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Research article

Synthesis of novel antibacterial and antifungal dithiocarbamate-containing piperazine derivatives via re-engineering multicomponent approach

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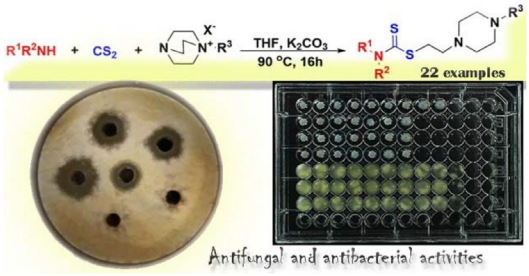
GRAPHICAL ABSTRACT



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ABSTRACT

A metal-free multicomponent synthetic route for the diverse preparation of dithiocarbamate-containing piperazine derivatives was developed through the C–N bond cleavage of DABCO ring. This multicomponent re-engineering approach proceeds *via* the reaction of amines, CS_2 and DABCO salts in one pot. Various DABCO salts and secondary amines are tolerated well in this protocol to afford a broad spectrum of dithiocarbamate-containing piperazines in good to high yields. Then, the selected compounds have been deployed against some critical types of bacteria and fungi. A certain number of synthesized compounds revealed not only appropriate antibacterial activity as investigated by disc fusion and minimum inhibitory concentration methods against bacteria (Gram-positive and Gram-negative), but also depicted good to excellent antifungal activity.

1. Introduction

Nowadays, the world is encountering the coronavirus disease 2019 (COVID-19) pandemic. It has been amply clear that this is a viral disease. Nevertheless, it could still weaken patients' immune systems, hence leading to secondary bacterial or fungal infections taking hold [1, 2]. For instance, the COVID-19 delta variant in some patients led to apparent of mucormycosis, previously called zygomycosis and also known as black fungus [3, 4]. Considering the extensive repercussion of this pandemic, scientists must come up with novel and effective antiviral drugs [5, 6], and need to find new antibacterial and antifungal compounds [7, 8]. Indisputably, discovering highly efficient remedies for these infectious

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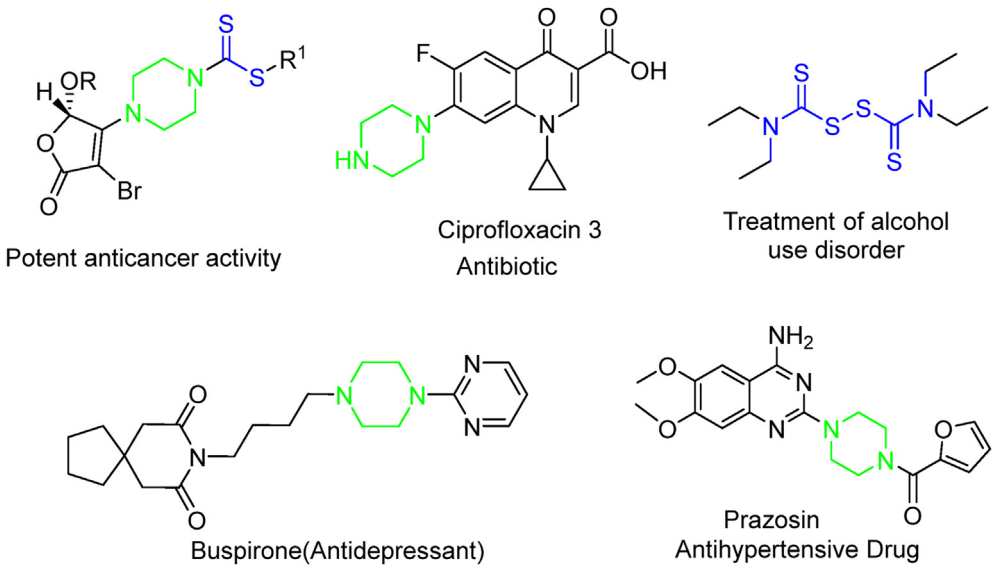
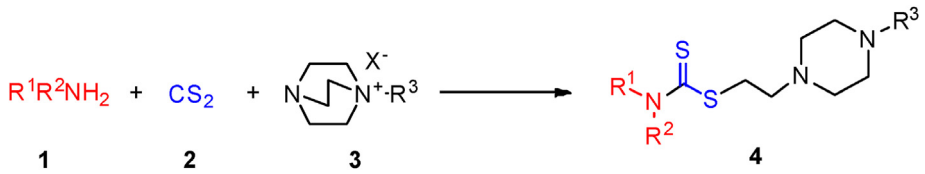


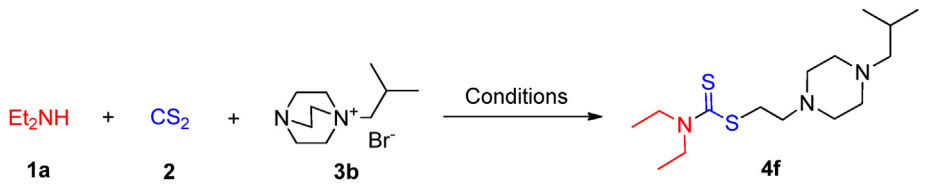
Figure 1. Representative piperazine- and dithiocarbamate-centered drugs and biologically active compounds.



Scheme 1. Single-pot three-component approach for the synthesis of dithiocarbamate-containing piperazines (**4**) using secondary amines (**1**), CS_2 (**2**) and DABCO salts (**3**).

diseases has exponentially emerged as an area of focus [9, 10, 11]. In this context, the synthesis of various dithiocarbamates (DTCs), which revealed remarkable properties and diverse applications in bioorganic and medicinal chemistry such as fungicides and pesticides, crop protection agents and anticancer agents, is thoroughly crucial [12, 13, 14, 15, 16, 17, 18]. For example, take Zineb, Maneb and disulfiram as imperative dithiocarbamate-based biologically active molecules (Figure 1) [19,20]. Further, piperazine is a six-membered heterocyclic compound encompassing two nitrogen atoms in the positions 1 and 4 [21]. On account of the importance of the substituted piperazines in many different biomedical applications, a swift approach to the direct synthesis of novel piperazines has been tremendously beneficial. Among various methods reported for the synthesis of piperazines, DABCO bond cleavage found widespread applications for the direct preparation of valuable piperazines scaffolds. A broad spectrum of nucleophiles such as carboxylic acids, amines, thiols, phenolates, indoles, azide, and alcohols were successfully deployed for the cleavage of C–N bond in DABCO [22]. Piperazine-based drugs such as Indinavir, an antiretroviral drug used to treat HIV, Ciprofloxacin, Buspirone, and Prazosin are available in the market (Figure 1). In addition, Vestipitant, a NK-1 receptor antagonist is in clinical trials to treat anxiety and tinnitus [23, 24]. Until now, MDL@Drug Data Report (MDDR) database includes approximately 11800 scaffolds bearing the piperazine heterocycles. Since piperazine compounds are normally applied as a linker between two portions of a bioactive molecules, combining piperazine along with dithiocarbamate moieties in a single structure may have synergistic effect for designing of novel and promising pharmacologically active compounds.

