are attracting attention. Additionally, the growth of synthetic approaches for these compounds has been prompted by their presence in a wide range of physiologically active chemicals [11], their crucial functions in agriculture [12] and their biological features [13]. Dithiocarbamates,
Dithiocarbamates are often synthesized using expensive, hazardous chemicals like thiophosgene, chloro-thioformates and isothiocyanates [9]. There have also been reports of amines reacting with carbon disulfide (CS₂) and alkyl halides (R-X) in the presence of strong bases like NaOH or KOH or Cs₂CO₃ and TBAI. These reactions require a catalyst as well as toxic organic solvents like DMF, DMSO or methanol. Although these methods work well to produce alkyl dithiocarbamate, but are not very efficient in producing aryl dithiocarbamate. Generally speaking, dithiocarbamate derivatives can result from the reaction of different amines with carbon disulfide and organyl thiocyanates [25], alkyl halides [26], allyl acetate [27], epoxide, Michael acceptors [28], tosyl hydrazone [29], etc. However, some of these methods have several drawbacks, such as handling of hazardous chemicals like isothiocyanates, the production of unwanted byproducts like urethane, the short-term stability of some precursors, lengthy and multistep processes, the requirement for high reaction temperatures and the yield of low to adequate yields. Because of its ecological friendliness, security and green chemistry attributes, preparing and extracting organic compounds in ethanol-water medium has received considerable attraction [30-32]. It is highly important and noteworthy to properly carry out various organic transformations in water-based systems in order to acquire goods in an environmental friendly manner, specifically from the environmental and industrial perspectives. Thus, during the past few decades, the employment of non-toxic, easily accessible, affordable and safe solvents has drawn increasing interest [30-32]. Hence, keeping our interest in dithiocarbamate synthesis, herein a green method to synthesize novel dithiocarbamates by a one-pot transformation of amines such as secondary amine, alkyl or aryl halides, and carbon disulfide in an ethanol-water medium is reported. This method is effective, catalyst-free and environmentally safe.

**EXPERIMENTAL**

For the synthesis of dithiocarbamate derivatives, analytical grade (A.R.) chemicals e.g. alkyl halides, aryl halides, carbon disulfide and secondary amines were obtained from SRL (India) and used without any further purification. The KBr pellets were used to acquire the FT-IR spectra (4000-400 cm⁻¹) using a Shimadzu 8201 PC, FT-IR spectrophotometer. The ¹³C NMR (125 MHz) and ¹H NMR (400 MHz) spectra were measured from the FT-NMR JEIL ECZS instrument in CDCl₃ using TMS as internal standard. The microanalyses for the elements C, H, N and S were recorded with the help of CHNS micro-analyzer. On silica gel plates of the TLC grade, the reactions development were observed.

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**General procedure for synthesis of dithiocarbamate derivatives:** A suitable quantity of the corresponding amine (1 mmol) and carbon disulfide (1.6 mmol) were added to a stirred 15 mL water-ethanol solvent (1:4) in a round-bottomed flask placed in an ice bath. The reaction medium’s temperature was maintained constant at 0 to 5 °C. The corresponding halide (1 mmol) was added dropwise after 2 h of stirring and then the reaction mixture again agitated at 25 °C. TLC was used to monitor the reaction progress using ethanol/n-hexane (1:4) solvent solution. To get the crude product, the derived products were separated from the mother liquor. By triturating the material in boiling ethanol, a pure product was obtained (Scheme-I).

**Scheme-I:** Synthesis of medicinally important dithiocarbamate derivatives by green approach

**Benzyl dicyclohexylcarbamodithioate (4i):** Yield: 90%; time: 6 h; FT-IR (KBr, νmax, cm⁻¹): 3052, 2998, 2945, 1587, 1480, 1427, 1235, 1097, 978, 836; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.29-7.25 (m, 5H) aromatic proton, 4.49 (s, 2H) S-CH₂-, 3.56-3.52 (d, 2H) N-CH₂-, 2.07-1.14 (m, 20H) cyclohexyl methylene (-CH₂-) proton; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 24.82, 32.31, 35.00, 42.58, 56.08, 128.75, 130.34, 130.95, 135.93, 195.27; Elemental analysis: Calcd. (found) % for C₃₀H₃₇NS₂: C, 75-90%; H, 8.41 (8.39); N, 4.03 (4.99); N, 18.45 (18.44).

