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SYNTHESIS OF NOVEL DOPAMINE DERIVED MULTIDIRECTIONAL LIGANDS FROM CYANURIC CHLORIDE: STRUCTURAL AND ANTIMICROBIAL STUDIES

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ABSTRACT

Two monopodal (2,4-dichloro-6-(3-hydroxytyramine)-1,3,5-triazine) and tripodal (2,4,6-(3-hydroxytyramine)-1,3,5-triazine) s-triazine derivatives were prepared through the reaction of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and 3-hydroxytyramine hydrochloride (dopamine hydrochloride). The structures of the compounds were identified by FT-IR, 1H NMR, 13C NMR, thermal analysis and elemental analysis. Their antimicrobial activities were carried out using the broth microdilution method in dimethyl sulfoxide (DMSO): Phosphate Buffered Saline (PBS) against eight bacteria and one yeast. The results of the test were compared with ampicillin. It was determined that CCDOP1, CCDOP3 and DOP have significant antibacterial and antifungal activity. These three chemicals revealed strong antibacterial activity against the *E. coli* and *S. aureus* strains used in the study. *S. aureus* was the most sensitive strain against dopamine hydrochloride and E. coli was the most sensitive bacteria against $CCDOP_1$.

Keywords: Cyanuric chloride,dopamine, antimicrobial activity, broth microdilution

INTRODUCTION

Important classes of nitrogenous compounds, such as substituted triazines (Agarwal et al., 2005a), pyrimidines (Srivastava et al., 1999), and quinolines (Srivastava et al., 1997), have been synthesized and screened for antimalarial activity (Jensen et al., 2001; Agarwal et al., 2005b). In addition, s-triazine derivatives have received considerable attention because of their potent biological activity, for example, as antiprotozoals (Baliani et al., 2005), anticancer drugs (Menicagli et al., 2004), estrogen receptor modulators (Henke et al., 2002), cyclin-dependent kinase inhibitors (Kuo et al., 2005), antivirals (Pandey et al., 2004; Srinivas et al., 2005), and antimalarials (Jensen et al., 2001; Ojha et al., 2011). It has been reported that s-triazine derivatives possess potent antimicrobial activity (Srinivas et al., 2005; McKay et al., 2006; Ghaib et al., 2002; Lübbers et al., 2000; Lebreton et al., 2003; Koç et al., 2010). These derivatives have also been studied as part of research aiming to uncover new natural products with improved biological activities (Kumar and Menon, 2009; Solankee et al., 2010), including antioxidant, anti-human immunodeficiency virus (HIV), and tumor growth inhibition activities (Chang et al., 2010; Naicker et al., 2004). Besides, many of the dopamine containing compounds exhibit antibacterial activities (Hadjipavlou-

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Litina et al., 2010; Pająk and Kańska, 2006). These are also used as bridging agents to synthesize herbicides and in the production of drugs or polymers (Patel and Patel, 2001; Xie et al., 2007; Koç, 2011). Because of these attractive characteristics, much effort has been devoted to the synthesis of s-triazine derivatives by different groups in the recent years (Koç and Uysal, 2010, 2011; Uysal and Koç, 2010; Mooibroek and Gamez, 2007).

The reaction of cyanuric chloride ($C_3N_3Cl_3$) with 3 or 1 equiv of dopamine hydrochloride in acetone gives the desired monopodal or tripodal in a single step, 2,4-dichloro-6-(3-hydroxytyramine)-1,3,5-triazine, 2,4,6-(3-hydroxytyramine)-1,3,5-triazine and 3-hydroxytyramine hydrochloride, coded to be $CCDOP_1$, $CCDOP_3$ and DOP (Koç, 2011). In this work, we have aimed to make two new s-triazine derivatives by using dopamine hydrochloride. We have called them "monopodal or tripodal s-triazine". As part of our ongoing research, here we report the characterization and antimicrobial activities of these compounds against several microorganisms.

MATERIALS AND METHODS

All the other chemicals were purchased from Aldrich. The linking agent, 2,4,6-trichloro-1,3,5-triazine (abbreviated as cyanuric chloride or cc, mp 145-146 ^oC), was obtained from Aldrich Chem. Co. Cyanuric chloride was purified using recrystallizations from pure petroleum ether (60-90 ^oC) (Koç, 2011). All solvents and dopamine hydrochloride used were reagent grade and were used without further purification. Melting points were measured using an Optimelt Automated Melting Point System (Digital Image Processing Technology) SRS apparatus. Elemental analyses (C, H, N) were performed using a Leco CHNS-932 model analyzer. ^1H NMR spectra were recorded at room temperature with a Varian 400 MHz spectrometer using TMS as an internal standard. FT-IR spectra were recorded with a Perkin-Elmer Spectrum 100 with Universal ATR Polarization Accessory. Thermal analyses were performed on a Shimadzu DTA 50 and TG 50 H on 5 mg samples. The DTA and TG curves were obtained at the heating rate of 10 ^oC/min from 22 to 900 ^oC under dry N_2. The pH values were measured with a WTW pH 537 pH meter.

