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Synthesis, Characterization and Evaluation of Antibacterial Activity of Several New pyromillitimides Containing Benzothiazole Moiety

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ABSTRACT

Starting from substituted-2-aminobenzothiazole a series of new pyromillitimides linked to benzothiazole moiety were synthesized by direct reaction of equimolar amounts of substituted-2-aminobenzothiazoles with pyromillitic anhydride in glacial acetic acid under reflux conditions for eight hours ^{1}HNMR and ^{13}C NMR spectral data which were in agreement with the proposed ones. Finally antibacterial activity of some of the prepared new cyclic imides were evaluated against two types of bacteria and the results showed that the most of the tested imides possess good biological activity against these organisms.

Keywords: Pyromillitimides, Benzothiazole, Cyclic imides.

INTRODUCTION

Cyclic imides have been attracted much more attention of organic and medicinal chemists due to their numerous applications in biological, synthetic, and polymer chemistry [1-4]. Thus a diversity of biological activities and pharmaceutical uses have been attributed to them such as antibacterial [5] antifungal and some of them are extensively used as analgesic [6], antinociceptive, [7,8] anticancer[9], anxiolytic[10] and anti-inflammatory [11] agents. Substituted benzothiazoles are known to cover a large domain of pharmacological activities serving as antitumor [12,13], antimicrobial [14,15] and anti-inflammatory [16,17] agents.

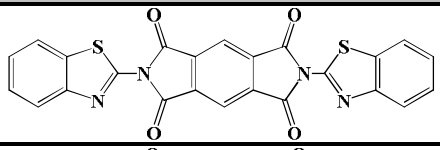
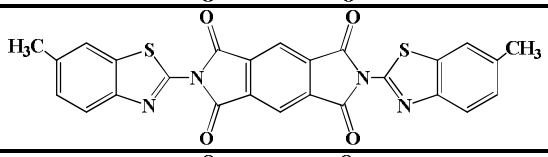
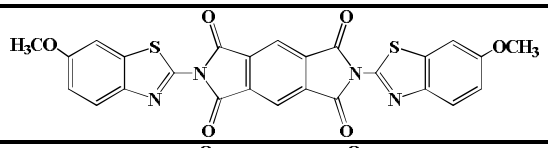
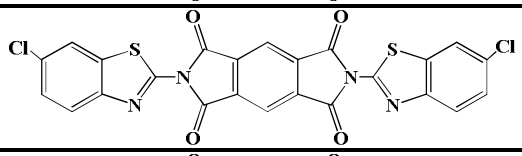
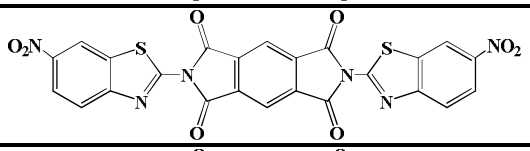
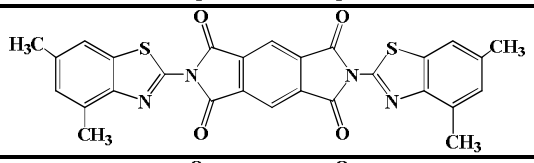
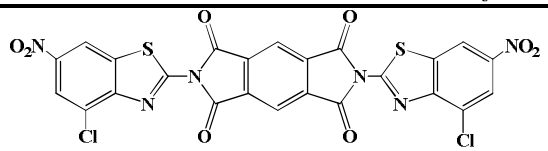
Thus many pyromillitimides have shown high anticancer activity[9,10] against a variety of murine and tumor cells, therefore plenty of pyromillitimide based anticancer drugs [11-14] have been synthesized and promising results have been obtained. Also, series of pyromillitimides exert pronounced analgesic or antinociceptive effects in mice [15,16] while other N-substituted pyromillitimides [15] showed antibacterial and antifungal activities.The therapeutic importance of these rings prompted us to synthesize new compounds by incorporating pyromillitimide and benzothiazole moieties in a single molecular framework. The new molecules were expected to possess biological activity.

