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# Synthesis of 1,4-Benzothiazine Compounds Containing Isatin Hydrazone Moiety as Antimicrobial Agent

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A series of novel 3-methyl-*N*″-(2-oxoindolin-3-ylidene)-4*H*-benzo[*b*][1,4]thiazine-2-carbohyrazides have been synthesized and studied on their *in vitro* antimicrobial activity potency to establish structure-activity relationship. Several compounds demonstrated promising antifungal and antibacterial activity; however, other tested compounds exhibited moderate to poor antimicrobial activity with respect to the reference drug against the test strains.

**Keywords** 1,4-benzothiazine, isatin, antifungal activity, antibacterial activity

## Introduction

Sulfur and nitrogen-containing heterocycles such as 1,4-benzothiazine and its derivatives play an important role in biochemical processes.[1] Clinical and pharmacological properties of 10*H*-phenothiazines and 4*H*-1,4-benzothiazines have been widely studied for a long time which appear in numerous biologically active natural products.[2] The compounds containing these basic moieties were wieldy used as antihistaminics,[3] antipsychotics,[4] antiemetics,[5] neuroleptics,[6] tranquilizers,[7] *etc*., (Figure 1).

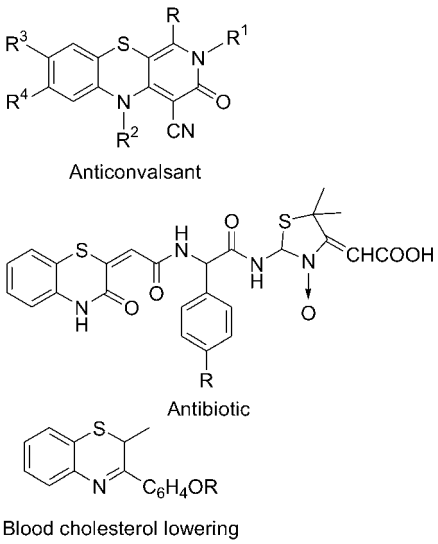


**Figure 1** Some of 1,4-benzothiazine based drugs.

Isatin (2,3-dioxoindole) is an endogenous compound with a long history and wide range of pharmacological actions. *N*-Mannich bases of isatin reduces the liability of the isatin nucleus towards bases, while maintaining its typical reactivity. Thus, *N*-substituted isatins have been frequently used as intermediates and synthetic precursors for the preparation of a wide variety of heterocyclic compounds.[8,9] Mannich bases of isatin and their derivatives were synthesized and reported for antibacterial,[10] antifungal,[11] anti-HIV,[12-19] anticonvulsant activities[20] and GAL3 receptor antagonist activity[21,22] and in recent years the compounds showing potent cytotoxicity *in vitro*[9] and antiviral activity[23] have been reported, among others (Figure 2).

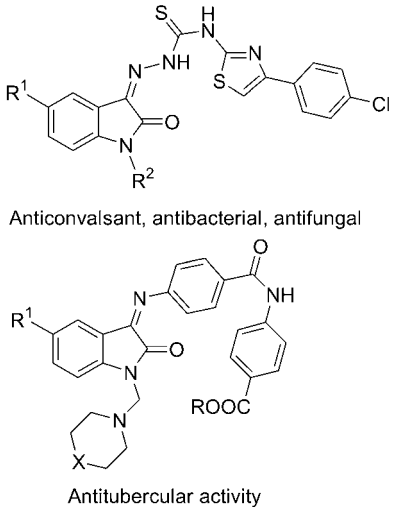


**Figure 2** Some of isatin based drugs.

In continuation of our work on bioactive isatin,[24] encouraged by the observations about biological properties of isatin derivatives and 1,4-benzothiazine, we decided to design and synthesize Mannich bases containing both 1,4-benzothiazine and isatin moieties to generate a series of newer 1,4-benzothiazine derivatives and screen them for potential biological activity. The results of such studies are presented in this article.