Antimicrobial activity

The antimicrobial activity of $CCDOP_1$, $CCDOP_3$ and DOP were determined using eight bacteria and one yeast including, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 6538, *Proteus mirabilis* ATCC 43071, *Pseudomonas aeruginosa* ATCC 15442, *Klebsiella oxytoca* ATCC 10031, *Bacillus cereus* ATCC 11778, *Listeria monocytogenes* Type 2 Pasteur Institute 5434, *Streptococcus salivarius* RSHE 606 and *Candida albicans* as test organisms. Bacterial strains and yeast were cultured overnight at 37 ^oC in nutrient broth. The broth microdilution method was employed for the determination of antimicrobial activity.

The minimal inhibition concentration (MIC) values of the chemical were studied for microorganisms. The inocula of microorganisms were prepared from 12 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity. The 96-well plates were prepared by dispensing into each well 100 µl of nutrient broth. 100 µl from chemicals initially prepared at the concentration of 10000 µg/ml were added into the first wells. Then, 100 µL from the first well was transferred into 11 consecutive wells and diluted and then, 100 µl inocula were distributed to each well. Ampicillin solution was used as the positive control. Then the plates were incubated at appropriate temperatures for 18 h and Candida was incubated for two days. Microbial growth was determined by adding 20 µl of 2,3,5-triphenyl-tetrazolium chloride (0.5 %) after incubation to each well and incubating for 30 min at 37 °C (Maltaş et al., 2010).

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Synthesis of compounds

Synthesis procedure for 2,4-dichloro-6-(3-hydroxytyramine)-1,3,5-triazine ($CCDOP_1$)

A solution of dopamine hydrochloride (1.90 g, 10 mmol) in ethanol (50 ml) was added dropwise to a cyanuric chloride suspension made by pouring slurry cyanuric chloride (1.84 g, 10 mmol) in 80 % (v/v) acetone/water (50 ml) and stirring for a further 5 h at 0 ^{o}C in an ice bath (Disley et al., 1999; Koç, 2011). The HCl generated during the reaction was neutralized through the periodic addition of $NaHCO_3$ (1.68 g, 20 mmol) to a total of two equivalents in water. Then the mixture was washed with $CHCl_3$ to remove excess cyanuric chloride (Naicker et al., 2004). The reaction was monitored by thin layer chromatography (TLC) (hexane–ethyl acetate, 4:2 v/v) (Teng et al., 2000) until substituted triazine could be detected and at these stages the *Fujiwara Test* (Fang et al., 2001; Koç, 2011) for dichlorotriazine was positive. The product was then precipitated out of solution by acidifying the pH 4 with (1 M) hydrochloric acid. A light yellow powder solid product was collected by filtration and was washed with cold water (3x100 ml) and acetone (Koç, 2011).

Data for ($CCDOP_1$)

Yield: (72 %); m.p.: 400 ^{o}C>; Elemental analysis (Found: C, 43.92; H, 3.33; N, 18.78 %). Calc. for $C_{11}H_{10}N_4O_2Cl_2$: C, 43.87; H, 3.35; N, 18. 61 %). IR (KBr) ν_{max}/cm^{-1}:3367 (N–H), 3340 (O-H), 2837 (C–H), 1551 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6), (δ: ppm): 6.84 (d, 1H, Ar-H), 6.81 (d, 1H, Ar-H), 6.65 (dd, 1H, Ar-H), 5.87 (s, 3H, NH and OH), 3.27 (t, 2H, Ar-C-CH_2-N), 2.56 (t, 2H, Ar-CH_2-C-N). ^{13}C NMR (100 MHz, DMSO-d_6), (δ: ppm): 170.78, 165.18, 164.26, 132.54, 122,44, 116.59, 115.63, 40.23, 35.50.

