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Designed Synthesis and Antimicrobial Studies of Novel Substituted Rhodanine Derivatives

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Abstract

New rhodanine derivatives were prepared from substituted primary amines as antimicrobial agents. All the synthesized compounds ((**IIa**–**IIh**)) were screened for antimicrobial activity using the micro dilution method recommended by the National Committee for Clinical Laboratory Standards, USA (CLSI 2006) to assess their antimicrobial activity. All the compounds were evaluated against gram positive bacteria: *Bacillus subtilis* MTCC 2756, *Staphylococcus aureus* MTCC 902; Gram negative bacteria: *Escherichia coli* MTCC 2622, *Pseudomonas aeruginosa* MTCC 2642, and *Klebsiella pneumoniae* MTCC 109. Fungal cultures used in the study were *Aspergillus niger* MTCC 282, *Candida albicans* MTCC 277, *Candida tropicalis* MTCC 230, *Candida glabrata* MTCC 3019 and *Candida parapsilosis* MTCC 6510.Allthe compounds exhibited potent anticandida activity against *Candida albicans* MTCC 277in the concentration range 2-16µg/ml and compound **IId** showed MIC value 2µg/ml against *candida albicans.* Considering these results it can be suggested these compounds may lead to the development of more potent antifungal drugs in the future.

Keywords: Microbicide, Anti-fungal, Rhodanine, Dithiocarbamate, Candidiasis.

1. Introduction

In spite of enormous progress in medicinal and pharmaceutical chemistry, infectious diseases still remain a biggest threat to society and have provided new challenges to researchers throughout world.[1] Incidence of lethal fungal infections has increased dramatically due to enhancement of immunocompromised individuals.[2-6] *Candida* and *Aspergillus* species are the most prominent fungal pathogens affecting human beings and *Candida albicans* remains the principal cause of invasive candidiasis.[7] There are several exciting therapeutics for the treatment of candidiasis, which include azoles namely fluconazole, ketoconazole, and clotrimazole. Furthermore, allyl amines like terbinafine, thiocarbamate stolciclate, fluoropyrimidines and polyenes (amphotericin B, nystatin) are also used frequently. [8,9] However, the azoles drugs are universally used for the treatment of Candidiasis but the widespread use of these azoles has led the problem due to development of resistance.[10] Nalidixic acid was developed in 1962 and no new classes of antimicrobials were developed till 2000 when linezolid entered the market. All the antimicrobials which have been developed during this time period were modifications of the existing molecules. [11]

In 1997, a data based study revealed that the occurrence of rhodanine-containing compounds of pharmaceutical interest is very small despite the fact that the compounds demonstrate a wide variety of biological activities.[12] In recent years, rhodanine derivatives have grabbed the attention of medicinal chemists because of their broad range of pharmacological activities as the number of scientific publications and patents unfolding various biological activities is increasing continuously.[13-15] Rhodanines have been reported for several biological

activities, such as antibacterial, antifungal, antimycobacterial, antidiabetic, anti-infective, pesticidal, antineoplastic, antitubercular, anti–human immunodeficiency virus (HIV), and antimalarial, and so on.[15-29] Numerous possibilities of structural derivatization of the rhodanine ring, probably will make their derivatives a privileged scaffold in drug discovery.[30]

The research based on structural based drug design to obtain new antimicrobial compounds is vitally important. Taking into account the studies done by other authors, we decided to synthesize a series of new derivatives having secondary amino substituted alkyl fragment at N-3 position of rhodanine (Figure 1) and evaluate their antimicrobial efficacy *in-vitro*.