Since the conventional synthesis encompassing the reaction of two reagents have limitations for preparing diverse and complex products, multicomponent reactions (MCRs) or one-pot three or more reactants procedures, making it viable to generate ensued molecules with more complexity and efficiency [25]. Besides, the re-engineering approach makes it possible to adopt specific nonelementary two-component reactions into higher-order MCRs. Implementing the re-engineering approach as a rational design culminated in increasing the dimensionality of MCRs and achieving diverse skeletal molecules [26]. In addition, in terms of the green chemistry criteria, MCRs enjoy excellent green properties such as pot, atom, and step economy and appropriate environmental impact factor (E-factor), as the lower amount of waste products were produced [27]. Consequently, in this project, dithiocarbamate-containing piperazine derivatives which were recently prepared with us *via* a two-component reaction [28], effectively were



Scheme 2. Model reaction for optimization of the reaction conditions for the synthesis of dithiocarbamate-containing piperazine (**4f**) using amine (**1a**), CS_2 (**2**) and DABCO salt (**3b**).

Table 1. Selected conditions for optimization of the model reaction of diethylamine (**1a**), CS_2 (**2**) and DABCO salt (**3b**) for the synthesis piprazine derivative (**4f**).

Entry	Base	Solvent	T (°C)	Time (h)	Yield (%)[a,b]
1	-	THF	120	24	40
2	NaOH	THF	120	24	37
3	KOH	THF	120	24	32
4	K_3PO_4	THF	120	24	66
5	Na_2CO_3	THF	120	24	54
6	K_2CO_3	THF	120	24	89
7	K_2CO_3	MeOH	120	24	83
8	K_2CO_3	EtOH	120	24	80
9	K_2CO_3	*n*-hexane	120	24	33
10	K_2CO_3	DMF	120	24	37
11	K_2CO_3	$CHCl_3$	120	24	26
12	K_2CO_3	CH_2Cl_2	120	24	NR[c]
13	K_2CO_3	DMSO	120	24	NR[c]
14	K_2CO_3	H_2O	120	24	8
15	K_2CO_3	THF	50	24	28
16	K_2CO_3	THF	70	24	35
17	K_2CO_3	THF	90	24	87
18	K_2CO_3	THF	90	12	82
19	**K_2CO_3**	**THF**	**90**	**16**	**95**

[a] Isolated yield.
[b] Reaction conditions: DABCO salt **3b** (0.5 mmol), diethylamine (0.5 mmol), carbon disulfide (0.75 mmol), base (0.5 mmol), solvent (3 mL).
[c] NR = no reaction.

synthesized through a novel re-engineering multicomponent approach and subsequently, their antifungal and antibacterial properties were investigated (Scheme 1).

2. Experimental

2.1. General

Starting materials and solvents were purchased from Merck and Fluka and were applied as received. All reactions were carried out in sealed vessel at high temperature for overnight. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 MHz device with tetramethylsilane (TMS) as internal standard for NMR solvents. Purity of products and progress of the reactions were checked by thin-layer chromatography using TLC silica gel 60 F254 plates and visualization was carried out using iodine or $KMnO_4$ solution. Melting points were measured by an electrothermal digital apparatus. HRMS (High Resolution Mass Spectra) was measured on a THERMO SCIENTIFIC Advantage and a THERMO SCIENTIFIC Exactive instrument equipped with an APCI source in the positive-ion mode.

2.2. General procedure for preparation of quaternary ammonium salts from DABCO

DABCO (10 mmol, 1.12 g) was dissolved in THF (20 mL) and then an alkyl halide such as isopropyl, isobutyl, allyl, benzyl, isopentyl halides (10 mmol) was added and the reaction mixture was heated at 70 °C for 24 h to afford a precipitate. Filtration of the precipitate, washing with diethyl ether (3 × 15 mL), and drying under vacuum afforded the corresponding product. In the case of *bis* ammonium salt of DABCO, 20 mmol of DABCO reacted with 10 mmol of the corresponding 1,3-dibromopropane.

2.3. General procedure for preparation of functionalized piperazines

In a round bottom flask, a DABCO salt (1 mmol), a secondary amine (1 mmol), carbon disulfide (1.5 mmol), potassium carbonate (1 mmol), and THF (5 mL) were added and the mixture was stirred at 90 °C for 16 h. At the end, the solvent was evaporated and the crude mixture was subjected to column chromatography (SiO_2, EtOAc/petroleum ether; 70/30) to afford pure products. The isolated compounds were well characterized by NMR spectroscopy and HRMS analysis.

2.3.1. 2-(4-isopropylpiperazin-1-yl)ethyldimethylcarbamodithioate (4a)

Yellow solid (192 mg, 70%); mp 53.5–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.48–3.41 (t, J = 6.9 Hz, 2H), 3.36 (s, 3H), 2.72–2.61 (m, 3H), 2.56 (brs, 8H), 1.04 (d, J = 6.5 Hz, 6H) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 56.8, 54.3, 53.2, 48.4, 45.2, 41.3, 34.5, 18.5 ppm; HRMS (ESI) calculated for $C_{12}H_{25}N_3S_2$ $[M+H]^+$: 276.1568; Found: 276.1566.

