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Research Article

Synthesis and Biological Evaluation of Some Novel Dithiocarbamate Derivatives

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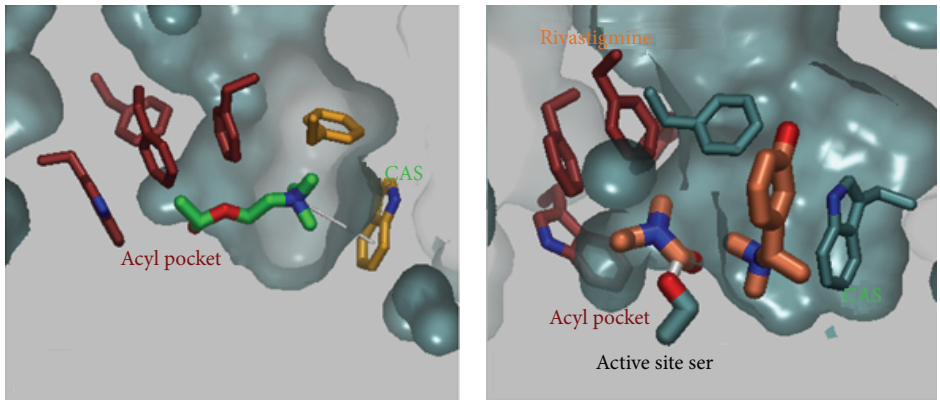
18 novel dithiocarbamate derivatives were synthesized in order to investigate their inhibitory potency on acetylcholinesterase enzyme and antimicrobial activity. Structures of the synthesized compounds were elucidated by spectral data and elemental analyses. The synthesized compounds showed low enzyme inhibitory activity. However, they displayed good antimicrobial activity profile. Antibacterial activity of compounds **4a**, **4e**, and **4p** (MIC = 25 μg/mL) was equal to that of chloramphenicol against *Klebsiella pneumoniae* (ATCC 700603) and *Escherichia coli* (ATCC 35218). Most of the compounds exhibited notable antifungal activity against *Candida albicans* (ATCC 10231), *Candida glabrata* (ATCC 90030), *Candida krusei* (ATCC 6258), and *Candida parapsilosis* (ATCC 7330). Moreover, compound **4a**, which carries piperidin-1-yl substituent and dimethylthiocarbamoyl side chain as variable group, showed twofold better anticandidal effect against all *Candida* species than reference drug ketoconazole.

1. Introduction

Alzheimer's disease (AD) is a an age associated neurodegenerative syndrome with clinical characteristic and pathological properties as loss of neurons in certain brain regions leading to deficiency of memory, cognitive dysfunction, behavioral disturbances, and deficits in activities of daily living, which eventually leads to death [1–3]. Although the underlying pathophysiological mechanisms are not clear, AD is firmly associated with impairment in cholinergic pathway, which results in reduced level of acetylcholine (Ach) that is hydrolysed by cholinesterases (ChE) in certain areas of brain [1, 2, 4, 5]. It is well known that there are two major forms of ChE in the brain of mammals. These are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) found in neurons and glial cells and in neuritic plaques and tangles in Alzheimer's disease (AD) patients [6].

Since the late 1970s the treatment of AD has proceeded and trended to a transmitter replacement strategy. Elevation of acetylcholine levels in brain through the use of AChE inhibitors has been established as the most effective treatment strategy against AD [3, 7]. Therefore, AChE and/or BuChE inhibitors have been recognised as the drug of choice in management of AD [8]. Several AChE inhibitors called as "cognitive enhancers" are being investigated for the symptomatic treatment of Alzheimer's disease [2, 7, 8]. These drugs increase the concentration of acetylcholine at the neurotransmitter sites or acts by regulating activity at nicotinic receptors [2, 4].

There are three important subsites in ChE; anionic site, oxyanion hole, and acyl pocket [9]. Carbamates as pyridostigmine, rivastigmine, and physostigmine constitute a class of ChE inhibitors. These compounds have been reported to direct their carbamate region towards the acyl pocket that includes esteratic site of the enzyme. This inhibition is subsequently reversed upon decarbamylation (Figure 1). However, carbamates have a relatively short duration of action and limited penetration to blood-brain barrier [10].



(a) (b)

Figure 1: (a) Ligand binding sites in acetylcholinesterase. Hydrophobic residues in the gorge are shown as orange sticks. The surface of the protein is shown in cadetblue. Acetylcholine (green sticks) is shown in the catalytic anionic site (CAS). π-Cation interactions and hydrogen bonds are shown as white dotted lines. The acyl pocket residues are shown as brown sticks. (b) Interaction between rivastigmine and acetylcholinesterase. After hydrolysis, rivastigmine, shown as coral sticks, releases the carbamate residue towards the acyl pocket and enzyme inhibition occurs. Images were taken from the official web site of European Bioinformatics Institute.

Dithiocarbamates have attracted a great deal of interest in medicinal chemistry due to the fact that new effective compounds can be gained by the bioisosteric replacement of carbamate moiety with dithiocarbamate moiety. They are also important pharmacophores because of their lipophilicity, which is essential for the delivery of central nervous system (CNS) drugs to their site of action through the blood-brain barrier [11–18]. Thus, evaluation of novel dithiocarbamate derivatives as potential AChE inhibitors will be rational.

The treatment of infectious diseases still remains a crucial problem because of the increasing number of multidrug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics existing for therapeutic use, the emergence of antibiotic resistance developed in the last decades has created a substantial medical need for new classes of antibacterial agents. A potential approach to overcome the resistance problem is to design novel agents with a different mode of action [19, 20].