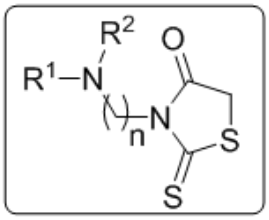


Figure 1: General structure of designed molecular framework

2. Experimental Section

2.1. Synthesis

In general, all reagents and solvents were commercial quality and were used without further purification. Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. IR spectra (ν_{max} in cm^{-1}) of the compounds were recorded on Perkin Elmer's FT-IR RX1 PC spectrophotometer. ^1H NMR & ^{13}C NMR spectra were recorded on Bruker AVANCE III spectrometers (operating at 500 MHz for ^1H; 50 and 75 MHz respectively for ^{13}C) in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, *J* in Hz.). Electro Spray Ionization High Resolution Mass spectra (ESI-HRMS) were recorded on Thermo Scientific Exactive Plus Orbitrap spectrometer. The reaction progress was routinely monitored by thin layer chromatography (TLC) on pre-coated silica gel plates (Merck India Ltd). Column chromatography was performed over Merck silica gel (100-200 Mesh). All compounds were characterized by TLC, ^1H and ^{13}C NMR, HRMS. All chemicals and solvents were procured from Sigma-Aldrich / Merck India Ltd. Rhodanine containing heterocycles (alkyl or aryl) are synthesized as per report procedure.[31]

3-(3-dimethylamino)propyl)-2-thioxothiazolidin-4-one (IIa)

The mixture of 3-(dimethyl amino)-1-propylamine (1g, 0.00978 mol), carbon disulphide (0.58ml, 0.00978mol), ethylbromo acetate (1.5ml, 0.01467 mol) in acetonitrile was stirred at room temperature till the reaction mixture get solidified. Then the solid product was washed with acetonitrile and dried. The residue was then treated with ethyl acetate and kept in freezer overnight. Then the residue obtained was evaporated under reduced pressure. Brown colour solid (65%); mp: 107°C; IR (KBr) ν (cm^{-1}): 2670,1697,1348,1324,1307; ^1H NMR (500 MHz, DMSO): δ4.06 (2H,s), 2.77-3.14 (8H d), 3.56-3.60 (2H m),1.12-1.15 (2H m); ^{13}C (125 MHz, DMSO):δ 201.81(C=S),174.02(C=O),57.52,42.29,39.97,35.47,22.45; HRMS(m/z) calculated for $C_8H_{14}N_2OS_2$: 218.0548 found:219.0623 (MH^+).

3-(2-(dimethylamino) ethyl)-2-thioxothiazolidin-4-one (IIb)

The title compound was synthesized from N,N,dimethyl ethylenediamine (1g,0.0113 mol) reacted with carbon disulphide (0.68ml,0.0113mol), ethylbromo acetate(1.75ml, 0.0169 mol) in acetonitrile at room temperature. Pale yellow solid (70%); mp145°C; IR (KBr) ν (cm^{-1}): 2644,1730,1674,1370,1332,1304; ^1H NMR (500 MHz, DMSO): δ 4.13-4.15 (2H,t), 4.02(2H s), 3.32-3.34(2H t),2.72(6H s); ^{13}C (125 MHz, DMSO):δ 202.29(C=S),174.89(C=O),54,43,40,39,38; HRMS(m/z) calculated for $C_7H_{12}N_2OS_2$: 204.039found:205.047 (MH^+).

3-(3-diethylamino) propyl)-2-thioxothiazolidin-4-one (IIc)

The title compound was synthesized from 3-(diethyl amino)-1-propylamine (1g, 0.0077 mol) reacted with carbon disulphide (0.46ml, 0.0077mol), ethylbromo acetate (1.19ml, 0.0115 mol) in acetonitrile at room temperature. Brown colour solid (65%); mp: 99 °C; IR (KBr) ν (cm^{-1}): 2671,1730,1342,1206,1131; ^1H NMR (500 MHz, DMSO): δ4.04-4.06 (4H,t), 2.19-3.13 (8H m), 1.34-1.37(6H,t);^{13}C(125MHz,DMSO):δ201.87(C=S),173.95(C=O), 9.13,46.73,41.59,35.92,21.85; HRMS(m/z) calculated for $C_{10}H_{18}N_2OS_2$: 246.08found:247.07 (MH^+).