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## Results and discussion

The synthesis of 3-methyl-*N*″-(2-oxoindolin-3-ylidene)-4*H*-benzo[*b*][1,4]thiazine-2-carbohyrazide was achieved through the versatile and efficient synthetic route as outlined in Scheme 1. The 3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carbohyrazide **1** was prepared via the reaction of ethyl 3-methyl-4*H*-benzo[*b*][1,4]-thiazine-2-carboxylate with hydrazine hydrate in ethanol which was then condensed with substituted isatin in ethanol in the presence of gl. acetic acid to obtain the desired products **3a**—**3l**. *N*-Mannich base of isatin derivatives were prepared from corresponding secondary amine according to a literature method.[25]

Physical constants and analytical data of compounds are summarized in Table 1.

**Scheme 1**

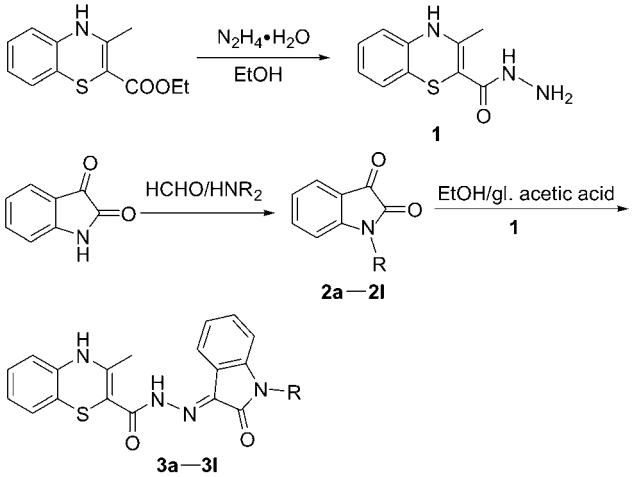
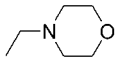
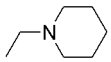
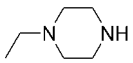
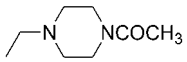
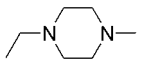
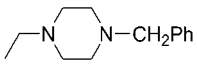



