



MICROWAVE-ASSISTED IONIC LIQUID CATALYZED ONE-POT SYNTHESIS OF HEXAHYDROQUINOLINE DERIVATIVES

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Ionic liquid catalyzed one-pot synthesis of hexahydroquinoline derivatives using substituted aryl aldehydes, dimedone, malononitrile and ammonium acetate has been described under microwave irradiation. The protocol has been utilized mild reaction conditions, excellent yield, shorter reaction time and simple workup procedure. The synthesized derivatives were obtained in 80-95% yields and were characterized by IR, ¹H NMR, and mass spectra.

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INTRODUCTION

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where all or most of the atoms contribute to the newly created product. In chemistry, a one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor.

Organic synthesis in an ionic liquid medium is a lucrative research area considering its cost, safety and significance to environmentally benign process development.¹⁻⁴ Ionic liquid (IL) is a salt in the liquid state. In some contexts, the term has been restricted to salts whose melting point is below some arbitrary temperature. While ordinary liquids such as water and gasoline are predominantly made of electrically neutral molecules, ionic liquids are primarily made of ions and short-lived ion pairs. These substances are variously called liquid electrolytes, ionic melts, ionic fluids, fused salts and liquid salts.⁵⁻⁷

Hexahydroquinoline has a broad spectrum of biological properties and it is well known structural scaffold of several natural products and artificial drugs.⁸ These are used due to their antibacterial and antifungal activity,⁹ anticancer activity,¹⁰ insecticidal activity,¹¹ and as antimicrobial,¹² anti-inflammatory agents,¹³ antioxidant,¹⁴ anti-anaphylactic and diuretic agent.

Several related approaches have been documented in the literature for the synthesis of 5-quinolinones, which generally involve the cyclocondensation of aldehyde, dimedone, an active methylene compound, and ammonium acetate.¹⁵⁻¹⁹ Microwave irradiation and solvent-free medium have been used as activation conditions, as well as various catalysts, such as nano-ZrO₂-SO₃H,²⁰ Fe₃O₄-TiO₂,²¹ nano MgO,²² and nano Fe₃O₄.²³ Pasha M.A. *et al.* reported

synthetic strategy for obtaining 2-amino-4-aryl-7, 7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles from aryl aldehydes, dimedone, malononitrile, and ammonium acetate using K₂CO₃ as a base in water with ultrasound treatment.²⁴ Jonnalagadda S.B. reported synthetic strategy by using TEA (triethylamine) as a base with microwave irradiation.²⁵

The literature survey also reveals that the published protocols suffer from one or several drawbacks, such as prolonged reaction time, harsh conditions, complicated preparation of the catalyst, reduced yield and lack of generality.

In the present study, we have developed an elegant, efficient, easy and direct procedure for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile and its nine derivatives under microwave irradiation using aryl aldehydes, dimedone, malononitrile and ammonium acetate and a catalytic amount of N-methylpyridinium tosylate (NMPyTs) ionic liquid.²⁶ The effect of catalyst and the green technique gives the excellent yield of the product under the aspect of environmentally benign processes. This methodology has numerous and significant advantages, such as atom economy, the use of a green solvent, mild catalyst-free conditions, short reaction time as well as a more comfortable workup procedure when compared with the conventional methods.

EXPERIMENTAL

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals. They were used without further purification. Melting points were recorded in open capillaries using a Buchi melting-point B-540 apparatus. ¹H NMR spectra were obtained on a Bruker instrument (400 MHz) and chemical shifts are reported in δppm. Mass spectra were measured using high-resolution ESI-MS (DFS) Thermo spectrometers (70 eV). Microwave irradiation was carried out in a Microwave Oven, Model No. MS2043DB DB1QILN (2450 MHz, 1050 W) equipped with Erlenmeyer flask.

MATERIAL AND METHODS

Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile and its derivatives (5a-e)

A mixture of substituted aryl aldehydes **1** (0.01 mol), dimedone **2** (0.01 mol), malononitrile **3** (0.01 mol), ammonium acetate **4** (0.01 mol) and catalytic amount of N-methylpyridinium tosylate (NMPyTs) as a ionic liquid were irradiated in microwave oven in an Erlenmeyer flask and irradiated until completion of the reaction. Reaction was monitored by TLC (ethyl acetate-hexane, 2:8). The reaction mixture was poured in crushed ice and filtered. The crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic techniques and compared with the standard method.

2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5a)

IR(KBr cm^{-1}): 3398, 3317, 3258, 2933, 2165, 1657, 1624, 1490; ^1H NMR (400 MHz, DMSO- d_6): δ 0.98(s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.93-2.13 (dd, 2H, $J=15$ Hz, CH_2), 2.33-2.55 (dd, 2H, $J=17.5$, CH_2), 4.39 (s, 1H, CH), 5.90 (s, 2H, NH_2), 6.95-7.30 (m, 5H, Ar-H), 7.25-7.50 (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 28.3, 30.4, 42.2, 53.8, 59.0, 111.7, 113.3, 120.9, 124.2, 126.2, 129.4, 131.4, 143.5, 149.0, 163.2, 198.2.; ESI-MS(m/z): 294.3 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(4-methylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5b)

IR(KBr cm^{-1}): 3390, 3312, 3248, 2923, 2175, 1670, 1610, 1488.; ^1H NMR (400 MHz, DMSO- d_6): δ 0.95(s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.95-2.18 (dd, 2H, $J=15$ Hz, CH_2), 2.35-2.45 (dd, 2H, $J=17.5$, CH_2), 4.45 (s, 1H, CH), 5.94 (s, 2H, NH_2), 6.92-7.30 (dd, 2H Ar-H), 6.90-7.00, (dd, 2H Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.9, 28.5, 30.5, 42.1, 52.4, 58.0, 111.2, 120.9, 124.9, 127.2, 129.4, 130.4, 145.5, 150.0, 162.2, 199.0; ESI-MS(m/z): 307 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5c)

IR(KBr cm^{-1}): 3375, 3310, 3170, 2960, 2675, 1660, 1490, 1378; ^1H NMR (400 MHz, DMSO- d_6): δ 0.90 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.90-2.10, 3.70-3.80 (s, 3H, $-\text{OCH}_3$) (dd, 2H, $J=15$ Hz, CH_2), 2.30-2.40 (dd, 2H, $J=17.0$, CH_2), 4.40 (s, 1H, CH), 5.95 (s, 2H, NH_2), 6.60-7.00, (dd, 2H Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 31.9, 37.5, 45.1, 55.4, 60.0, 111.0, 121.9, 124.9, 128.2, 130.4, 131.4, 150.5, 153.0, 166.2, 198.0; ESI-MS(m/z): 324 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(4-hydroxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5d)

IR(KBr cm^{-1}): 3425, 3314, 3174, 2970, 2680, 1676, 1493, 1380.; ^1H NMR (400 MHz, DMSO- d_6): δ 0.91(s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.90-2.86 (dd, 2H, $J=15$ Hz, CH_2), 2.70-2.90 (dd, 2H, $J=17.0$, CH_2), 4.45 (s, 1H, CH), 5.97 (s, 2H,

NH_2), 6.60-7.00, (dd, 2H Ar-H), 6.60-7.00, (dd, 2H, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.5, 32.3, 38.1, 43.2, 51.3, 57.0, 111.9, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 198.4; ESI-MS(m/z): 309.3 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(2-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5e)

IR(KBr cm^{-1}): 3488, 3343, 3129, 2970, 2687, 1686, 1490, 1390, 740; ^1H NMR (400 MHz, DMSO- d_6): δ 0.95(s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.92-2.96 (dd, 2H, $J=15$ Hz, CH_2), 2.70-2.95 (dd, 2H, $J=17.0$, CH_2), 4.55 (s, 1H, CH), 5.87 (s, 2H, NH_2), 6.60-7.00, (m, 4H, Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.5, 32.3, 38.1, 43.2, 51.3, 57.0, 111.9, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 198.4; ESI-MS(m/z): 311.3 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(2-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5f)

IR(KBr cm^{-1}): 3445, 3330, 3133, 2924, 2667, 1690, 1440, 1388, 724.; ^1H NMR (400 MHz, DMSO- d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.95 (dd, 2H, $J=15$ Hz, CH_2), 2.70-2.95 (dd, 2H, $J=17.0$, CH_2), 4.65 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m, 4H, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 31.3, 39.1, 43.3, 51.5, 57.0, 111.5, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 197.4; ESI-MS(m/z): 327.8 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5g)