3-(2-(diethylamino) ethyl)-2-thioxothiazolidin-4-one (IId)

The title compound was synthesized from N,N,diethyl ethylenediamine (1g,0.0086 mol) reacted with carbon disulphide (0.52ml,0.0086mol), ethylbromo acetate(1.33ml, 0.0129 mol) in acetonitrile at room temperature. Yellowish brown solid (68%); mp: 92 °C; IR (KBr) ν (cm^{-1}): 2564,2470,1727,1471,1435,1199; ^1H NMR (500 MHz, DMSO): δ 4.34-4.37 (2H,t), 4.17(2Hs), 3.35-3.38(2H t),3.23-3.27(4H m), 1.38-1.41(6H t); ^{13}C (125 MHz, DMSO):δ 202.13(C=S),174.60(C=O),47.43,47.23,38.15,36.85,8.53; HRMS(m/z) calculated for $C_9H_{16}N_2OS_2$: 232.07found:233.07 (MH^+).

3-(3-(piperidin-1-yl) propyl)-2-thioxothiazolidin-4-one (IIe)

The title compound was synthesized from 1-(3-aminopropyl) piperidine (1g,0.0070mol) reacted with carbon disulphide (0.42ml,0.0070mol), ethylbromo acetate(1.08ml, 0.0105 mol) in acetonitrile at room temperature. Brown colour solid (62%); mp: 178 °C; IR (KBr) ν (cm^{-1}): 2627,1725,1431,1356,1310,1291; ^{1}H NMR (500 MHz, DMSO): δ 4.10-4.13 (4H,t), 2.77-3.57(6H d), 2.32-2.36(5H m)1.87-1.89(3H d); ^{13}C (125 MHz, DMSO):δ 201.97(C=S),174.08(C=O),54,51,41,36,22,21; HRMS(m/z) calculated for $C_{11}H_{18}N_2OS_2$: 258.086found:259.093 (MH^+).

3-(2-(piperidine-1-yl) ethyl)-2-thioxothiazolidin-4-one (IIf)

The title compound was synthesized from 1-(2-aminoethyl) piperidine (1g, 0.0078 mol) reacted with carbon disulphide (0.46ml, 0.0078mol), ethylbromo acetate (1.21ml, 0.0117 mol) in acetonitrile at room temperature. Light brown solid (68%); mp: 204 °C; IR (KBr) ν (cm^{-1}): 2634,1741,1344,1284,1215; ^{1}H NMR (500 MHz, DMSO): δ 4.22-4.25 (4H,t), 3.58-3.60(2Hd), 2.51-3.39(6H s),1.65-1.85(4H d); ^{13}C (125 MHz, DMSO):δ 203.93(C=S),175.28(C=O),52.95,52.45,40.45,40.28,40.12,39.95,39.78,39.62,39.45,36.96,22.88,21.59; HRMS(m/z) calculated for $C_{10}H_{16}N_2OS_2$: 244.07found:245.07 (MH^+).

3-(2-(pyrrolidine-1-yl) ethyl)-2-thioxothiazolidin-4-one (IIg)

The title compound was synthesized from 1-(2-aminoethyl) pyrrolidine (1g,0.0087mol) reacted with carbon disulphide (0.53ml,0.0087mol), ethylbromo acetate(1.36ml, 0.0131 mol) in acetonitrile at room temperature. Yellowish brown solid (70%); mp:177 °C; IR (KBr) ν (cm^{-1}): 2590,17201678,1322,1212; ^{1}H NMR (500 MHz, DMSO): δ 4.21-4.24 (4H,m), 3.66(2H s), 3.50-3.51(2H d),3.12(2H s),2.06(2H s)1.92-1.95(2H t); ^{13}C (125 MHz, DMSO):δ 203.25(C=S), 175.07(C=O), 54,50,40,39,36,23; HRMS(m/z) calculated for $C_9H_{14}N_2OS_2$: 230.054found:231.06 (MH^+).

