Synthesis of Benzofuran Derivatives and their Evaluation of Antimicrobial Activity

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Abstract: 2-Acetyl benzofuran (**1**) was synthesized by refluxing salicylaldehyde and dry chloroacetone in presence of potassium carbonate. The product formed was reacted with 2-aminobenzothiazole with catalyst *p*-toluene sulphonic acid to form *N*-[(1*Z*)-1-(benzofuran-2-yl)ethylidene]1,3-benzothiazol-2-amine (**2**). In cold condition, Staudinger reaction was carried out for compound (**2**) with various acid chlorides in presence of triethylamine to synthesize 4-[1-benzofuran-2-yl]-1-[1, 3-benzothiazol-2-yl]-4-methylazetidin-2-one (**3a-3j**). All the synthesized compounds were characterized on the basis of analytical data. The compounds were screened for their antimicrobial activities. Compound **3b**, **3c** and **3d** exhibited moderate activity.

Keywords: Benzofuran, Benzothiazol, Azetidinone, Antimicrobial activity.

Introduction

Benzofuran derivatives possess a wide range of biological activities. They have been reported to possess antimicrobial¹⁻⁴, antitumour^{5, 6}, anti-inflammatory⁷ activity *etc.* Benzothiazoles play a significant role as antibacterial⁸⁻¹⁰ and antifungal activity. Azetidinones with heterocyclic molecule has created an excellent drug for antimicrobial¹¹⁻¹³ activity. Based on these findings and in continuation of our research work, we report herein synthesis of a tri-heterocyclic molecule containing benzofuran, benzothiazole and azetidinone for enhanced activity.

Experimental

Melting points were determined in open capillary tube and are uncorrected. The TLC was taken in silica gel G pre-coated TLC plates. The solvents and reagents used for synthesis were of laboratory grade. The IR was recorded with Perkin Elmer FTIR spectrophotometer using KBr press pellet technique. The NMR was recorded in Bruker 400 MHz FTNMR spectrometer using DMSO as solvent and TMS as internal standard.

Synthesis of 2-acetyl benzofuran (1)

The mixture of salicylaldehyde (0.1 mole), chloroacetone (0.1 mole) and anhydrous potassium carbonate (30 g) were gently refluxed in dry acetone (150 mL) for 13 h. The reaction product after cooling was filtered and the filtrate on the removal of the solvent under reduced pressure furnished 2-acetyl benzofuran as dark yellow colored solid. The product obtained was recrystallized from petroleum ether. Yield 55% IR cm^{-1} : 1674 (C=O), 3088 (CH phenyl), 2900 (CH_3) ^1H NMR δ ppm CHCl_3 (400MHz): 7.46 to 7.73 aromatic protons, 2.2 (3H,s, CH_3).

Synthesis of 2- aminobenzothiazole

To a solution of aniline (0.2 mole) and potassium thiocyanate (0.8 mole) in 360 mL of 96% acetic acid was added drop wise, with stirring, 0.2 mole of bromine dissolved in 250 mL of glacial acetic acid while the temperature was kept below 35 °C. After all the bromine solution had been added the mixture was stirred for 10 h and was then filtered and the residue washed with water. The combined filtrate and washings were neutralized with ammonium hydroxide. The precipitate was collected on a filter and dried. Yield 70% IR cm^{-1} : 3056 (CH aromatic), 3397 (NH) ^1H NMR δ ppm (400MHz): 7.14 to 7.6 aromatic protons, 5.55(1H, s, NH).

Synthesis of N-[(1Z)-1-(benzofuran-2-yl)ethylidene]1,3-benzothiazol-2-amine (2)

A mixture of 2- acetyl benzofuran and 2-aminobenzothiazole and a small pinch of *p*-toluene sulphonic acid were gently refluxed in ethanol (30 mL) for 6 h. After the completion of the reaction the mixture was poured into crushed ice, filtered and then dried and recrystallised from ethanol. Yield 60% IR cm^{-1} : 2929(CH_3), 3058(CH aromatic), 3119(CH aromatic), 1643(C=N) ^1H NMR δ ppm CHCl_3 (400MHz) aromatic protons 7.28 to 7.68, 2.1 (3H, s, CH_3).