2.3.2. 2-(4-isopropylpiperazin-1-yl)ethyl diethylcarbamodithioate (4b)

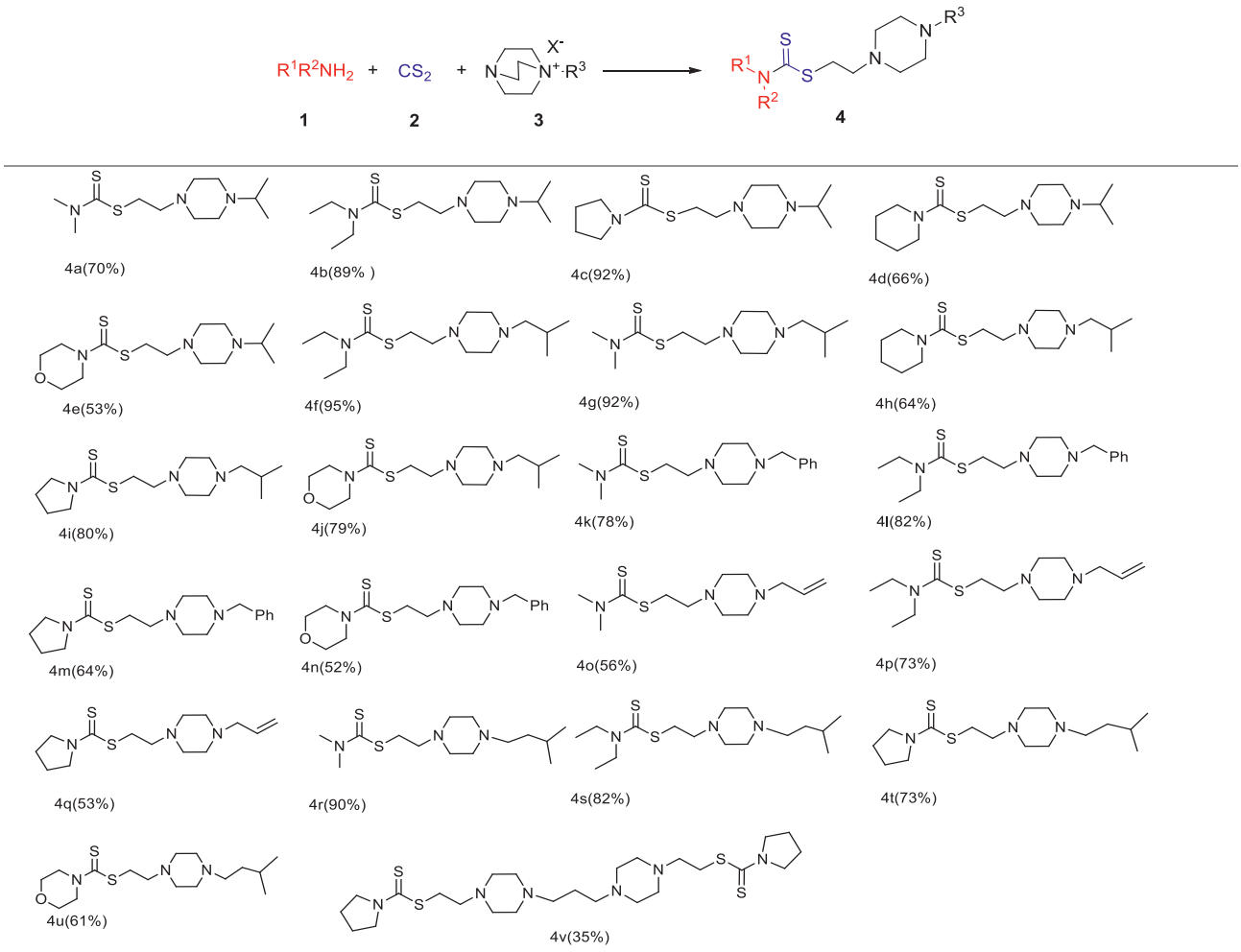
Colorless viscous oil (270 mg, 89%);^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (q, J = 6.7 Hz, 2H), 3.74 (q, J = 6.8 Hz, 2H), 3.49 (t, J = 7.6 Hz, 2H), 2.76–2.64 (m, 3H), 2.61 (brs, 8H), 1.27 (t, J = 6.8 Hz, 6H), 1.07 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 56.9, 54.6, 52.9, 49.4, 48.4, 46.5, 33.9, 18.4, 12.4, 11.5 ppm; HRMS (ESI) calculated for $C_{14}H_{29}N_3S_2$ $[M+H]^+$: 304.1881; Found: 304.1873.

2.3.3. 2-(4-isopropylpiperazin-1-yl)ethylpyrrolidine-1-carbodithioate (4c)

Pale yellow solid (277 mg, 92%); mp 53–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (t, J = 6.9 Hz, 2H), 3.55 (t, J = 6.9 Hz, 2H), 3.35 (t, J = 7.4 Hz, 2H), 2.62–2.53 (m, 3H), 2.46 (brs, 8H), 1.92–1.88 (m, 4H), 0.94 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 56.7, 54.6, 54.0, 52.9, 50.2, 48.1, 33.0, 25.6, 23.9, 18.3 ppm; HRMS (ESI) calculated for $C_{14}H_{27}N_3S_2$ $[M+H]^+$:302.1725; Found: 302.1718.

2.3.4. 2-(4-isopropylpiperazin-1-yl)ethylpiperidine-1-carbodithioate (4d)

Cream solid (208 mg, 66%); mp 84–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (brs, 2H), 3.89 (brs, 2H), 3.47 (t, J = 7.2 Hz, 2H), 2.74–2.63 (m, 3H), 2.56 (brs, 8H), 1.68–1.62 (m, 6H), 1.03 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 57.0, 54.3, 53.2, 52.7, 51.3, 48.4, 34.0, 25.8, 25.3, 24.2, 18.5 ppm; HRMS (ESI) calculated for $C_{15}H_{29}N_3S_2$ $[M+H]^+$: 316.1881; Found: 316.1877.



Scheme 3. Diversity in the synthesis of piperazines containing dithiocarbamate motif [a,b] (4) from secondary amines (1), CS_2 (2) and DABCO salts (3). [a] Isolated yield. [b] Reaction conditions: DABCO salt (1 mmol), secondary amine (1 mmol), carbon disulfide(1.5 mmol), K_2CO_3 (1 mmol), solvent (5 mL), 90 °C and 16 h.

2.3.5. 2-(4-isopropylpiperazin-1-yl)ethylmorpholine-4-carbodithioate (4e)

Pale yellow solid (168 mg, 53%); mp 70–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (brs, 2H), 3.91 (brs, 2H), 3.75–3.66 (m, 4H), 3.51–3.37 (m, 2H), 2.68–2.62 (m, 3H), 2.55 (brs, 8H), 1.01 (d, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 66.1, 66.0, 56.5, 54.2, 52.7, 50.8, 50.5, 48.1, 33.7, 18.2 ppm; HRMS (ESI) calculated for $C_{14}H_{27}N_3OS_2$ $[M + H]^+$: 318.1674; Found: 318.1673.