In addition to their potential AChE inhibitory activity, dithiocarbamate derivatives are important compounds in antimicrobial chemotherapy due to their antibacterial and antifungal properties. First, Miller and Elson [21] and Kligman and Rosensweig [22] determined the activity of dimethyl dithiocarbamate salts against several pathogenic fungi and commented on their possible application in human therapy. In the last decade, dithiocarbamate moiety combined heterocyclic ring systems were studied widely, and now these compounds form a promising group of novel antifungal agents [23].

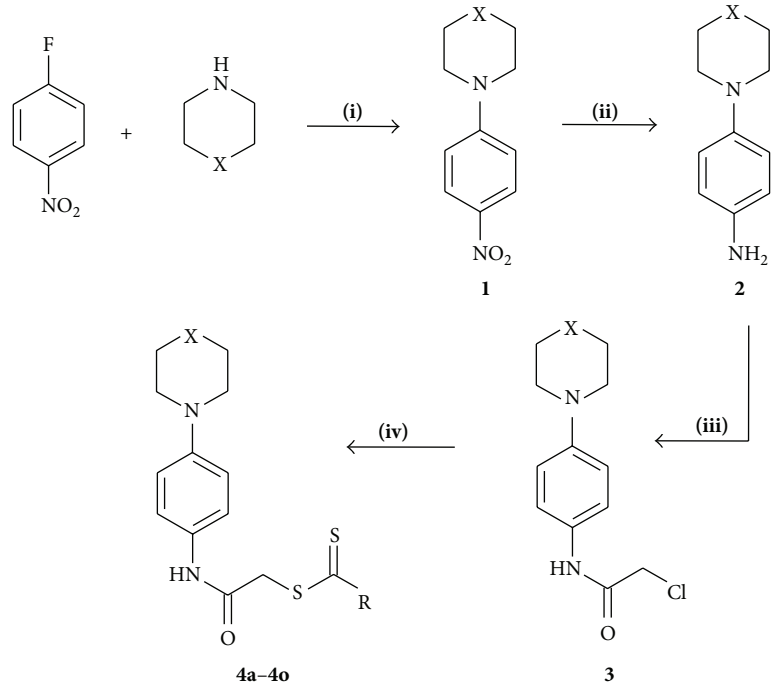
Cyclic amines as piperidine, piperazine, and morpholine possess antimicrobial importance and thus they are often subjected to new antimicrobial agents development studies. For instance, quinoline drugs as norfloxacin and ciprofloxacin carry piperazine nucleus and show broad antibacterial activity spectrum [24]. Linezolid, used for the treatment of infections caused by gram-positive bacteria, includes morpholine group [25–27]. Piperidine based chemical entities with aryl substituents have been documented as potent microbial agents [28, 29].

On the basis of above findings, in the present study we report the synthesis and biological evaluation of some novel dithiocarbamate derivatives as probable anticholinesterase and antimicrobial agents.

2. Experiment

2.1. Materials. All reagents were purchased from commercial suppliers and were used without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus (Weiss-Gallenkamp, Loughborough, UK) and were uncorrected. IR spectra were recorded on Shimadzu 8400 FT-IR spectrophotometer (Shimadzu, Tokyo, Japan). ^{1}H-NMR spectra were recorded on a Bruker 500 MHz spectrometer (Bruker, Billerica, USA). Mass spectra were recorded on a VG Quattro mass spectrometer (Agilent, Minnesota, USA). Elemental analyses were performed on a Leco CHNS-932 analyser (Leco, Michigan, USA). The TLC was performed to monitor reactions on silica gel 60 F_{254} (Merck) layer using petroleum ether : ethyl acetate (3 : 1 v/v) for the first and third reaction steps and petroleum ether : ethyl acetate (1 : 1 v/v) for the second and fourth reaction steps (Scheme 1).

*2.2. General Procedure for 4-Substituted-1-nitrobenzene Derivatives **(1a–1c)**.* 4-Fluoro-1-nitrobenzene (4.24 mL, 0.04 mol), K_2CO_3 (5.52 g 0.04 mol), appropriate cyclic secondary amine (0.04 mol), and DMF (10 mL) were added into a vial (30 mL) of microwave synthesis reactor (Anton-Paar Monowave 300, Graz, Austria). The reaction mixture was heated under conditions of 200°C and 10 bars for 15 min. After cooling, the mixture was poured into iced-water; precipitated product was washed with water, dried, and recrystallized from ethanol.



Scheme 1: The synthetic route for the preparation of dithiocarbamate derivatives. Reagents and conditions: (**i**) K_2CO_3, DMF microwave irradiation, 15 min; (**ii**) Zn powder, 25% HCl/EtOH, room temperature 1 h, and then reflux for 1 h; (**iii**) $ClCH_2COCl$, TEA, THF ice bath and then room temperature 1 h; (**iv**) corresponding dithiocarbamic acid sodium salt, acetone, reflux for 12 h.

*2.3. General Procedure for 4-Substituted Aniline Derivatives **(2a–2c)**.* Corresponding 4-substituted-1-nitrobenzene derivative (**1a–1c**) (0.035 mol) was dissolved in ethanol (100 mL) and 25% HCl (100 mL) mixture. Zinc powder (22.75 g, 0.35 mol) was divided into ten equal portions (2.275 g × 10) and each portion was added to the stirring solution in 15 min intervals. Once the addition of the zinc was completed reaction mixture was refluxed for 1 h. Hot solution was allowed to cool down, poured into ice water, and then neutralized with 10% NaOH solution. The precipitate was extracted with chloroform (3 × 100 mL). The extracts were combined and filtered over anhydrous Na_2SO_4. The solvent was evaporated and the residue was recrystallized from ethanol to give the 4-substituted aniline derivatives (**2a–2c**).

