Journal of Saudi Chemical Society (2014) **18**, 262–268

King Saud University

**Journal of Saudi Chemical Society**

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ORIGINAL ARTICLE

# Synthesis of novel dipodal-benzimidazole, benzoxazole and benzothiazole from cyanuric chloride: Structural, photophysical and antimicrobial studies

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Received 17 May 2011; accepted 1 July 2011
Available online 13 July 2011

**KEYWORDS**

Benzimidazole;
Cyanuric chloride;
Antimicrobial study;
Photo-physics;
Thermal stability;
Triazine

**Abstract** In the present study, new benzimidazole, benzoxazole and benzothiazole derivatives were prepared and screened for antimicrobial activity. The structure of 4,4′-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis(oxy))dibenzaldehyde (DIPOD) **5** was established from *p*-hydroxy benzaldehyde **4** and 4-(4,6-dichloro-1,3,5-triazin-2-yl)-*N*,*N*-diethylaniline **3**. The reaction of DIPOD **5** with different *o*-phenylenediamine or *o*-amino phenol or *o*-amino thiophenol in ethanol gave benzimidazole, benzoxazole and benzothiazole **7**. Novel heterocycles showed excellent broad-spectrum antimicrobial activity against bacterial strain (*Escherichia coli*, *Staphylococcus aureus*) and fungal strain (*Candida albicans*, *Aspergillus niger*) cultures. Activity data was compared with standard Streptomycin and Fluconazole drug. Photophysical and thermal properties of synthesized compounds were also studied.
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Peer review under responsibility of King Saud University.
doi:10.1016/j.jscs.2011.07.001

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## 1. Introduction

*s*-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals (Balini et al., 2005), anticancer agents (Menicagli et al., 2004), estrogen receptor modulators (Henke et al., 2002), antimalarials (Jensen et al., 2001; Agarwal et al., 2005), cyclin-dependent kinase modulators (Kuo et al., 2005), and antimicrobials (Koc et al., 2010. It has been reported that *s*-triazine derivatives are used as templates for molecular imprinting (Tahmassebi and Sasaki, 1994) and for the construction of three-helix bundle protein (Tahmassebi and Sasaki, 1998).

It is also important to note that compounds containing benzimidazole, benzoxazole and benzothiazoles moieties often exhibit diverse biological activities. These heterocycles are known to have antibiotic (Evans et al., 1979), antiviral (Song et al., 2005), anticancer (Kumar et al., 2002), and antimicrobial (Yildiz-Oren et al., 2004) activities. These heterocycles have also been used as ligands for complexes used in asymmetric transformations (Figge et al., 2002). Benzimidazole derivatives are an unique class of broad-spectrum antirhino/enteroviral agents (Nakano et al., 2000), effective against the human cytomegalovirus (HCMV) (Zhu et al., 2000) and efficient selective neuropeptide YY1 receptor antagonists (Zarrinmayeh et al., 1998).

In this paper, we have reported the novel benzimidazole, benzoxazole and benzothiazole derivatives from 4,4′-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis(oxy))dibenzaldehyde (DIPOD). The DIPOD was prepared by reacting cyanuric chloride with *N*,*N*-diethyl aniline, followed by reaction of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-*N*,*N*-diethylaniline with 2 equivalents of 4-hydroxybenzaldehyde. The compounds are characterized by spectral analysis. Thermal properties and antimicrobial activities of these compounds are studied.

## 2. Experimental

### 2.1. Materials and methods

All reagents and solvents were procured from s.d. fine chemicals (India) and were used without purification. The reaction was monitored by TLC using on 0.25 mm E-Merck silica gel 60 $F_{254}$ precoated plates, which were visualized with UV light. The FT-IR spectra were recorded on a Perkin–Elmer 257 spectrometer using KBr disks. $^{1}$H-NMR and $^{13}$C NMR spectra were recorded on a VXR 400-MHz instrument using TMS as an internal standard. Mass spectra were recorded on a Finnigan Mass spectrometer. The UV–visible absorption spectra of the compounds were recorded on a Spectronic Genesys 2 UV–visible spectrophotometer. Simultaneous DSC-TGA measurements were performed on SDT Q 600 v8.2 Build 100 model of Waters (India) Pvt. Ltd.

### 2.2. Biological activity

All compounds were evaluated for in vitro antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* strains and in vitro antifungal activity against *Candida albicans* and *Aspergillus niger* strains by using serial dilution method.