IR(KBr cm^{-1}): 3495, 3321 and 3223, 2174, 1690, 1440, 1330, 745; ^1H NMR (400 MHz, DMSO- d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.30 (dd, 2H, $J=15$ Hz, CH_2), 2.40-2.95 (dd, 2H, $J=17.0$, CH_2), 4.35 (s, 1H, CH), 5.78 (s, 2H, NH_2), 7.31, (d, 2H, $J=8.0$ Hz, Ar-H), 7.15, (d, 2H, $J=8.0$ Hz, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 31.3, 38.4, 43.3, 51.5, 57.3, 111.6, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 197.4.; ESI-MS(m/z): 327 [$\text{M}+\text{H}$] $^+$

2-Amino-4-(2-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5h)

IR(KBr cm^{-1}): 3450, 3340, 3163, 2944, 2677, 1650, 1420, 1382, 750; ^1H NMR (400 MHz, DMSO- d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.95 (dd, 2H, $J=15$ Hz, CH_2), 2.70-2.95 (dd, 2H, $J=17.0$, CH_2), 4.65 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m, 4H, Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 31.3, 39.1, 43.3, 52.5, 59.0, 111.5, 114.4, 113.7, 130.3, 135.2, 150.5, 162.0, 199.4; ESI-MS(m/z): 372 [$\text{M}+\text{H}$] $^+$

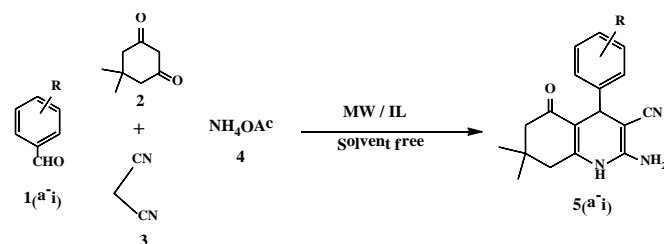
2-Amino-4-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5i)

IR(KBr cm^{-1}): 3420, 3325, 3263, 2964, 2177, 1650, 1470, 1362, 670; ^1H NMR (400 MHz, DMSO- d_6): δ 0.91 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.94-2.95 (dd, 2H, $J=15$ Hz, CH_2), 2.75-2.90 (dd, 2H, $J=17.0$, CH_2), 4.75 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m, 4H Ar-H), 7.20-8.50, (br, s 1H,

NH); ^{13}C NMR (75 MHz, DMSO- d_6): 27.2, 31.4, 39.3, 43.4, 52.8, 59.2, 111.2, 114.3, 115.7, 132.3, 138.2, 155.5, 161.0, 198.9; ESI-MS(m/z); 372 [$\text{M}+\text{H}$] $^+$

RESULTS AND DISCUSSION

Here an attempt has been made to develop one-pot synthesis and a new synthetic protocol for selectively substituted hexahydroquinoline derivatives using dimedone, aryl aldehydes, malononitrile, and ammonium acetate in a catalytic amount of ionic liquid. To study of this green protocol and reaction leading to the desired product by using microwave irradiation (Scheme 1).



Scheme 1. Synthetic route for compound **5a-5i**

A literature survey reveals that all the derivatives in scheme consumed a long time (nearly 180 min and more) for the completion with relatively lower yield (60-98 %). The same transformation could be accomplished under microwave-assisted with shorter reaction time (3-8 min) with moderate to excellent yield (80-95 %) in (Table 1).

Table 1. Synthesis of hexahydroquinoline derivatives catalyzed by ionic liquid under microwave irradiation (120 °C/300 W).

Pro- duct	R	Time, min	Yield, %	Melting point, °C	
				Found	Reported ^{Ref}
5a	H	8	80	272	275-277 ²⁷
5b	4-CH ₃	5	84	298	294-295 ²⁷
5c	4-OCH ₃	4	87	290	289-293 ²⁷
5d	4-OH	7	85	290	293-295 ²⁸
5e	2-F	5	92	297	299-300 ²⁷
5f	2-Cl	8	90	270	273-276 ²⁸
5g	4-Cl	3	95	288	290-291 ²⁸
5h	2-Br	5	88	280	285-287 ²⁸
5i	4-Br	4	92	290	295-296 ²⁸

Initially, the mixture of substituted aryl aldehydes, dimedone, malononitrile, ammonium acetate (0.01 mol each) was taken in an 50 mL vessel and subjected to microwave irradiation under neat conditions in the absence of catalyst and solvent, and the reaction was failed to get the product under this condition. The reaction was repeated in the presence of catalyst in the range of 2-10 mol %. We have optimized the amount of catalyst for the synthesis of (**5g**, Table 1) under microwave irradiation and excellent yield was obtained in only 3 minutes when 6 mol % catalysts are introduced (Table 2, entry 4).

Table 2. Optimization of catalyst concentration for the synthesis of (**5g**) under M.W. Irradiation.

Entry	Catalyst mol %	Time, min	Yield, ^a %
1	No catalyst	15	-
2	2	7	76
3	4	5	89
4	6	3	95
5	8	4	85
6	10	6	70

^aisolated yield

CONCLUSION

The microwave-assisted reaction is an efficient and beneficial protocol leading to the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives. The reaction is influenced under highly efficient, effortless, cheaply and recyclable homogenous catalyst (ionic liquid) for the one-pot multicomponent reaction of substituted aryl aldehydes, dimedone, malononitrile, and ammonium acetate under solvent-free condition. The advantages of the current protocol include its efficiency, high product yield, short reaction time and operational simplicity.

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EATON'S REAGENT CATALYZED SYNTHESIS, IN VITRO α -AMYLASE INHIBITORY ACTIVITY AND MOLECULAR DOCKING STUDY OF SOME SCHIFF'S BASES AS DIABETIC-II INHIBITORS

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A series of Schiff's bases of p-tolylsulphonyl hydrazide were synthesized by using Eaton's reagent under solvent-free condition, characterized by spectroscopic data and for evaluated α -amylase inhibitory activity *in vitro*. Four among the studied compounds exhibited varying degrees of α -amylase inhibitory activity with IC₅₀ values in the range of 115.48 to 169.42 $\mu\text{g mL}^{-1}$. The observed results were supported by the molecular docking study performed to understand the binding interaction of the title compounds with the active site of α -amylase enzyme. Results suggest that Schiff's bases of p-tolylsulphonyl hydrazide derivatives can act as potential antidiabetic drugs.

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converted by other enzymes to glucose that acts as a source of energy to the body. Inhibitors of α -amylase function by modulating the blood glucose level after a meal.⁴ The ability of a drug to delay the production and absorption of glucose by inhibiting carbohydrate hydrolyzing enzymes - α -amylase and α -glucosidase is an important therapeutic approach for the development of antidiabetic drugs. Thus α -amylase functioning as a key enzyme for the digestion and absorption of starch in the blood is one of the targets in the treatment of T2DM.

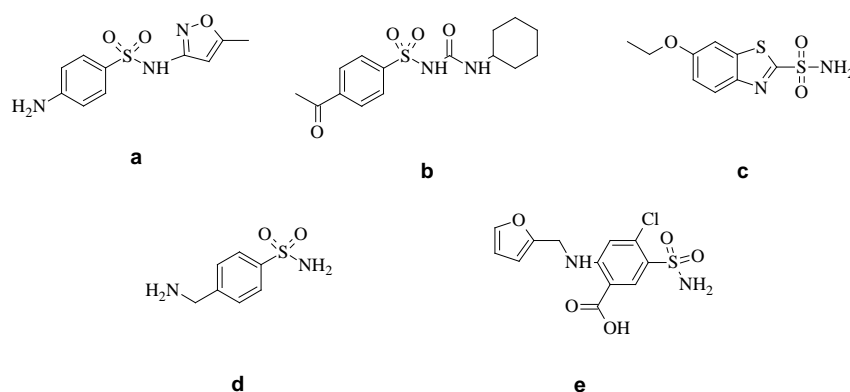
INTRODUCTION

Diabetes mellitus, a metabolic disorder characterized by chronic hyperglycemia condition, has become a significantly growing disease all over the world due to changing lifestyles and increasing junk food in the diet. As per the reports of the International Diabetes Federation (IDF), approximately 366 million people have diabetes and the number may be doubled by 2030.¹ It is mainly caused by the lack of insulin, which includes increased morbidity, disability, mortality and represents a threat to the economies of all countries, especially in developing ones like India.² In diabetic patients, the immune system becomes weak by destroying insulin-producing cells, leading to a high level of blood glucose, which significantly increases the risk of long-term heart disease, stroke, dysfunction and kidney failure.³

