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# SYNTHESIS AND ANTIFUNGAL SCREENING OF BENZOTHIAZOLE DERIVATIVES CONTAINING THIAZOLIDINONE MOIETY

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## ABSTRACT

A series of novel benzothiazol-2-amine (1), ethylbenzo[d]thiazol2-ylcarbamate (2), (benzo[d]thiazol2-y)hydrazinecarboxamide (3), N-(benzo[d]thiazol2-yl)2-substitutedbenzylidene hydrazinecarboxamide (4-7), 1-(benzo[d]thiazol-2yl)-3-(2-(substitutedphenyl)-4-oxothiazolidin-3yl)urea (8-11) have been prepared. First compound obtained with reaction of aniline, ammonium thiocynate and bromine. After treated with ethyl chloformate, compound 1 was change compound 2. In the next step compound 2 was introduced in reaction with hydrazine producing compound 3. Then it was treated with different aldehydes and give compounds 4-7. Compounds 4-7 were reacted with thioglycolic acid to yield compounds 8-11. Structure of these compounds cleared from IR, NMR and biological properties were tested against some fungi.

**KEYWORDS**: Benzothiazole, thiazolidinone, antifungal activity, fluconazole.

## INTRODUCTION

The heterocyclic nitrogen and sulphur like benzothiazole derivatives has a vital role in synthetic drugs. Benzothiazole derivative possess in broad spectrum of biological and pharmacological activities such as antifungal[1], antimicrobial[2-4] antibacterial[5,6], anticancer[7], antitumor[8,9], anticonvulsant[10] anti-inflammatory[11] etc. Literature studies on thiazolidinones have shown that these derivatives possess biological activities, like antimicrobial[12,13], antifungal[14,15], antibacterial[16,17], anticancer[18], and anti-inflammatory[19] activities. Hence, it was thought interesting to explore the study of such molecules. The survey of literature reveals the antifungal activity possessed by most of the benzothiazole and thiazolidinone derivatives. Therefore, we think it is worthful to assess biological activity of these compounds.

## MATERIAL AND METHODS

M.P. of synthesized drugs clarified from m. p. apparatus. Purity of all these compounds was regularly cleared using TLC. The percentage of C,H & N,IR spectra and $^1$H NMR spectra of these compounds was determined. The structure of drugs has shown in scheme 1.

## RESULTS AND DISCUSSION

### Chemistry

Synthesis of benzo[d]thiazol-2-amine (1)

Aniline (0.01mol) was taken in a 250 ml beaker with magnetic stirrer and covered with watch glass. It was placed into hotplate, and added HCl (5ml) with water (20ml). Then it was stirred at temperature 80$^0$C for 15 min and added $NH_4SCN$ (0.01 mol) with stirred about 1 hr. The reaction mixture in 20 ml chloroform was taken in a beaker and stirring at temperature 50$^0$C for 20 min. Then bromine (0.01mol) was mixed, during the addition of bromine, a temp of reaction mixture was maintained below 10$^0$C. It was refluxed until the evaluation of HBr ceased (about 30 min) chloroform was separate. The filtrate was neutralized with aq. Ammonia. The precipitate of 2-amino benzothiazole was filtered and recrystallised from $C_2H_5OH$ with 73% yield.

(Acetone); m.p.132$^0$C. IR spectra: 689 (-C-S-C), 1339(CN-), 1558(-C=C), 1609(CC Ar), 1634 (-C=N-), 3044 (-C-H), 3429(-N-H); $^1$HNMR ($CDCl_3$ + DMSO-$d_6$) δ in ppm: 7.35 (s,2H, $NH_2$), 7.51-8.52 (m,4H, ArH); $C_7H_6N_2S$: Calcd. C, 55.97; H, 4.03; N, 18.65; Found: C, 55.95; H, 4.06; N, 18.69%.

Synthesis of Ethylbenzo[d]thiazol-2-ylcarbamate (2)

Compound 1 (0.01mol), $C_2H_5OH$ (30ml), $K_2CO_3$ (2g) and $ClCOOC_2H_5$ (0.001mole), were added at 0-5 $^0$C and refluxed 8 hr about 70$^0$ C. The mixture was separated from the solvent and recrystalised by ethanol.

Yield 65%; (ethanol); m.p.148$^0$C. IR spectra: 688 (-C-S-C), 1337(-CN-), 1558 (C=C), 1620(-C-C Ar), 1632 (-C=N), 1680 (-C=O), 3041 (C-H ring), 3420 (N-H); $^1$HNMR spectra: 2.27 (s, 2H, $CH_3$), 3.39 (s, 3H, $CH_2$), 6.58 (s, 1H,N-H), 7.55-8.53 (m, 4H, ArH); $C_{10}H_{10}N_2O_2S$:

Calculated. C,54.04; H,4.53;N,12.60; Found:C,54.06; H,4.56; N,12.63%.