3-(3-(azepan-1-yl)propyl)-2-thioxothiazolidin-4-one (IIh)

The title compound was synthesized from 3-(azepan-1-yl)propan-1-amine (1g,0.0064 mol) reacted with carbon disulphide (0.40ml,0.0064mol), ethylbromo acetate (0.992ml, 0.0105 mol) in acetonitrile at room temperature. Brown colour solid (65%); mp: 157 °C; IR (KBr) ν (cm^{-1}): 2599,1723,1683,1433,1349,1317; ^{1}H NMR (500 MHz, DMSO): δ 4.03-4.05 (4H,t), 3.41-3.51(2H s), 2.24-3.11(6H m), 1.62-2.11(8H s); ^{13}C (125 MHz, DMSO):δ 201.92(C=S),174.04(C=O),54,41,35,26,23,22; HRMS(m/z) calculated for $C_{12}H_{20}N_2OS_2$: 272.10 found:273.10 (MH^+).

2.2. Antifungal assay:

2.2.1 Test fungal pathogens:

Fungal cultures used in the study were *Aspergillus niger* (MTCC 282), *Candida albicans* MTCC 277, *Candida tropicalis* MTCC 230, *Candida glabrata* MTCC 3019 and *Candida parapsilosis* MTCC 6510. All the MTCC strains were procured from Microbial Type Culture Collection, CSIR- Institute of Microbial Technology, Chandigarh, India which is traceable to American Type Culture Collections (ATCC).

2.2.2 Sub-culturing of test organisms:

All reference fungal cultures were subcultured on Potato dextrose agar. The fungal slant was incubated for 48 h at 30◦C. Mcfarland density (0.5 on the McFarland scale) of fungal culture was adjusted in normal saline to achieve the final concentration of 1×10^6 cfu/mL of each test organism individually. In case of *Aspergillus niger*, conidial suspensions were harvested after isolates were subcultured on PDA at 30°C to 7 days and were suspended in normal saline. *Aspergillus niger* inocula were then prepared spectrophotometrically and further diluted in normal saline in order to obtain a final inoculum concentration of 1×10^6. This had been used as adjusted inoculum for all the further studies.

2.2.3 Determination of MIC:

MIC was done by broth microdilution method conferring to the reference of clinical& Laboratory standards Institute 2012, USA, using 96 well ELIZA plates. [32-34] To determine MIC the compounds and standard drug ketoconazole (reference antimycotic drug) were dissolved in 0.5% DMSO to give stock concentration of 1000µg/ml. RPMI 1640 broth (Sigma-Aldrich, Castle Hill, Australia) with L-glutamine and without sodium bicarbonate was used for susceptibility testing. The medium was buffered to pH 7.0 at 25°C with 0.165 M 3-(*N*-morpholino)-propanesulfonic acid (MOPS; Sigma-Aldrich). Sterility was confirmed prior to use. Serial dilutions of the test compounds and ketoconazole (reference antimycotic drug) were prepared in appropriate medium conc. ranging from 0.5 to 1000 µg/ml. Each well was inoculated with 20µlof fungal suspension at a density of 10^6CFU/ml. The microtitre plates were incubated at 37^0C for 48 hrs. The fungal growth was measured by taking the absorbance at 600nm using a micro titer plate reader.0.5% DMSO and sterile RPMI medium were used as blank control which do not inhibit the growth of fungus.MIC was defined as the lowest concentration of drug showing no growth. The experiment was performed in triplicate.

2.3 Anti-bacterial assay

2.3.1 Test bacterial pathogens

The bacterial pathogens used in the study were Gram positive bacteria *Bacillus subtilis* MTCC 2756, *Staphylococcus aureus* MTCC 902; Gram negative bacteria *Escherichia coli* MTCC 2622, *Pseudomonas aeruginosa* MTCC 2642, and *Klebsiella pneumoniae* MTCC 109. All the MTCC strains were procured from Microbial Type Culture Collection, CSIR- Institute of Microbial Technology, Chandigarh, India which is traceable to American Type Culture Collections (ATCC).