*2.4. General Procedure for 2-Chloro-N-(4-substituted-phenyl) acetamide **(3a–3c)**.* Appropriate 4-substituted aniline (**2a–2c**) (0.022 mol) and triethylamine (3.2 mL, 0.22 mol) were dissolved in THF (100 mL). This mixture was allowed to stir on an ice bath. Chloroacetyl chloride (1.8 mL, 0.022 mol) in THF (10 mL) was added drop by drop. After this stage, the content was stirred for 1 h at room temperature. THF was evaporated and the product was recrystallized from ethanol.

*2.5. N-[(4-Substituted-phenyl)-2-substitutedthiocarbonylthio] acetamide Derivatives **(4a–4s)**.* The compounds **3a–3c** (0.001 mol) were stirred with appropriate sodium salt of dithiocarbamic acid (0.0011 mol) in acetone (30 mL) for 3 h. The precipitated product was filtered, washed with water, and recrystallized from ethanol to gain the title products **4a–4s**.

*2.5.1. N-[4-(Piperidin-1-yl)phenyl]-2-(dimethylaminothiocarbonylthio)acetamide **(4a)**.* IR (KBr) ν_{max} (cm^{-1}): 3288 (N–H), 1651 (C=O), 1217 (C=S), 821 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.51–1.62 (m, 6H, piperidine, $C_{3,4,5}$–H), 3.05 (s, 6H, –N $(CH_3)_2$), 3.41–3.47 (m, 4H, piperidine, $C_{2,6}$–H), 4.17 (s, 2H, –$COCH_2$), 6.87 (d, 2H, J = 8.35 Hz, phenyl, $C_{3,5}$–H), 7.40 (d, 2H, J = 8.54 Hz, phenyl, $C_{2,6}$–H), 10.00 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 338.16. Anal. Calcd. for $C_{16}H_{23}N_3OS_2$: C, 56.94; H, 6.87; N, 12.45; Found: C, 56.63; H, 6.85; N, 12.49.

*2.5.2. N-[4-(Piperidin-1-yl)phenyl]-2-(diethylaminothiocarbonylthio)acetamide **(4b)**.* IR (KBr) ν_{max} (cm^{-1}): 3289 (N–H), 1659 (C=O), 1236 (C=S), 824 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.31 (t, 6H, J = 7.14 Hz, –$N(CH_2\underline{CH_3})_2$), 1.51–1.63 (m, 6H, piperidine, $C_{3,4,5}$–H), 3.03 (q, 4H, J = 7.21 Hz, –$N(\underline{CH_2}CH_3)_2$), 3.39–3.49 (m, 4H, piperidine, $C_{2,6}$–H), 4.18 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.53 Hz, phenyl, $C_{3,5}$–H), 7.41 (d, 2H, J = 8.62 Hz, phenyl, $C_{2,6}$–H), 10.05 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 366.18. Anal. Calcd. for $C_{18}H_{27}N_3OS_2$: C, 59.14; H, 7.44; N, 11.49; Found: C, 59.07; H, 7.42; N, 11.50.

*2.5.3. N-[4-(Piperidin-1-yl)phenyl]-2-(pyrrolidin-1-yl-thiocarbonylthio)acetamide **(4c)**.* IR (KBr) ν_{max} (cm^{-1}): 3291 (N–H), 1659 (C=O), 1236 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.51–1.62 (m, 6H, piperidine, $C_{3,4,5}$–H), 1.91–2.06 (m, 4H, pyrrolidine, $C_{3,4}$–H), 3.04–3.09 (m, 4H, pyrrolidine, $C_{2,5}$–H), 3.41–3.47 (m, 4H, piperidine,

$C_{2,6}$–H), 4.20 (s, 2H, –$COCH_2$), 6.87 (d, 2H, J = 8.31 Hz, phenyl, $C_{3,5}$–H), 7.40 (d, 2H, J = 8.39 Hz, phenyl, $C_{2,6}$–H), 9.99 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 364.11. Anal. Calcd. for $C_{18}H_{25}N_3OS_2$: C, 59.47; H, 6.93; N, 11.56; Found: C, 59.22; H, 6.91; N, 11.59.

2.5.4. N-[4-(Piperidin-1-yl)phenyl]-2-(piperidin-1-yl-thiocarbonylthio)acetamide ***(4d)***. IR (KBr) ν_{max} (cm^{-1}): 3287 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.51–1.66 (m, 12H, 2 × piperidine, $C_{3,4,5}$–H), 3.04–3.08 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.47 (m, 4H, piperidine, $C_{2,6}$–H), 4.20 (s, 2H, –$COCH_2$), 6.87 (d, 2H, J = 8.36 Hz, phenyl, $C_{3,5}$–H), 7.40 (d, 2H, J = 8.29 Hz, phenyl, $C_{2,6}$–H), 10.01 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 378.19. Anal. Calcd. for $C_{19}H_{27}N_3OS_2$: C, 60.44; H, 7.21; N, 11.13; Found: C, 60.70; H, 7.19; N, 11.15.