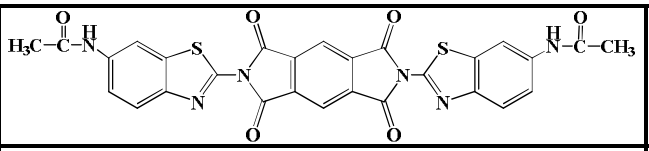
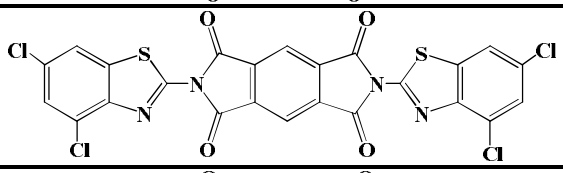
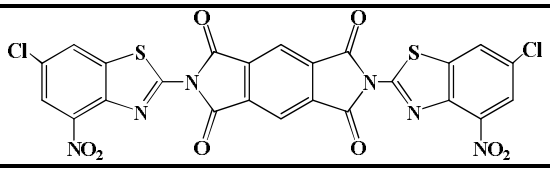
MATERIALS AND METHODS

Chemicals used in this work are supplied from BDH and Fluka companies and are used without further purification. Melting points were determined on Gallenkamp capillary melting point apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer using KBr discs. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300MHz instrument using DMSO-d_6 as a solvent and TMS as internal reference.

Synthesis of N-(Substituted benzothiazole-2-yl)-pyromillitimides (1-10): The titled compounds were prepared according to literature procedures [18]. A mixture of pyromillitic anhydride (0.01 mol), substituted-2-aminobenzothiazole 0.01 mol and 50 mL of glacial acetic acid was refluxed for eight hours with stirring. The resulted solution was cooled to room temperature before pouring into cold water and the obtained solid was filtered off, dried then recrystallized from a suitable solvent. Physical properties of compounds 1-10 are listed in table 1.

Table 1: Physical properties of benzothiazolyl pyromilltimides 1-10

Comp. No.	Compound structure	color	Melting points °C	Yield %	Solvent of Recrystallization
1		Yellow		90	Ethanol
2		Faint yellow		87	Ethanol
3		Violet		85	Ethanol
4		White		80	Acetone
5		Yellow		82	Ethanol
6		Light brown		85	Ethanol
7		Yellow		75	Acetone

8		Faint yellow		80	Ethanol
9		Greenish yellow		75	Acetone
10		Deep yellow		70	Ethanol

Biological Study: The cup plate method [19] using nutrient agar medium was employed in studying the antimicrobial activity of the prepared imides against four types of bacteria, *Staphylococcus aureous*, *Streptococcus pyogenes*, (Gram positive) , *Escherichia coli* and *Pseudomonas aureginosa* (Gram negative) and *Candida albicans* fungi. DMF was used as sample solution and sample size for all the compounds was fixed at 0.1 mL. Using a sterilized cork borer cups were scooped out of agar medium contained in a Petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added, the cups and the Petri dishes were subsequently incubated at 37°C for 48 h. Zones of inhibition produced by each compound was measured in mm and the results are listed in table 2.

Table 2: Antibacterial activity for some of the prepared compounds

Comp. No.	Gram-positive bacteria		Gram-negative		Fungi
	Staphylococcus aureus	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*
1	-	+	++	++	++
2	+	+	+	++	+
3	++	+	-	+	-
4	+	-	++	+	+
5	+	+	+	-	-
6	+	+	-	++	++
7	+	+	++	-	-
8	+	++	++	++	+++
9	+	-	+	-	+
10	++	+	-	++	+

Key to symbols: inactive = (-) inhibition zone < 6 mm ,Slightly active = (+) inhibition zone 6-9 mm , Moderately active = (++) inhibition zone 9-12 mm, Highly active = (+++) inhibition zone 13-17 mm, Very high activity = (++++) inhibition zone > 17 mm.