2.3.6. 2-(4-isobutylpiperazin-1-yl)ethyl diethylcarbamodithioate (4f)

Colorless viscous oil (301 mg, 95%);^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (q, J = 7.1 Hz, 2H), 3.74 (q, J = 7.1 Hz, 2H), 3.44 (t, J = 7.6 Hz 2H), 2.66 (t, J = 6.3 Hz 2H), 2.55 (brs, 4H), 2.41 (brs, 4H), 2.06 (d, J = 7.4 Hz, 2H), 1.78 (m, 1H), 1.26 (q, J = 6.5 Hz, 6H), 0.87 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 66.8, 57.0, 53.3, 52.9, 49.3, 46.5, 34.0, 25.2, 20.8, 12.3, 11.5 ppm; HRMS (ESI) calculated for $C_{15}H_{31}N_3S_2$ $[M + H]^+$: 318.2038; Found: 318.2033.

2.3.7. 2-(4-isobutylpiperazin-1-yl)ethyldimethylcarbamodithioate (4g)

Colorless viscous oil (266 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (brs, 3H), 3.44 (t, J = 6.5 Hz, 2H), 3.36 (brs, 3H), 2.67 (t, J = 7.4 Hz, 2H), 2.52 (brs, 4H), 2.42 (brs, 4H), 2.07 (d, J = 7.3 Hz, 2H), 1.76 (m, 1H), 0.88 (d, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 66.7, 56.9, 53.3, 52.9, 45.3, 41.3, 34.4, 25.2, 20.8 ppm; HRMS (ESI) calculated for $C_{13}H_{27}N_3S_2$ $[M + H]^+$: 290.1725; Found: 290.1718.

2.3.8. 2-(4-isobutylpiperazin-1-yl) ethyl piperidine-1- carbamodithioate(4h)

Yellow solid (210 mg, 64%); mp 64–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30–4.20 (brs, 2H), 3.90–3.80 (brs, 2H), 3.47 (t, J =7.3Hz, 2H), 2.68 (t, J =7.3Hz, 2H), 2.62–2.50 (brs, 4H), 2.50–2.35 (brs, 4H), 2.05 (d, J = 7.3 Hz, 2H), 1.85–1.70 (m, 1H), 1.70–1.55 (brs, 6H), 0.86 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 66.9, 57.0, 53.3, 53.1, 51.1 (2C), 33.9, 25.8, 25.3, 25.2, 24.2, 20.8 ppm; HRMS (ESI) calculated for $C_{16}H_{31}N_3S_2$ $[M + H]^+$: 330.2038; Found: 330.2032.

2.3.9. 2-(4-isobutylpiperazin-1-yl)ethyl pyrrolidine-1-carbodithioate (4i)

Colorless viscous oil (252 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (t, J = 6.8 Hz, 2H), 3.58 (t, J = 6.8 Hz, 2H), 3.42 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.49 (brs, 4H), 2.35 (brs, 4H), 2.06–1.86 (m, 6H), 1.68 (m, 1H), 0.81 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 66.7, 56.8, 54.6, 53.1, 52.7, 50.2, 33.1, 25.7, 25.0, 23.9, 20.6 ppm; HRMS (ESI) calculated for $C_{15}H_{29}N_3S_2$ $[M + H]^+$: 316.1881; Found: 316.1873.

2.3.10. 2-(4-isobutylpiperazin-1-yl)ethyl morpholine-4-carbodithioate (4j)

White solid (261 mg, 79%); mp 68–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27–4.01 (brs, 4H), 3.76 (t, J = 4.9 Hz, 4H), 3.53–3.46 (m, 2H), 2.73–2.67 (m, 2H), 2.56 (brs, 4H), 2.43 (brs, 4H), 2.08 (d, J = 7.4 Hz, 2H), 1.77 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 66.7, 66.1, 66.1, 56.7, 53.3, 52.9, 50.9, 50.5, 33.9, 25.2, 20.8 ppm; HRMS (ESI) calculated for $C_{15}H_{29}N_3OS_2$ $[M + H]^+$: 332.1830; Found: 332.1827.

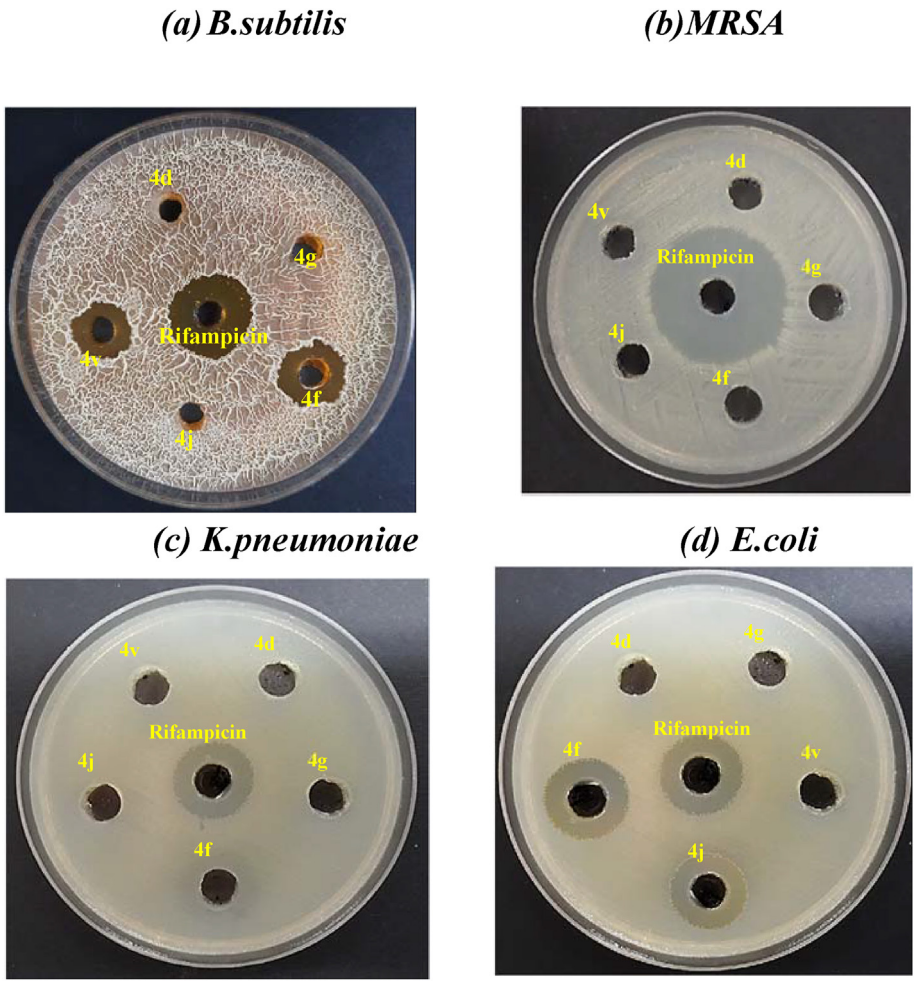


Figure 2. Antibacterial effects of synthetic compounds on bacteria: (a) *B.subtilis* was sensitive to **4f** (20 ± 1 mm inhibition zone) and intermediate to **4j** (18 mm ± 1 inhibition zone), (b) *MRSA* was resistant to all of synthetic compounds, (c) *K.pneumoniae* was resistant to all of synthetic compounds, and (d) *E.coli* was sensitive to **4f** (22 ± 0.6 mm inhibition zone) and intermediate to **4j** (15 ± 0.7 mm inhibition zone).