2.5.5. N-[4-(Piperidin-1-yl)phenyl]-2-(4-methylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4e)***. IR (KBr) ν_{max} (cm^{-1}): 3291 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 0.93 (d, 3H, J = 7.11 Hz, –CH_3), 1.50–1.64 (m, 11H, 2 × piperidine, $C_{3,4,5}$–H), 3.04–3.09 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.46 (m, 4H, piperidine, $C_{2,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.87 (d, 2H, J = 8.33 Hz, phenyl, $C_{3,5}$–H), 7.40 (d, 2H, J = 8.43 Hz, phenyl, $C_{2,6}$–H), 10.02 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 392.14. Anal. Calcd. for $C_{20}H_{29}N_3OS_2$: C, 61.34; H, 7.46; N, 10.73; Found: C, 61.42; H, 7.45; N, 10.70.

2.5.6. N-[4-(Piperidin-1-yl)phenyl]-2-(4-benzylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4f)***. IR (KBr) ν_{max} (cm^{-1}): 3289 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.44–1.63 (m, 11H, 2 × piperidine, $C_{3,4,5}$–H), 2.54 (d, 2H, J = 7.14 Hz, –$\underline{CH_2}C_6H_5$), 3.04–3.10 (m, 4H, piperidine, $C_{2,6}$–H), 3.42–3.48 (m, 4H, piperidine, $C_{2,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.87 (d, 2H, J = 8.22 Hz, phenyl, $C_{3,5}$–H), 7.19–7.31 (m, 5H, –$CH_2\underline{C_6H_5}$), 7.41 (d, 2H, J = 8.30 Hz, phenyl, $C_{2,6}$–H), 10.02 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 468.17. Anal. Calcd. for $C_{26}H_{33}N_3OS_2$: C, 66.77; H, 7.11; N, 8.98; Found: C, 66.59; H, 7.09; N, 9.00.

2.5.7. N-[4-(Morpholin-4-yl)phenyl]-2-(dimethylaminothiocarbonylthio)acetamide ***(4g)***. IR (KBr) ν_{max} (cm^{-1}): 3287 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 3.04 (s, 6H, –$N(CH_3)_2$), 3.41–3.47 (m, 4H, morpholine, $C_{3,5}$–H), 3.72–3.74 (m, 4H, morpholine, $C_{2,6}$–H), 4.18 (s, 2H, –$COCH_2$), 6.89 (d, 2H, J = 8.32 Hz, phenyl, $C_{3,5}$–H), 7.44 (d, 2H, J = 8.44 Hz, phenyl, $C_{2,6}$–H), 10.01 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 340.15. Anal. Calcd. for $C_{15}H_{21}N_3OS_2$: C, 53.07; H, 6.24; N, 12.38; Found: C, 53.33; H, 6.25; N, 12.36.

2.5.8. N-[4-(Morpholin-4-yl)phenyl]-2-(diethylaminothiocarbonylthio)acetamide ***(4h)***. IR (KBr) ν_{max} (cm^{-1}): 3289 (N–H), 1659 (C=O), 1235 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.23 (t, 6H, J = 7.18 Hz, –$N(CH_2\underline{CH_3})_2$), 3.04 (q, 4H, J = 7.16 Hz, –$N(\underline{CH_2}CH_3)_2$), 3.39–3.49 (m, 4H, morpholine, $C_{3,5}$–H), 3.72–3.76 (m, 4H, morpholine, $C_{2,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.89 (d, 2H, J = 8.33 Hz, phenyl, $C_{3,5}$–H), 7.45 (d, 2H, J = 8.29 Hz, phenyl, $C_{2,6}$–H), 10.06 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 368.12. Anal. Calcd. for $C_{17}H_{25}N_3O_2S_2$: C, 55.56; H, 6.86; N, 11.43; Found: C, 56.62; H, 6.85; N, 11.41.

2.5.9. N-[4-(Morpholin-4-yl)phenyl]-2-(pyrrolidin-1-yl-thiocarbonylthio)acetamide ***(4i)***. IR (KBr) ν_{max} (cm^{-1}): 3287 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.93–2.07 (m, 4H, pyrrolidine, $C_{3,4}$–H), 3.03–3.06 (m, 4H, pyrrolidine, $C_{2,5}$–H), 3.41–3.48 (m, 4H, morpholine, $C_{3,5}$–H), 3.73–3.82 (m, 4H, morpholine, $C_{2,6}$–H), 4.21 (s, 2H, –$COCH_2$), 6.89 (d, 2H, J = 8.36 Hz, phenyl, $C_{3,5}$–H), 7.44 (d, 2H, J = 8.31 Hz, phenyl, $C_{2,6}$–H), 10.05 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 336.17. Anal. Calcd. for $C_{17}H_{23}N_3O_2S_2$: C, 55.86; H, 6.34; N, 11.50; Found: C, 55.94; H, 6.37; N, 11.51.

2.5.10. N-[4-(Morpholin-4-yl)phenyl]-2-(piperidin-1-yl-thiocarbonylthio)acetamide ***(4j)***. IR (KBr) ν_{max} (cm^{-1}): 3289 (N–H), 1651 (C=O), 1217 (C=S), 821 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.56–1.64 (m, 6H, piperidine, $C_{3,4,5}$–H), 3.03–3.06 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.48 (m, 4H, morpholine, $C_{3,5}$–H), 3.73–3.86 (m, 4H, morpholine, $C_{2,6}$–H), 4.20 (s, 2H, –$COCH_2$), 6.89 (d, 2H, J = 8.42 Hz, phenyl, $C_{3,5}$–H), 7.44 (d, 2H, J = 8.38 Hz, phenyl, $C_{2,6}$–H), 10.05 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 380.15. Anal. Calcd. for $C_{18}H_{25}N_3O_2S_2$: C, 56.96; H, 6.64; N, 11.07; Found: C, 57.10; H, 6.67; N, 11.08.

