Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (3): 1239-1245

(International Peer Reviewed Journal)

Synthesis and Antimicrobial Study of Some Substituted 2-Amino Benzothiazole Derivatives

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Accepted on 17th May 2014

ABSTRACT

The amide derivatives were synthesized by facile synthetic procedure, in which substituted 2-aminobenzothiazoles reacts with acid chlorides of substituted phenoxyacetic acid in basic condition. All the derivatives were screened for their antimicrobial activity against Azotobacter sp., Pseudomonas aeruginosa, Aspergillus niger, Fusarium moniliforme, Phanerochaete chrysosporium. Chloramphenicol and Amphotericin B were used as standard drugs for evaluation of antibacterial and antifungal activity respectively. Some derivatives have exhibited good antifungal activity.

Keywords: 2-aminobenzothiazole, amide, antibacterial, antifungal.

INTRODUCTION

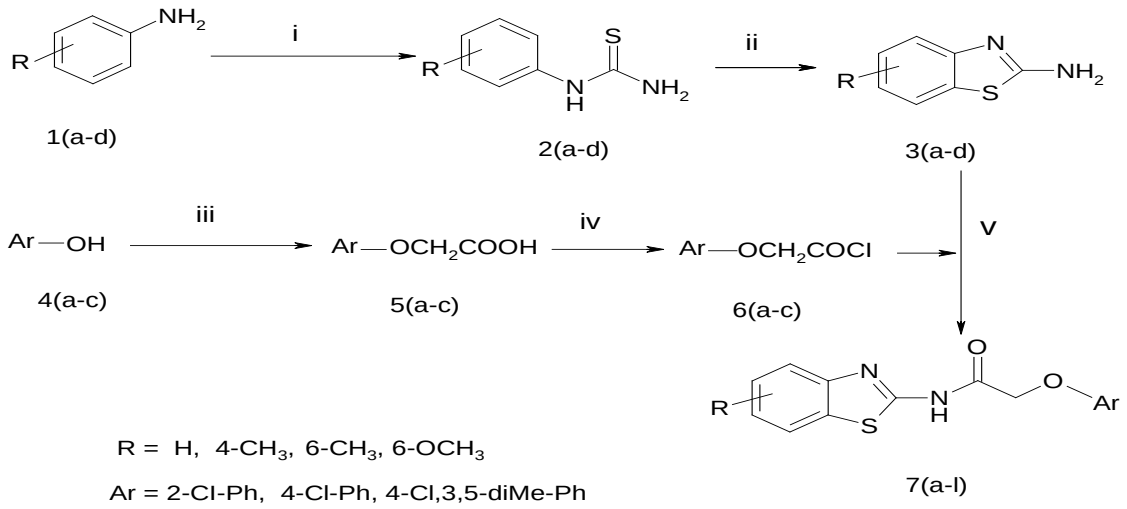
Nitrogen and sulfur containing rings are involved in several biologically active compounds. Benzothiazole and its derivatives represent a large group of heterocyclic compounds, some of which have already found application in medicine and agriculture. 2-Aminobenzothiazole plays a fundamental role in the field of pharmaceutical chemistry by regulating different pharmacological activities. Literature survey reveals that benzothiazole ring is present naturally in various marine organisms [1], which have various useful biological activities. The benzothiazole derivatives have been shown to possess antibacterial [2-4], antifungal [5-8], anti-inflammatory [9,10], anticonvulsant [11,12], antitumor [13,14], anti-HIV [15], antiproliferative [16], acaricidal [17], plant growth regulator [18-20] and herbicidal [21,22] activities.

In the previous work, the synthesis and plant growth regulator activity of same 2-amino benzothiazole derivatives were reported. In continuation of this study we have screened these compounds for their possible antimicrobial activities because, benzothiazole derivatives have been shown to exhibit diverse biological activities. In the present work, we report here the synthesis and antimicrobial activity of 2-amino benzothiazole derivatives.