**Table 1** Physical constants and analytical data of compounds

| Comp. | R | m.p./℃ | Yield/% | Molecular formula | IR $\nu$/cm$^{-1}$ | $^1$H NMR ($\delta$) | EI-MS (M+1) |
|---|---|---|---|---|---|---|---|
| **3a** | H | 152—154 | 79 | $C_{18}H_{14}O_2N_4S$ | 3400, 3398, 3030, 2800, 1690, 1630, 1590, 1550, 1480, 610. | 1.21 (s, 3H, $CH_3$), 4.25 (bs, 1H, NH), 5.28 (s, 1H, NHCO), 6.50 (s, 1H, CONHN), 6.89—7.20 (m, 4H, ArH), 7.30—7.95 (m, 4H, ArH). | 252 |
| **3b** | $CH_2N(CH_3)_2$ | 228—230 | 72 | $C_{21}H_{21}O_2N_5S$ | 3410, 3390, 3020, 2810, 1680, 1640, 1590, 1550, 1480, 600. | 1.39 (s, 3H, $CH_3$), 2.45 (s, 6H, $2CH_3$), 3.59 (s, 2H, $CH_2$), 5.19 (bs, 1H, NH), 7.20—7.80 (m, 8H, ArH), 8.60 (s, 1H, NHCO). | 310 |
| **3c** | $CH_2N(CH_2CH_3)_2$ | 215—218 | 69 | $C_{23}H_{25}O_2N_5S$ | 3415, 3380, 3020, 2840, 1690, 1660, 1610, 1580, 1495, 640. | 1.19 (s, 6H, $2CH_3$), 1.70 (t, $J$=7.0 Hz, 3H, $2CH_3$), 2.35—2.40 (m, 4H, $2CH_2$), 4.20 (s, 2H, $CH_2$), 5.20 (bs, 1H, NH), 6.39 (bs, 1H, NHCO), 6.80—7.19 (m, 4H, ArH), 7.59—7.94 (m, 4H, ArH). | 338 |
| **3d** | $CH_2N[CH(CH_3)_2]_2$ | 110—112 | 72 | $C_{25}H_{29}O_2N_5S$ | 3400, 3395, 3030, 2830, 1670, 1660, 1600, 1580, 1490, 620. | 1.30 (d, $J$=6.0 Hz, 12H, $4CH_3$), 1.63 (s, 3H, $CH_3$), 2.25—2.41 (m, 2H, $CH_2$), 4.45 (s, 2H, $CH_2$), 5.30 (bs, 1H, NH), 6.70 (s, 1H, NHCO), 7.60—7.80 (m, 4H, ArH), 8.15—8.40 (m, 4H, ArH). | 366 |
| **3e** | $CH_2N[(CH_2)_3CH_3]_2$ | 232—234 | 75 | $C_{27}H_{33}O_2N_5S$ | 3410, 3385, 3010, 2890, 1680, 1650, 1600, 1510, 1500, 620. | 0.80 (t, $J$=6.10 Hz, 6H, $2CH_3$), 1.20 (q, $J$=6.00 Hz, 8H, $4CH_2$), 1.80 (s, 3H, $CH_3$), 2.6—2.70 (m, 4H, $2CH_2$), 3.95 (s, 2H, $CH_2$), 6.59—6.80 (m, 4H, ArH), 7.00—7.30 (m, 4H, ArH), 7.40 (bs, 1H, NH), 9.80 (s, 1H, NHCO). | 394 |
| **3f** | $CH_2N(C_6H_{11})_2$ | 212—214 | 78 | $C_{31}H_{37}O_2N_5S$ | 3420, 3380, 3020, 2900, 1680, 1660, 1610, 1570, 1450, 640. | 1.00—1.40 (m, 12H, $6CH_2$), 1.61—1.63 (m, 4H, $2CH_2$), 1.65 (s, 3H, $CH_3$), 1.90—1.99 (m, 4H, $2CH_2$), 2.60—2.80 (m, 2H, 2NCH), 3.90 (bs, 1H, NH), 4.60 (s, 2H, $CH_2$), 5.40 (s, 1H, NHCO), 7.00—7.49 (m, 4H, ArH), 7.50—7.80 (m, 4H, ArH). | 446 |

