SYNTHESIS AND ANTIMICROBIAL ACIVITY OF 4 – THIOMORPHOLINE - 4YLBENZOHYDRAZIDE DERIVATIVES

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ABSTRACT: The purpose of this research was to development of new potent bioactive molecule with less toxic, safer and easy available. Modern therapeutic is based on scientific observation supported by systematic assessment of activity of drug is simulated and clinical condition. The integrity of the drug molecule, optimization of biological effect, uniform and consistent availability of drug from the dosage.

Present work deals with the preparation of thiomorpholie derivatives by nucleophilic substitution reaction. Thiomorpholine (I) and P-chlorobenzonitrile (II) on reflux gives 4–thiomorpholin–4ylbenzonitrile (III) then this upon hydrolysis by using sodium hydroxide and methanol gives corresponding 4–thiomorpholin–4ylbenzoic acid (IV).This acid on treatment with thionyl chloride gives corresponding 4–thiomorpholin–4ylbenzoyl chloride (V).This is treated with hydrazine hydrate gives 4–thiomorpholin–4ylbenzohydrazide (VI) then this hydrazide is treated with various substituted heterocyclic compound to form thiomorpholine derivatives.

Aromatic and Heterocyclic derivatives were synthesized to increase Log P value by increasing microbial intracellular concentration and to decrease microbial resistance. The newly synthesized compounds were tested for its antimicrobial activity. The structures of newly synthesized compounds were established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data.

Key words: Antimicrobial activity, Thiomorpholine and Microbial intracellular concentration.

INTRODUCTION

During past decades, compounds bearing heterocyclic nuclei have received much attention due to their potent biological value in the development of novel antimicrobials[1], analgesic[2] and anti-inflammatory[3]. Thiomorpholine analogs are associated with a variety of pharmacological activities including antimycobacterial[4], antibacterial[5], and antimalarial[6], and analgesic[7], anti-inflammatory[8].

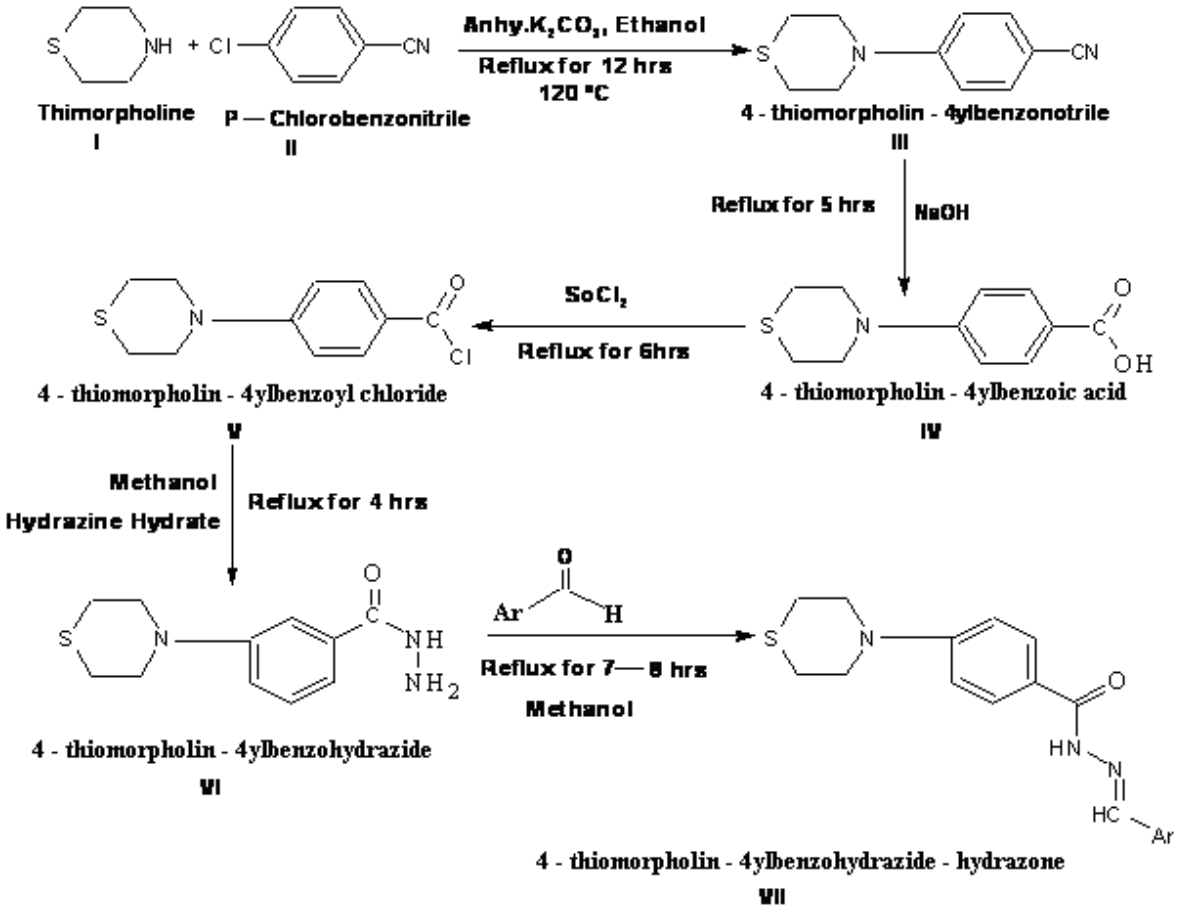
Thiomorpholine is a heterocyclic compound containing nitrogen and sulfur. It can be considered a thio derivative of morpholine. The thiomorpholine chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically[9]. In view of these, a project was undertaken to synthesize a new series of 4- thiomorpholine – 4ylbenzohydrazide-hydrazone by conventational method and to evaluate the new compounds for their antimicrobial activity.