α -Amylase is an enzyme that catalyzes the hydrolysis of carbohydrates and starch into glucose in human blood, resulting in hyperglycemic condition and eventually type-II Diabetes mellitus (T2DM). It is present in the saliva of human beings, where it begins the chemical process of digestion. Pancreas and salivary glands make α -amylase to hydrolyze dietary starch into disaccharides which are then

Schiff's bases are the condensation products of primary amines with carbonyl compounds, named after the scientist Hugo Schiff. Schiff's bases possess imine or azomethine ($\text{C}=\text{N}-$) functional group and constitute a versatile pharmacophore and reaction intermediates for the design, synthesis, and development of various bioactive lead compounds of various biological interest such as 4-thiazolidinone,⁵ inorganic metal complexes⁶ and azetidinones.⁷ Furthermore, they are also well known to exhibit numerous biological activities such as antimicrobial,⁸ antitubercular,⁹ antioxidant,¹⁰ anticonvulsant,¹¹ anti-inflammatory,¹² and anticancer activity.¹³ They are also useful in pigments and dyes,¹⁴ intermediates for organic synthesis,¹⁵ polymer stabilizers¹⁶ and corrosion inhibitors.¹⁷

Sulfonamide functionality is the basis of several drugs. Sulfamethoxazole (**a**) is an antibacterial sulfa drug. Acetohexamide (**b**) is a sulfonylurea used to treat diabetes mellitus. Ethoxzolamide (**c**) is a sulfonamide drug that acts on carbonic anhydrase inhibitors and widely used in the treatment of glaucoma and ulcers.¹⁸ Mafenide (**d**), also known as sulfamylon, is a sulfonamide type medication that is used as an antibiotic. Furosemide (**e**) is used to treat fluid build-up due to heart failure, liver scarring or kidney disease and also in the treatment of high blood pressure.

**Figure 1:** Some biologically active sulphonamide drugs**Table 1.** Yields of Eaton's reagent catalyzed synthesis of Schiff's bases

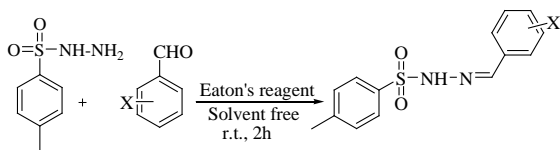
Entry	Aldehyde	Schiff's base	Code	Yield*, %	M. P., °C
1			1	91	133
2			2	90	178-180
3			3	89	142-143
4			4	90	134-136
5			5	80	133-135
6			6	90	182-183
7			7	92	177-179

*Yields isolated in case of p-toluenesulfonyl hydrazide (5 mmol), aldehyde (5 mmol) using Eaton's reagent (5 mol %) under solvent-free conditions.

Eaton's reagent [P_2O_5 : methane sulphonic acid] (1:10 by weight) is used as an alternative to the polyphosphoric acid (PPA) in organic synthesis.¹⁹ It is inexpensive, easy to handle, easy to separate, less viscous than PPA and commercially available reagent. Philip Eaton firstly synthesized it in 1973. Eaton's reagent has been used for the

synthesis of phenanthrolines,²⁰ tetrahydroisoquinoline-2-ones,²¹ quinolones,²² 3,4-dihydropyrimidin-2(1H)-ones,²³ polyamides²⁴ and chalcones.²⁵ Thus, considering the widespread applications, biological significance of Schiff's bases in various fields and in continuation of our successful attempts in the development of bioactive heterocyclic

compounds,²⁶⁻²⁷ in the present article we report the synthesis of some Schiff's bases from p-tolyl sulphonyl hydrazide and various aldehydes using Eaton's reagent under solvent-free conditions (Scheme 1).



Scheme 1. Eaton's reagent catalyzed synthesis of Schiff's bases.

The synthesized compounds were screened for *in vitro* α -amylase enzyme inhibitory antidiabetic activity whose observed results were supported by computational studies of molecular docking in terms of possible interactions with the active site of the α -amylase enzyme and high free energy of binding.

RESULTS AND DISCUSSION

In the present work, we synthesized some Schiff's bases of p-toluenesulphonyl hydrazide with various aldehydes under solvent-free conditions at room temperature. p-Toluenesulphonyl hydrazide is a solid compound. After the addition of aldehyde to p-toluenesulphonyl hydrazide, initially, the reaction mixture was difficult to stir at room temperature, particularly in the case of solid aldehydes. But as soon as Eaton's reagent was added to the above mixture, an exotherm was observed, the contents turned into the liquid phase for a while and then a white or yellow solid mass appeared which was stirred at room temperature for 2 h.

Initially, we tried the reaction of benzaldehyde with p-toluene sulphonyl hydrazide using Eaton's reagent (5 mol%) under solvent-free conditions. When tried with different amounts of Eaton's reagent from 5 to 10, 15 and 20 mol %, 5 mol % of the reagent was found to be appropriate for this transformation. Commonly ethanol is the best solvent for the synthesis of Schiff's bases. However, the use of ethanol in this reaction required slightly more time (3 h) for completion. Thus the use of 5 mol% of Eaton's reagent under solvent-free conditions was found to be the best condition for this reaction. Although the synthesis of Schiff's bases is fast and straightforward, comparatively more time was required for completion of the reaction (2 h) which could be most probably due to the presence of a sulphonamide group adjacent to the reaction center - NH₂.

Under these reaction conditions, various aldehydes were treated with p-toluene sulphonyl hydrazide to afford the corresponding Schiff's bases in excellent yields in almost all cases. Electron withdrawing groups reacted more smoothly, providing higher yields as compared to those with electron-donating groups. To our delight, methoxy groups in the Schiff's bases remained intact under these reaction conditions (Table 1).

The synthesized compounds were evaluated for amylase inhibitory activity and the results were compared with the standard acarbose. Among all the synthesized Schiff's bases, compounds **1** (4-chlorophenyl), **3** (3-nitrophenyl), **5** (fluorophenyl substituted indole) and **6** (2-methoxynaphthyl ring) had significant amylase inhibitory activity, but less than the standard acarbose at all the concentrations i.e. 20, 40, 60, 80 and 100 $\mu\text{g mL}^{-1}$ (Table 2).

Molecular docking study of human pancreatic α -amylase:

α -Amylase is an enzyme that catalyzes the hydrolysis of α -1,4 glucan linkages in starch. In human beings, α -amylase is composed of 496 amino acids in a single polypeptide chain and occurs as different isozymes synthesized in either salivary glands or the pancreas.