2.5.11. N-[4-(Morpholin-4-yl)phenyl]-2-(4-methylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4k)***. IR (KBr) ν_{max} (cm^{-1}): 3288 (N–H), 1659 (C=O), 1234 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 0.94 (d, 3H, J = 7.14 Hz, –CH_3), 1.50–1.65 (m, 5H, piperidine, $C_{3,4,5}$–H), 3.03–3.09 (m, 4H, piperidine, $C_{2,6}$–H), 3.40–3.46 (m, 4H, morpholine, $C_{3,5}$–H), 3.71–3.77 (m, 4H, morpholine, $C_{2,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.31 Hz, phenyl, $C_{3,5}$–H), 7.42 (d, 2H, J = 8.39 Hz, phenyl, $C_{2,6}$–H), 10.02 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 394.18. Anal. Calcd. for $C_{19}H_{27}N_3O_2S_2$: C, 57.98; H, 6.91; N, 10.68; Found: C, 58.08; H, 6.92; N, 10.69.

2.5.12. N-[4-(Morpholin-4-yl)phenyl]-2-(4-benzylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4l)***. IR (KBr) ν_{max} (cm^{-1}): 3289 (N–H), 1659 (C=O), 1233 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.51–1.62 (m, 5H, piperidine, $C_{3,4,5}$–H), 2.52 (d, 2H, J = 7.22 Hz, –$\underline{CH_2}C_6H_5$), 3.05–3.08 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.47 (m, 4H, morpholine, $C_{3,5}$–H), 3.72–3.78 (m, 4H, morpholine, $C_{2,6}$–H), 4.18 (s, 2H, –$COCH_2$), 6.89 (d, 2H, J = 8.38 Hz, phenyl, $C_{3,5}$–H), 7.19–7.31 (m, 5H, –$CH_2\underline{C_6H_5}$), 7.41 (d, 2H, J = 8.43 Hz, phenyl, $C_{2,6}$–H), 10.04 (s, 1H, –NHCO). MS (ESI)

Table 1: Some physicochemical properties of the synthesized compounds.

Comp.	X	R	Yield (%)	M.p. (°C)	M.p. (°C) [Lit.]	Molecular formula	Molecular weight (g/mol)	Appearance
1a	CH_2	—	73	97	95 [31]	$C_{11}H_{14}N_2O_2$	206	Yellow
1b	O	—	69	161	158-159 [32]	$C_{10}H_{12}N_2O_3$	208	Yellow
1c	N–CH_3	—	79	106	105-106 [33]	$C_{11}H_{15}N_3O_2$	221	Yellow
2a	CH_2	—	42	41	40 [34]	$C_{11}H_{16}N_2$	176	White
2b	O	—	51	131	129.5–130.5 [35]	$C_{10}H_{14}N_2O$	178	Brown
2c	N–CH_3	—	49	92	93 [36]	$C_{11}H_{17}N_3$	191	White
3a	CH_2	—	79	132	—	$C_{13}H_{17}ClN_2O$	252.5	Brown
3b	O	—	81	171	170–172 [37]	$C_{12}H_{15}ClN_2O_2$	254.5	Brown
3c	N–CH_3	—	76	186	—	$C_{13}H_{18}ClN_3O$	267.5	Brown
4a	CH_2	–$N(CH_3)_2$	75	142	—	$C_{16}H_{23}N_3OS_2$	337	Cream-colored
4b	CH_2	–$N(C_2H_5)_2$	83	127	—	$C_{18}H_{27}N_3OS_2$	365	Brown
4c	CH_2	Pyrrolidin-1-yl	85	163	—	$C_{18}H_{25}N_3OS_2$	363	Cream-colored
4d	CH_2	Piperidin-1-yl	82	235	—	$C_{19}H_{27}N_3OS_2$	391	Cream-colored
4e	CH_2	4-Methylpiperidin -1-yl	79	212	—	$C_{20}H_{29}N_3OS_2$	405	Brown
4f	CH_2	4-Benzylpiperidin-1-yl	84	220	—	$C_{26}H_{33}N_3OS_2$	481	Brown
4g	O	–$N(CH_3)_2$	87	148	—	$C_{15}H_{21}N_3OS_2$	339	Brown
4h	O	–$N(C_2H_5)_2$	78	97	—	$C_{17}H_{25}N_3O_2S_2$	367	White
4i	O	Pyrrolidin-1-yl	73	175	—	$C_{17}H_{23}N_3O_2S_2$	365	Cream-colored
4j	O	Piperidin-1-yl	77	171	—	$C_{18}H_{25}N_3O_2S_2$	393	Brown
4k	O	4-Methylpiperidin -1-yl	69	165	—	$C_{19}H_{27}N_3O_2S_2$	407	Cream-colored
4l	O	4-Benzylpiperidin-1-yl	72	150	—	$C_{25}H_{31}N_3O_2S_2$	483	Cream-colored
4m	N–CH_3	–$N(CH_3)_2$	70	185	—	$C_{16}H_{24}N_4OS_2$	352	Brown
4n	N–CH_3	–$N(C_2H_5)_2$	78	152	—	$C_{18}H_{26}N_4OS_2$	380	White
4o	N–CH_3	Pyrrolidin-1-yl	73	175	—	$C_{19}H_{28}N_4OS_2$	378	Cream-colored
4p	N–CH_3	Piperidin-1-yl	75	147	—	$C_{20}H_{30}N_4OS_2$	406	Brown
4r	N–CH_3	4-Methylpiperidin-1yl	71	179	—	$C_{26}H_{34}N_4OS_2$	420	Brown
4s	N–CH_3	4-Benzylpiperidin-1-yl	82	155	—	$C_{16}H_{24}N_4OS_2$	496	Cream-colored

(m/z): $[M + 1]^+$ 470.21. Anal. Calcd. for $C_{25}H_{31}N_3O_2S_2$: C, 63.93; H, 6.65; N, 8.95; Found: C, 63.75; H, 6.63; N, 8.98.