The title compounds were screened for antimicrobial activity by cup plate method .Synthesis of title compounds was shown in Scheme 1 and 2. The physical constants, yield and analytical data of 4-thiomorpholine – 4ylbenzohydrazide derivatives. VII a–h and VI a-h are given in table No. I, II and III.

MATERIALS AND METHODS

The melting points were determined in open capillary tube using Precision melting point apparatus and uncorrected. Thin-layer chromatography was performed with fluorescent silica gel plates HF_{254} (Merck), plates were viewed under UV 254 and 265 light. Infrared spectra's (v-cm^{-1}) were recorded on a Shmadzu FT-IR 4000; using KBr disks.^{1}H-NMR spectra were recorded on Bruker Spectrophotometer at 300MHz frequency in CDCl3 as well as DMSO using TMS as internal standard reference. Peaks are reported in ppm downfield of TMS. Mass spectra were recorded on 'GCMS-QP2010s' instrument by direct injection method.

SCHEME 1:



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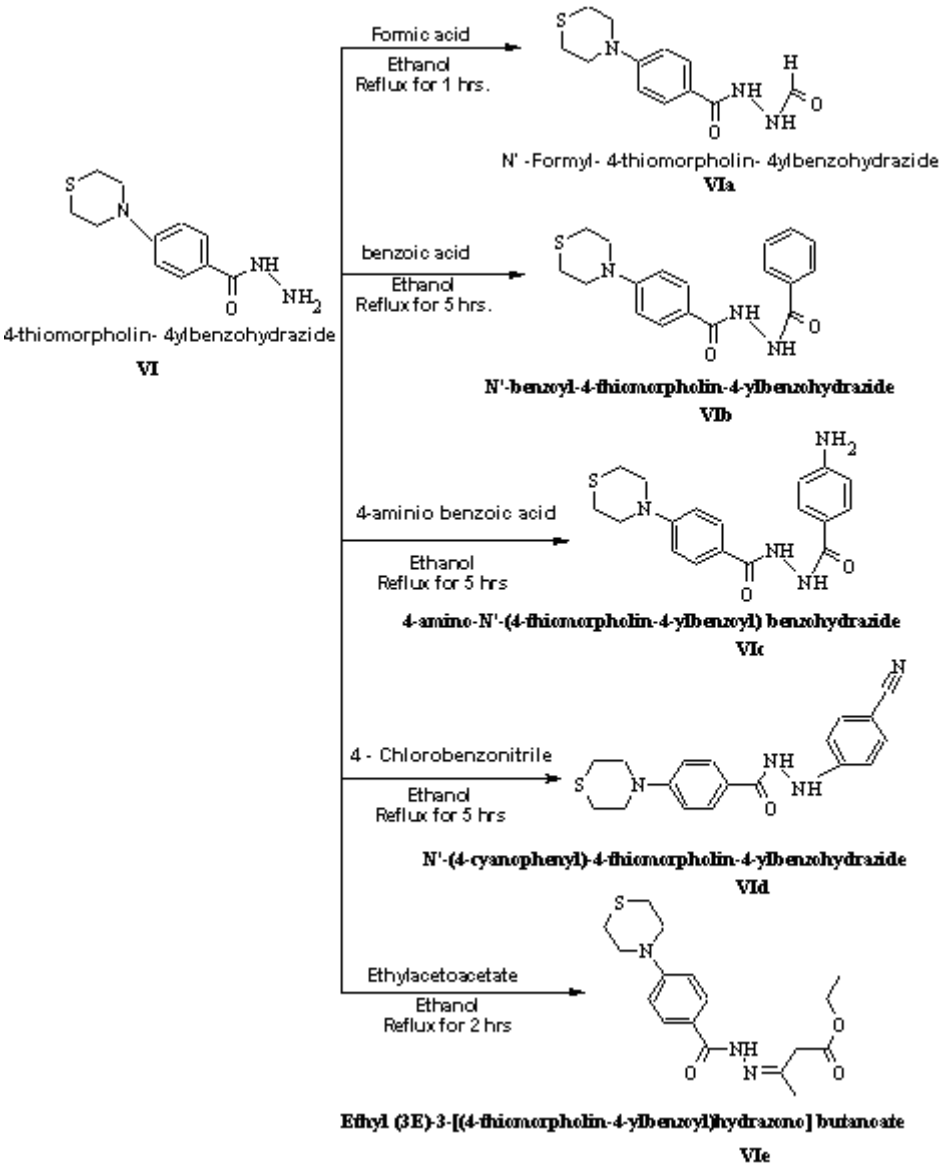
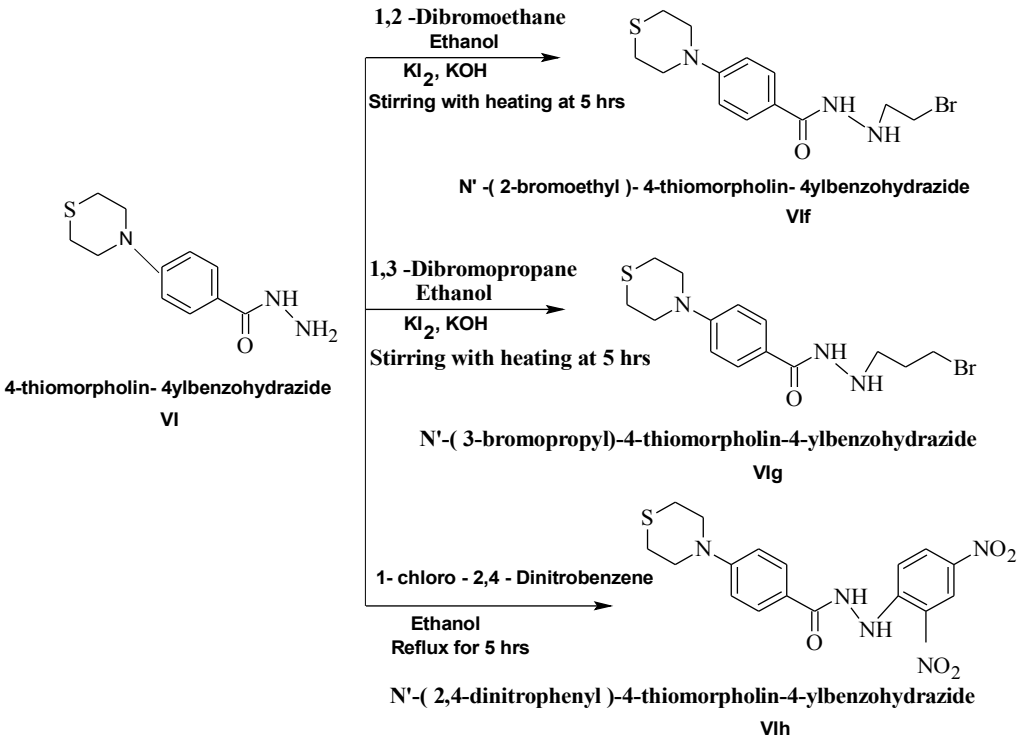


Preparation of 4-thiomorpholin -4 ylbenzonitrile (III):

A mixture of thiomorpholine (I) (4gm, 0.14 mol) in ethanol (25ml) and 4-chlorobenzonitrile (II) (3.2gm, 0.05 mole) in 250 ml round bottom flask and also added anhydrous potassium carbonate (3gm) for the purpose of increasing rate of reaction. Then was heated at 120°C .The conversion of the 4-chlorobenzontrile (2) was complete after 12hrs.Water (25ml) was then added into the reaction mixture. The precipitate was filtered off, washed with water and dried under vacuum (30°C) to give title compound. Recrytallized from 50% aqueous ethanol.