MATERIALS AND METHODS

All the chemicals and solvents used in studies were of GR grade and were dried and purified before use. The synthesized compounds were purified by recrystallisation with appropriate solvents and purity was checked by TLC. Melting points were determined by open capillary method and are uncorrected. IR

spectra were recorded using Nujol with FT-IR Perkin-Elmer model Spectrum One Spectrophotometer, ^{1}H NMR & ^{13}C NMR spectra were recorded using $CDCl_3$ & DMSO respectively with Varian-300 NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on WATERS, Q-TOF MICROMASS (LC/MS) spectrometer. For antimicrobial activity, Nutrient agar (Hi- media) was used as microbiological media for bacteria, Composition (gL^{-1}): Sodium chloride 5.0; Beef extract 10.0; Peptone 10.0 (pH 7.2) and Potato dextrose agar (Hi- media) was the microbiological media for fungi, Composition (gL^{-1}): Potatoes infusion 200.0; Dextrose 20.0 (pH 5.2). The species used for the activity are *Azotobacter sp* (Gram-negative bacteria), *Pseudomonas aeruginosa* NCIM 2036 (Gram-negative bacteria) and *Aspergillus niger* NCIM 545 (Fungi), *Fusarium moniliforme* NCIM 1099 (Fungi) and *Phanerochaete chrysosporium* NCIM 1197 (Fungi). General procedure is depicted in scheme 1.



Scheme 1
Reagents and conditions: (i) H_2O, HCl, KSCN, Heat; (ii) Br_2, CCl_4, 15-20°C;
(iii) Chloroacetic acid, NaOH, Boil; (iv) $SOCl_2$, $CHCl_3$, Reflux; (v) Et_3N, $CHCl_3$, < 10°C.

.

General Procedures: Synthesis of phenyl thiourea 2(a-d), **2-aminobenzothiazole 3(a-d)**, **phenoxyacetic acid 5(a-c)** and **phenoxyacetyl chloride 6(a-c).** All the compounds were synthesized by the reported procedure [18].

Synthesis of amide 7(a-l) : A mixture of 2-aminobenzothiazole (0.01 mol) and triethylamine (0.02 mol) in chloroform (20 mL) was stirred for 5 minutes. To it phenoxyacetyl chloride (0.01 mol) in chloroform was added drop wise. During addition the reaction temperature was maintained below 10°C and the mixture was stirred for 4 h. The mixture was concentrated and small quantity of ethanol was added. The solid separated was washed with cold ethanol to get pure product.

2-(2-Chlorophenoxy)-N-(benzothiazol-2-yl) acetamide (7a) : Brown yellow solid, yield 70%, m.p. 178-180°C, IR cm^{-1} ; 3362(N-H), 1746(C=O), 1597(C=N), 1456(C=C), ^{1}H NMR; ($CDCl_3$) δ: 4.91 (s, 2H, O CH_2-), 7.03-7.08 (t, 1H, Ar-H), 7.26-7.29 (d, 4H, Ar-H), 7.43-7.48 (t, 1H, Ar-H), 7.54-7.60 (t, 1H, Ar-H), 7.86-7.92 (t, 1H, Ar-H), >11 (s, 1H, NH), MS (ESI) *m/z*: 319

2-(2-Chlorophenoxy)-N-(4-methylbenzothiazol-2-yl) acetamide (7b): Yellow solid, yield 72%, m.p. 182-184°C, IR cm^{-1}; 3428(N-H), 1649(C=O), 1589(C=N), 1460(C=C), ^{1}H NMR; ($CDCl_3$) δ: 2.71(s, 3H, -CH_3), 4.80 (s, 2H, OCH_2-), 7.01-7.66 (m, 7H, Ar-H), >11 (s, 1H, NH), MS (ESI) *m/z*: 333

2-(2-Chlorophenoxy)-N-(6-methylbenzothiazol-2-yl) acetamide (7c): Brown solid, yield 68%, m.p. 196-198°C, IR cm^{-1}; 3379(N-H), 1716(C=O), 1683(C=N), 1462(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.50 (s, 3H, -CH_3), 4.86 (s, 2H, OCH_2-), 7.01-7.07 (m, 2H, Ar-H), 7.24-7.34 (m, 2H, Ar-H), 7.43-7.46 (d, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.74-7.76 (d, 1H, Ar-H), >11 (s, 1H, NH), ^{13}C NMR; (DMSO-d_6) δ: 20.9, 66.6, 113.8, 120.2, 121.3, 122.2, 122.9, 127.6, 128.3, 130.2, 131.5, 133.3, 146.3, 153.2, 156.4, 167.2, MS (ESI) *m*/*z*: 333

2-(2-Chlorophenoxy)-N-(6-methoxybenzothiazol-2-yl) acetamide (7d): Brown solid, yield 69%, m.p. 190-192°C, IR cm^{-1}; 3362(N-H), 1732(C=O), 1673(C=N), 1482(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 3.88 (s, 3H, -OCH_3), 4.88 (s, 2H, OCH_2-), 7.01-7.99 (m, 7H, Ar-H), >11 (s, 1H, NH), MS (ESI) *m*/*z*: 349