*2.5.13. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(dimethylaminothiocarbonylthio)acetamide **(4m)**.* IR (KBr) ν_{max} (cm^{-1}): 3273 (N–H), 1654 (C=O), 1221 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 2.22 (s, 3H, –NCH_3), 3.06 (s, 6H, –$N(CH_3)_2$), 3.39–3.57 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.18 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.25 Hz, phenyl, $C_{3,5}$–H), 7.42 (d, 2H, J = 8.28 Hz, phenyl, $C_{2,6}$–H), 10.02 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 353.11. Anal. Calcd. for $C_{16}H_{24}N_4OS_2$: C, 54.51; H, 6.86; N, 15.89; Found: C, 54.38; H, 6.84; N, 15.84.

*2.5.14. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(diethylaminothiocarbonylthio)acetamide **(4n)**.* IR (KBr) ν_{max} (cm^{-1}): 3292 (N–H), 1654 (C=O), 1234 (C=S), 820 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.23 (t, 6H, J = 7.11 Hz, –$N(CH_2\underline{CH_3})_2$), 2.24 (s, 3H, –$NCH_3$), 3.06 (q, 4H, J = 7.16 Hz, –$N(\underline{CH_2}CH_3)_2$), 3.39–3.62 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.18 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.19 Hz, phenyl, $C_{3,5}$–H), 7.42 (d, 2H, J = 8.32 Hz, phenyl, $C_{2,6}$–H), 10.03 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 381.16. Anal. Calcd. for $C_{18}H_{28}N_4OS_2$: C, 56.81; H, 7.42; N, 14.72; Found: C, 56.58; H, 7.44; N, 14.75.

*2.5.15. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(pyrrolidin-1-yl-thiocarbonylthio)acetamide **(4o)**.* IR (KBr) ν_{max} (cm^{-1}): 3287 (N–H), 1654 (C=O), 1234 (C=S), 820 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 2.06–2.10 (m, 4H, pyrrolidine, $C_{3,4}$–H), 2.22 (s, 3H, –NCH_3), 3.04–3.08 (m, 4H, pyrrolidine, $C_{2,5}$–H), 3.42–3.65 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.20 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.12 Hz, phenyl, $C_{3,5}$–H), 7.41 (d, 2H, J = 8.23 Hz, phenyl, $C_{2,6}$–H), 10.00 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 379.17. Anal. Calcd. for $C_{18}H_{26}N_4OS_2$: C, 57.11; H, 6.92; N, 14.80; Found: C, 57.42; H, 6.94; N, 14.75.

*2.5.16. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(piperidin-1-yl-thiocarbonylthio)acetamide **(4p)**.* IR (KBr) ν_{max} (cm^{-1}): 3291 (N–H), 1661 (C=O), 1234 (C=S), 820 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.56–1.68 (m, 6H,

piperidine, $C_{3,4,5}$–H), 2.24 (s, 3H, –NCH_3), 3.03–3.08 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.68 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.24 Hz, phenyl, $C_{3,5}$–H), 7.42 (d, 2H, J = 8.31 Hz, phenyl, $C_{2,6}$–H), 10.03 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 393.13. Anal. Calcd. for $C_{19}H_{28}N_4OS_2$: C, 58.13; H, 7.19; N, 14.27; Found: C, 58.42; H, 7.21; N, 14.25.

2.5.17. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(4-methylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4r)***. IR (KBr) ν_{max} (cm^{-1}): 3293 (N–H), 1661 (C=O), 1234 (C=S), 820 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 0.96 (d, 3H, J = 7.08 Hz, –CH_3), 1.52–1.65 (m, 5H, piperidine, $C_{3,4,5}$–H), 3.04–3.08 (m, 4H, piperidine, $C_{2,6}$–H), 3.41–3.75 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.19 (s, 2H, –$COCH_2$), 6.88 (d, 2H, J = 8.26 Hz, phenyl, $C_{3,5}$–H), 7.41 (d, 2H, J = 8.24 Hz, phenyl, $C_{2,6}$–H), 10.01 (s, 1H, –NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 407.16. Anal. Calcd. for $C_{20}H_{30}N_4OS_2$: C, 59.08; H, 7.44; N, 13.78; Found: C, 59.22; H, 7.46; N, 13.71.

2.5.18. N-[4-(4-Methylpiperazin-1-yl)phenyl]-2-(4-benzylpiperidin-1-yl-thiocarbonylthio)acetamide ***(4s)***. IR (KBr) ν_{max} (cm^{-1}): 3275 (N–H), 1659 (C=O), 1221 (C=S), 822 (1,4-disubstituted benzene). ^{1}H-NMR (500 MHz, DMSO-d6): 1.51–1.62 (m, 5H, piperidine, $C_{3,4,5}$–H), 2.61 (d, 2H, J = 7.16 Hz, –$\underline{CH_2}C_6H_5$), 3.05–3.09 (m, 4H, piperidine, $C_{2,6}$–H), 3.44–3.75 (m, 8H, piperazine, $C_{2,3,5,6}$–H), 4.18 (s, 2H, $COCH_2$), 6.88 (d, 2H, J = 8.11 Hz, phenyl, $C_{3,5}$–H), 7.17–7.30 (m, 5H, –$CH_2\underline{C_6H_5}$), 7.42 (d, 2H, J = 8.27 Hz, phenyl, $C_{2,6}$–H), 10.04 (s, 1H, NHCO). MS (ESI) *(m/z)*: $[M + 1]^+$ 483.15. Anal. Calcd. for $C_{26}H_{34}N_4OS_2$: C, 64.69; H, 7.10; N, 11.61; Found: C, 64.77; H, 7.12; N, 11.58.