Synthesis of 4-[1-(benzofuran-2-yl)-1-[1,3-benzothiazol-2-yl]-3-azetidin-2-one (3a-3j)

N-[(1Z)-1-(benzofuran-2-yl)ethylidene]1,3-benzothiazol-2-amine(**2**) (0.01 mole) was added to triethylamine (0.02 mol) in dioxane (30 mL) at 0 to 5 °C. To this mixture various acid chloride (0.012 mol) was added drop wise. This mixture was stirred for 5 h at 0 to 5 °C. The precipitate formed was filtered off and the filtrate was refluxed for 6 h. The reaction mixture was left for 24 h at room temperature and it was poured into crushed ice. The product (**3a-3j**) was precipitated, which was filtered, dried and recrystallised from ethanol.

Table 1. Physical data of synthesized compounds (**3a-3j**).

Compound	Molecular formula & (Molecular weight)	R (Acid chlorides)	Yield, %	M.P, °C
3a	$\text{C}_{18}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}$ (55)	ClCH_2-	55	220
3b	$\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (320)	CH_3-	58	235
3c	$\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ (334)	CH_3CH_2-	63	240
3d	$\text{C}_{19}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}$ (413)	BrCH_2-	53	210
3e	$\text{C}_{18}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ (389)	$\text{Cl}_2\text{CH}-$	54	215
3f	$\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (362)	Pentanoyl chloride	50	225
3g	$\text{C}_{20}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$ (445)	Oxalylacetyl chloride	40	240
3h	$\text{C}_{20}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$ (396)	Succinyl chloride	42	245
3i	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ (48)	<i>n</i> -Butyryl chloride	44	243
3j	$\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ (350)	Methoxy acetyl chloride	47	230

All compounds gave satisfactory CH and N analysis.

Spectral values**4-(1-Benzofuran-2-yl)-1-(1,3-benzothiazol-2-yl)-3-chloro-4-methylazetidin-2-one (3a)**

IR cm^{-1} : 2926 (CH_3), 3057 (CH Ar), 3119 (CH Ar), 743 (CCl), 1673 (CO cyclic amide) ^1H NMR δ ppm CHCl_3 : 2.61 (3H,s, CH_3), 4.56 (1H,s,Azetidinone), 7.16 (1H,s,CH), 7.31to7.71 (8H,m,Ar).

4-(1-Benzofuran-2-yl)-1-(1,3-benzothiazol-2-yl)-4-methylazetidin-2-one (3b)

IR cm^{-1} : 2772 (CH_2), 2958 (CH_3), 3057 (CH Ar), 3072 (CH Ar), 1695 (CO cyclic amide) ^1H NMR δ ppm CHCl_3 : 2.28 (3H,s, CH_3), 2.61(2H,s, CH_2), 7.26 (1H,s,CH), 7.33to7.86 (8H,m,Ar).

4-(1-Benzofuran-2-yl)-1-(1,3-benzothiazol-2-yl)-3,4-dimethylazetidin-2-one (3c)

IR cm^{-1} : 2938 (CH_3), 2975 (CH Ar), 3043 (CH Ar), 1682 (CO cyclic amide) 2734 (CH, Azetidinone), ^1H NMR δ ppm CHCl_3 : 1.24 (3H,d, CH_3), 2.61(3H,s, CH_3), 7.26 (1H,s,CH), 7.31to7.71 (8H,m,Ar), 2.52 (1H,q,CH Azetidinone), ESI MS (m/z) = $M + H = 349$, $M^+ = 348$, fragmented ion at 215 and 216.

4-(1-Benzofuran-2-yl)-1-(1,3-benzothiazol-2-yl)-3-bromo-4-methylazetidin-2-one (3d)

IR cm^{-1} : 2850 (CH), 2908 (CH_3), 2957 (CH Ar), 3055 (CH Ar), 754 (CBr), 1637 (CO cyclic amide) ^1H NMR δ ppm CHCl_3 : 1.41 (3H,s, CH_3), 4.48(1H,s,CH), 7.13 (1H,s,CH), 7.15to7.69 (8H,m,Ar) ESI MS (m/z) = $M + H = 414$, $M^+ = 413$, fragmented ion at 285.