Synthesis of 2,4,6-(3-hydroxytyramine)-1,3,5-triazine ($CCDOP_3$)

Cyanuric chloride (1.84 g, 10.00 mmol) was dissolved in THF (150 ml). N-ethyldiisopropylamine (DIPEA) (5.22 ml, 30.00 mmol) was added and the two-necked round bottomed flask was cooled to 0 °C. Dopamine hydrochloride (5.67 g, 30.00 mmol) was added portionwise. After the completion of the addition, the suspension mixture was warmed to room temperature and then heated under reflux for 48 h. The solid obtained was filtered under reduced pressure and washed with THF (3x20 ml) and ethanol (3x25 ml) to remove N-ethyldiisopropylamine. The brown product, 2,4,6-(3-hydroxytyramine)-1,3,5-triazine **($CCDOP_3$),** was dried overnight at 50 °C under reduced pressure.

*Data for**($CCDOP_3$)***

Yield: (67 %); m.p.: 360 ^{o}C dec.; Elemental analysis (Found: C, 60.70; H, 5.86; N, 15.78 %). Calc. for $C_{27}H_{30}N_6O_6$: C, 60.66; H, 5.66; N, 15.72 %). IR (KBr) ν_{max}/cm^{-1}: 3378 (NH), 3358 (OH), 2897 (CH), 1567 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6), (δ: ppm): 6.97 (d, 3H, Ar-H), 7.07 (d, 3H, Ar-H), 6.78 (dd, 3H, Ar-H), 5.91 (s, 9H, NH and OH), 3.38 (t, 6H, Ar-C-CH_2-N), 2.78 (t, 6H, Ar-CH_2-C-N).

RESULTS AND DISCUSSION

The usual strategy employed for the synthesis of $CCDOP_1$ and $CCDOP_3$ ligands based on 1,3,5-trichloro-sym-triazine or cyanuric chloride entails reacting the least reactive amine with the first chlorine atom and the most reactive amine with the last chlorine atom, since the chlorine atoms on cyanuric chloride become progressively deactivated as substitution of the triazine ring with amines ensues (Koç, 2011) (Figure 1). In the ^{1}H NMR spectra of s-triazine derivatives signals at about 5.87 and 5.91 ppm for compounds $CCDOP_1$ and $CCDOP_3$ were detected, respectively. All signals appeared as singlet and were attributed to the N-H in the $CCDOP_1$ and $CCDOP_3$.

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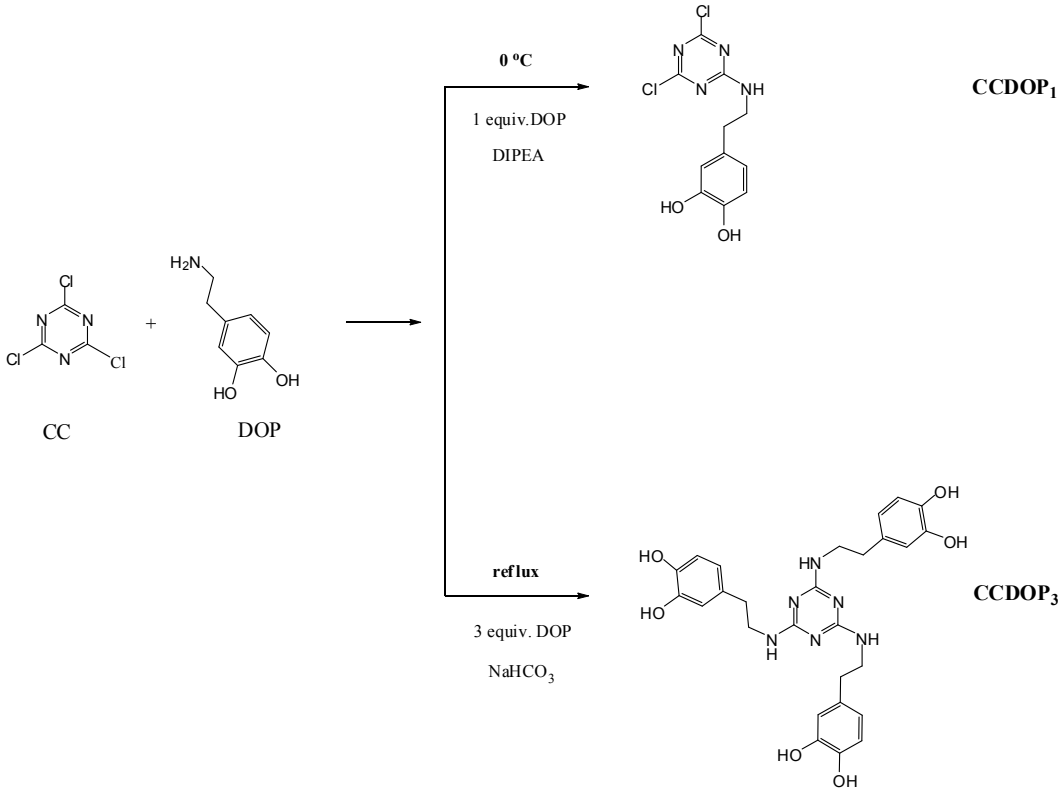