Continued

| Comp. | R | m.p./℃ | Yield/% | Molecular Formula | IR $\nu$/cm$^{-1}$ | $^1$H NMR ($\delta$) | EI-MS (M+1) |
|---|---|---|---|---|---|---|---|
| **3g** |  | 182 | 75 | $C_{23}H_{23}O_3N_5S$ | 3410, 3380, 3030, 2920, 1640, 1600, 1590, 1550, 1410, 1080, 640 | 1.40 (s, 3H, $CH_3$), 2.39 (t, $J$=7.80 Hz, 4H, $2CH_2N$), 3.25 (t, $J$=7.10 Hz, 4H, $2CH_2O$), 4.50 (s, 2H, $CH_2$), 6.70 (s, 1H, NH), 7.20—7.50 (m, 4H, ArH), 7.79—7.89 (m, 4H, ArH), 8.40 (s, 1H, NHCO). | 352 |
| **3h** |  | 132 | 73 | $C_{24}H_{25}O_2N_5S$ | 3400, 3390, 3040, 2850, 1690, 1630, 1580, 1540, 1480, 690 | 1.00—1.40 (m, 6H, $3CH_2$), 1.40 (s, 3H, $CH_3$), 2.49 (t, $J$=6.50 Hz, 4H, $2CH_2$), 4.30 (s, 2H, $CH_2$), 6.60—7.00 (m, 4H, ArH), 7.49—7.69 (m, 4H, ArH), 8.00 (bs, 1H, NH), 9.00 (s, 1H, NHCO). | 350 |
| **3i** |  | 110 | 70 | $C_{23}H_{24}O_2N_6S$ | 3410, 3380, 3030, 2900, 1680, 1660, 1620, 1580, 1490, 670 | 1.59 (s, 3H, $CH_3$), 2.38 (t, 4H, $J$=7.10 Hz, $2CH_2N$), 2.69 (t, 4H, $J$=7.00 Hz, $2CH_2$), 4.50 (s, 2H, $CH_2$), 5.39 (s, 1H, NH), 6.65 (s, 1H, NH), 6.90—7.20 (m, 4H, ArH), 7.40—8.00 (m, 4H, ArH), 8.30 (s, 1H, NHCO). | 351 |
| **3j** |  | 270—272 | 73 | $C_{25}H_{26}O_3N_5S$ | 3430, 3395, 3040, 2850, 1720, 1690, 1630, 1590, 1550, 1450, 600 | 1.39 (s, 3H, $CH_3$), 2.19 (s, 3H, $COCH_3$), 2.50 (t, $J$=7.00 Hz, 4H, $2CH_2N$), 2.95 (t, $J$=6.50 Hz, 4H, $2CH_2N$), 4.30 (s, 2H, $CH_2$), 6.95—7.20 (m, 4H, ArH), 7.40 (s, 1H, NH), 7.50—7.80 (m, 4H, ArH), 8.10 (s, 1H, NHCO). | 393 |
| **3k** |  | 228—230 | 70 | $C_{25}H_{26}O_2N_5S$ | 3400, 3380, 3010, 2900, 1680, 1660, 1620, 1650, 1600, 700 | 1.40 (s, 3H, $CH_3$), 2.00 (s, 3H, $NCH_3$), 2.37 (t, $J$=7.00 Hz, 4H, $2CH_2N$), 2.70 (t, $J$=7.01 Hz, 4H, $2CH_2N$), 4.59 (s, 2H, $CH_2$), 6.89 (s, 1H, NH), 7.10—7.39 (m, 4H, ArH), 7.19—7.90 (m, 4H, ArH), 9.80 (s, 1H, NHCO). | 365 |
| **3l** |  | 215—218 | 77 | $C_{30}H_{30}O_2N_5S$ | 3410, 3390, 3030, 2800, 1690, 1640, 1590, 1550, 1500, 650 | 1.30 (s, 3H, $CH_3$), 2.35 (t, $J$=7.00 Hz, 4H, $2CH_2N$), 2.70 (t, $J$=7.02 Hz, 4H, $2CH_2N$), 3.50 (s, 2H, $NCH_2Ph$), 4.20 (s, 2H, $CH_2$), 6.59 (s, 1H, NH), 7.00 (s, 1H, NHCO), 7.10—7.39 (m, 3H, ArH), 7.35—7.60 (m, 5H, ArH), 7.63—7.95 (m, 5H, ArH). | 441 |

## Experimental

Melting points of all the synthesized compounds were determined by an open capillary method and are uncorrected. The synthesized compounds were crystallized using proper solvent and the purities were ascertained on the basis of thin-layer chromatography, mass and spectral data. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel (Merck) glass plates, visualized by

iodine-vapour. Developing solvents were hexane-ethyl acetate (8∶2, *V*/*V*). IR spectra were recorded on an FTIR spectrophotometer (Perkin Elmer) using nujol mull. $^1$H NMR spectra were obtained at 300 MHz on a Varian Mercury YH-300 FT NMR spectrometer in $CDCl_3$/DMSO-$d_6$ using tetramethylsilane as an internal standard. Mass spectra were recorded from an HP 1100 MSD mass spectral instrument (positive and negative APCI ion source, 50—200 V, nitrogen). All the chemicals and solvents used were of synthetic grade (S. D. Fine chemicals, Mumbai, India). The compounds **1** and **2a**—**2l** were prepared in the laboratory.[26,27]

### General synthesis of *N*-Mannich bases of isatin

Formaldehyde solution (2.0 mmol) and secondary amine (1.0 mmol) were dissolved in ethanol (20 mL) and stirred for 30 min. The iminiun ion formed *in situ* was then refluxed with isatin (1.0 mmol) in ethanol (Scheme 1). The reaction was monitored by TLC and the mixture cooled to room temperature, refrigerated for 48 h to form crystals. The crystalline products were separated by filtration, washed and vacuum dried. Recrystallization from ethanol rendered desired products in pure form.