4-(1-Benzofuran-2-yl)-1-(1,3-benzothiazol-2-yl)-3,3-dichloro-4-methylazetidin-2-one(3e)

IR cm^{-1} : 2850 (CH_3), 2918 (CH Ar), 3059 (CH Ar), 754 (CCl), 1696 (CO cyclic amide) ^1H NMR δ ppm CHCl_3 : 1.18 (3H,s, CH_3), 7.19 (1H,s,CH), 7.23to7.78 (8H,m,Ar).

Antimicrobial activity

The minimum inhibitory concentration was determined by the method of serial dilutions and found to be 100 $\mu\text{g/mL}$ for bacteria and 200 $\mu\text{g/mL}$ for fungi. The newly synthesized compounds were screened for antibacterial activity using cup plate diffusion method; *B. subtilis* and *E. coli* were taken as test organisms. Among the tested compounds **3b**, **3c** and **3d** were moderately active against standard Ampicillin while the remaining compounds were weakly active. The fungicidal activity of the compounds was evaluated against *C. albicans* using griseofulvin as standard, compounds **3b**, **3c** and **3d** exhibited moderate activity.

Table 2. Antimicrobial activity of benzofuran derivatives (**3a-3j**)

Compound code	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Candida albicans</i>
Zone of inhibition, diameter in mm			
3a	9	7	5
3b	15	14	9
3c	17	16	12
3d	16	15	11
3e	11	8	2
Ampicillin	20	20	
Control	.04	.03	
Griseofulvin	-	-	17
Control	-	-	.04

Results and Discussion

The scheme of synthesis of titled compounds is depicted in the (Scheme 1). All the intermediate and targeted molecules were confirmed by TLC, IR, NMR and mass data. 2-acetyl benzofuran was synthesized by reacting salicylaldehyde and chloroacetone in presence of anhydrous potassium carbonate as reported. 2-Aminobenzothiazole was prepared by stirring aniline and potassium thiocyanate in presence of bromine and acetic acid in cold condition. *N*-[(1*Z*)-1-(benzofuran-2-yl)ethylidene]1,3-benzothiazol-2-amine (**2**) was obtained by refluxing 2-acetyl benzofuran and 2-aminobenzothiazole in presence of *p*-toluene sulphonic acid. The IR spectra of compound (**2**) showed presence of C=N stretching vibrations at 1643 cm^{-1} and disappearance of NH absorption bands. The targeted molecule 4-[1-benzofuran-2-yl]-1-[1,3-benzothiazol-2-yl]-3-bromo-4-methylazetidin-2-one (**3d**) was synthesized by mixing compound (**2**) with triethylamine in dioxane and bromoacetyl chloride in cold condition. The IR spectra revealed the peak at 1637 cm^{-1} showing the presence of C=O stretching vibration of cyclic amide. The C-H stretching frequency was at 2850 cm^{-1} and C-Br stretching frequency at 754 cm^{-1} indicated their presence in azetidinone ring.

From ^1H NMR spectra δ value 1.41 was assigned to methyl protons, a singlet at δ value 4.48 was integrated to methine of azetidinone and the multiplet δ value at 7.15 to 7.69 was due to aromatic protons. The structure of compound (**3d**) was further supported by its ESI MS Spectra indicating molecular ion peak was at 413 m/z and fragmented ion peak at 285 m/z .

Scheme 1

Conclusion

Various tri-heterocyclic compounds **3a** to **3j** of benzofuran derivatives were synthesized containing benzofuran, benzothiazol and azetidinone rings. The compounds were characterized by IR, NMR and ESI MS spectral data. They were evaluated for antimicrobial activity, compounds **3b**, **3c** and **3d** exhibited moderate activity when compared to standard Ampicillin and Griseofulvin.

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