2.3.11. 2-(4-benzylpiperazin-1-yl) ethyldimethyl -4-carbodithioate (4k)

Pale yellow solid (252 mg, 78%); mp 65–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H), 3.55 (s, 3H), 3.52 (s, 2H), 3.45 (t, J = 7.5 Hz, 2H), 3.37 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 2.66–2.54 (brs, 4H), 2.54–2.38 (brs, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 137.9, 129.2, 128.1, 127.0, 62.9, 56.8, 52.8, 45.3, 41.4, 34.4 ppm; HRMS (ESI) calculated for $C_{16}H_{25}N_3S_2$ $[M + H]^+$: 324.1568; Found: 324.1565.

2.3.12. 2-(4-benzylpiperazin-1-yl) ethyldiethyl -4-carbodithioate (4l)

Yellow viscous oil (287 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.17 (m, 5H), 4.03 (q, J = 7.0 Hz, 2H), 3.75 (q, J = 7 Hz, 2H), 3.53 (s, 2H), 3.45 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.65–2.55 (brs, 4H), 2.55–2.44 (brs, 4H), 1.28 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 137.9, 129.2, 128.1, 127.0, 62.9, 57.0, 52.8 (2C), 49.4, 46.6, 34.1, 12.4, 11.2 ppm; HRMS (ESI) calculated for $C_{18}H_{29}N_3S_2$ $[M + H]^+$: 352.1881; Found: 352.1875.

2.3.13. 2-(4-benzylpiperazin-1-yl) ethyl pyrrolidine-1-carbodithioate (4m)

Yellow oil (223 mg, 64%);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 3.93 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.52 (s, 2H), 3.47 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.64–2.54 (brs, 4H), 2.54–2.36 (brs, 4H), 2.14–2.02 (m, 2H), 2.02–1.89 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 137.9, 129.2, 128.2, 126.9, 62.9, 57.0, 54.9, 52.8 (2C), 50.5, 33.2, 25.9, 24.2 ppm; HRMS (ESI) calculated for $C_{18}H_{27}N_3S_2$ $[M + H]^+$: 350.1725; Found: 350.1719.

2.3.14. 2-(4-benzylpiperazin-1-yl)ethyl morpholine-4-carbodithioate (4n)

Colorless viscous oil (190 mg, 52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H), 4.30–4.01 (brs, 4H), 3.76 (t, J = 4.8 Hz, 4H), 3.53 (s, 2H), 3.49 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.54–2.47 (m, 8H) ppm.^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 137.9, 129.0, 128.0, 126.9, 66.3, 66.1, 62.9, 56.7, 52.8, 50.6, 45.8, 33.9, 29.5 ppm; HRMS (ESI) calculated for $C_{18}H_{27}N_3OS_2$ $[M + H]^+$: 366.1674; Found: 366.1671.

2.3.15. 2-(4-allylpiperazin-1-yl)ethyl dimethylcarbamodithioate (4o)

Colorless viscous oil (153 mg, 56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.13–5.00 (m, 2H), 3.44 (s, 3H), 3.35 (t, J = 7.4 Hz, 2H), 3.27 (s, 3H), 2.90 (d, J = 6.5 Hz, 2H), 2.59 (t, J = 2.25 Hz, 2H), 2.49 (brs, 4H), 2.40 (brs, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 134.5, 117.6, 61.3, 56.5, 52.5, 52.4, 45.0, 41.1, 34.1 ppm; HRMS (ESI) calculated for $C_{12}H_{23}N_3S_2$ $[M + H]^+$: 274.1412; Found: 274.1402.

2.3.16. 2-(4-allylpiperazin-1-yl) ethyl diethylcarbamodithioate (4p)

Colorless viscous oil (219 mg, 73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.81 (m, 1H), 5.21–5.13 (m, 2H), 4.02 (q, J = 7 Hz, 2H), 3.75 (q, J = 7.0 Hz, 2H), 3.54–3.35 (t, J = 7.4 Hz, 2H), 3.01–3.00 (m, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.64–2.54 (brs, 4H), 2.54–2.38 (brs, 4H), 1.27–1.25 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 134.9, 118.0, 61.7, 56.9, 52.9 (2C), 49.4, 46.6, 33.9, 12.40, 11.5 ppm; HRMS (ESI) calculated for $C_{14}H_{27}N_3S_2$ $[M + H]^+$: 302.1725; Found: 302.1722.