2-(4-Chlorophenoxy)-N-(benzothiazol-2-yl) acetamide (7e) : Brown solid, yield 77%, m.p. 219-220°C, IR cm^{-1}; 3446(N-H), 1704(C=O), 1666(C=N), 1463(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 4.76 (s, 2H, OCH_2-), 6.97-7.00 (d, 2H, Ar-H), 7.29-7.34 (d, 2H, Ar-H), 7.39-7.44 (t, 1H, Ar-H), 7.50-7.55 (t, 1H, Ar-H), 7.83-7.88 (m, 2H, Ar-H), >11 (s, 1H, NH), MS (ESI) *m*/*z*: 319, ^{13}C NMR; (DMSO-d_6) δ: 67, 115.9, 120.9, 121.5, 124.6, 126.6, 127.8, 129.9, 131.8, 147.4, 155.2, 156.9, 166.4, MS (ESI) *m*/*z*: 319

2-(4-Chlorophenoxy)-N-(4-methylbenzothiazol-2-yl) acetamide (7f) : Brown yellow solid, yield 70%, m.p. 215-217°C, IR cm^{-1}; 3379(N-H), 1721(C=O), 1571(C=N), 1463(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.78 (s, 3H, -CH_3), 4.84 (s, 2H, OCH_2-), 7.04-7.74 (m, 7H, Ar-H), 13.40 (s, 1H, NH), MS (ESI) *m*/*z*: 333

2-(4-Chlorophenoxy)-N-(6-methylbenzothiazol-2-yl) acetamide (7g) : Brown yellow solid, yield 82%, m.p. 188-190°C, IR cm^{-1}; 3374(N-H), 1688(C=O), 1605(C=N), 1464(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.49 (s, 3H, -CH_3), 4.72 (s, 2H, OCH_2-), 6.92-7.69 (m, 7H, Ar-H), >11(s, 1H, NH), MS (ESI) *m*/*z*: 333

2-(4-Chlorophenoxy)-N-(6-methoxybenzothiazol-2-yl) acetamide (7h) : Light yellow solid, yield 61%, m.p. 198-200°C, IR cm^{-1}; 3376(N-H), 1686(C=O), 1654(C=N), 1466(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 3.88 (s, 3H, -OCH_3), 4.72 (s, 2H, OCH_2-), 6.91-6.93 (d, 2H, Ar-H), 7.05-7.09 (d, 1H, Ar-H), 7.31 (s, 1H, Ar-H), 7.32-7.34 (d, 2H, Ar-H), 7.69-7.72 (d, 1H, Ar-H), 9.72 (s, 1H, NH), MS (ESI) *m*/*z*: 349

2-(4-Chloro-3, 5-dimethylphenoxy)-N-(benzothiazol-2-yl) acetamide (7i): Light yellow solid, yield 82%, m.p. 196-198°C, IR cm^{-1}; 3396(N-H), 1697(C=O), 1642(C=N), 1455(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.36 (s, 6H, 2-CH_3), 4.72 (s, 2H, OCH_2-), 6.68 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 7.26-7.86 (m, 4H, Ar-H), 11.92 (s, 1H, NH)
MS (ESI) *m*/*z*: 347

2-(4-Chloro-3, 5-dimethylphenoxy)-N-(4-methylbenzothiazol-2-yl) acetamide (7j): Yellow solid, yield 74%, m.p. 230-232°C, IR cm^{-1}; 3398(N-H), 1703(C=O), 1589(C=N), 1464(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.37 (s, 6H, 2-CH_3), 2.65 (s, 3H, -CH_3), 4.70 (s, 2H, OCH_2-), 6.74 (s, 2H, Ar-H), 7.21-7.30 (m, 2H, Ar-H), 7.66-7.68 (m, 1H, Ar-H), 9.83 (s, 1H, NH), ^{13}C NMR; (DMSO-d_6) δ: 17.8, 20.4, 66, 114.3, 118.3, 123.3, 126.2, 129.8, 131, 136.4, 147.2, 156.2, 167, MS (ESI) *m*/*z*: 361