**4-Chlorobenzyl dicyclohexylcarbamodithioate (4ii):** Yield: 87%; time: 7 h; FT-IR (KBr, νmax, cm⁻¹): 3050, 2998, 2945, 1587, 1480, 1427, 1235, 1097, 978, 836; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.29-7.25 (m, 5H) aromatic proton, 4.49 (s, 2H) S-CH₂-, 3.56-3.52 (d, 2H) N-CH₂-, 2.07-1.14 (m, 20H) cyclohexyl methylene (-CH₂-) proton; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 24.82, 32.31, 35.00, 42.58, 56.08, 128.75, 130.37, 130.75, 135.93, 195.27; Elemental analysis: Calcd. (found) % for C₃₀H₃₇NS₂Cl: C, 69.11 (69.14); H, 8.41 (8.39); N, 4.03 (4.99); N, 18.45 (18.44).

**Benzyl dicyclohexylcarbamodithioate (4i):** Yield: 87%; time: 7 h; FT-IR (KBr, νmax, cm⁻¹): 3052, 2998, 2945, 1587, 1480, 1427, 1235, 1097, 978, 836; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.29-7.25 (m, 5H) aromatic proton, 4.49 (s, 2H) S-CH₂-, 3.56-3.52 (d, 2H) N-CH₂-, 2.07-1.14 (m, 20H) cyclohexyl methylene (-CH₂-) proton; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 24.82, 32.31, 35.00, 42.58, 56.08, 128.75, 130.37, 130.75, 135.93, 195.27; Elemental analysis: Calcd. (found) % for C₃₀H₃₇NS₂: C, 69.11 (69.14); H, 8.41 (8.39); N, 4.03 (4.99); N, 18.45 (18.44).

**Ethyl dicyclohexylcarbamodithioate (4iv):** m.f.: Yield: 86%; time: 12 h; FT-IR (KBr, νmax, cm⁻¹): 3031, 2991, 1427, 1235, 1097, 978, 836; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.29-7.25 (m, 5H) aromatic proton, 4.49 (s, 2H) S-CH₂-, 3.56-3.52 (d, 2H) N-CH₂-, 2.07-1.14 (m, 20H) cyclohexyl methylene (-CH₂-) proton; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 24.82, 32.31, 35.00, 42.58, 56.08, 128.75, 130.34, 130.95, 134.93, 198.27; Elemental analysis: Calcd. (found) % for C₂₀H₂₈NS₂Cl: C, 62.88 (62.91); H, 7.39 (7.37); N, 16.79 (16.75).
1228, 1080, 855; ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.12 (s, 2H) N-CH₃, 3.13 (q, 2H) S-CH₂-, 2.10-1.28 (m, 20H) cyclohexyl methylene (-CH₂-) proton, 1.22 (m, 3H) -CH₃; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 13.16, 24.60, 27.42, 30.55, 31.66, 42.45, 56.18, 200.15; Elemental analysis: Calcd. (found) % for C₁₃H₂₃NS₂: C, 61.94 (61.97); H, 9.28 (9.32); N, 5.16 (5.11); N, 23.62 (23.59).

Methyl dicyclohexylcarbamodithioate (4vi): Yield: 88%; time: 10 h; FT-IR (KBr, νmax cm⁻¹): 3045, 2990, 2955, 1581, 1485, 1437, 1249, 1086, 967, 848; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.39-7.14 (m, 15H) aromatic proton, 4.42 (s, 2H) S-CH₂-; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 42.62, 128.65, 128.72, 129.11, 129.46, 130.15, 130.41, 134.63, 140.55, 198.58; Anal. calcd. (found) % for C₁₃H₂₃NS₂: C, 69.14 (69.17); H, 9.28 (9.32); N, 5.16 (5.11); N, 23.62 (23.59).

Benzyl diphenylcarbamodithioate (4vii): Yield: 88%; time: 11 h; FT-IR (KBr, νmax cm⁻¹): 3051, 2996, 2955, 1581, 1485, 1437, 1249, 1086, 967, 848; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.39-7.14 (m, 15H) aromatic proton, 4.42 (s, 2H) S-CH₂-; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 42.62, 128.65, 128.72, 129.11, 129.46, 130.15, 130.41, 134.63, 140.55, 198.58; Anal. calcd. (found) % for C₁₃H₂₃NS₂: C, 69.14 (69.17); H, 9.28 (9.32); N, 5.16 (5.11); N, 23.62 (23.59).

