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Synthesis and Antimicrobial Activity of Novel Benzisothiazolin-3-one Acetamide Derivatives

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A series of novel 2-(3-oxobenzo[d]isothiazol-2(3H)-yl)-N-substituted phenylacetamide (**4a-4e**) have been synthesized from benzo [d]isothiazol-3(2H)-one (**BIT**) and substituted aniline. These benzisothiazolin-3-one acetamide derivatives (**4a-4e**) were identified by IR, ^{1}H NMR and elemental analyses. Their antimicrobial activities were also evaluated.

Keywords: Synthesis, Antimicrobial activity, Benzisothiazolin-3-one, Acetamide.

INTRODUCTION

The chemistry of 1,2-benzisothiazolin-3-one and their fused heterocyclic derivatives has received considerable attention due to the synthetic and effective biological importance. These derivatives have shown various fungistatic, antimicrobial and antipsychotic biological activities[1,2]. 1,2-Benzisothiazolin-3-one and 2-methyl-4-isothiazolin-3-one are among the most important industrial biocides[3,4]. Synthesis of isoxazoline derivative remains a main focus of medicinal chemists[5-7].

Acetamide linkage is found to be active in many important drugs and there are varieties bioactive acetamide derivatives which have been developed in recent years. Acetamide are found to be potential agents for anthelmintic, antioxidant, anti-inflammatory, anti-arthritic, anticancer, antibacterial and antifungal activities[8-13].

The aim of this study is to design, synthesis a series of novel benzisothiazolin-3-one acetamide derivatives. The antimicrobial activity of these novel derivatives is also described. The results show that theses compounds exhibit a good spectrum of activity against heterotrophic bacteria.

EXPERIMENTAL

Reagents, solvents and starting materials were purchased from standard sources and purified using literature procedures. Reactions were monitored by silica-gel-coated thin-layer chromatography (TLC). Silica gel (200-300 mesh) was used for column chromatography.

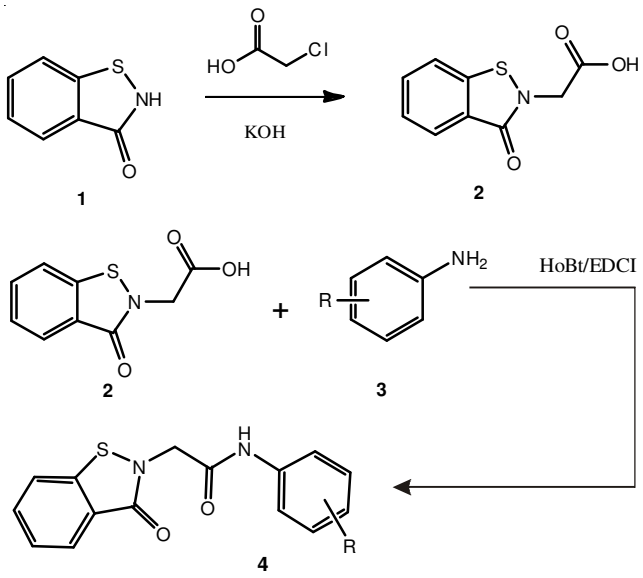
General procedure: To a mixture of KOH (11 mmol) and H_2O (30 mL) was added benzo[d]isothiazol-3(2H)-one (BIT, 10 mmol) at room temperature. The mixture was heated to 50 °C and stirred for 1 h. Chloroacetic acid (10 mmol) dissolved in H_2O (5 mL) was added dropwise within 20 min to the mixture. After completion of the dropwise, the mixture was heated to 90 °C and stirred for 4 h. The crude product was obtained by concentrated the solvent. After recrystallized to afford compound **2** as white solid, m.p.: 232-233 °C.

To a mixture of substituted aniline (0.005 mol), compound **2** (0.005 mol), 1-hydroxybenzotriazole (0.006 mol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide·HCl (0.006 mol) was added DMF (15 mL). Then the mixture was stirred for another 24 h at room temperature. After completion of the reaction, precipitate solids was obtained by adding water to the mixture. After filtration, washing, drying and column chromatography to obtain compound **4**.

Detection method: Melting points were recorded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm were reported with TMS as the internal standard. IR spectra in KBr were recorded by a Perkin-Elmer PE-683 infrared spectrometer. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. The bioactivity was evaluated by disk diffusion method.

RESULTS AND DISCUSSION

The title compound was synthesized according to Fig. 1. In this paper, the 2-(3-oxobenzo[d]isothiazol-2(3H)-yl)-N-



4a= 4-CH_3 **4b**=3-Cl **4c**= 4-F **4d**=2,4-dimethyl **4e**=2,6-dimethyl

Fig. 1. Synthetic route of compounds **4a-4e**

substituted phenylacetamide (**4a-4e**) were designed and prepared by the reaction of benzo[d]isothiazol-3(2H)-one (BIT) and substituted aniline. The results are reported in Table-1.