### General procedure for preparing compounds 3a—3l

The equimolar mixture of isatin or *N*-substituted isatin (0.2 g, 1.35 mmol) and compound **1** (0.27 g, 1.35 mmol) containing 1—1.5 mL of glacial acetic acid in ethanol (20 mL) was refluxed for 4—6 h. The progress of reaction was monitored by TLC and excess of solvent was removed under vacuum and the obtained semisolid was treated with ice-water and separated solid was filtered, washed with water and purified by column chromatography affording desired products (**3a**—3**l**) in pure form.

## Microbiology

### *In vitro* antimicrobial activity

All the synthesized compounds **3a**—3**l** were tested for *in vitro* antimicrobial activity. The lowest concentration (highest dilution) required to arrest the growth of microorganism was regarded as minimum inhibitory concentration (MIC) by an agar well diffusion method.[28] Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful particular fungal strain was transferred to 3 mL of saline to get a suspension of corresponding species. Twenty milliliters of agar media were poured into each Petri-dish. Excess of suspension was decanted and the plates were dried in an incubator at 37 ℃. Inhibition zones were measured after 48 h and compared with the control.

Percent change in antifungal activity of different derivatives over parent compound, 3-methyl-*N*′′-(2-oxoindolin-3-ylidene)-4*H*-benzo[*b*][1,4]thiazine-2-carbohyrazide (**3a**) was calculated using the following formula.

$$\text{Percent change in antifungal activity} = \frac{D-P}{P} \times 100$$

where *D* is the zone of inhibition for derivative and *P* is the zone of inhibition for parent compound. The same methodology for evaluation of antibacterial activity was performed as described for antifungal activity, with only the plates being incubated at 37 ℃ for 24 h.

**Table 2** Quantitative antimicrobial activity of compounds **3a**—**3l** (zone of inhibition in mm)[a]

| Compound | Antibacterial activity | | Antifungal activity | |
|---|---|---|---|---|
| | *E. coli* | *S. aureus* | *A. niger* | *P. marneffei* |
| **3a** | 11.5 | 10.3 | 14.25 | 12.50 |
| **3b** | — | 8.0 | 10.5 | 08.0 |
| **3c** | — | — | 11.75 | 10.20 |
| **3d** | — | — | 08.75 | 11.20 |
| **3e** | 13.5 | 11.2 | 13.75 | 12.0 |
| **3f** | 10.7 | 09.8 | 12.5 | 11.50 |
| **3g** | 11.4 | 16.0 | 14.0 | 15.50 |
| **3h** | 10.7 | 10.2 | 15.25 | 16.20 |
| **3i** | 14.4 | 13.2 | 16.10 | 15.10 |
| **3j** | 12.7 | 13.5 | 17.0 | 16.75 |
| **3k** | 15.3 | 12.8 | 15.50 | 14.75 |
| **3l** | 13.5 | 12.3 | 16.25 | 15.50 |
| Cloxacilline | 18.0 | 19.0 | | |
| Fluconazole | | | 19.0 | 20.0 |

[a] The quantitative antimicrobial data of compounds **3a**—**3l** at MIC value 100 μg/mL concentration and cloxacilline used as a standard at MIC value 50 μg/mL.