The compound III was confirmed by IR (KBr) (cm $^{-1}$): 3081 (Aromatic C-H Stretch), 2925 (Aliphatic C-H Stretch), 2225 (C ≡ N Stretch), 1583 (Aromatic C = C Stretch), 1230 (C – N Stretch), 620(C – S Stretch of C-S-C). ^{1}H-NMR spectrum: ^{1}H-NMR (DMSO-d_6, 300 MHz), δ (ppm): 2.27(s, 4H, N(CH_2)$_2$), 2.59 (s, 4H, S (CH_2)$_2$) , 6.8-7.9 (m, 6H, Ar-H).LC-MS (m/z): 206.29 (M+1).



Preparation of 4-thiomorpholin-4ylbenzoic acid (IV):

To 4-thiomorpholin–4ylbenzonitrile (III) (3gm, 0.01mol), water (120ml) and sodium hydroxide (6gm, 0.3mol) were added. Small amount of methanol was added to increase the rate of the reaction. The reaction mixture was refluxed on water bath for 5 hrs; it was cooled to room temperature and make acidic by the addition of HCL (10%) with efficient stirring. The precipitate was filtered off, washed with water and dried under vacuum (60°C) to give the title compound. Recrytallized from ethanol.
The compound IV was confirmed by IR (KBr) (cm $^{-1}$): 3084 (Aromatic C-H Stretch), 3051 (O – H Stretch), 2915 (Aliphatic C-H Stretch), 1680 (C = O Stretch), 1582 (Aromatic C = C Stretch), 1282 (C – N Stretch), 681 (C – S Stretch of C-S-C). ^{1}H-NMR spectrum: ^{1}H-NMR (DMSO-d_6, 300 MHz), δ (ppm): 1.1 (s, 1H,-COOH), 2.51 (s, 9H, 3CH_3), 2.09-2.31(m, 8H, 4(CH_2)), 6.65 (s, 1H, - CH). LC-MS (m/z): 225.29 (M+1).

Preparation of 4-thiomorpholin-4ylbenzoyl chloride (V):

A mixture of 4-thiomorpholin– 4ylbenzoic acid (IV) (6gm, 1 mol) in ethanol (25ml) and thionyl chloride ($SOCl_2$) (3.3ml, 0.5 mol) was refluxed on water bath for 6 hrs. Excess of thionyl chloride was removed by distillation under reduced pressure or by adding formic acid dropwise as required and the residue so collected was used for the next step.

The compound V was confirmed by IR (KBr) (cm $^{-1}$): 3084 (Aromatic C-H Stretch), 3051 (O – H Stretch), 2915 (Aliphatic C-H Stretch), 1680 (C = O Stretch), 1582 (Aromatic C = C Stretch), 1282 (C – N Stretch), 681 (C – S Stretch of C-S-C).^{1}H-NMR spectrum: ^{1}H-NMR (DMSO-d_6, 300 MHz), δ (ppm): 2.51 (s, 9H, 3CH_3), 2.09-2.31(m, 8H, 4(CH_2)), 6.65 (s, 1H, - CH). LC-MS (m/z): 243.74 (M+1).

Preparation of 4-thiomorpholin -4ylbenzohydrazide (VI):

To the solution of 4-thiomorpholin– 4ylbenzoyl chloride (V) (6gm, 0.01 mole) in 15ml of methanol, 99% hydrazine hydrate (1.94ml, 0.03 mol) was added and the mixture was refluxed with on water bath for 4hrs. After cooling the precipitate was collected, washed with distilled water, and recrytallized from ethanol.

The compound VI was confirmed by IR (KBr) (cm $^{-1}$): 3100 (N-H Stretch of 1° amine), 3051 (Aromatic C-H Stretch), 2915 (Aliphatic C-H Stretch), 1600 (C = O Stretch), 1491 (Aromatic C = C Stretch), 1100 (C – N Stretch), 835 (N-H Bend), 660 (C - S Stretch).^{1}H-NMR spectrum: ^{1}H-NMR (DMSO-d_6, 300 MHz), δ (ppm): 2.51 (s, 9H, 3CH_3), 2.09-2.31(m, 8H, 4(CH_2)), 6.65 (s, 1H, - CH), 4.4 (s, 2H, NH2), 9.1 (s, 1H, NH). LC-MS (m/z): 238.32 (M+1).