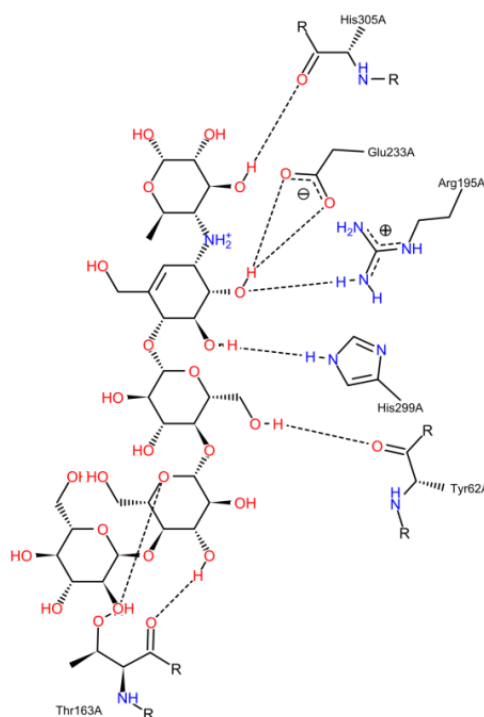
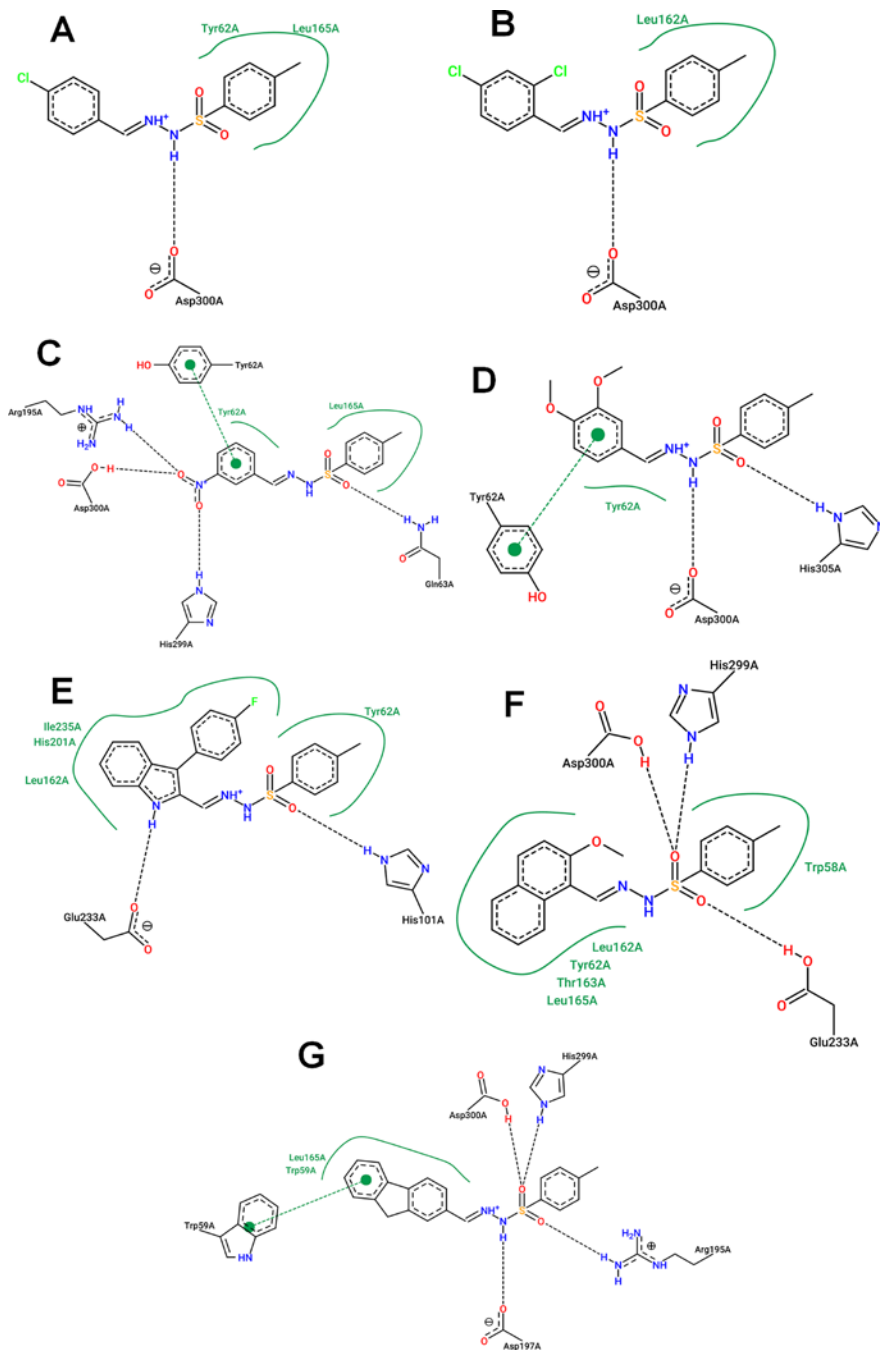


Figure 2. Interactions of acarbose with key residues at the binding site.

The screening of synthesized Schiff's bases showed that the compounds **1**, **2**, **3**, **5** and **6** possess good α -amylase inhibitory activity with IC₅₀ values less than 200 μM . The remaining compounds with IC₅₀ higher than 200 μM possess moderate α -amylase inhibitory activity. Docking results were found in good agreement with the experimentally observed α -amylase inhibitory activity. For the α -amylase inhibitory activity, the hydrogen bond interactions with residues HIS305, GLU233, ARG195, HIS299, TYR62, and THR163 were observed to be important as shown by α -amylase inhibitor Acarbose (Figure 2).

Table 2. % Results of amylase inhibitory activity and molecular docking study

Entry	Compound	% Inhibition at concentration, $\mu\text{g mL}^{-1}$					IC_{50} , $\mu\text{g mL}^{-1}$	Free Energy of binding, kcal mol^{-1}
		20	40	60	80	100		
1	1	5.56	11.83	23.07	34.43	39.17	115.48	-8.06
2	2	19.76	23.66	27.57	35.97	14.79	190.69	-8.58
3	3	22.60	26.62	34.79	35.85	40.71	169.42	-8.72
4	4	10.76	15.73	13.37	22.13	29.23	226.22	-7.29
5	5	31.36	39.40	45.79	51.47	52.89	154.17	-7.79
6	6	45.79	50.88	60.35	63.07	69.70	126.70	-8.82
7	7	33.96	39.40	43.43	46.50	47.92	253.97	-7.14
8	Acarbose	35.14	50.88	62.13	69.94	76.09	70.656	-12.52

**Figure 3.** 2D-Interaction diagrams for all compounds. A) Compound **1**; B) Compound **2**; C) Compound **3**; D) Compound **4**; E) Compound **5**; F) Compound **6**; and G) Compound **7** .

Most of the synthesized Schiff's bases showed similar hydrogen bond interactions and the aromatic rings of these Schiff's bases were found to occupy the binding pockets at the active site of α -amylase. Aromatic rings attached to imino nitrogen in compounds **1**, **6**, **5**, **3**, and **2** were found to make crucial hydrophobic interactions with TYR62, whereas the 4-methylphenyl ring in compound **5** and **3** showed significant hydrophobic interactions with the residues HIS201, LEU162 and ILE235 (Figure 3).

For **2**, **3** and **6** Schiff's bases, hydrogen bonding was observed with residues like ASP197, GLU233, HIS299, ASP300, THR163 as the key interactions similar in the case of standard acarbose. For Schiff's bases **4** and **7**, the crucial hydrophobic interaction with TYR62 were not found, but instead, the aromatic rings attached to imino nitrogen were found to occupy the pocket surrounded by the residues TRP59, TRP58 (Figure 3). These compounds form hydrogen bonds with the residues ASP300, HIS299, ASP197, and GLU233. The crucial hydrophobic interaction at the pocket with TYR62 residues was not found in these compounds which may be responsible for their less α -amylase inhibitory activity. This suggests that the presence of naphthyl, 2-indolyl, m-nitrophenyl and ortho-substituted rings were favorable for α -amylase inhibitory activity. The electronegative chloro and nitro groups on the phenyl ring were found to be beneficial for α -amylase inhibitory activity. The aromatic rings in these compounds were found to burry in the pockets made of residues like TYR62, LEU165.

EXPERIMENTAL

Chemicals used were SD fine or Aldrich made and used without further purification. The reaction progress was monitored by using silica gel pre-coated on aluminum TLC plates using 40 % ethyl acetate in n-hexane. Melting points of the products were measured in capillaries open at one end and were uncorrected. The products were purified by recrystallization from ethanol and confirmed by analysis of spectroscopic data (^1H NMR, ^{13}C NMR, IR and mass spectra).

General procedure for the solvent-free synthesis of Schiff's bases using Eaton's reagent

A mixture of p-toluenesulfonyl hydrazide (5 mmol) and aldehyde (5 mmol) was stirred with Eaton's reagent (5 mol %) at room temperature under the solvent-free condition for 2 h. Progress of the reaction was monitored by TLC in 40 % ethyl acetate in n-hexane. After completion of the reaction as confirmed by TLC, the reaction mass was poured into ice-cold water, resulting in solid was separated by filtration under vacuum and further purified by recrystallization from ethanol as the pure Schiff's base. □

1-(4-Chlorobenzylidene)-2-tosylhydrazine (1)

^1H NMR (400 MHz, CDCl_3): δ ppm 2.39 (s, 3H), 7.24-7.31 (dd, 4H), 7.47 (d, 2H), 7.7 (s, 1H), 7.86 (d, 2H), 8.35 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl_3): δ ppm 78.65, 127.12, 127.74, 128.55, 129.34, 132.43, 134.63, 136.11, 143.16, 145.27; Mass 309.1 (M+1) $^+$.

1-(2,4-Dichlorobenzylidene)-2-tosylhydrazine (2)

^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3H), 7.4-7.46 (m, 3H), 7.66 (s, 1H), 7.7-7.76 (dd, 3H), 8.19 (s, 1H), 11.82 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ ppm: 78.77, 127.11, 127.56, 129.04, 129.84, 133.49, 135.09, 136.00, 141.31, 143.36; Mass: 343.1 (M+1) $^+$.