**Table 3** Percent change in antibacterial and antifungal activity of compounds **3a**—**3l**[a]

| Compound | Antibacterial activity | | Antifungal activity | |
|---|---|---|---|---|
| | *E.coli* | *S. aureus* | *A. niger* | *P. marneffei* |
| **3a** | — | — | — | — |
| **3b** | −14.81 | −22.33 | −26.31 | −36.00 |
| **3c** | — | — | −17.54 | −18.0 |
| **3d** | — | — | −38.59 | −10.4 |
| **3e** | 17.39 | 8.7 | −3.50 | −4.0 |
| **3f** | −6.9 | −4.85 | −12.25 | −8.0 |
| **3g** | −0.86 | 55.33 | −1.75 | 24.0 |
| **3h** | −6.95 | −0.97 | 7.0 | 29.6 |
| **3i** | 25.21 | 28.15 | 14.0 | 20.8 |
| **3i** | 10.53 | 31.06 | 19.29 | 34.0 |
| **3k** | 33.04 | 24.27 | 8.77 | 18.00 |
| **3l** | 17.39 | 19.41 | 14.0 | 24.0 |

[a] Percent change in antibacterial and antifungal activity of 1,4-benzothiazine derivatives over parent compound **3a**.

## Antibacterial activity

The synthesized compounds were screened for their

antibacterial activity against *E. coli* (ATCC-25923) (gram-negative) and *S. aureus* (gram-positive) bacterial strains. Cloxaciline was used as a standard and DMSO as a negative control. The approximate MIC values of the test derivatives indicate that most compounds exhibit good activity against *E. coli* and *S. aureus* bacteria.

Antibacterial screening of compounds **3a**—**3l** against *E. coli* reveals that compounds **3e**, **3i**, **3k** and **3l** exhibited the good activity ＞100 μg/mL, whereas compounds **3a**, **3f**, **3g**, **3h**, and **3j** were respectable as compared to the standard.

Most tested compounds had appreciable *in-vitro* antibacterial activity against the *S. aureus*, the most active compound **3g** excellent activity＞100 μg/mL as compared to the standard. Whereas compounds **3a**, **3b**, **3e**, **3f**, **3h**—**3i** showed good activity, compounds **3c** and **3d** did not show any improvement of bacterial activity against *S. aureus* (Figure 3).

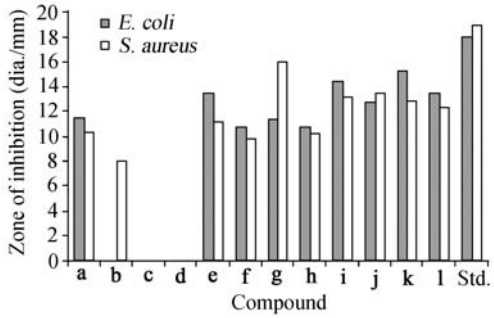



**Figure 3** Graphical representation of antibacterial activity of compounds **3a**—**3l** at MIC value 100 μg/mL concentration and cloxacilline used as a standard at MIC value 50 μg/mL.

The derivatives **3e**, **3g**, **3i**—**3l** of **3a** were found to be more effective. While **3b**, **3f** showed lower percent change in antibacterial activity than the parent molecule **3a** and compounds **3c** and **3d** did not show any percent change in antibacterial activity (Figure 4).

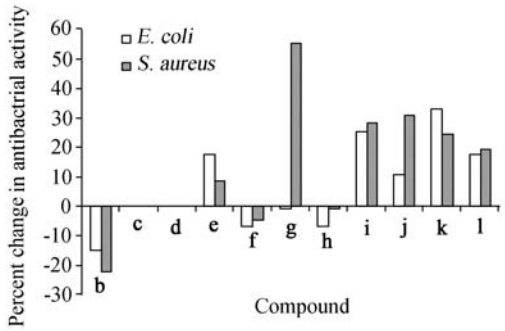



**Figure 4** Percent change in antibacterial activity of 1,4-benzothiazine derivatives over parent compound **3a**.

## Antifungal activity

The synthesized compounds were tested for their antifungal activity against *A. niger* and *P. marneffei.* Fluconazole was used as a positive control and DMSO as a negative control.