Figure 1: Proposed structures of the monopodal and tripodal s-triazines

The NH was also identified by FT-IR spectroscopy as a sharp band at about 3367–3378 cm^{-1} (Koç, 2011). The vibrations of the triazine C=N and O-H of the $CCDOP_1$ and $CCDOP_3$ were observed at 1551, 1567 and 3340, 3358 cm^{-1} range, respectively (Disley et al., 1999; Koç, 2011).

The thermal stabilities of compounds $CCDOP_1$ and $CCDOP_3$ were also thermally investigated and their plausible degrading (Koç, 2011; Koç and Uysal, 2010, 2011; Uysal and Koç, 2010) schemes are presented in Table 1. Thermal decomposition of the anhydrous compounds starts in the range of 98–412 °C and completes in the range 900 °C. The observed weight losses for all compounds are in good agreement with the calculated values.

In this study, the antimicrobial activities of $CCDOP_1$, $CCDOP_3$ and DOP were investigated by microbroth dilution method according to Maltaş et al. (2010) against eight bacteria and one yeast. The obtained results are presented in Table 2 and Figure 2.

Table 1: Decomposition steps with the temperature range and weight loss for monopodal and tripodal s-triazines

Compound	Temp. Range (°C)	Weight loss Found (Calc.) (%)
$C_{11}H_{10}N_4O_2Cl_2$ ($CCDOP_1$)	98-125	11.07 (11.29)
	132-231	34.57 (34.92)
	235-397	28.30 (28.53)
$C_{27}H_{30}N_6O_6$ ($CCDOP_3$)	110-155	18.98 (19.09)
	165-225	58.85 (59.01)
	228-412	08.22 (08.43)

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Table 2: Results of antimicrobial activities of $CCDOP_1$, $CCDOP_3$, DOP and standard antibiotic

Tested microorganisms	MIC values of chemicals (µg/ml)			MIC values of Ampicillin (µg/ml)
	$CCDOP_1$	$CCDOP_3$	DOP	
***Escherichia coli* ATCC 25922**	39	625	156	39
***Staphylococcus aureus* ATCC 6538**	39	625	19	39
***Proteus mirabilis* ATCC 43071**	2500	2500	2500	2500
***Pseudomonas aeruginosa* ATCC 15442**	2500	2500	2500	-
***Klebsiella oxytoca* ATCC 10031**	2500	1250	1250	1250
***Bacillus cereus* ATCC 11778**	2500	1250	1250	78
***Listeria monocytogenes* Type 2 Past. Inst. 5434**	2500	1250	2500	-
***Streptococcus salivarius* RSHE 606**	1250	1250	1250	-
Candida albicans	2500	1250	1250	2500