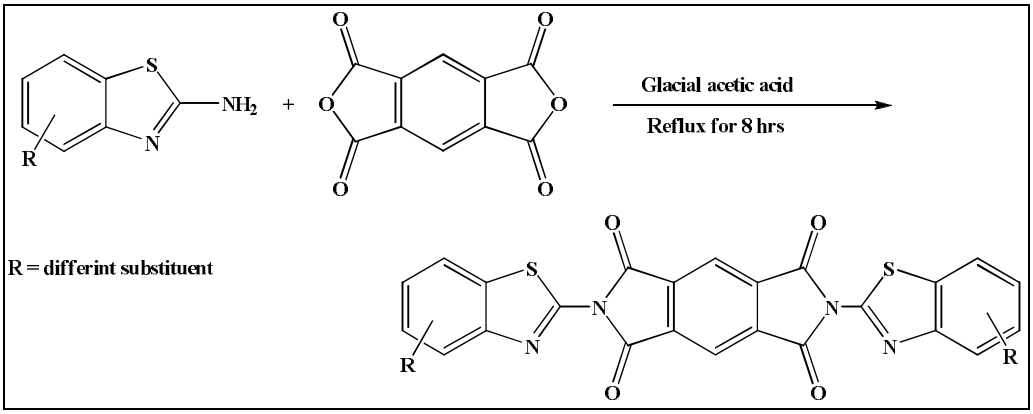
RESULTS AND DISCUSSION

Since both pyromillitimides and benzothiazoles are biologically active components having wide spectrum of medicinal and pharmacological applications, the present work is directed toward synthesis of new compounds containing these two active moieties with expected biological activity.

A new series of N-(substituted benzothiazol-2-yl)-pyromillitimides were synthesized via direct reaction between pyromillitic anhydride and substituted-2-aminobenzothiazoles in the presence of glacial acetic

acid under reflux conditions at high temperature for eight hours. 2-aminobenzothiazoles substituted with different substituents are used here as primary amines which introduced successfully as active nucleophiles attacked carbonyl groups in the cyclic anhydride (pyromillitic anhydride) producing N-(benzothiazol-2-yl) pyromillitamic acids which intrun introduced directly in dehydration reaction under the influence of glacial acetic acid and heat affording the desirable pyromillitimides (1-10).

The starting materials (substituted-2-amino benzothiazoles) used in this work were prepared according to literature [20] via reaction of primary aromatic amines with ammonium thiocyanate and bromine in glacial acetic acid.



Structures of the prepared compounds were confirmed by FTIR, ^{1}HNMR and ^{13}CNMR spectra data.

FTIR spectra of pyromillitimides (1-10) showed clear absorption bands at (1681-1739) cm^{-1} and (1595-1647) cm^{-1} due to ν(C=O) imide and ν(C=N) in thiazol ring. Other bands appeared at (1550-1600) cm^{-1}, (1338-1373) cm^{-1} and (620-655) cm^{-1} which attributed to ν(C=C) aromatic, ν(C-N) imide and ν(C-S) in thiazole ring respectively [21] (Table 3).

Table 3: FTIR spectral data of pyromillitimides 1-10

Comp. No.	ν(C=O) imide	ν(C=N) thiazole	ν(C=C) aromatic	ν(C-N) imide	ν(C-S) thiazole	others
1	1739	1595	1550	1338	625	
2	1739	1647	1600	1338	624	
3	1739	1630	1600	1338	625	ν(C-O-C) 1178, 1269
4	1681	1635	1597	1334	655	ν(C-Cl) 1237
5	1732	1612	1595	1346	628	ν(C-NO_2) 1527
6	1724	1620	1573	1373	644	
7	1733	1622	1585	1348	630	ν(C-NO_2) 1527 ν(C-Cl) 1200

8	1732	1600	1566	1338	655	ν(NH)amide 3248 ν(C=O)amide 1651
9	1733	1640	1595	1334	620	ν(C-Cl) 1080
10	1730	1620	1590	1342	628	ν(C-NO_2) 1530 ν(C-Cl) 1210

^{1}HNMR spectrum of compound 3 showed clear signals at δ = 3.7ppm (s, 6H, 2 CH_3) signal and at δ = (7.0-8.3)ppm (m, 8H, aromatic) signal due to CH_3 and aromatic protons respectively while ^{13}CNMR spectrum of the same compound 3 showed signals at δ = 56.3, (105-156), 162.2 and 165.2 ppm due to CH_3, aromatic carbons, C=N and C=O respectively. These evidences confirm the formation of the compound.
^{1}HNMR spectrum of compound 8 showed signals at δ = 2.2ppm (s, 6H, 2CH_3),δ = 7.65-8.8 ppm,(m,8H, aromatic) and at δ = 10.5 ppm(s, 2H, NH) due to CH_3, aromatic protons and NH (amide) respectively, while ^{13}CNMR of this compound showed signals at δ = 24.55, (112.9-148), 161.5, 165.8 and 168.7 ppm belong to CH_3, aromatic carbons, C=N, C=O imide and C=O amide respectively. These evidences confirm the formation of the compound.