4-Chlorobenzyl diphenylcarbamodithioate (4viii): Yield: 89%; time: 14 h; FT-IR (KBr, νmax cm⁻¹): 3051, 2996, 2955, 1581, 1485, 1442, 1258, 1079, 961, 827, 738; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.38-7.16 (m, 14H) aromatic proton, 4.12 (s, 2H) S-CH₂-; ¹³C NMR (125 MHz, CDCl₃) δ ppm: 42.48, 128.72, 129.24, 129.55, 130.24, 130.42, 133.32, 134.38, 141.21, 199.08; Anal. calcd. (found) % for C₁₃H₂₃NS₂Cl: C, 64.93 (64.90); H, 4.36 (4.42); N, 3.79 (3.81); N, 19.12 (19.08).

Methyl diphenylcarbamodithioate (4ix): Yield: 88%; time: 10 h; FT-IR (KBr, νmax cm⁻¹): 3032, 2985, 1421, 1226, 1086, 845; ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.19 (s, 2H) N-CH₃, 3.19 (s, 3H) S-CH₃, 2.10-1.16 (m, 20H) cyclohexyl methylene (-CH₂-) proton, ¹³C NMR (125 MHz, CDCl₃) δ ppm: 19.26, 24.62, 27.39, 31.70, 42.58, 56.08, 201.24; Elemental analysis: Calcd. (found) % for C₁₃H₂₅NS₂: C, 61.94 (61.97); H, 9.28 (9.32); N, 5.16 (5.11); N, 23.62 (23.59).

Biological evaluation

Antibacterial and antifungal activity: Test chemicals were dissolved in DMSO solvent, sterilized by filtering using sintered glass filters and stored at 4 °C. The bioactivity of the synthesized compounds was confirmed using the well-diffusion technique on a nutritional agar medium. On the nutrient agar plates, microorganisms were cultured over night at 37 °C. Kanamycin, amoxicillin and DMSO were employed as reference substances. On potato dextrose agar plates, fungi were cultivated for 5 days at 30 °C. The zones of inhibition (mm) exhibited by the synthesized dithiocarbamate were compared to standards amoxicillin and kanamycin (30 µg/disc) as well as other common antibiotics.

RESULTS AND DISCUSSION

The utilization of environmental friendly solvents and atom-economical catalytic methods represents noteworthy methodologies in organic chemistry reactions, owing to the increasing emphasis on the development of environmentally sustainable reactions. This work is part of our ongoing research into the development of green organic chemistry by using water-ethanol as the reaction medium and catalyst-free conditions [33].

To find the optimal solvent for reaction progression, the process was optimized using the reaction of amine, CS₂ and alkyl halide as a straightforward model substrate in various solvents. The intended product was found to be produced in good yields in a water-ethanol medium without the need for a catalyst by simply combining carbon disulfide (1.6 mmol), amine (1.0 mmol) and alkyl halide (1.0 mmol) at ambient temperature. Although the reaction produces good to outstanding yields in organic solvents, the approach is most favourable when used with water. The process used to obtain product 4i was chosen as a representative model for this purpose. Table-1 provides a summary of the outcomes of this assessment of the model reaction.

### Table 1: Evaluation of Reaction Progress in Existence of Various Solvents

<table>
<thead>
<tr>
<th>Solvent Used</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>Ether</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Toluene</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Water</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>Chloroform</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>Water and ethanol (1:1)</td>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>Water and ethanol (1:2)</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Water and ethanol (1:3)</td>
<td>7</td>
<td>87</td>
</tr>
<tr>
<td>Water and ethanol (1:4)</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>Water and ethanol (1:5)</td>
<td>6</td>
<td>90</td>
</tr>
</tbody>
</table>

It is clear that employing a solution of water and ethanol at a ratio of 1:4 produced a fantastic product yield. The addition of starting compounds in one pot to gain desired dithiocarbamate derivative products in good to excellent yield represents further advantages of this procedure. Additionally, performing the organic transformations in a water-ethanol as a non-toxic solvent makes this pathways environmentally compliant and safe with green chemistry. Additionally, it is clear from the data acquired that no acidic or basic catalyst was required for the reaction to proceed in an appropriate manner, which is another benefit of this method.