Compounds **3a**, **3h**—**3l** and **3g**, **3h**—**3l** showed better antifungal activity against *A. niger* and *P. marneffei* at 100 μg/mL than the standard. While other compounds exhibited good to poor activity as compared to the standard (Figure 5).

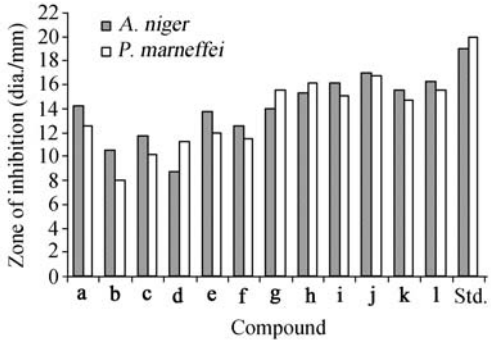



**Figure 5** Graphical representation of antifungal activity of compounds **3a**—**3l** at MIC value 100 μg/mL concentration and flucanazole used as a standard at MIC 50 μg/mL.

The derivatives **3g**—**3l** of **3a** were found to be more effective (Figure 6). While derivatives **3b**—**3f** exhibited lower percent change in antifungal activity than the parent molecule **3a** against all tested fungal species (Figure 6).

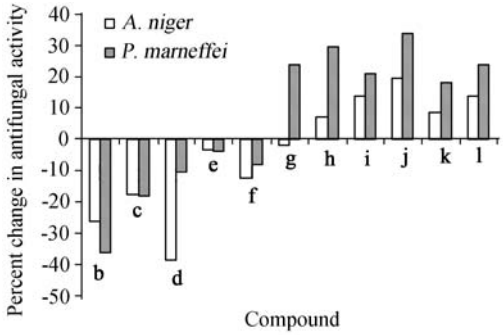



**Figure 6** Percent change in antifungal activity of 1,4-benzothiazine derivatives over parent compound **3a**.

The literature survey reveals that variation in the length of aliphatic chain produces varied pharmacological effect; for example in homologous series, group of compounds that differ by a constant unit, generally a $CH_2$ group, show increase or decrease in biological properties.[1] In some cases, the chain branching lowers the potency of a compound because the branched alkyl chain is less lipophilic than the corresponding straight chain as a result of larger molar volume and shapes of branched compound.[1] By examination of structure-activity relationship for **3a**, the antibacterial coverage and the overall pharmacokinetics largely depend upon the substitution.

It is seen that, introduction of aliphatic chain to isatin results in the decrease of **3b**—**3e**. It may be attributed to reduction in lipophilicity with increase in the number of methylene groups from **3b** — **3e**. Moreover chain

branching may interfere with receptor binding than the corresponding straight chain analogue.

The structural modification of **3a** was found to be more effective for morpholin, piperazine, *N*-acetyl piperazine, *N*-methyl piperazine, *N*-benzyl piperazine derivatives **3f**—**3l** against tested antifungal species than those against the antibacterial species. For these compounds presence of extra N and O increases lipophilicity or decreases the tendency of metabolism due to increase in hydrophilicity and thus making the compound more effective, also connecting substituents into a ring, pharmacodynamics properties could be enhanced by constraining the groups into a particular by favorable conformation.

These factors may be responsible for variation in activity for **3b**—**3l**.

The results of structural activity relationship indicated on the basis of bioassay could be used to model the toxicity effect due to substitution of newer groups.

## Conclusion

In conclusion, we have synthesized a series of isatin derivatives linked to 1,4-benzothiazine moiety and found that compounds **3a**, **3h**—**3l** and **3g**, **3h**—**3l** showed appreciable *in vitro* antimicrobial activity with respect to the reference. The modification of the *N*-1 substituent of piperazine ring produced relatively major changes in terms of activity. However, other compounds exhibited moderate to poor antibacterial as well as antifungal activity.

The results of present study are encouraging to define and optimize the antifungal effect of the tested compounds. Further investigations are currently in progress to verify the susceptibility of the other fungi to these compounds and to outline their pharmacokinetic profile.

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