Preparation of 4-thiomorpholin -4 ylbenzohydrazide - hydrazones (VII a – h):

A mixture of 4-thiomorpholin– 4ylbenzohydrazide (VI) (0.01mmole) and aromatic aldehyde (0.01mmol) with 2-3 drops of con.sulphuric acid in methanol (50ml) was refluxed on water bath for about 7-8 hrs.The solvent was removed under vaccum to give products viz,VII a – h.

Table I: Physical data of 4-thiomorpholin -4 ylbenzohydrazide – hydrazones (VII a – h).

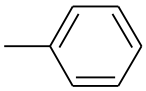
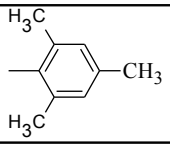
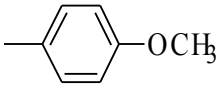
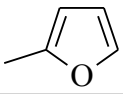
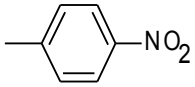
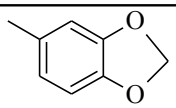
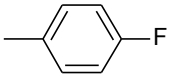
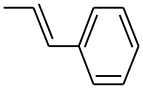
Code	-Ar	Molecular formula	Mol.wt	M.P. (°C) Uncorrected	% yield
VII a		$C_{18}H_{19}N_3OS$	325	122	94
VII b		$C_{21}H_{25}N_3O_2S$	367	159	87
VII c		$C_{19}H_{21}N3O_2S$	355	218	88
VII d		$C_{16}H_{17}N_3O_2S$	315	176	75
VII e		$C_{18}H_{18}N_4O_2S$	370	150	86
VII f		$C_{19}H_{19}N_3O_3S$	369	235	95
VII g		$C_{18}H_{18}FN_3OS$	343	211	78
VII h		$C2_0H_{21}N_3OS$	351	140	89

Table II: Analytical data of 4-thiomorpholin -4 ylbenzohydrazide - hydrazones (VII a – h).

Code	Molecular formula	IR Spectrum (cm $^{-1}$)	^{1}H-NMR Spectrum δ (ppm)	LC-MS (m/z)
VII a	$C_{18}H_{19}N_3OS$	3150,3030,2930,1650,1580,1580,750,690		123
VII b	$C_{21}H_{25}N_3O_2S$	3250, 2995, 2920, 1690, 1280, 860, 685	2.51(s, 9H, $3CH_3$), 2.09-2.31) (m, 8H, 4 CH_2), 6.65(s, 1H, - CH), 6.91-7.99(m, 6H, Ar-H), 8.97(s, 1H, -CONH)	160
VII c	$C_{19}H_{21}N3O_2S$	3280, 3000, 2935, 1605, 1506, 1180, 1035, 825, 615		219
VII d	$C_{16}H_{17}N_3O_2S$	3100, 3080, 2925, 1590, 1500, 1180, 845, 680	1.83-2.25(m, 8H, 4(CH_2)), 6.58(s, 1H, - CH), 6.71-8.06(m, 4H, Ar-H), 8.63(s, 1H, -CONH)	177
VII e	$C_{18}H_{18}N_4O_2S$	3050, 2930, 2850, 1600, 1510, 1350, 1100, 845, 670		151
VII f	$C_{19}H_{19}N_3O_3S$	3100, 2920, 2800, 1630, 1500, 1120, 1030, 810, 610	2.17(t , 2H, - CH_2), 3.19(s, 4H, N ($CH_2)_2$), 4.78(s, 4H, S ($CH_2)_2$), 6.05(s, 1H, - N=CH), 6.72-8.00 (m,7H ,Ar-H), 8.54 (s, 1H, - CONH)	236
VII g	$C_{18}H_{18}FN_3OS$	3380, 2850, 2850, 1650, 1505, 1215, 1150, 830, 615	2.17 (s, 4H ,N ($CH_2)_2$), 2.59(s, 4H, S ($CH_2)_2$), 4.00 (s, 1H,- CH), 7.15-7.86(m, 8H, Ar-H), 8.62(s, 1H, - CONH)	212
VII h	$C2_0H_{21}N_3OS$	3250, 3100, 2945, 1620, 1590, 1100, 800, 700		141

Preparation of N'-Formyl-4-thiomorpholin- 4ylbenzohydrazide (VI a):

A solution of 4-thiomorpholin-4ylbenzohydrazide (VI) (1.17gm, 5.0 moles) in formic acid (20ml) was refluxed for 1 hr. The solvent was evaporated and the residue was recrystallized from ethanol to give compound (VIa).Recrystallized from ethanol.