TABLE-1
REACTION OF 2-[3-OXOBENZO[D]ISOTHIAZOL-2 (3H)-YL]ACETIC ACID WITH SUBSTITUTED ANILINE

Product	R	Reaction time	Temp.	Yield (%)
4a	4-CH_3	24 h	rt	74.8
4b	3-Cl	24 h	rt	69.4
4c	4-F	24 h	rt	67.5
4d	2,4-Dimethyl	24 h	rt	73.3
4e	2,6-Dimethyl	24 h	rt	72.9

2-[3-Oxobenzo[d]isothiazol-2(3H)-yl]-N-(*p*-tolyl)acetamide (4a): m.p.: 159-160 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): 2.23 (S, 3H, CH_3), 5.11 (s, 2H, CH_2), 7.09-8.08 (m, 8H, Hring), 10.11 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3250, 3020, 1670, 1642, 1595, 1286, 1150, 648; Anal. Calcd. for $C_{16}H_{14}N_2O_2S$:C 64.41, H 4.73, N 9.39; found: C 64.21, H 4.89, N 9.03.

N-(3-Chlorophenyl)-2-[3-oxobenzo[d]isothiazol-2(3H)-yl]acetamide (4b): m.p.: 176-177 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): 5.14 (s, 2H, CH_2), 7.52-8.11 (m, 8H, Hring), 10.28 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3280, 3052, 1680, 1642, 1598, 1297, 1230, 1148, 648; Anal. Calcd. for $C_{15}H_{11}N_2O_2SCl$: C 56.52, H 3.48, N 8.79; found: C 56.98, H 3.54, N 8.47.

N-(4-Fluorophenyl)-2-[3-oxobenzo[d]isothiazol-2(3H)-yl]acetamide (4c): m.p.: 144-145 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): 5.13 (s, 2H, CH_2), 7.13-8.11 (m, 8H, CH), 10.27 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3277, 3055, 1679, 1640, 1608, 1296, 1221, 1148, 646; Anal. Calcd. for $C_{15}H_{11}N_2O_2SF$: C 59.59, H 3.67, N 9.27; found: C 59.90, H 3.79, N 9.03.

N-(2,4-Dimethylphenyl)-2-[3-oxobenzo[d]isothiazol-2(3H)-yl]acetamide (4d): m.p.: 179-181 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): 3.31 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 6.96-8.10 (m, 7H, H ring), 9.54 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3245, 3021, 1672, 1614, 1593, 1275, 1151, 648; Anal. calcd. for $C_{17}H_{16}N_2O_2S$: C 65.36; H 5.16; N 8.97; found: C 65.50, H 5.23, N 9.03.

N-(2,6-Dimethylphenyl)-2-[3-oxobenzo[d]isothiazol-2(3H)-yl]acetamide (4e): m.p.: 207-209 °C; (DMSO-d_6, 300 MHz): 2.14 (s, 6H, CH_3), 5.15 (s, 2H, CH_2), 7.06-8.12 (m, 7H, Ar-H), 9.57 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3255, 3039, 1671, 1614, 1594, 1277, 1153, 647; Anal. calcd. for $C_{17}H_{16}N_2O_2S$: C 65.36, H 5.16, N 8.97; found: C 65.12, H 5.44, N 8.79.

The antimicrobial activity was evaluated using the disk diffusion method[14]. The values of antimicrobial activities were listed in Table-2. The organisms used in the present investigation was *heterotrophic bacteria*. The results show that the title compounds have good antimicrobial activities against the tested organisms. When the solution concentration was below 100 ppm, the antimicrobial activities drop gradually, but still batter than the contrast test sample.

TABLE-2
ANTIMICROBIAL ACTIVITIES OF THE TITLE COMPOUNDS (%)

Product	Heterotrophic bacteria		
	400 ppm (%)	100 ppm (%)	50 ppm (%)
4a	98.9	89.3	70.2
4b	100.0	97.7	85.7
4c	100.0	99.1	91.3
4d	97.7	90.0	84.0
4e	96.2	81.6	50.0
BIT	100.0	80.1	42.8

Conclusion

A new series of 2-[3-oxobenzo[d]isothiazol-2(3H)-yl]-N-substituted phenylacetamide (**4a-4e**) were designed and synthesized from benzo[d]isothiazol-3(2H)-one (**BIT**) and substituted aniline. The antimicrobial activities of these compounds **4a-4e** were evaluated. The preliminary bioassay show the title compound exhibited a favorable antimicrobial activity against heterotrophic bacteria.

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