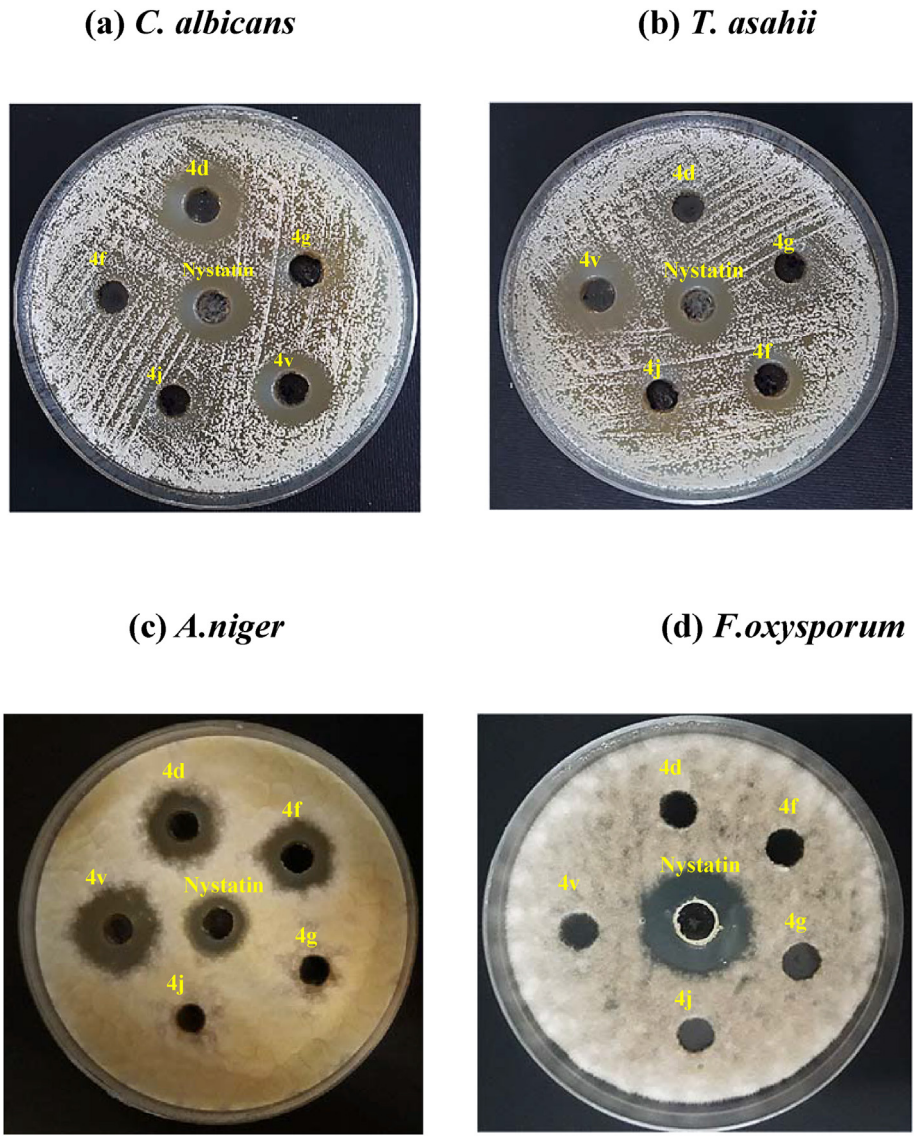


Figure 3. Antifungal activity of synthetic compounds: (a) **4d** and **4v** were affected on *C.albicans* with zone inhibition of 23 ± 1 and 22 ± 0.5 mm respectively, (b) **4f** and **4v** had 19 ± 1 and 22 ± 1 mm inhibition zone on *T.asahii.* (c) **4d**, **4f** and **4v** with 19 ± 0.7, 19 ± 0.5 and 25 ± 1 mm inhibition zone were effect on *A.niger* respectively. (d) The selected compounds had no effect on *F.oxysporum.*

2.3.17. 2-(4-allylpiperazin-1-yl) ethyl pyrrolidine-1-carbamodithioate (4q)

Yellow viscous oil (158 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.80 (m, 1H), 5.16 (t, J = 13.0 Hz, 2H), 3.92 (t, J = 6.8 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 7.3 Hz, 2H), 2.99 (d, J = 6.5 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.64–2.54 (brs, 4H), 2.54–2.38 (brs, 4H), 2.12–2.01 (m, 2H), 2.01–1.90 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 134.9, 118.0, 61.7, 57.0, 54.9, 52.8, 50.5, 33.3, 25.9, 24.2 ppm; HRMS (ESI) calculated for $C_{14}H_{25}N_3S_2$ $[M + H]^+$: 300.1568; Found: 300.1565.

2.3.18. 2-(4-isopentylpiperazin-1-yl)ethyl dimethyl carbamodithioate (4r)

Pale yellow viscous oil (272 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.41 (t, J = 7.2 Hz, 2H), 3.34 (s, 3H), 2.65 (t, J = 7.2 Hz, 2H) 2.56 (brs, 4H), 2.47 (brs, 4H), 2.31 (t, J = 5.4 Hz, 2H), 1.54 (m, 1H), 1.41–1.30 (m, 2H), 0.86 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 56.7, 56.7, 52.9, 52.5, 45.2, 41.3, 35.3, 34.4, 26.5, 22.5 ppm; HRMS (ESI) calculated for $C_{14}H_{29}N_3S_2$ $[M + H]^+$: 304.1881; Found: 304.1881.

2.3.19. 2-(4-isopentylpiperazin-1-yl) ethyl diethyl carbamodithioate (4s)

Yellow viscous oil (271 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (q, J = 6.9 Hz, 2H), 3.74 (q, J = 7.0 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.64–2.39 (brs, 8H), 2.33 (t, J = 7.8 Hz, 2H), 1.64–1.48 (m, 1H), 1.43–1.32 (m, 2H), 1.30–1.20 (m, 6H), 0.88 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 56.9, 53.1, 52.8, 49.4, 46.5, 35.7, 33.9, 26.6, 22.7, 12.3, 11.5 ppm; HRMS (ESI) calculated for $C_{16}H_{33}N_3S_2$ $[M + H]^+$: 332.2194; Found: 332.2188.

2.3.20. 2-(4-isopentylpiperazin-1-yl) ethyl pyrrolidine-1- carbamodithioate (4t)

Pale yellow solid (240 mg, 73%); mp 49–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (t, J = 6.8 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.64–2.38 (brs, 8H), 2.36–2.27 (m, 2H), 2.12–2.01 (m, 2H), 2.01–1.90 (m, 2H), 1.62–1.47 (m, 1H), 1.48–1.25 (m, 2H), 0.88 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 57.0, 56.9, 54.9, 53.0, 52.9, 50.5, 35.8, 33.3, 26.6, 25.9, 24.2, 22.7 ppm; HRMS (ESI) calculated for $C_{16}H_{31}N_3S_2$ $[M + H]^+$: 330.2038; Found: 330.2032.

2.3.21. 2-(4-isopentylpiperazin-1-yl) ethyl morpholine-4- carbamodithioate (4u)

White solid (210 mg, 61%); mp 51–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.4–4.1 (brs, 2H), 4.10–3.80 (brs, 2H), 3.84–3.61 (m, 4H), 3.53–3.41 (t, J = 7.5 Hz, 2H), 2.71–2.63 (t, J = 7.5 Hz, 2H), 2.64–2.38 (brs, 8H),

Table 2. Numerical results of inhibition diameter zones for synthetic compounds.

Microorganism	B.subtillis	*E. coli*	C.albicans	T.asahii	A.niger
inhibition diameter zones in millimeters (mm)	(4f) 20 ± 1	(4f) 22 ± 0.6	(4d) 23 ± 1 (4v) 22 ± 0.5	(4f) 19 ± 1 (4v) 22 ± 1	(4d)19 ± 0.7 (4f) 19 ± 0.5 (4v) 25 ± 1

2.41–2.30 (m, 2H), 1.64–1.44 (m, 1H), 1.44–1.29 (m, 2H), 0.86 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 67.6, 66.0, 52.9, 52.6, 50.5, 46.1, 35.5, 33.8, 26.5, 22.6 ppm; HRMS (ESI) calculated for $C_{16}H_{31}N_3OS_2$ $[M + H]^+$: 346.1987; Found: 346.1980.