2-(4-Chloro-3, 5-dimethylphenoxy)-N-(6-methylbenzothiazol-2-yl) acetamide (7k): Brown yellow solid, yield 76%, m.p. 202-204°C, IR cm^{-1}; 3397(N-H), 1714(C=O), 1590(C=N), 1465(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.36 (s, 6H, 2-CH_3), 2.49 (s, 3H, -CH_3), 4.71 (s, 2H, OCH_2-), 6.77 (s, 2H, Ar-H), 7.26 (s, 1H, Ar-H), 7.64-7.69 (m, 2H, Ar-H), >11 (s, 1H, NH), MS (ESI) *m*/*z*: 361

2-(4-Chloro-3, 5-dimethylphenoxy)-N-(6-methoxybenzothiazol-2-yl) acetamide (7l) : Brown solid, yield 63%, m.p. 154-156°C, IR cm^{-1}; 3394(N-H), 1710(C=O), 1605(C=N), 1472(C=C), ^{1}H NMR; ($CDCl_3$) *δ*: 2.36 (s, 6H, 2-CH_3), 3.88 (s, 3H, -OCH_3), 4.69 (s, 2H, OCH_2-), 6.70 (s, 2H, Ar-H), 7.04-7.07 (d, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.67-7.70 (d, 1H, Ar-H), 9.74 (s, 1H, NH), MS (ESI) *m*/*z*: 377

RESULTS AND DISCUSSION

Spectrum: In general, the IR spectra of the synthesized acetamide derivatives show the N–H absorption bands at 3362-3446 cm^{-1}. The absorption bands of the C=O group were observed in the range 1649-1746 cm^{-1}. The IR absorptions for the C=N group were observed at 1571-1683 cm^{-1} and that for C=C group in range 1455- 1482 cm^{-1}. As evident from the spectrum of the individual derivative, these bands are dependent on the substituent.

In the ^{1}H NMR spectra the signals of protons of the OCH_2-CO group appeared as singlets in the region of 4.69-4.91 ppm. The signals of aromatic protons appeared as multiplets in the range 7.01-7.86 ppm. The NH protons were observed at 9.71-13.40 ppm as singlets and were D_2O- exchangeable. In case of compounds **7b**, **7f** and **7j** the -CH_3 (4-position of benzothiazole ring) protons signals were observed at 2.71, 2.78 and 2.65 ppm respectively. While, in compounds **7c**, **7g** and **7k** the -CH_3 (6-position of benzothiazole ring) protons signals were observed at 2.50, 2.49 and 2.49 ppm respectively. In case of compound **7d**, **7h** and **7l** the -OCH_3 protons signals appeared at the same position 3.88 ppm. For compounds **7i**, **7k** and **7l** the signals of 2-CH_3 protons of phenoxy group were observed at 2.36 ppm, while, that for **7j** at 2.37 ppm. The effects of the synthesized amide derivatives **7a-l** were tested on the microbes.
From MIC values for the antimicrobial studies, it is observable that all the compounds showed inhibition of *Azotobacter sp. & Pseudomonas aeruginosa* at the tested concentration 1024 μg mL^{-1}. The compounds **7c**, **7d**, **7f**, **7j** & **7k** showed inhibition of *A. niger* at 32 μg mL^{-1}. The compounds **7j** & **7k** showed inhibition of *F. moniliforme* at 32 μg mL^{-1}. All the compounds do not showed inhibition of *P. chrysosporium* at 32 μg mL^{-1}.

APPLICATIONS

Antimicrobial activity: All the compounds were tested for their *in-vitro* antimicrobial activity against *Azotobacter sp*, *P. aeruginosa* (bacteria) (Table 1) *and A. niger*, *F. moniliforme*, *P. chrysosporium* (fungi)(Table 2 and Fig.1). Double dilution method/tube-dilution method was used to find minimum inhibitory concentration (MIC, μg mL^{-1}) [23]. Nutrient broth and potato dextrose broth were used to culture bacteria and fungi respectively. Stock solution (1024 μg mL^{-1}) of each compound was prepared in DMSO. Sterile test tubes containing 5 mL of the appropriate broth were supplemented with varying concentrations of the compounds (0.125-1024 μg mL^{-1}), and were inoculated with 2% (v/v) inoculums containing 10^5 cells and incubated at 37°C for 24 h for the bacteria and 7 days for the fungi. After incubation, the growth of bacteria and fungi was visually observed and monitored by measuring absorbance at 540 nm. The Chloramphenicol and Amphotericin B (standard drugs) were used as positive controls for evaluation of antibacterial and antifungal activity respectively. DMSO was used as negative control.