2.3.2 Sub-culturing of test organism:

All reference bacterial and fungal cultures were subcultured on Nutrient agar. The bacterial slants were incubated overnight at 37°C. Mcfarland density (0.5 on the McFarland scale) of bacterial culture was adjusted in normal saline to achieve the final concentration of 1×10^6 cfu/mL of each test organism individually.

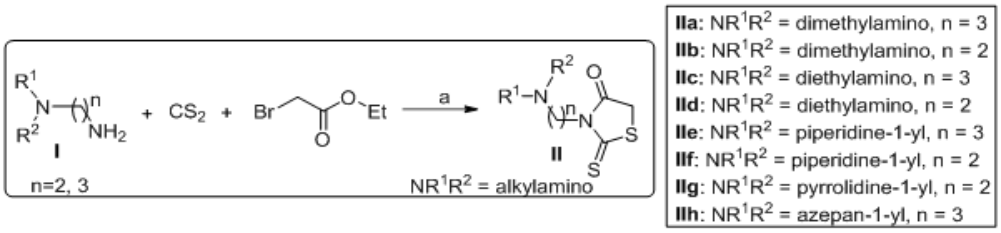
2.3.3 Determination of MIC antibacterial activity:

MIC was done by broth microdilution method recommended by National Committee for Clinical Laboratory Standards, USA. To determine MIC the compounds and standard drug Ampicllin were dissolved in 0.5% DMSO to give stock concentration of 1000µg/ml. RPMI 1640 broth (Sigma-Aldrich, Castle Hill, Australia) with L-glutamine and without sodium bicarbonate was used for susceptibility testing. The medium was buffered to pH 7.0 at 25°C with 0.165 M 3-(*N*-morpholino)-propanesulfonic acid (MOPS; Sigma-Aldrich). Sterility was confirmed prior to use. Serial dilutions of compounds were made with test media to give concentrations ranging from 0.5 to 1000µg/ml. Colony suspensions equivalent to 0.5 Mc Farland standard were prepared and inoculated to yield a final inoculum of 1×10^6 CFU/ml. The microtitre plates were incubated at 37°C for 24 hrs. MIC was defined as the lowest concentration of drug showing no growth.MIC was attained from three independent tests that were performed in triplicate.

3. Result & Discussion

3.1. Chemistry:

In this effort, the new chemical entity (NCE), 3-(dialkylamino) alkyl)-2-thioxothiazolidin-4-one (**II**, Scheme 1) has been synthesized as shown in scheme 1. [31]



Scheme 1: (a) = Acetonitrile, room temperature

Different derivatives (**IIa-IIh**) are prepared by the reaction of substituted primary amine (**I**), carbon disulphide and ethylbromoacetate in acetonitrile. The reaction mixture is stirred at room temperature till the reaction mixture gets solidified. After completion of the reaction (observed on TLC), crude product was purified by column chromatography to get **II** in good to excellent yield.

3.2. Structure-Activity Relationship (SAR)

(a) Antifungal Activity:

All the synthesized compounds (**IIa-IIh**; Table 1) were screened for their *in vitro* antifungal activity against various fungal strains of *Candida* and *Aspergillus niger*. Ketoconazole was taken as reference standard. Compounds with MIC > 250µg/ml were considered as inactive.MIC between 250-125µg/ml were indicative of low activity and MIC between 64 to 32µg/ml exhibited moderate activity. MIC less than 16µg/ml can be considered as the activities which are used in clinical situation. Among these, all the compounds showed potent activity against *Candida albicans* (MIC 2-16µg/ml) and are considered of great interest for further development. All the compounds were inactive against *Aspergillus niger*.