Synthesis of N(benzo[d]thiazol2-y)hydrazinecarboxamide (3)
Compound 2 (0.02mole) was added in hydrazine (4ml) and ethanol (30ml) then refluxed it about 5 h. The separated mixture was filtered, washed then recrystallized by alcohol.

Yield 61%; (methanol); m.p.154$^0$C. IR spectra: 683 (-C-S-C), 1289(-NN), 1346 (-CN), 1566 (-C=C), 1616 (C-C Ar), 1639(CN), 1688 (-CO), 3041 (-C-H ), 3426 (NH); $^1$HNMR spectra: 6.46 (s, 2 x 1H,NH), 7.10 (s, 2H, $NH_2$), 7.51-8.50 (m,4H,Ar); $C_8H_8N_4OS$: CalcdC,46.14; H,3.87; N, 26.90; Found:C,46.17; H,3.85; N, 26.92%.

N(benzo[d]thiazol-2yl)2-benzylidene hydrazine carboxamide (4)
Compound 3 (0.01mole) in methanol (50ml) reacted with substituted aromatic aldehyde (0.01mole) then refluxed approximate 9h. The product recrystallized by solvent to obtain product.

Yield 58%; (ethanol); m. p.160$^0$C. IR spectra: 686 (-C-S-C), 1287 (-N-N), 1347 (-CN), 1574 (-C=C), 1616(CC Ar), 1631 (-C=N), 1685(-CO), 3039 (CH), 3427 (NH); $^1$HNMR spectra: 6.55(s, 2x1H, NH),6.96 (d, 1H,CH-Ar), 7.50-8.52 (m, 9H, ArH); $C_{15}H_{12}N_4OS$; Calcd:C,60.79; H,4.08; N,18.91; Found: C,60.76; H,4.06; N,18.93%.

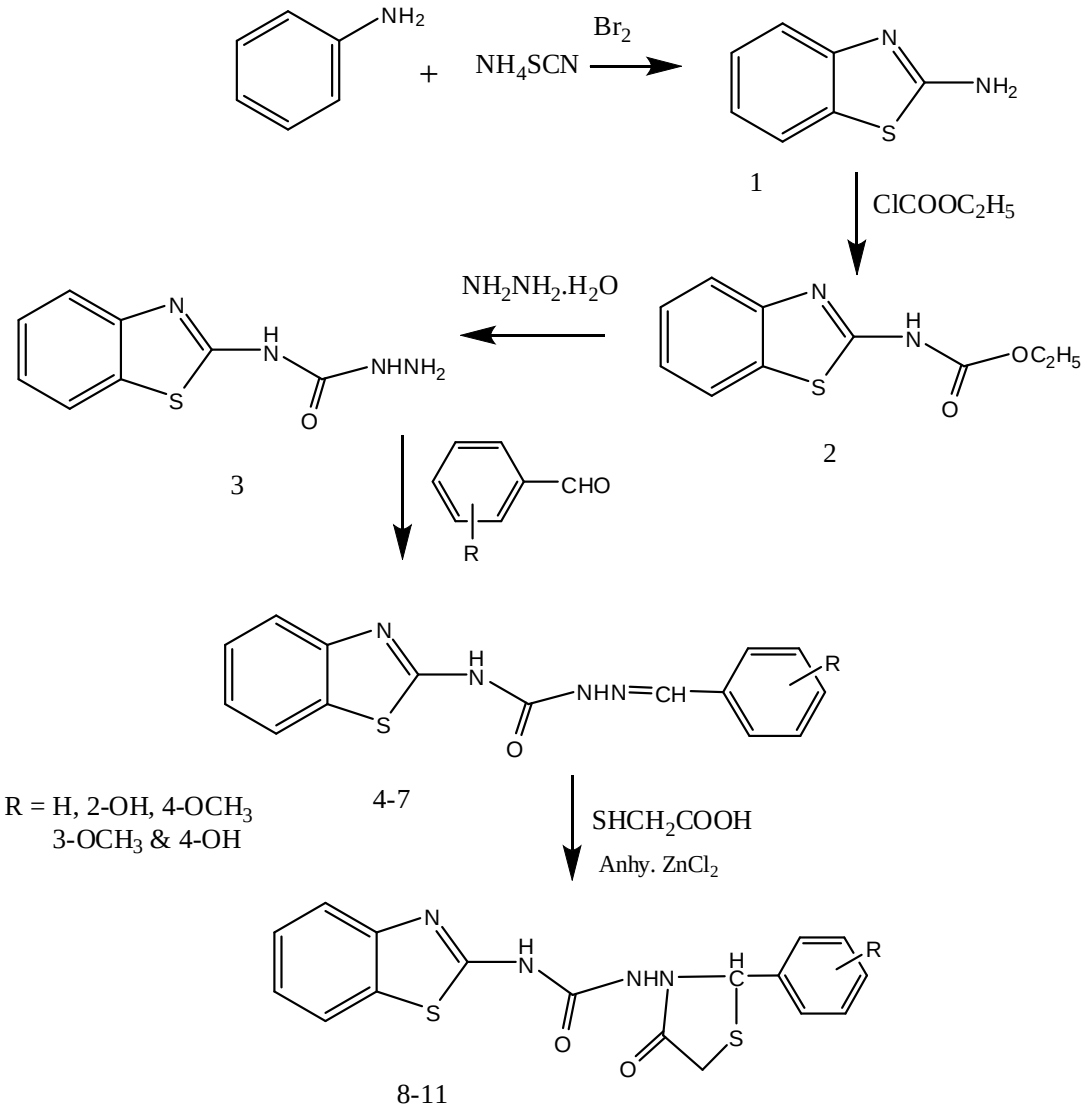
Compounds (5-7) were synthesized by using similar method of compound 4. Elemental and spectral analysis is described below.
N-(benzo[d]thiazol-2yl)2(2hydroxybenzylidene)hydrazinecarboxamide (5)
Yield 50%; (ethanol); m.p.158$^0$C. IR spectra: 679 (-C-S-C), 1280 (-NN), 1349 (-CN), 1560 (--C=C-), 1618 (CC Ar), 1635(-C=N), 1683 (-CO), 3048 (CH), 3425 (NH), 3465 (-OH); $^1$HNMR spectra: 6.49(s, 2x1H, NH),6.95(d,1H, CH-Ar), 7.54-8.53 (m, 8H, ArH), 12.24(s, 1H, -OH); $C_{15}H_{12}N_4O_2S$;Calcd:C,57.68;H,3.87;N,17.94;Found:C, 57.65 H,3.84, N,17.96%.