The compound VIa was confirmed by IR (KBr) (cm $^{-1}$): 3184 (0-H Stretch), 3100 (Aromatic C-H Stretch), 2995 (Aliphatic C-H Stretch), 1600 (C = O Stretch), 1450 (C = N Stretch), 1100 (C – N Stretch), 850 (N-H Bend), 640 (C - S Stretch).

Preparation of N'-Benzoyl-4-thiomorpholin-4ylbenzohydrazide (VI b):

A solution of 4-thiomorpholin– 4ylbenzohydrazide (VI) (1.17gm, 0. 5 mole) in Benzoic acid (1gm, 0.03 mole) was refluxed for 5 hrs. The solvent was evaporated and the residue was recrystallized from ethanol to give compound (VIb).Recrystallized from ethanol.

The compound VIb was confirmed by IR (KBr) (cm $^{-1}$): 3000 (Aromatic C-H Stretch), 2950 (Aliphatic C-H Stretch), 1600 (C = O Stretch), 1445 (C = N Stretch), 1100 (C – N Stretch), 850 (N-H Bend), (690 C - S Stretch).

Preparation of N'-Benzoylamine-4-thiomorpholin-4ylbenzohydrazide (VI c):

A solution of 4-thiomorpholin– 4ylbenzohydrazide (VI) (1.17gm, 0.5 mole) in 4-amino benzoic acid (1gm, 0.03 moles) was refluxed for 5 hrs. The solvent was evaporated and the residue was recrystallized from ethanol to give compound (VIc).Recrystallized from ethanol.

The compound VIc was confirmed by IR (KBr) (cm $^{-1}$): 3350 (N-H Stretch of 1° amine), 3000 (Aromatic C-H Stretch), 2920 (Aliphatic C-H Stretch), 1600 (Aliphatic C-H Stretch), 1440 (C=N Stretch), 1100 (C–N Stretch), 850 (N-H Bend), 690(C - S Stretch).

Preparation of N'-Benzonitrile-4-thiomorpholin-4ylbenzohydrazide (VI d):

A mixture of 4-thiomorpholin– 4ylbenzohydrazide [VI] (1gm, 1.0 mole) in ethanol (25ml) and 4-chlorobenzonitrile ((0.5gm, 0.01 mole) in 250ml RBF and also added Anhydrous potassium carbonate(3 gm) for the purpose of increasing rate of reaction. Then was heated at 120°C .The conversion of the 4-chlorobenzontrile (2) was complete after 12hrs.Water (25ml) was then added into the reaction mixture. The precipitate was filtered off, washed with water and dried under vacuum (30°C) to give title compound (VId). Recrytallized from 50% aqueous ethanol.

The compound VId was confirmed by IR (KBr) (cm $^{-1}$): 3100 (Aromatic C-H Stretch), 2950 (Aliphatic C-H Stretch), 1600 (C = O Stretch), 1500(C = N Stretch), 2225 (C ≡ N Stretch), 1100 (C – N Stretch), 850 (N-H Bend), 680 (C - S Stretch).

Preparation of Ethyl (3E)-3-[(4-thiomorpholin-4ylbenzoyl) hydrazono] butanoate (VI e):

A mixture of 4-thiomorpholin–4ylbenzohydrazide (VI) (0.37gm, 0.01 mole) and ethyl acetoacetate (0.208gm, 0.01mmole) was condensed without solvent at 145-155°C for 10 min. The reaction mixture was cooled and refluxed in ethanol (25ml) for 2hrs. The precipitate formed after cooling was cooling was collected by filtration and recrystallization from ethanol to give title compound (VIe).

The compound VIe was confirmed by IR (KBr) (cm $^{-1}$): 3220 (N-H Stretch of 2^0 amine), 3100 (Aromatic C-H Stretch), 2950 (Aliphatic C-H Stretch), 1750 (C = O Stretch), 1500 (C = N Stretch), 1085 (C – N Stretch), 865 (N-H Bend), 645 (C – S Stretch).