#### 2.2.1. General

Incubator at 35 and 37 °C; pipettes of various sizes (Gilson); sterile tips 5, 10, 50, 100, 200 μL sterile normal saline; sterile isosensitest agar (Southern Group Laboratory, SGL); antibiotic solutions (Sigma–Aldrich); sterile solution of 10% (v/v) DMSO in water (Sigma–Aldrich) were used for microbial studies.

#### 2.2.2. Medium

Isosensitest medium was used throughout the assay, as it is pH buffered. Although NCCLS recommends the use of Mueller Hinton medium for susceptibility testing, the isosensitest medium had comparable results for most of the tested bacterial strains (Koeth et al., 2000).

#### 2.2.3. Preparation of the plates

Plates were prepared under aseptic conditions. A sterile 96 well plate was labeled. A volume of 100 μL of test material in 10% (v/v) DMSO (usually a stock concentration of 4 mg/mL) was pipetted into the first row of the plate. To all other wells, 50 μL of nutrient broth was added. Serial dilutions were performed using a multichannel pipette. Tips were discarded after use such that each well had 50 μL of the test material in serially descending concentrations. To each well, 10 μL of resazurin indicator solution was added, using a pipette of 30 μL strength isosensitized, both added to each well to ensure that the final volume was the single strength of the nutrient broth. Finally, 10 μL of bacterial suspension ($5 \times 10^6$ cfu/mL) was added to each well to achieve a concentration of $5 \times 10^5$ cfu/mL. Each plate was wrapped loosely with cling film to ensure that bacteria did not become dehydrated. Each plate had a set of controls: a column with a broad-spectrum antibiotic as positive control, a column with all solutions with the exception of the test compound, and a column with all solutions with the exception of the bacterial solution, adding 10 μL of nutrient broth instead. The plates were prepared in triplicate, and placed in an incubator set at 37 °C for 18–24 h. The color change was then assessed visually. Any color changes from purple to pink or colorless were recorded as positive. The lowest concentration at which color change occurred was taken as the MIC value. The average of three values was calculated and that was the MIC for the test material and bacterial or fungal strain (Sarkar et al., 2007).

### 2.3. Synthesis of compounds

#### 2.3.1. Synthesis of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline (3)

A mixture of *N*,*N*-diethylaniline (27 g, 0.2 mol) and cyanuric chloride (18.4 g, 0.1 mol) was heated at 70 °C for 8 h under a slow stream of dry nitrogen, the reaction was monitored by TLC, after completion the reaction mixture was extracted with hot chloroform (200 mL) and the white crystals of hydrochloride salt of *N*,*N*-diethylaniline were removed by filtration. Slow cooling and evaporation of the chloroform extract to a volume of 50 mL yielded good crystals of **3**. The product was recrystallized two times from acetone.

Yield: 11.68 g, 40%; m.p. (Crystallized from acetone) 156 °C.

FT-IR (KBr) $\upsilon_{max}$ cm$^{-1}$: 824 (C–Cl), 1232 (C–N), 1515 (C═N), 1610 (C═C), 2967 (C–H).

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C) ($\delta$: ppm): 1.23 (t, 6H, –$CH_3$, $J$ = 6.8, 7.2, 14.0, Hz), 3.46 (q, 4H, –$CH_2$, $J$ = 6.8, 7.2, 14.0, 14.4 Hz), 6.65–6.69 (dd, 2H, Ar–H, $J$ = 9.2 Hz, 2.8 Hz), 8.29–8.33 (dd, 2H, Ar–H, $J$ = 9.2, 2.8 Hz).

$^{13}$C NMR (75 MHz, DMSO–$d_6$, 25 °C) ($\delta$: ppm): 15.6, 49.0, 114.6, 125.6, 130.7, 154.2, 172.3, 179.5.

Mass: m/e = 298 ($M^+ + 1$), 299 ($M^+ + 2$).

#### 2.3.2. 4,4′-((6-(4-(Diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis(oxy))dibenzaldehyde (5)

*p*-Hydroxybenzaldehyde (**4**) (2.426 g, 0.022 mol) and 4-(4, 6-dichloro-1,3,5-triazin-2-yl)-*N*,*N*-diethylaniline (**3**) (3 g, 0.011 mol) were added to a suspension of $K_2CO_3$ (3.04 g,

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