N-(benzo[d]thiazol-2yl)2-(4-methoxybenzylidene) hydrazine carboxamide (6)
Yield 46%; (methanol); m.p.165$^0$C. IR spectra: 689 (-C-S-C), 1284 (-NN), 1345 (-CN), 1557(-C=C),1610 (CC Ar), 1633 (-C=N),1679 (-CO), 3039 (CH), 3423 (NH); $^1$HNMR spectra: 4.58 (s, 3H, $OCH_3$), 6.59 (s, 2 x 1H,NH), 6.91 (d,1H,CH-Ar), 7.53-8.49 (m,8H,ArH); $C_{16}H_{14}N_4O_2S$,Calcd C,58.88;H,4.32;N,17.17;Found C,58.86; H,4.35; N,17.14%.

N(benzo[d]thiazol-2yl)-2-(4-hydroxy-3-methoxybenzylidene) hydrazine carboxamide (7)
Yield 41%; (acetone); m.p.169$^0$C. IR spectra: 684 (-C-S-C), 1279 (-NN), 1343 (-CN), 1560 (-C=C), 1610 (CC Ar), 1631 (-C=N), 1689 (-CO), 3040 (CH), 3421 (NH), 3460 (-OH); $^1$HNMR spectra: 4.59 (s, 3H, -$OCH_3$), 6.49 (s, 2x1H, N-H), 6.89 (d,1H,CHAr), 7.52-8.51 (m,7H,Ar-H), 12.65 (s, 1H, -OH); $C_{16}H_{14}N_4O_3S$:C,56.13;H,4.12;N,16.36; Found:C,56.16; H, 4.15; N,16.34%.

Synthesis of 1-(benzo[d]thiazol-2yl)3(4-oxo-2phenylthiazolidin-3yl)urea (8)
A methanol solution of compound 4 (0.01mole) with $SHCH_2COOH$ (0.02mole) was refluxed for 8-12 hr. Put the product in ice, filtered and then recrystallized to obtain drug 8.
Yield 38%; (methanol); m.p.190$^0$C. IR spectra: 683 (-C-S-C), 1281 (-NN), 1349 (-CN), 1561 (-C=C), 1616 (CC Ar), 1625(-C=N), 1681 (-C=O), 3047 (CH), 3419 (NH); $^1$HNMR spectra: 4.30(s,2H,$SCH_2$-CO), 6.52 (s, 2x1H,-NH),6.95 (d,1H,CH-Ar), 7.50-8.50 (m, 9H, ArH); $C_{17}H_{14}N_4O_2S_2$ Calcd.C, 55.12;H, 3.81; N, 15.12; Found:C, 55.16; H,3.85; N, 15.14%.