1-(3-Nitrobenzylidene)-2-tosylhydrazine (3)

^1H NMR (400 MHz, CDCl_3) δ ppm 2.43 (s, 3H), 7.27-7.37 (dd, 2H), 7.55-7.59 (dd, 1H), 7.84-7.95 (m, 4H), 8.19 (d, 1H), 8.37 (s, 1H), 8.49 (d, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ ppm: 62.99, 120.96, 122.84, 124.19, 127.63, 129.68, 132.57, 135.41, 136.01, 138.08, 144.50, 148.04; Mass 320.0 (M+1) $^+$.

1-(3,4-Dimethoxybenzylidene)-2-tosylhydrazine (4)

^1H NMR (400 MHz) δ ppm: 2.38 (s, 3H), 3.8 (s, 6H), 6.98 (s, 1H), 7.7 (dd, 2H), 7.4 (s, 2H), 7.8 (dd, 3H), 11.2 (s, 1H); ^{13}C NMR (100.6 MHz) δ ppm: 20.94, 55.50, 108.57, 111.45, 120.91, 126.39, 127.25, 129.55, 136.12, 143.14, 147.18, 148.96, 150.59; IR (neat) cm^{-1} : 3196, 2970, 2930, 1598, 1550, 1029; Mass: 335.2 (M+1) $^+$.

1-[3-(4-Fluorophenyl)-1H-indol-2-yl)methylene]-2-tosylhydrazine (5)

^1H NMR (400 MHz) δ ppm: 2.43 (s, 3H), 7.10-7.18 (dd, 3H), 7.27-7.34 (m, 6H), 7.77 (s, 2H), 7.82-7.86 (dd, 4H); ^{13}C NMR (100.6 MHz, CDCl_3) δ ppm: 47.65, 112.91, 115.63, 120.15, 121.05, 123.93, 126.69, 127.36, 1237.86, 129.14, 129.65, 132.17, 135.77, 136.39, 140.10, 143.63, 160.14, 162.56; Mass 408.11 (M+1) $^+$.

1-(2-Methoxynaphthalen-1-yl)methylene)-2-tosylhydrazine (6)

^1H NMR (400 MHz, DMSO-d_6) δ ppm: 2.37 (s, 3H), 3.6 (s, 3H), 7.4-7.46 (m, 3H), 7.66 (s, 1H), 7.7-7.76 (m, 6H), 8.19 (s, 1H), 11.7 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ ppm 56.46, 113.09, 113.54, 123.89, 125.00, 127.76, 128.55, 129.64, 130.33, 132.59, 136.17, 143.51, 144.61, 157.31; Mass 355.11 (M+1) $^+$.

(9H-Fluoren-2-yl)methylene)-2-tosylhydrazine (7)

^1H NMR (400 MHz) δ ppm: 2.39 (s, 3H), 3.98 (s, 2H), 7.4 (d, 3H), 7.6 (s, 2H), 7.85 (m, 6H), 11.45 (s, 1H); ^{13}C NMR (100.6 MHz) δ ppm: 20.93, 36.25, 120.15, 123.04, 125.14, 126.13, 126.83, 127.22, 129.64, 132.21, 136.29, 140.31, 142.96, 143.44, 143.59, 147.40; IR (KBr) cm^{-1} : 3194, 2970, 2927, 1595; Mass: 363.2 (M+1) $^+$.

α -Amylase inhibitory activity

Antidiabetic activity of the synthesized compounds was determined in terms of % α -amylase inhibition using the literature method.²⁸ Starch solution (0.5 % w/v) was prepared using 20 mM sodium phosphate buffer with 6.7 mM sodium chloride (pH 6.9; 25 mL) in a boiling water

bath for 15 minutes. The α -Amylase solution was prepared by mixing 1U mL⁻¹ of α -amylase in the same buffer. The colorimetric reagent was prepared by mixing an equal volume of sodium potassium tartrate tetrahydrate solution and 96 mM 3,5-dinitrosalicylic acid (DNS) solution. Starch solution (1000 μ L) was mixed with increasing concentration of an enzyme inhibitor. 1000 μ L of the α -amylase solution was added to the synthesized compounds at different concentrations (20, 40, 60, 80, and 100 μ g mL⁻¹) or acarbose (20-100 μ g mL⁻¹) and incubated at 25 °C for 3 minutes to react with the starch solution. A 1000 μ L of 96 mM DNS reagent was added to the above solution and the contents were heated for 15 minutes in the boiling water bath. The final volume was made up with distilled water and absorbance was measured at 540 nm using a spectrophotometer. The percentage inhibition and 50 % inhibitory concentration (IC₅₀) values were then determined (Table 2).

Molecular Docking

Molecular docking study was performed to explore binding affinity, binding mode and possible molecular interactions of the synthesized compounds against the active site of the α -amylase enzyme and the results were expressed in terms of binding energies. The crystal structure of human pancreatic α -amylase complexed with Acarbose ((PDB: 2QV4) downloaded from www.rcsb.org was used for docking studies. Autodock Vina²⁹ was used to perform docking simulations. Marvin Sketch 5.6.0.0 (2011) was used to draw 2D structures of the compounds which were converted into 3D geometry using the same interface. The geometry of 3D molecules was optimized through energy minimization using UCSF Chimera 1.8³⁰ during which Gasteiger charges were added and energy minimization was carried out with the combination of steepest descent and conjugate gradient geometry search criteria until gradient converges to 0.05 and 0.01 respectively. The protein was processed by removing water and other nonstandard residues. The resulting clean protein was further optimized by energy minimization in UCSF Chimera with the Amber ff12SB force field and similar geometry search criteria. During the docking simulation, polar hydrogen was added to protein structure with MGLtools1.5.4. All torsion angles for the compounds were set free to perform flexible docking. Grid box of size 18 x 18 x 18 with 1Å spacing with x, y and z centers 12.94, 47.17 and 26.2 respectively was chosen, which was large enough to cover the active site of the protein. The results of docking simulations were analyzed in terms of estimated binding free energy in kcal mol⁻¹ and interactions of ligands with residues at the active site.

CONCLUSION

In summary, we synthesized various Schiff's bases of p-toluenesulphonyl hydrazide using Eaton's reagent (5 mol %) under solvent-free conditions. The synthesis is simple, solvent-free, beneficial and economical from the commercial point of view. The Schiff's bases **1**, **3**, **5** and **6** exhibited good amylase inhibitory activity and high free binding energies; but less than the standard Acarbose at different concentrations 20, 40, 60, 80 and 100 μ g mL⁻¹ highlighting the future scope in the development of p-

toluenesulphonyl hydrazide based compounds as possible diabetic inhibitors as per the pharmaceutical requirement.

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ONE-POT SYNTHESIS OF PHTHALAZIN-4-HETEROARYL-4H-PYRAN DERIVATIVES IN [BMIM][OH]

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Keywords: Phthalic acid, ethyl cyanohydrazide, active methylene compounds, heteroaromatic aldehydes, [bmim][OH].

A [bmim][OH] mediated, green and efficient synthesis of phthalazines derivatives have been developed by condensing phthalic acid (**1**), ethyl cyanohydrazide (**2**), heteroaromatic aldehydes (**3a-3f**) and active methylene compounds (**4**) at 60-65 °C for 60-90 min. The importance of this method includes shorter reaction time and high yield.

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INTRODUCTION

Nowadays ionic liquids (ILs) are used widely as reaction medium in organic chemistry. ILs have non-volatile nature at room temperature and have been used to develop eco-friendly methods for synthesis of organic compounds including heterocycles.²⁻⁴ Multicomponent reactions (MCR) are one-pot reactions which contains three to more components in single reaction vessel to give a final desired product containing substantial components of all the reactants.⁵ One of great challenges in modern medicinal chemistry is design and discovery of pharmaceutical active molecules.

Heterocyclic products which have nitrogen atom are well known and their use as pharmaceutical active compounds and agrochemicals are increasing.⁶ Heterocyclic compounds having phthalazine moiety have received considerable attention because of their biological active properties and clinical applications.⁷ Phthalazine compounds possess anti-convulsant,⁸ cardiotonic,⁹ and vasorelaxant,¹⁰ properties. This has led to a large number of reports about the synthesis of phthalazine compounds.¹¹ Nevertheless the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge.

Therefore, we decide to prepare phthalazine containing pyran moiety. Here, we report one-pot four component reaction for title compounds in weakly basic 1-butyl-3-methylimidazolium hydroxide ([bmim][OH]) medium.