Table 1: Antibacterial activity

Compounds	Minimum Inhibitory Concentration (μg/mL)	
	Azotobacter sp	***P. aeruginosa***
7a	1024	1024
7b	1024	1024
7c	1024	1024
7d	1024	1024
7e	1024	1024
7f	1024	1024
7g	1024	1024
7h	1024	1024
7i	1024	1024
7j	1024	1024
7k	1024	1024
7l	1024	1024
Chloramphenicol	0.2	8
Control	--	--

Table 2: Antifungal activity

Compounds	Minimum Inhibitory Concentration (µg/mL)		
	A. niger	*F. moniliforme*	*P. chrysosporium*
7a	64	128	256
7b	128	64	512
7c	32	128	256
7d	32	128	256
7e	128	128	128
7f	32	256	128
7g	64	128	256
7h	64	128	128
7i	64	128	128
7j	32	32	128
7k	32	32	64
7l	128	64	128
Amphotericin B	1	4	1
Control	--	--	--

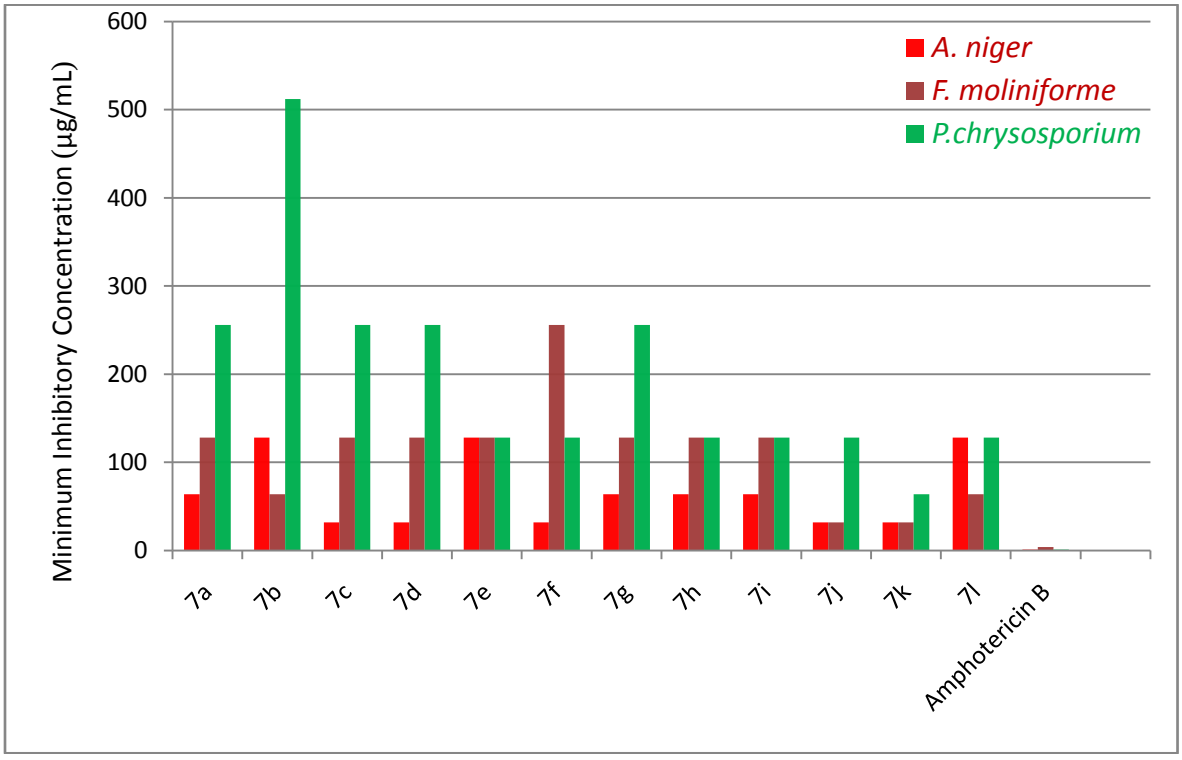


Figure 1: Antifungal activity

CONCLUSIONS

From the results, we conclude that the amide derivatives of benzothiazole are having moderate to good fungicidal activity against tested microbes as compared to the standard, however, they were not much effective as bactericidal agents. Among the series, **7(h-l)** were found to be more effective. 4-Cl,3,5-dimethyl-phenoxy ring was found to be somewhat more effective for antimicrobial activities. However, from the results no adequate structure activity relationship could be derived, this might be due to presence of two rings with different substituents.

ACKNOWLEDGEMENTS

DPM thanks to the Department of Science and Technology, New Delhi, for "INSPIRE Fellowship".

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