After the reaction conditions optimization, the applicability of these conditions was tested with various amines and alkyl/aryl halides. This three-component organic transformation was conducted using a variety of carbon disulfide, secondary amines and several different alkyl or aryl halides in one pot while the mixture of H₂O/EtOH (1:4) was present to evaluate the simplification and broaden the opportunity of the reaction.
Different secondary amines, including diphenylamine and dicyclohexyl amine, produced outstanding yields.

**FT-IR studies:** The dithiocarbamate compounds show bands in the region 3052-2945 cm\(^{-1}\) corresponding to the C-H moiety stretching frequency of aliphatic and aromatic carbon. Moreover, the synthesized compounds show different bands in the range of 1587-1480 cm\(^{-1}\), which is predicted for the C=C bond stretch of the aromatic ring and another peak observed 1427 cm\(^{-1}\) assigned due to the C-S bond stretch. The peak observed at 1235 cm\(^{-1}\) is assigned for the C-N bond stretch while another peak at 1097 cm\(^{-1}\) is assigned due to the C=S bond stretch. The synthesized compound exhibited a peak at 978 cm\(^{-1}\) predicted due to the C-H bond bend. The dithiocarbamate ligand absorbs at 836 cm\(^{-1}\) is assigned to the C-S bond stretch.

**\(^{1}\)H NMR studies:** In the \(^{1}\)H NMR of compound 4i, five protons of the aromatic ring appear as a multiplet at δ 7.29-7.25 ppm. A singlet at δ 4.49 ppm corresponds to the benzyllic -CH\(_2\)- group. The two protons belonging to N-CH\(_2\)- moiety appears at δ 3.56-3.52 ppm as a doublet in the spectra of the compound. Also, a multiplet was observed at δ 2.07-1.14 ppm due to ten protons, which are predicted for methylene (-CH\(_2\)-) proton of cyclohexyl ring.

**\(^{13}\)C NMR studies:** The \(^{13}\)C NMR spectra of compound 4i exhibit ten different peaks which are in good agreement with the respective compound structure. The four peaks observed at δ 128.75, 130.37, 130.75 and 135.93 ppm correspond to aromatic carbon, while the benzyllic -CH\(_2\)- group appears at δ 42.58 ppm. The C=S bond peak was observed at δ 195.27 ppm. The remaining four peaks at δ 24.82, 32.31, 35.00 and 56.08 ppm correspond to carbon of the cyclohexyl ring.

**Biological activity:** The synthesized dithiocarbamate derivatives (4i-4iv) were tested against three pathogens, including one fungus, one Gram-positive (E. coli) and one Gram-negative (S. aureus) bacteria. The bioactivity of test substances was investigated using the well diffusion method. For both bacterial and fungal strains, dithiocarbamate derivatives showed a distinct zone of inhibition surrounding the well. Compound 4i exhibited good antibacterial activity against S. aureus with an inhibition zone of 12 mm, while compound 4ii and 4iv exhibited prominent antibacterial activity against E. coli (Table-2). Compound 4iii exhibited more antifungal activity against C. albicans as compared with other tested compounds but found to be less than the standard drug.

**Conclusion**

A simple, extremely effective and ecologically friendly method for synthesizing dithiocarbamate derivatives in a water-ethanol medium utilizing three different reactants viz. alkyl/ benzyl halides, carbon disulphide and alkyl/aryl amines is presented. All the products were well characterized by various spectral data. By employing water as both a solvent and a promoter, this methodology obviates the necessity for alkaline and hazardous substances, as well as organic solvents such as DMF or DMSO, and catalysts. Some of the remarkable benefits of this process include the high to excellent product yield, reaction at room temperature (energy efficient), atom economy, clean reaction conditions, catalyst-free, potentially remarkable and medicinally significant molecules and the use of readily accessible starting reactant materials. It is a practical and appealing technique for multi-component reactions in combinational chemistry due to the straightforward experimental procedures. This method has several environmentally friendly features, will be a desirable option for the synthesis of various dithiocarbamate derivatives. The synthesized compound also exhibited good bioactivity against tested pathogens.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

**REFERENCES**

4. A. Chanda and V.V. Fokin, Chem. Rev., 109, 725 (2009); https://doi.org/10.1021/cr800448q