Compounds (9-11) were synthesized by using similar method of compound 8. Elemental and spectral analysis is described below.
1-(benzo[d]thiazol-2yl)-3(2-(2-hydroxyphenyl)4-oxothiazolidin-3yl)urea (9)
Yield 36%; (acetone); m.p.187$^0$C. IR spectral: 679 (-C-S-C), 1280 (-NN), 1344 (-CN),
1566 (-C=C),1619(CC Ar), 1640(C=N), 1680 (-CO),3051 (CH), 3422 (N
H), 3457 (OH); $^1$HNMR spectral: 4.27 (s, 2H, -S-$CH_2$-CO), 6.60 (s, 2x1H, NH),6.89 (d,1H,CHAr),7.51-8.50 (m,8H,ArH), 12.80 (s, 1H,-OH); $C_{17}H_{14}N_4O_3S_2$, Calcd C, 52.84;H,3.65; N,14.50; Found:C, 52.87; H,3.64; N,14.54%.
1(benzo[d]thiazol-2yl)-3(2(4-methoxyphenyl)-4oxothiazolidin-3-yl)urea (10)
Yield 32%; (methanol); m.p.199$^0$C. IR spectra: 678 (-C-S-C), 1284 (-NN),1351(-CN), 1563 (-C=C), 1610 (CC Ar), 1632 (-C=N), 1682 (CO), 3049 (CH), 3420 (NH); $^1$HNMR spectra : 4.25 (s, 2H, -S-$CH_2$-CO), 4.50 (s, 3H, $OCH_3$), 6.51(s, 2x1H,NH), 6.92 (d,1H, CHAr), 7.52-8.49(m, 8H, ArH), $C_{18}H_{16}N_4O_3S_2$:C,53.98;H,4.03;N,13.99;FoundC,53.96; H,4.06; N, 13.95%.
1-(benzo[d]thiazol-2yl)3(2-(4hydroxy-3-methoxyphenyl)-4oxothiazolidin-3yl)urea (11)




**Scheme - I**

Yield 33%; (ethanol); m.p. 203$^0$C. IR spectra: 689 (-C-S-C), 1282 (-NN), 1339 (-CN), 1569 (-C=C), 1613 (CC Ar), 1634 (-C=N),1679 (-CO), 3047 (CH), 3423 (NH), 3456 (OH); $^1$HNMR spectra: 4.27 (s, 2H, -S-$CH_2$-CO), 4.55 (s, 3H, $OCH_3$), 6.57 (s, 2x1H, NH),6.95 (d,1H,CHAr),7.52-8.52 (m,7H,ArH), 12.76 (s, 1H,OH); $C_{18}H_{16}N_4O_4S_2$ Calcd,C,51.91;H,3.87;N, 13.45;Found:C,51.93; H,3.89; N,13.42%.

**Pharmacological Studies**

New compounds were performed antifungal activity. Activity was determined by using disc diffusion method[20] against C.albicans, C. albicans ACCT and C. krusei G03. Inhibition of each strain was recorded in mm. Activity of these compounds was compared with standard drug like fluconazole.

The biological record has shown in table1. Compounds having thiazolidinone moiety with benzothiazoles exhibited better antifungal activity. Compound 11 was found more potent antifungal agents against c. albicans and c. krusei compared with standard drug fluconazole. Compounds 7, 8, 9, and 10 exhibited moderate and rest compounds have shown mild activity against different stains.

**Table 1 Activity of drugs 4-11.**

| Compds | R | fungal inhibition/mm | | |
|---|---|---|---|---|
| | | C. albican | C. albicans ATCC | C. krusei |
| 4 | H | 13 | 10 | - |
| 5 | 2-OH | 18 | 15 | 9 |
| 6 | 4-$OCH_3$ | 19 | 14 | 7 |
| 7 | 4-OH, 3-$OCH_3$ | 22 | 17 | 11 |
| 8 | H | 25 | 15 | 13 |

| | | | | |
|---|---|---|---|---|
| 9 | 2-OH | 28 | 20 | 16 |
| 10 | 4-$OCH_3$ | 27 | 22 | 18 |
| 11 | 4-OH, 3-$OCH_3$ | 31 | 24 | 20 |
| Fluconazole | | 29 | 25 | 19 |

## CONCLUSION

The derivatives of novel heterocyclic compounds (1-11) were synthesized. The structures of new drugs were cleared by spectral & analytical data. Antifungal activity was tested against various fungi such as c. albican, c. albican ATCC and c. krusei. From biological data it has been observed that compounds containing –OH and –$OCH_3$ group are more active than the remaining compounds.

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