Table 1: **MIC (in µg/ml) of DTC compounds against fungi.**

Test microbes	MIC µg/ml								
	IIa	IIb	IIc	IId	IIe	IIf	IIg	IIh	Ketoconazole
A. niger	>1000*	>1000	>1000	>1000	>1000	>1000	1000	>1000	1
C. albicans	8	4	16	2	8	8	4	8	0.5
C. tropicalis	64	64	125	32	125	125	125	250	1
C. glabrata	64	125	125	64	125	64	250	125	0.5
C. parapsilosis	125	250	250	64	250	125	125	125	0.5

*Recorded no activity up to 1000 mg/ml

A closer look into structure activity relationship revealed that the most potent compound **IId** against *Candida albicans* (causative agent for vaginal candidiasis) possessed the structure of 3–(2-(dielhyl amino) ethyl)-2-thioxothiazolidin-4-one with MIC 2µg/ml.

On analysis of the effect of substituents showed that all the different substitutions showed potent anti-candidal activity against *Candida albicans* whereas all the compounds were less active against other *candidal* species. All of the compounds were inactive against *Aspergillus niger*.

(b) Anti-bacterial activity:

The synthesized compounds (**IIa-IIh**; Table 2) were also been evaluated for their anti-bacterial activities against different species. Ampicillin was taken as reference standard. Compounds with MIC> 250µg/ml were considered as inactive and MIC between 250and 125µg/ml were indicative of low activity.MIC between 64 to 32µg/ml showed moderate activity. MIC less than 16µg/ml was supposed to be the activity which can be used in clinical situation but unfortunately, none of the compound demonstrated the efficacy at this concentration.

Table 2: **MIC (in µg/ml) of DTC compounds against different bacterial species**

Test microbes	MIC µg/ml								
	IIa	**IIb**	**IIc**	**IId**	**IIe**	**IIf**	**IIg**	**IIh**	**Ampicillin**
B. subtilis	125	125	125	64	64	125	64	32	2
S. aureus	64	500	125	250	250	250	125	64	0.5
E. coli	125	250	500	500	125	250	500	64	1
P. aeruginosa	32	32	125	32	125	64	125	64	1
K. pneumonia	125	125	250	64	125	125	64	500	1

Among the eight compounds, **IIa**, **IIb**, **IId** displayed MIC of 32µg/ml against *Pseudomonas aeruginosa* and they showed moderate anti-bacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumonia*. Compound **IIh** showed MIC 32-64µg/ml for bacterial species *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli and Pseudomonas aeruginosa* and **IId**, **IIe**, **IIg** exhibited moderate activity against *B. subtilis.*

(c) Safety profile of compounds:

All the compounds were screened for their safety towards human cervical cell line (HeLa). The compounds (**IIa-IIh**; Table 3) showed same IC_{50} value 222.67 ± 6.31 µg/ml. The synthesized compounds have no effect on the viability of HeLa cells over a 24 h incubation period.

Table 3: Safety profile of compounds against HeLa cell line

Test microbes	IC_{50} µg/ml							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	**IIf**	**IIg**	**IIh**
HeLa Cell Line	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31	222.67 ± 6.31

4. Conclusions

In search of a novel microbicidal agent, different rhodanine derivatives (**IIa-IIh**) were designed, synthesized and screened for biological activity *in-vitro*. The compounds were screened for their antimicrobial activity (both antibacterial & antifungal) against 10 different microbial species. All the compounds exhibited high antifungal activity against *Candida albicans* displaying lowest MIC activity (MIC 2µg/ml) for compound **IId**. It is worth to take into account that we have found eight promising compounds that appear to be good antifungal candidates for future research and compound **IId** could be an interesting molecule for the development of dithicarbamate derived antifungal candidate. Compound **IIa**, **IIb**, **and IId** exhibited moderate antibacterial activity as well and can be used for designing of novel anti-bacterial agents for further studies.

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