Preparation of N'-(2-bromoethyl–4-thiomorpholin-4ylbenzohydrazide (VIf) :

A mixture of 4-thiomorpholin– 4ylbenzohydrazide (VI) (1.37gm, 10 moles) in ethanol (25ml) added into the 1, 2-dibromoethane also added potassium iodide and potassium hydroxide using as catalyst. Stirring the mixture with heating at 60-70°C for 5 hrs.Then resulting mixture is added into the cold water and the precipitate is filtered and to give title compound (VIf).Recrystallized from ethanol.

The compound VIe was confirmed by IR (KBr) (cm $^{-1}$): 3200 (N-H Stretch of 2° amine), 3220 (Aromatic C-H Stretch), 2875 (Aliphatic C-H Stretch), 1600 (C = O Stretch), 1420 (C = N Stretch), 1010 (C – N Stretch), 910 (N-H), 730 (C - Br Stretch), 650 (C – S Stretch).

Preparation of N'-(3-bromopropyl) – 4-thiomorpholin- 4ylbenzohydrazide (VIg):

A mixture of 4-thiomorpholin–4ylbenzohydrazide (VI) (1.37gm, 10 moles) in ethanol (25ml) added into the 1, 3-dibromopropane also added potassium iodide and potassium hydroxide using as catalyst. Stirring the mixture with heating at 60-70°C for 5 hrs.Then resulting mixture is added into the cold water and the precipitate is filtered and to give title compound (VIg).Recrystallized from ethanol.

The compound VIg was confirmed by IR (KBr) (cm $^{-1}$): 3220 (N-H Stretch of 2° amine), 3020 (Aromatic C-H Stretch), 2875(Aliphatic C-H Stretch), 1575 (C = O Stretch), 1500 (C = N Stretch), 1100 (C – N Stretch), 850 (N-H Bend), 750 (C - Br Stretch), 663 (C – S Stretch).

Preparation of N'-2, 4 –dinitrophenyl – 4-thiomorpholin- 4ylbenzohydrazide (VIh):

A mixture of 4-thiomorpholin– 4ylbenzohydrazide (VI) (1gm, 1.1 mole) in ethanol (25ml) and 1-chloro-2,4-dinitrobenzen (0.5gm, 0.01 mole) in 250ml RBF and also added.

Anhydrous potassium carbonate(3 gm) for the purpose of increasing rate of reaction. Then was heated at 120°C.The conversion of the 4-chlorobenzontrile (2) was complete after 12hrs.Water (25ml) was then added into the reaction mixture. The precipitate was filtered off, washed with water and dried under vaccum (30°C) to give title compound (VIh). Recrytallized from 50% aqueous ethanol.

The compound VIh was confirmed by IR (KBr) (cm $^{-1}$): 3520 (N – H Stretch of 2° amine), 3100 (Aromatic C-H Stretch), 2950 (Aliphatic C-H Stretch), 1650 (C = O Stretch), 1595 (C = N Stretch), 1350 (- NO_2 Stretch), 1100 (C – N Stretch), 850 (N-H Bend), 650 (C - S Stretch).

Table III: Physical data of 4-thiomorpholin -4 ylbenzohydrazide derivative (VI a – k).

Code	Molecular formula	Mol.wt	M.P. (°C) Uncorrected	% yield
VI a	$C_{12}H_{15}N_3O_2S$	265	249	70%
VI b	$C_{18}H_{19}N_3O_2S$	341	253	75%
VI c	$C_{18}H_{20}N_4O_2S$	356	259	74%
VI d	$C_{18}H_{18}N_4OS$	338	244	48.42%
VI e	$C_{17}H_{23}N_3O_3S$	349	235	79.6%
VI f	$C_{13}H_{18}BrN_3Os$	344	227	98.34%
VI g	$C_{14}H_{20}BrN_3OS$	358	257	95%
VI h	$C_{17}H_{17}N_5O_5S$	403	241	80%

RESULTS AND DISCUSSION

From the literature survey it reveals that the thiomorpholine have been reported for number of pharmacological activities and some molecules have shown significant activities and some compounds shows moderate and good activities. Here we have synthesized some novel 4-thiomorpholin-4ylbenzohydrazide analogues and screened them for their antimicrobial activities.