2.3.22. (propane-1,3-diylbis(piperazine-4,1-diyl))bis(ethane-2,1-diyl) bis(pyrrolidine-1-carbodithioate) (4v)

White solid (195 mg, 35%); mp 112–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, J = 6.8 Hz, 4H), 3.67 (t, J = 6.8 Hz, 4H), 3.48 (t, J = 7.3 Hz, 4H), 2.70 (t, J = 7.4 Hz, 4H), 2.59 (brs, 8H), 2.49 (brs, 8H), 2.37 (t, J = 7.7 Hz, 4H), 2.08–1.98 (m, 8H), 1.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 57.0, 56.6, 54.9, 53.1, 52.9, 50.5, 33.4, 26.0 (2C), 24.2 ppm; HRMS (ESI) calculated for $C_{25}H_{46}N_6S_4$ $[M + H]^+$: 559.2745; Found: 559.2740.

2.4. Biological evaluations

2.4.1. Microorganisms strains

For antibacterial assays Gram-positive bacteria, *Bacillus subtilis* (ATTC 6633), *Methicillin Resistance Staphylococcus aureus* (ATTC 33593), and Gram-negative bacteria, *Escherichia coli* (ATTC 25922), *Klebsiella pneumonia* (ATTC 10031) were used. For antifungal assays molds, *Aspergillus niger* (DSM 1957) and *Fusarium oxysporum* (DSM 62338) and yeasts, *Candida albicans* (ATTC 10231), *Trichosporon asahii* (CBC 8904) were used. Bacterial strains were cultured in nutrient agar and fungi were cultured in Sabouraud dextrose agar.

2.4.2. Antimicrobial Tests

Antibacterial and antifungal activities were evaluated with CLSI [29, 30] and EUCAST [31] standard methods by the agar well diffusion and the microbroth dilution techniques. Microbroth dilution method was applied for minimum inhibitory concentration (MIC) determination. All experiments were performed in three biological replicates. A stock solution was prepared by dissolving 10 mg of the hydrochloride salt of each compound (10 mg) in 1 mL of distilled water or related culture media as solvent and then sterilized by microbial filter with 0.22 μm pore size.

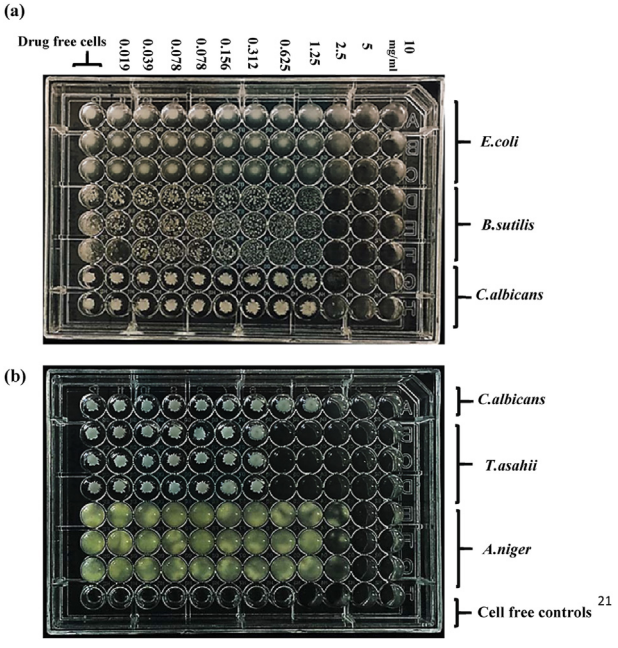


Figure 4. The results of MIC test for **4f** and **4v**. All experiments had three replicates. (a) **4f** was tested for bacteria and (b) **4v** was tested for fungi.

2.4.3. Agar well diffusion method for antibacterial activity assay

Bacterial homogenous suspensions were prepared by transferring the fresh grown bacteria from the plates into sterile normal saline solution and vortexing. In continue, the turbidity was adjusted to 0.5 McFarland standard units, containing 1–2 * 10^8 cell/ml, and was spread over the entire Mueller Hinton agar (MHA) surface plates with sterile swab. Next, by the aid of a sterile tip, a hole of 6–8 mm diameter is punched aseptically, and 100 μL of the prepared stock of each compound was introduced into the well. A well was poured with Refampicin as positive control. Eventually, the plates were incubated at 37 °C for 24 h. Diffusion of the antimicrobial agent in the agar medium inhibits the growth of the tested microbial strain. The inhibition zones were measured in millimeter [32].

2.4.4. Agar well diffusion method for antifungal activity assay

The fungal strains were cultured on Sabouraud dextrose agar and incubated at 35 °C (for yeasts) and 28 °C (for molds). A microbial suspension of yeast was prepared in sterile normal saline and adjusted to 0.5 McFarland standard units, containing 1–5 $\times 10^6$ cell/ml. For the mold, a sterile tissue paper putted on the surface of the Sabouraud dextrose agar containing each mold, then sterile normal saline (1 mL) supplemented with 0.1% Tween 20 was implemented to cover them. The spores (without any hypha) were collected through tissue paper with sterile tip. After that, by applying a hemocytometer, the suspension was adjusted to 1–5$\times 10^6$ conidia/mL and was spread over the entire Mueller Hinton agar containing %2 glucose surface plates by the aid of a sterile swab. Then, a hole of 6–8 mm diameter is punched aseptically with a sterile tip, and 100 μL of the tested compounds (10 mg/mL dissolved in water) is introduced into the well. Nystatin was used as positive control standard antifungal drug and incubated at 35 °C and 28 °C for 48 h.

2.4.5. Determination of minimum inhibitor concentration of synthetic compounds

The MIC is the minimum concentration of antimicrobial compound that completely prevents the growth of the microorganism in culture medium as detected by the unaided eye [33]. The procedure involved preparing two-fold dilutions of the antimicrobial agent in MHB or MHB containing %2 glucose dispensed in 96-well microtitration plate (microdilution). Therefore, the compounds that could impact on microorganisms (**4f** for bacteria and **4v** for fungi) in agar well diffusion method were selected and diluted. Therefore, each well was poured with 50 μl of e.g. 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, 0.078, 0.039 and 0.019 mg/mL of proper medium of effective compounds. Then, each well is inoculated

Table 3. Numerical results of MIC for synthetic compounds.