RESULTS AND DISCUSSION

First, we have studied a one pot, four-component reaction of phthalic acid (**1**) (1 mmol), ethyl cyanohydrazide¹² (**2**) (1 mmol), furfuraldehyde (**3a**) (1 mmol), and malononitrile (**4**) (1 mmol) in different ionic liquid medium at different

temperatures to form 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(furan-2-yl)-4H-pyran-3,5-dicarbonitrile (**5a**) as a model reaction. It was found that the reaction in the presence of [bmim][OH] as medium for 1 h at 60-65 °C gave the highest yield (88 %) and the clean product **5a** (Table 1, entry 1). Here, initially compound **1** was reacted with **2** in [bmim][OH] at 60-65 °C for 18 min to form 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile as intermediate **6** (confirmed by TLC, showing the absence of starting materials). Then to this reaction mixture added **3a** and **4** and again heated at 60-65 °C for 1.5 h to form **5a** excellent yield (88 %) on simple work-up of the reaction mixture. The structure of the compound **5a** has been confirmed by ¹H NMR, IR and mass spectroscopy.

Table 1. Effect of ionic liquid and temperature on the synthesis of **5a**.

Entry	Ionic liquid	Temp., °C	Time, h/h	Yield of, 5a , %
1	[bmim][OH]	60-65	1	88
6	[bmim][Br]	60-65	3	70
5	[DBUH][OAc]	60-65	2	83
4	[bmim][OH]	80-85	1	80
5	[bmim][OH]	40-45	2	75
6	[bmim][OH]	30-35	6	70

Table 2. The effect of amount of [bmim][OH] on the yield of **5a**.

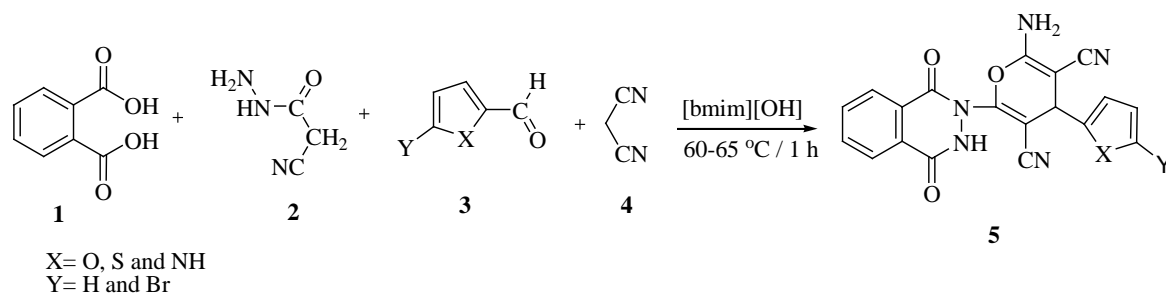
Entry	mmol of [bmim][OH]	Time, h	Yield of 5a (%)
1	0.5	4	80
2	1	2	88
3	2	2	82

After finalizing the above optimization conditions, the one-pot reaction has been carried out at different temperature (room temperature, 40, 60 and 80 °C) in the presence of [bmim][OH] to get desired compound **5a**. It was found that the one-pot reaction of **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and **4a** (1 mmol) in the presence of [bmim][OH] as medium (1 mmol) for 120 min at 60-65 °C gave the highest yield (88 %) and the clean product **5a** (Table 1, entry 1). In order to examine effect of different quantity of [bmim][OH], the one-pot reaction has been carried out at different quantity (0.5, 1 and 2 mmol) of

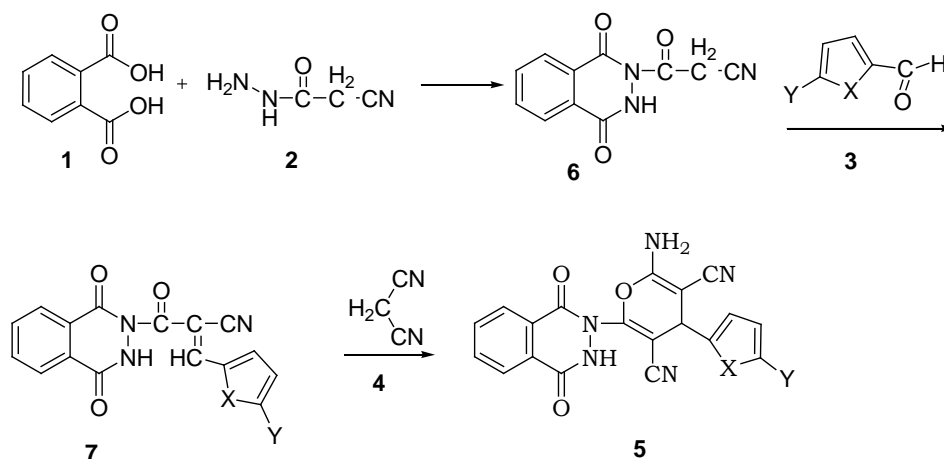
[bmim][OH] with respect of phthalic acid **1**. However, it was found that the one-pot reaction of **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and **4a** (1 mmol) in the presence of [bmim][OH] (1 mmol) as medium for 2 h at 60-65 °C gave the highest yield (88 %) (Table 2, entry 2).

After having optimized the reaction conditions, the generality of the reaction was investigated by carrying out

the condensation of several others heteroaromatic aldehydes (**3b-3f**) respectively in [bmim][OH] medium at 60-65 °C for 2 h giving **5b-5f** in very good yields and no side product formation was detected. It was found that this method works with a wide variety of substrates. It is worthy to mention that the reaction of **1**, **2**, **3a-3f** and **4** could get high yield and require short reaction time for formation of **5a-5f**. (Scheme 1).



Scheme 1. One-pot synthesis of **5a-f**.



Scheme 2. Step-wise synthesis of **5**.

The synthesis of **5** could also be achieved in step-wise syntheses. Thus, a mixture of **1** and **2** was heated at 60-65 °C for 0.5 h in [bmim][OH] medium to form intermediate **6**.¹³ Then, **6** was reacted with **3** at 60-65 °C for 0.5 h in [bmim][OH] medium to form intermediate **7**¹³ then **7** was reacted with **4** at 60-65 °C for 0.5 h in [bmim][OH] medium to form **5**. The reaction was monitored by TLC.

The structures of these products have been established earlier on the basis of their spectral data (Scheme 2).

Furthermore, the compound **5** was assigned E-configuration on the presumption that bulky groups in a trans position would confer thermal stability on the molecule. This has been found to be case by a careful examination of the Frame-work molecular models of both E and Z-configurations of **5** wherein it was observed that there was minimum number of steric interactions in the E-configuration.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using iodine vapour or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument on KBr pellets. ¹H NMR spectra were recorded in DMSO-*d*₆ using TMS as internal standard at 400 MHz operating frequency. Mass spectra were recorded on Agilent-LCMS instrument. All reagents were purchased from Merck or Aldrich and used without further purification. [bmim][OH] was prepared as reported elsewhere.¹³

Preparation of 5a-5f from 1, 2, 3a-3f and 4

A mixture of **1** (1 mmol) and **2** (1 mmol) was heated at 60-65 °C for 0.5 h in [bmim][OH] (1 mmol) for 0.5 h, when

no starting materials was detected by TLC. To this reaction mass added compounds **3** and **4** and again heated at 60–65 °C for 1 h, when no starting materials was detected by TLC. After the reaction was complete, cold water was added to the reaction mixture and solid part was separated by filtration. The product was recrystallized from ethanol to obtain **5**.

2-Amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(furan-2-yl)-4H-pyran-3,5-dicarbonitrile (5a)

Yield 88 %, m.p. 206–208 °C. IR (KBr): 3302–3406 (br, medium, -NH-), 2211 (s, strong, -CN-), 1715 (s, strong, -CO- of amide group), 1655 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.2 (s, 1H, -CH), 7.0–8.2 (m, 7H, Ar-H), 9.6 (s, 2H, -NH₂), 11.4 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ = 44.7, 74.6, 85.4, 113.7, 114.3, 123.6, 126.7, 127.8, 129.6, 131.8, 133.2, 137.1, 155.4, 157.5, 163.1, 163.8. $M^+ + 1 = 374$.