The purity and homogeneity of the synthesized compounds were preliminary checked by their physical constant. The final compounds were found to be soluble in organic solvents. These compounds were characterized by spectral studies for structural elucidation and studies showed satisfactory results.

Biological Evaluation

All the newly synthesized -thiomorpholin-4ylbenzohydrazide were assayed in vitro for their antibacterial activity against *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria) and antifungal activity against *Aspergillus niger* and *Candida albicans*. The minimum inhibitory concentration (MIC) value for antibacterial activity of compounds was determined by the cup plate method by using nutrient agar media (NAM).

The minimum inhibitory concentration (MIC) values for antifungal activity were determined by using broth double dilution method (Serially diluted method) in Sabourauds dextrose broth at P^H 7.4. For comparison, Ciprofloxacin was used as the reference antibacterial agents; Ketoconazole was employed as the reference antifungal agent. The antibacterial and antifungal MIC values for test compound as well as reference standard are given in Table. No. IV, V, VI, VII respectively.

The obtained results revealed that the nature of substituent and substitution pattern on the benzene ring may have a considerable impact on the antibacterial and antifungal activities of the synthesized compounds. Of particular importance, a nitro group has a considerable impact on antibacterial and antifungal activity. Lipophilicity plays an important role in the preparation of these compounds into bacterial cell.

Antibacterial Activity:

The minimum inhibitory concentration (MIC) was determined by the cup plate method. Ciprofloxacin was employed during the test procedures as reference. The MIC of the synthesized compounds ranges between 25-200 µg/ml. VIIc, VIId, VIIf and VIe were found moderately active, while VIIb, VIIe, VIIh and VIb, VIc, VId VIf were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards Staphylococcus aureus (Gram-positive bacteria) and Escherichia coli (Gram-negative bacteria)

Table IV: Minimum inhibitory concentration of 4-thiomorpholin -4 ylbenzohydrazide – hydrazones (VIIa-h).

Sr.No	compound	MIC in µg/ml	
		E.coli	*S.Aureus*
1	VII a	100	150
2	VII b	62.5	50
3	VII c	31.5	31.5
4	VII d	31.5	31.5
5	VII e	100	100
6	VII f	31.5	31.5
7	VII g	100	100
8	VII h	62.5	62.5
9	S	25	25
10	C	-	-

Note: -Standard(S) = Ciprofloxacin Control (C) = DMF

Table V: Minimum inhibitory concentration of 4-thiomorpholin -4 ylbenzohydrazide (VI a-h).

Sr.No	compound	MIC in µg/ml	
		E.coli	*S.Aureus*
1	Via	150	150
2	Vib	100	150
3	Vic	100	100
4	Vid	50	62.5
5	Vie	31.5	31.5
6	Vif	50	50
7	Vig	150	150
8	Vih	150	150
9	S	25	31
10	C	-	-

Note: - Standard(S) = Ciprofloxacin control (C) = DMF

Antifungal Activity:-

The minimum inhibitory concentration (MIC) was determined by the broth dilution method (Serially diluted method). Ketoconazole was employed du6d ring the test procedures as references.MIC of the synthesized compounds ranges between 15.6-500µg/ml. VIIc, VIId and VIe was found moderately active, while VIIe and VIa, VIb, VIc, VId were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards *Aspergillus niger* and *Candida albicans*.

Table VI: Minimum inhibitory concentration of 4 -thiomorpholin -4 ylbenzohydrazide – hydrazones (VIIa-h).

Sr.No	compound	MIC in µg/ml	
		C.albicans	*A.niger*
1	VII a	100	100
2	VII b	150	150
3	VII c	31.5	50
4	VII d	62.5	62.5
5	VII e	100	100
6	VII f	150	150
7	VII g	100	150
8	VII h	150	150
9	S	25	25
10	C	-	-

Note: - Standard(S) = Ketoconazole Control (C) = DMF

TableVII: Minimum inhibitory concentration of 4 -thiomorpholin -4 ylbenzohydrazide (VIIa-h).

Sr.No	compound	MIC in µg/ml	
		C.albicans	*S.Aureus*
1	VIa	100	100
2	VIb	100	150
3	VIc	100	100
4	VId	100	100
5	VIe	62.5	50
6	VIf	150	150
7	VIg	150	150
8	VIh	150	150
9	VIi	62.5	50
10	S	25	25
11	C	-	-

Note: - Standard(S) = Ketoconazole Control (C) = DMF

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