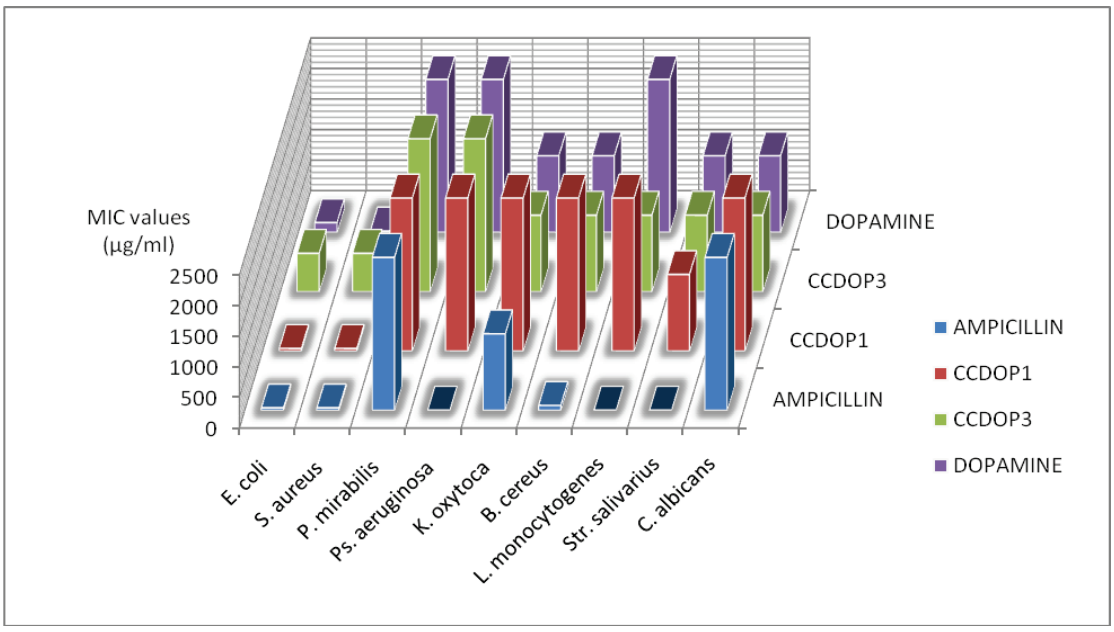

Figure 2: Graphic of antimicrobial activity test results

$CCDOP_1$ was found to be strongly antibacterial against *E. coli* and *S. aureus* at a 0.0396 mg/ml dose level. Ampicillin control antibiotic was equally effective against these two bacteria. The MIC value of chemical was determined as 1.25 mg/ml for *Streptococcus salivarius*. While Ampicillin had no effect on this strain, our chemical was found to be more effective than the antibiotic. For *P. mirabilis* the MIC value was determined as 2.50 mg/ml. The control antibiotic influenced this strain at a 1.25 mg/ml dose level. Although *P. aeruginosa* was found to be resistant to the con-

trol antibiotic at all test doses, it was affected by $CCDOP_1$ at a 2.50 mg/ml dose level. The MIC value was 2.50 mg/ml for *K. oxytoca* and *B. cereus*, too. It has been seen that $CCDOP_1$ revealed a similar effect against *K. oxytoca* when compared with the standard antibiotic. Though *L. monocytogenes* was resistant to the antibiotic, $CCDOP_1$ had antimicrobial capacity against this strain at a 2.50 mg/ml dose level. In addition to its antibacterial effect, our chemical had antifungal capacity against *Candida albicans* which is yeast and used in the study at a concentration of 2.50 mg/ml.

The MIC values of $CCDOP_3$ were determined as 0.625 mg/ml against *E. coli* and *S. aureus*. $CCDOP_3$ was more effective than $CCDOP_1$ against *K. oxytoca, B. cereus, L. monocytogenes* and *Candida albicans* at a concentration of 1.25 mg/ml. This chemical had strong antibacterial and antifungal activities as well as the control antibiotic against *K. oxytoca* and *Candida albicans*, respectively. The MIC values were determined as 2.50 mg/ml for *P. mirabilis* and *P. aeruginosa.*

Dopamine hydrochloride exhibited strong antibacterial activity against *S. aureus* at a concentration of 0.0195 mg/ml. It was found to be more effective than Ampicillin. *E. coli* was affected by dopamine hydrochloride at a dose of 0.156 mg/ml. It had similar antimicrobial activity against other bacteria and *Candida* when compared with $CCDOP_3$.

CONCLUSION

In this study, $CCDOP_1$, $CCDOP_3$ were synthesized by the reaction of cyanuric chloride and dopamine hydrochloride according to the literature (Naicker et al., 2004; Koç, 2011; Disley et al., 1999; Teng et al., 2000; Fang et al., 2001). The structures of the compounds were identified by FT-IR, ^{1}H NMR, ^{13}C NMR, thermal analysis and elemental analysis. According to the results obtained from the broth microdilution test, it has been determined that $CCDOP_1$, $CCDOP_3$ and DOP revealed strong antibacterial activity against the *E. coli* and *S. aureus* strains used in the study. $CCDOP_1$ and DOP have significant antimicrobial activity and these effects are close to the control antibiotic used. *S. aureus* was the most sensitive strain against dopamine hydrochloride and *E. coli* was the most sensitive bacteria against $CCDOP_1$. $CCDOP_3$ was more effective than the other chemicals tested against all microorganisms except for *E. coli* and *S. aureus*. Although they were resistant to the antibiotic, *P. aeruginosa, L. monocytogenes* and especially *Str. salivarius* were significantly affected by $CCDOP_1$, $CCDOP_3$ and DOP. It was determined that these chemicals have antifungal capacities, too.

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