2.6. Enzymatic Assay. All compounds were subjected to a slightly modified method of Ellman's test [30, 31] in order to evaluate their potency to inhibit the AChE. Donepezil hydrochloride was used as a positive control (Table 2). Enzyme solutions were prepared in gelatin solution (1%), at a concentration of 2.5 units/mL. AChE and compound solution (50 μL) which is prepared in 2% DMSO at 0.1 and 1 mM concentrations were added to 3.0 mL phosphate buffer (pH 8 ± 0.1) and incubated at 25°C for 5 min. The reaction was started by adding DTNB (50 μL) and ATC (10 μL) to the enzyme-inhibitor mixture. The production of the yellow anion was recorded for 10 min at 412 nm. As a control, an identical solution of the enzyme without the inhibitor is processed following the same protocol. The blank reading contained 3.0 mL buffer, 50 μL 2% DMSO, 50 μL DTNB, and 10 μL substrate. All processes were assayed in triplicate. The inhibition rate (%) was calculated by the following equation:

$$\text{Inhibition\%} = \frac{\left[\left(A_C - A_B\right) - \left(A_I - A_B\right)\right]}{\left(A_C - A_B\right)} \times 100, \quad (1)$$

where A_I is the absorbance in the presence of the inhibitor, A_C is the absorbance of the control, and A_B is the absorbance of blank reading. Both of the values are corrected with blank-reading value. SPSS for Windows 15.0 was used for statistical analysis. Student's t-test was used for all statistical calculations. Data were expressed as mean ± SD inactive in culture medium.

Table 2: % Inhibition potency of the compounds on AChE at 10^{-3}–10^{-4} M concentrations.

Comp.	Inhibition %	
	10^{-3} M	10^{-4} M
4a	16.95	16.45
4b	16.21	14.36
4c	41.93	12.98
4d	31.39	9.78
4e	41.48	11.47
4f	9.54	8.37
4g	7.56	2.42
4h	8.58	1.97
4i	15.56	1.02
4j	15.55	1.49
4k	12.11	3.01
4l	6.31	3.86
4m	9.47	2.43
4n	12.11	2.17
4o	28.81	9.31
4p	37.78	2.36
4r	7.65	7.43
4s	7.40	5.10
Donepezil	98.37	92.31

2.7. Broth Microdilution Assay. The antimicrobial activities of compounds were tested using the microbroth dilution method [32]. MIC readings were performed twice for each chemical agent. Final products were tested for their in vitro growth inhibitory activity against *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 700603), *Escherichia coli* (ATCC 35218), *Escherichia coli* (ATCC 25923), *Candida albicans* (ATCC 10231), *Candida glabrata* (ATCC 90030), *Candida krusei* (ATCC 6258), and *Candida parapsilosis* (ATCC 7330). Chloramphenicol and ketoconazole were used as control drugs.

The cultures were obtained from Mueller-Hinton broth (Difco) for the bacterial strains after overnight incubation at 35 ± 1°C. The yeasts were maintained in Sabouraud dextrose broth (Difco) after overnight incubation 35 ± 1°C. The inocula of test microorganisms were adjusted to match the turbidity of a MacFarland 0.5 standard tube as determined with a spectrophotometer and the final inoculum size was 0.5–2.5 × 10^5 cfu/mL for antibacterial and antifungal assays. Testing was carried out in Mueller-Hinton broth and Sabouraud dextrose broth (Difco) at pH 7 and the twofold serial dilution technique was applied. The last well on the microplates containing only inoculated broth was kept as controls and the last well with no growth of microorganism was recorded to represent the MIC expressed in μg/mL. For both the antibacterial and antifungal assays the compounds were

Table 3: Antimicrobial activities of the compounds as MIC values (μg/mL).

Comp.	A	B	C	D	E	F	G	H	I
4a	25	50	25*	25*	25*	25**	25**	25**	25**
4b	200	50	50	50	200	50*	25**	50*	50*
4c	25	50	50	50	50	50*	50*	25**	50*
4d	200	50	50	50	200	50*	50*	50*	25**
4e	50	50	25*	25*	50	25**	50*	25**	50*
4f	25	50	50	50	50	50*	50*	50*	50*
4g	200	200	200	200	200	50*	50*	50*	200
4h	50	50	50	50	200	200	100	400	400
4i	200	200	200	200	200	400	50*	400	400
4j	200	200	200	200	200	400	50*	400	400
4k	200	50	50	50	200	400	50*	400	400
4l	200	200	50	50	200	400	50*	400	200
4m	200	50	50	50	200	400	50*	50*	200
4n	200	200	50	50	50	400	50*	50*	200
4o	200	50	50	50	200	400	50*	50*	200
4p	200	200	25*	25*	200	400	50*	200	200
4r	50	50	50	50	50	400	50*	400	50*
4s	200	200	50	50	200	400	100	200	400
Ref-1	6.125	25	25	25	25	—	—	—	—
Ref-2	—	—	—	—	—	50	50	50	50

A: *Enterococcus faecalis* (ATCC 29212), B: *Pseudomonas aeruginosa* (ATCC 27853), C: *Klebsiella pneumoniae* (ATCC 700603), D: *Escherichia coli* (ATCC 35218), E: *Escherichia coli* (ATCC 25923), F: *Candida albicans* (ATCC 10231), G: *Candida glabrata* (ATCC 90030), H: *Candida krusei* (ATCC 6258), and I: *Candida parapsilosis* (ATCC 7330). **Ref-1**: chloramphenicol, **Ref-2**: ketoconazole. *Equal activity to reference. **Better activity than reference.

dissolved in DMSO. Further dilutions of the compounds and standard drugs in test medium were prepared at the required quantities of 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.13, and 1.63 μg/mL concentrations with Mueller-Hinton broth and Sabouraud dextrose broth [32, 33]. Each experiment in the antimicrobial assays was replicated twice in order to define the MIC values given in Table 1.