2-Amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(thiophen-2-yl)-4H-pyran-3,5-dicarbonitrile (5b)

Yield 86 %, m.p. 182–190 °C; IR (KBr) : 3306–3401 cm^{-1} (br, medium, -NH-), 2218 cm^{-1} (s, strong, -CN-), 1706 cm^{-1} (s, strong, -CO- of amide group), 1659 cm^{-1} (s, strong, -CO- of amide group); ^1H NMR (DMSO- d_6 , 400 MHz): δ 6.5 (s, 1H, -CH), 7.4–8.1 (m, 7H, Ar-H), 9.8 (s, 2H, -NH₂), 12.1 (s, 1H, -NH, D₂O exchangeable); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 49.5, 74.5, 87.3, 113.9, 115.1, 124.2, 127.8, 128.6, 129.1, 130.7, 134.3, 137.0, 155.8, 157.3, 163.0, 163.5; $M^+ + 1 = 390$.

2-Amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(1H-pyrrol-2-yl)-4H-pyran-3,5-dicarbonitrile (5c)

Yield 84 %, m.p. 193–195 °C. IR (KBr): 3303–3405 (br, medium, -NH-), 2217 (s, strong, -CN-), 1704 (s, strong, -CO- of amide group), 1658 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.0 (s, 1H, -CH), 7.2–8.4 (m, 7H, Ar-H), 9.3 (s, 2H, -NH₂), 11.4 (s, 1H, -NH, D₂O exchangeable), 11.9 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ = 47.5, 74.6, 86.3, 115.7, 116.2, 123.4, 126.7, 127.4, 128.8, 132.4, 133.2, 134.1, 154.5, 156.3, 163.1, 163.4. $M^+ + 1 = 373$.

2-Amino-4-(5-bromofuran-2-yl)-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4H-pyran-3,5-dicarbonitrile (5d)

Yield 83 %, m.p. 211–212 °C. IR (KBr): 3305–3405 (br, medium, -NH-), 2215 (s, strong, -CN-), 1716 (s, strong, -CO- of amide group), 1658 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.1 (s, 1H, -CH), 7.0–8.2 (m, 6H, Ar-H), 9.5 (s, 2H, -NH₂), 11.2 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ = 44.9, 74.9, 85.8, 113.9, 114.9, 123.1, 126.2, 127.1, 129.2, 131.4, 133.5, 137.2, 155.2, 157.6, 163.2, 163.1. $M^+ + 1 = 451$.

2-Amino-4-(5-bromothiophen-2-yl)-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4H-pyran-3,5-dicarbonitrile (5e)

Yield 82 %, m.p. 192–194 °C. IR (KBr): 3302–3401 (br, medium, -NH-), 2213 (s, strong, -CN-), 1702 (s, strong, -CO- of amide group), 1655 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.1 (s, 1H, -CH), 7.4–8.1 (m, 6H, Ar-H), 9.5 (s, 2H, -NH₂), 12.2 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ = 49.1, 74.3, 87.2, 113.6, 115.2, 124.1, 127.4, 128.8, 129.2, 130.5, 134.8, 137.2, 155.6, 157.4, 163.1, 163.3. $M^+ + 1 = 469$.

2-Amino-4-(5-bromo-1H-pyrrol-2-yl)-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4H-pyran-3,5-dicarbonitrile (5f)

Yield 88 %, m.p. 186–188 °C. IR (KBr): 3301–3402 (br, medium, -NH-), 2214 (s, strong, -CN-), 1701 (s, strong, -CO- of amide group), 1659 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.3 (s, 1H, -CH), 7.2–8.4 (m, 6H, Ar-H), 9.5 (s, 2H, -NH₂), 11.3 (s, 1H, -NH, D₂O exchangeable), 11.8 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ = 47.3, 74.8, 86.2, 115.1, 116.1, 123.8, 126.8, 127.8, 128.9, 132.1, 133.3, 134.2, 154.3, 156.1, 163.2, 163.1. $M^+ + 1 = 452$.

Preparation of 6 from 1 and 2 via stepwise reactions

A mixture of **1** and **2** was heated at 60–65 °C in [DBU] [OAc] (1 mmol) for 0.5 h. After the completion of the reaction, as monitored by TLC, the reaction mixture was poured into ice-cold water. The precipitated product was filtered, washed with water, dried and recrystallized from ethanol. Yield 75 %, m.p. 152–154 °C [lit.¹³ m.p. 150–152 °C].

Preparation of compounds 7 from 6 and compounds 3

A mixture of **6** (1 mmol), **3a–3f** (1 mmol) and [DBU] [OAc] (1 mmol) were heated at 60–65 °C for 0.5 h. After the completion of the reaction, as monitored by TLC, the reaction mixture was poured into ice-cold water. The precipitated product was filtered, washed with water, dried and recrystallized from ethanol. Yield ~ 86 %.

(E)-2-(1,4-Dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(furan-2-yl)acrylonitrile (7a)

M.p. 169–171 °C. IR (KBr): 3140–3438 (broad, medium, -NH-), 2258 (sharp, strong, -CN-), 1743 (sharp, strong, -CO-group), 1730 (sharp, strong, -CO-group), 1683 (sharp, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.8 (s, 1H, -CH), 7.5–8.2 (m, 7H, -ArH), 11.3 (s, 1H, -NH, D₂O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.2, 81.2, 117.2, 122.4, 124.2, 127.4, 128.2, 128.6, 129.1, 129.1, 129.3, 133.1, 136.2, 164.3, 164.4, 164.8. $M^+ + 1 = 308$.

(E)-2-(1,4-Dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(thiophen-2-yl)acrylonitrile (7b)

M.p. 160–162 °C. IR (KBr): 3294-3519 (broad, medium, -NH-), 2258 (sharp, strong, -CN-), 1794 (sharp, strong, -CO- group), 1748 (sharp, strong, -CO- of amide group), 1682 (sharp, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 7.3 (s, 1H, -CH), 7.9-8.6 (m, 7H, -ArH), 11.3 (s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.3, 81.3, 117.2, 122.8, 124.0, 127.2, 128.2, 128.5, 129.0, 129.1, 129.5, 133.1, 136.0, 164.4, 164.4, 164.7. $M^+ + 1 = 324$.

(E)-2-(1,4-Dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-pyrrol-2-yl)acrylonitrile (7c)

M.p. 169–171 °C. IR (KBr): 3046-3444 (broad, medium, -NH-), 2258 (sharp, strong, -CN-), 1773 (sharp, strong, -CO- group), 1730 (sharp, strong, -CO- group), 1673 (sharp, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.5 (s, 1H, -CH), 7.4-8.1 (m, 7H, -ArH), 11.1 (s, 1H, -NH, D_2O exchangeable), 12.1 (s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.0, 81.2, 117.1, 122.6, 124.5, 127.2, 128.2, 128.7, 129.1, 129.2, 129.3, 133.1, 136.2, 164.3, 164.6, 164.8. $M^+ + 1 = 307$.

(E)-3-(5-Bromofuran-2-yl)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)acrylonitrile (7d)

M.p. 156–159 °C. IR (KBr): 3145-3432 (br, medium, -NH-), 2259 (s, strong, -CN-), 1748 (s, strong, -CO- group), 1735 (s, strong, -CO- group), 1685 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 6.9 (s, 1H, -CH), 7.5-8.2 (m, 6H, -ArH), 11.8 (s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.1, 81.6, 117.1, 122.3, 124.8, 127.6, 128.3, 128.9, 129.3, 129.6, 129.9, 133.2, 136.4, 164.5, 164.8, 164.9. $M^+ + 1 = 387$.

(E)-3-(5-Bromothiophen-2-yl)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)acrylonitrile (7e)

M.p. 165–167 °C. IR (KBr): 3295-3512 (br, medium, -NH-), 2245 (s, strong, -CN-), 1793 (s, strong, -CO- group), 1749 (s, strong, -CO- of amide group), 1680 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz) δ = 7.1 (s, 1H, -CH), 7.9-8.6 (m, 6H, -ArH), 11.2 (s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.1, 81.5, 117.1, 122.4, 124.2, 127.3, 128.1, 128.3, 129.1, 129.5, 129.6, 133.2, 136.1, 164.2, 164.6, 164.8. $M^+ + 1 = 403$.

(E)-3-(5-Bromo-1H-pyrrol-2-yl)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)acrylonitrile (7f)

M.p. 171–173 °C. IR (KBr): 3048-3440 (br, medium, -NH-), 2252 (s, strong, -CN-), 1775 (s, strong, -CO- group), 1731 (s, strong, -CO- group), 1675 (s, strong, -CO- of amide group) cm^{-1} . ^1H NMR (DMSO- d_6 , 400 MHz): δ 6.3 (s, 1H, -CH), 7.4-8.1 (m, 6H, -ArH), 11.4 (s, 1H, -NH, D_2O exchangeable), 12.2 (s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 81.3, 81.5, 117.4, 122.8, 124.8, 127.1, 128.5, 128.8, 129.2, 129.4, 129.8, 133.2, 136.3, 164.5, 164.6, 164.8. $M^+ + 1 = 386$.