Microorganism	*E.coli* (4f)	*B.subtilis* (4f)	*C.albicans* (4v)	*T.asahii* (4v)	*A.niger* (4v)
MIC mg/mL (Average)	2.5	2.5	2.5	0.625	5

with 50 μl of microbial inoculum prepared in MHB or and MHB+ %2 glucose after dilution with culture media, 1:150 v:v of standardized microbial suspension adjusted to 0.5 McFarland scale. After complete mixing, the inoculated 96-well microtitration plates were incubated in 37 °C for 24–48 h [29,30,33].

Optical density measuring was used for MIC determination. Thus, by using an ELISA reader, the absorbance of microtiter plates at 570 nm and 530 nm was evaluated for bacteria and yeasts, respectively. The drug free wells were considered as positive control and the lowest concentration with optical density of less than 0.1 was considered as MIC. For molds, MIC was determined visually.

3. Results and discussion

3.1. Chemistry

Here, a straightforward and three-component procedure for the synthesis of dithiocarbamate-containing piperazines **4** is reported *via* the reaction of secondary amines **1,** carbon disulfide **2**, and quaternized derivatives of DABCO **3**. Normally, design and discovery of a direct step-economy synthetic route to generate substituted piperazine rings is partly complicated; as a result, it has been garnered widespread attention in recent years. In this regard, 1,4-diazabicyclo [2.2.2]octane (DABCO) which has universally known as a base in organic reactions [28, 34], has been deployed as a reagent in C–N bond cleavage synthetic routes for the straightforward preparation of unsymmetrical piperazine compounds [22].

To optimize the reaction conditions, a model reaction was considered (Scheme 2). Initially, we observed that the reaction of DABCO salt **3b** (0.5 mmol) with diethylamine (0.5 mmol) and CS2 (0.75 mmol) in THF for 24 h at 120 °C without a base provided the product **4f** in 40% isolated yield (Table 1, entry 1). Under these conditions, various bases such as NaOH, KOH, K_3PO_4, Na_2CO_3 and K_2CO_3 were used in the model reaction (Table 1, entries 2–6) and the elevated yield (89 %) was achieved using K_2CO_3 (Table 1, entry 6). By screening the model reaction in various protic and aprotic solvents in the presence of K2CO3, we observed that higher yields were obtained in MeOH and EtOH (Table 1, entries 7–8) compare to DMF, *n*-hexane and $CHCl_3$ (Table 1, entries 9–11). Using aqueous media gave inferior results (Table 1, entry 14). No desired product was obtained in CH_2Cl_2 and DMSO (Table 1, entry 12–13). By decreasing the reaction temperature to 50, 70 and 90 °C, the corresponding product was obtained in 25, 37 and 87 %, respectively (Table 1, entries 15–17). Besides that, we observed that by decreasing the reaction time to 16 h, the yield was improved to 95% (Table 1, entry 19). At the end, deploying THF as a solvent and heating the reaction mixture to 90 °C for 16 h in the presence of K_2CO_3 as a base was used as optimal conditions for the direct synthesis of a wide range of piperazine derivatives.

The generality of the reaction was investigated using various DABCO salts and secondary amines and the results are shown in Scheme 3. Various linear and cyclic secondary amines encompassing diethylamine, dimethylamine, morpholine, pyrrolidine, and piperidine were successfully deployed in this synthetic route to give the desired 1,4-disubstituted piperazines **4a-u** in good to excellent yields. In addition, DABCO salts with primary and secondary alkyl groups are compatible with this protocol. By using *bis*-ammonium salt of DABCO, the corresponding *N, N′-bis* piperazine **4v** containing two dithiocarbamate groups was obtained in moderate yield. In this MCRs, the regioselectivity seems to be related to the alkyl moiety attached to the nitrogen in DABCO salts. In the case of allyl and benzyl salts of DABCO, due to the competition between the carbon of the bridge and the alkyl group for nucleophilic attack, the corresponding alkyl dithiocabamates were obtained as main byproduct in the reaction mixture. The structures of all products were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analyses (Figures S1–S44 in supplementary material).

3.2. Biological studies

Based on the results, the selected synthetic compounds were effective antifungal compounds because they could inhibit yeasts and molds.

3.2.1. Antimicrobial effects of the synthetic compounds with the disk diffusion test

As shown in Figure 2, **4f**, **4j** and **4v** were affected on different bacteria. But, based on zone inhibition diameter, only **4f** was affected on *B.subtillis* and *E.coli* with zone inhibition diameter of 20 ± 1 and 22 ± 0.6 mm, respectively and had no effect on *MRSA* and *K.pneumoniae*.

Addition antifungal effects of these synthetic compounds were shown in Figure 3. **4d**, **4f** and **4v** had antifungal activity. **4d** and **4v** were affected on *C.albicans* with zone inhibition of 23 ± 1 and 22 ± 0.5 mm, respectively, **4f** and **4v** had 19 ± 1 and 22 ± 1 mm inhibition zone for *T.asahii.* **4d**, **4f** and **4v** with 19 ± 0.7, 19 ± 0.5 and 25 ± 1 mm inhibition zone were effected on *A.niger*, respectively. The results of zone inhibition diameter were summarized in Table 2.

3.2.2. Minimum inhibitory concentration (MIC) results of the selected synthetic molecules

For determination of MIC, we selected **4f** (effect on both bacteria) and **4v** (effect on three fungi). Figure 4 shows the MIC results of the **4f** and **4v** on sensitive microorganisms. The results of MIC were summarized in Table 3. As shown in Figure 4, compound **4f** illustrated antibacterial activity with MIC values of 2.5 mg/mL against *E.coli* and B.sutilis and also compound **4v** showed antifungal activity with MIC values of 2.5, 0.625 and 5 mg/mL against *C.albicans*, *T.asahii* and *A.niger*, respectively.

4. Conclusion

In conclusion, expansion of modern biologically active molecules inspired the organic chemists to render DABCO bond cleavage technique. In this project, a one-pot three-component reaction based on re-engineering approach has been devised for the synthesis of dithiocarbamate-containing piperazine scaffolds by *in situ* reaction of amines, CS_2 and DABCO salts. The reaction proceeds *via* C–N bond cleavage of DABCO ring. A certain number of synthesized compounds revealed appropriate antibacterial activity against both Gram-positive as well as Gram-negative bacteria and depicted good to excellent antifungal activity. Finally, this synthetic route enjoys various merits namely easy workup procedure, operator friendliness, economical use of reagents, provided satisfactory yields of the small molecules.

Declarations

Author contribution statement

Azim Ziyaei Halimehjani: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Faezeh Dehghan, Yazdanbkhsh Lotfi Nosood: Performed the experiments; Analyzed and interpreted the data.

Vida Tafakori, Elaheh Amini: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Seyyed Emad Hooshmand: Conceived and designed the experiments; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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