Biological activity: The prepared compounds were screened for their antibacterial activity against four bacteria including *Staphylococcus aureous*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aureginosa* respectively and *Candida albicans* fungi. The tested compounds showed different biological activities against the studied types of bacteria as shown in table 2. It was noticeable that biological activity of these compounds depend on nature of substituents in their molecules thus compounds 1,4,7,8 showed moderatly activity against E.coli, compounds 1,2,6,8,10 showed moderatly activity against *Pseudomonas aureginosa*, while compound 8 showed moderate activity against *Streptococcus pyogenes* and compounds 3,10 showed moderatly activity against *Staphylococcus aureous*. On the other hand compound 8 showed high activity against *Candida albicans* fungi.

APPLICATIONS

The synthesized pyromillitic imides derivatives showed significant antibacterial activities and are promising lead molecules for the development of new drugs. Several other pyromillitic imides derivatives can be synthesized to evaluate their biological activity.

CONCLUSIONS

In the present research, some novel pyromillitic imides compounds were synthesized and screened for their antimicrobial activities. The most prepared compounds possessed significant activity against the tested bacteria which may be due to the presence of halogens, nitro and acitamido groups in benzothiazol ring system.

REFERENCES

[1] S. Shinde, S. Tekale, S. Kauthale and S. Deshmukh, Int. *J. Indian Chem*, **2011,** 2 (2), 2228.
[2] R. Shimazawa, H. Takayama, F. Kato and Y. Hashimoto, *Bioorg. Med. Chem. Lett*, **1999,** 9, 559.
[3] T. Vidal, A. Petit, A. Loupy and R. Gedye, *Tetrahedron*, **2000,** 56, 5473.
[4] R. Jayakumar, R. Balaji and S. Nanjudan, *Eur. Polym. J*, **2000,** 36, 1659.
[5] M. Struga, J. Kossakowski, J. Stefanska, A. Zimmiak and A. Koziol, *Eur.J.Med.Chem*, **2008,** 43, 1309-1314.
[6] D.M. Borchhardt and A.D. Andricopulo, *Med. Chem*, **2009**, 5, 66-73.

[7] L. Zhang, G.F. Hao, Y. Tan, Z. Xi., M.Z. Huang and G.F. Yang, *Bioorg. Med. Chem*, **2009**, 17, 4935-4942.
[8] M.M. De Souza, R. Correa, V.C. Filho, I. Grabchev and V. Bojinov, *Pharmazie*, **2002**, 56, 430.
[9] J.A. Yunesa, A.A. Cardoso, R.A. Yunes, R. Correa and V.C. Filho, *Z. Naturforsch*, **2008,** 63, 675.
[10] A.J. Bojarski, B. Kuran, J. Kossakowski, A. Koziol and A. Chodkowska, *Eur. J. Med. Chem*, **2009**, 44, 152-164.
[11] S.M. Sondhi, R. Rani, P. Roy, S.K. Agrawal and A.K. Saxena, *Bioorg. Med. Chem. Lett*, **2009**, 19, 1534-1538.
[12] D.F. Shi, T.D. Bradshaw, M.S. Chua, A.D. Westwell and M.F.G. Stevens, *Bioonrg. Med. Chem. Lett*, **2001**, 11, 1093.
[13] M.A. El-Sherbeny, *Arzneim-Forsch*, **2000,** 50, 843.
[14] I. Yildiz-Oren, I. Yalcin, E. Aki-Sener and N. Ucartruk, *Eur. J. Med. Chem*, **2004**, 39, 291.
[15] A. Latrofa, M.L.A. Franco, A. Rosato, D. Carone and C. Vitali, *IL Farmaco*, **2005,** 60, 291.
[16] R. Paramashivappa, P.P. Kumar, S.P.V. Rao and S. Rao, *Bioorg. Med. Chem. Lett*, **2003**, 13, 657.
[17] K. Oketani, N. Nagakura, K. Harada and T. Inoue, *Eur. J. Pharm*, **2001**, 422, 209.
[18] A. Chavan and N. Pai. *Molecules*, **2007,** 12, 2467.
[19] O.V. Prezhdo, B.V. Uspenskii, V.V. Prezhdo, W. Boszczyk and V. B. Distanov, *Dyes and Pigments*, **2007**, 72, 42.
[20] N. Patel and S. Agravat, *Orient J. Chem*, **2006,** 22, 333.
[21] R. Silverstein, F. Webster, and D. Kiemle, Spectrometric Identification of Organic Compounds, 7th Edition, John Wiley & Son, INC, NEW JERSEY, USA, **2005**.