3. Results and Discussion

In the present study some N-[(4-substituted-phenyl)-2-substitutedthiocarbonylthio]acetamide derivatives (**4a**–**4s**) were synthesized in order to evaluate their biological activities. Target compounds were prepared in four steps. Initially, 4-fluoro-1-nitrobenzene in DMF was reacted with appropriate cyclic secondary amine under microwave irradiation to obtain 4-substituted-1-nitrobenzene derivatives **(1a**–**1c)**. In the second step, nitro group reduction of **1a**–**1c** gave 4-substituted aniline derivatives (**2a**–**2c**), which were acetylated in further step by chloroacetyl chloride to gain 2-chloro-N-(4-substituted-phenyl)acetamides (**3a**–**3c**). Finally, compounds **3a**–**3c** were reacted with appropriate dithiocarbamic acid sodium salt to obtain target compounds (**4a**–**4s**). Synthetic route for the preparation of target compounds is outlined in Scheme 1. Some physicochemical properties of the compounds are given in Table 1.

Structure elucidations of the final compounds (**4a**–**4s**) were performed with IR, ^{1}H-NMR, and ES-MS spectroscopic methods and elemental analysis. Characteristic stretching absorptions of C=O groups and N–H bonds were observed at 1651–1661 cm^{-1} and 3273–3493 cm^{-1}, respectively. The stretching absorptions at about 1230 cm^{-1} were assigned to C=S bond. In the ^{1}H-NMR spectra, all of the aromatic and aliphatic protons were observed at the estimated chemical shifts. The N–H proton of the acetylamino group gave a singlet signal at 9.99–10.06 ppm. The aromatic protons of 1,4-disubstituted phenyl ring were found at 6.87–7.45 ppm. The $-COCH_2$ protons appeared as singlet signals at 4.17–4.21 ppm. The M + 1 peaks in ES-MS spectra were in agreement with the calculated molecular weight of the target compounds (**4a**–**4s**). Elemental analysis results for C, H, and N elements were satisfactory within 0.4% calculated values of the compounds.

The anticholinesterase effects of the compounds (**4a**–**4s**) were determined by modified Ellman's spectrophotometric method (Table 2). Donepezil was used as a standard AChE inhibitor. The tested compounds showed low enzyme inhibitory activity. However, the compounds **4c** and **4e**, which carry piperidine ring on fourth position of phenyl, displayed better inhibitory activity than other compounds.

Contrary to their enzyme inhibitory potency synthesized compounds displayed good antimicrobialy activity profile. Antibacterial activity of the compounds **4a**, **4e**, and **4p** (MIC = 25 μg/mL) was equal to that of chloramphenicol against *Klebsiella pneumoniae* (ATCC 700603) and *Escherichia coli* (ATCC 35218). Most of the compounds (**4b**–**4d**, **4f**, **4h**, **4k**–**4o**, **4r**, and **4s**) showed moderate antibacterial activity against these two bacterial strains (Table 3).

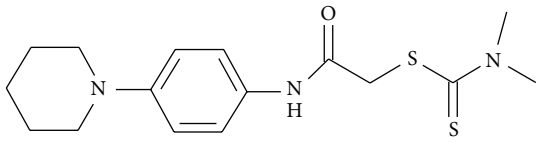


Figure 2: Chemical structure of compound **4a**.

When compared with bacterial strain, *Candida* species were found to be more sensitive to synthesized compounds. Compound **4a** (Figure 2) which carries piperidin-1-yl substituent and dimethylthiocarbamoyl side chain as variable groups exhibited twofold better anticandidal effect than reference drug ketoconazole. Furthermore, the other piperidin-1-yl substituted compounds **4b**–**4f** showed significant antifungal activity (Table 3). Although morpholin-4-yl and 4-methylpiperazin-1-yl substituted compounds **4g**–**4l** and **4m**–**4s** showed equal activity to reference drug against *Candida glabrata* (ATCC 90030), their potency against the other *Candida* species was not the same with reference. This finding suggests that piperidin-1-yl substitution has good influence on antifungal activity. Besides, dimethylthiocarbamoyl side chain raises the antifungal activity significantly.

4. Conclusion

In an effort to develop potent anticholinesterase and antimicrobial agents, we described the synthesis of a series of N-[(4-substituted-phenyl)-2-substitutedthiocarbonylthio]acetamide derivatives (**4a**–**4s**) and focused on their biological activity evaluation. Anticholinesterase activity of the synthesized compounds was not as notable as antimicrobial activity. When compared with antibacterial activity, target compounds displayed better antifungal effect profile. Among these derivatives, compound **4a** can be identified as the most promising antifungal agent against all tested *Candida* species with a twofold lower MIC value (25 μg/mL) than ketoconazole. This result may have a good impact on medicinal chemists to synthesize more active compounds that contain similar chemical structure.

Conflict of Interests

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

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