Preparation of compounds 5 from 7 and 4

A mixture of **7** (1 mmol), **4** (1 mmol) and [DBU] [OAc] (1 mmol) were heated at 60–65 °C for 1.0 h. After the completion of the reaction, as monitored by TLC, the reaction mixture was poured into ice-cold water. The precipitated product was filtered, washed with water, dried and recrystallized from ethanol to form **5**. Yield ~ 80%.

CONCLUSION

In summary, we have successfully devised a simple and green one pot as well as step-wise and tandem process for synthesis of novel 2-amino-6(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl-4-heteroyl-4H-pyran-3,5-dicarboxitriles with simple work up procedures.

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COMPARISON OF INTENSITY-MODULATED RADIOTHERAPY (IMRT) AND 3D TANGENTIAL BEAMS TECHNIQUE USED AT PATIENTS WITH BREAST CANCER

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Keywords: Oncology; radiotherapy; breast cancer; intensity-modulated radiotherapy (IMRT), three-dimensional conformal radiotherapy (3D-CRT); QA; dosimetry.

Radiotherapy is one of the most effective treatments for breast cancer. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) are two recently developed radiotherapy techniques. IMRT is believed to be more effective than 3D-CRT in target coverage, dose homogeneity and reducing toxicity to healthy organs. However, these advantages have not been demonstrated in the treatment of breast cancer. This meta-analysis was performed to compare IMRT and 3D-CRT in the treatment of breast cancer in terms of dose-volume histograms and outcomes, including survival and toxicity. □

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INTRODUCTION

Radiotherapy nowadays, together with chemotherapy and surgery, is a way to treat the patients who have different kinds of tumors. The radiotherapy aims to give the prescribed dose to the tumor and to protect as much as possible the organs and surrounding healthy tissue at risk. Intensity-modulated radiation therapy (IMRT) is an advanced technique of high-precision radiotherapy that uses a computer-controlled linear accelerator to deliver precise radiation doses to a malignant tumor or specific areas within the tumor.¹ IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the tumor by modulating or controlling the intensity of the radiation beam in multiple small volumes² and high radiation doses to be focused to regions within the tumor while minimizing the dose to surrounding normal critical structures.

The process of radiotherapy starts with scanning of the patients, delineating areas of interest, creating the treatment plans and sending all the data to the machine through a verification system, mosaic. An essential part of this chain is the plan which is created in the treatment planning system. This system can create 3D CRT and IMRT plans.³ Even the process of these two techniques is similar, and the design plan differs significantly. Conventional 3D CRT treatment planning is manually optimized. This means that the treatment planner chooses all beams parameters, such as the number of beams, beam directions, shapes, weights, etc., and the computer calculates the resulting dose distribution.⁴ In the case of IMRT dose distribution is inversely determined, meaning that the treatment planner has to decide before the dose distribution he wants and the

computer then calculates a group of beam intensities that will be produced, as nearly as possible, the desired dose distribution.⁵ It is necessary to compare and to know the advantages and disadvantages of these two methods, and so to choose the right method for every single patient. □

The purpose of this article is to compare the intensity-modulated radiotherapy (IMRT) with the 3D tangential beams technique in respect of dose distribution in target volume and critical organs they generate in patients with early-stage breast cancer who received breast-conserving therapy.

EXPERIMENTAL

In this study, five patients with breast tumors have been taken into account. The patients are scanned in the CT simulator. They are positioning with the help of immobilization devices such as breast step ELKETA. On the body, three orientated points in the crosses of lasers' room are put. These are some marks (cross). The slices' thickness is 3 mm and then the images are sent to the Monaco TPC. Monaco is the system where the doctors delineate the target volumes and the organs at risk. A treatment planning system that is in use Monte Carlo algorithm, which is a family of two and three-dimensional treatment plans systems.⁶ It is composed of several modules; the most important module of patients' data, including patient demographics and anatomic data and the teletherapy planning module.⁷

The treatment planning system can create plans with both techniques three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. The plans with the first technique treatment are done in two phases. In the first phase, the plan is a simple box technique with four beams. Each beam has the energy 6 MV. The beams are conformed with the help of MLC to the treatment planning volume PTV dose distribution.

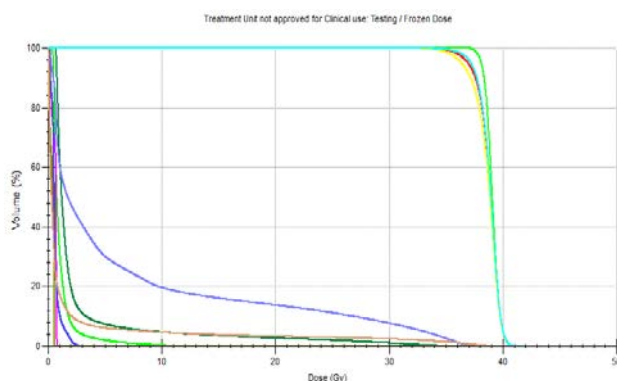


Figure 1. A case of IMRT treatment plan DVH.

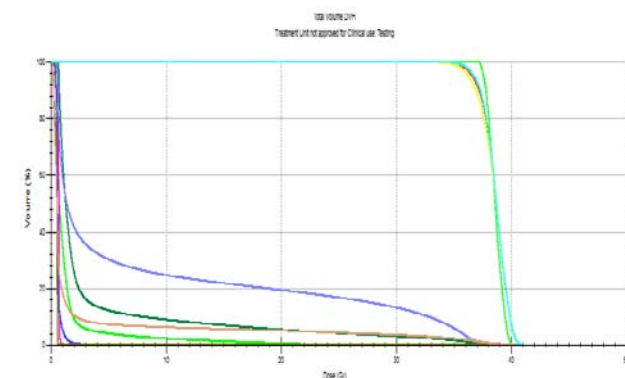


Figure 2. A case of 3D CRT.

The second technique (IMRT) is done with one phase. The number of beams is fixed. There are six beams, with energy 6 MV, in different angles, which are used to create the plan. All the beams are created by more small beams to modulate the intensity in such a way to have the desire. When the plans are finished, they are compared for both methods, first according to the dose-volume histogram and then according to time-consuming for quality control procedures. The checks for the position of the patients, so the giving of the right dose to the right part of the body, for 3D CRT and IMRT are done in the machine according to the set-up beams with the help of IGRT. The time which is needed to treat the patients with the first technique is much shorter than the second technique. □

RESULTS AND DISCUSSIONS

These plans were done with both techniques, three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for five patients with breast tumors. Their comparison is done first according to dose-volume histograms and then according to time-consuming for QC checks. For all organs at risk, the comparison is made for the mean doses. It is observed that the average doses, for all patients, are a little lower in the IMRT technique than in 3D (Figures 1 and 2). Table 1 gives a picture of such results. The mean doses are in Gy.

Table 1. Means radiation doses at various organs.

	Mean dose			Heterogeneity index CTV (vol. 95 %)
	Heart	Lung	cont. breast	
IMRT	2.486	6.737	1.092	1.08
3D	3.579	8.146	1.418	1.10

From the obtain histograms (Figures 1 and 2), it is seen that the conformity to planning target volume does not differ very much. Anyway, a bit better conformity it is observed with the IMRT technique. Regarding the doses to the organs at risk, it is not a big difference between doses taken by organs at risk in the IMRT and 3D CRT technique. So according to the histograms we can say that the IMRT technique is better for protection of the organs at risk and irradiating with the best coverage the treatment planning volume, because in the 3D CRT due to the dose limits for the organs at risk it should be irradiate first the planning target volume as the doctors delineate and then a smaller planning target volume. So in the IMRT technique, it is irradiated the appropriate planning target volume with the maximum protection of the organs at risk and not only a part of it.

CONCLUSIONS

The work done in this investigation stresses the advantages and disadvantages of two treatment methods for breast tumors. To choose between two techniques, it is necessary to see the patients' characteristics case by case. It is important to determine the total dose, which has to be given to the planning target volume. It is preferable to use the 3D CRT technique while planning treatment with a volume of dose within the safe limits for the organs at risk because it is less time consuming for QC and more comfortable for the patient which in this case has to spend less time in the machine during the treatment. For the cases where the doses which have to be given for the procedure will not be significant, say around 40 Gy, it will be preferable to use the IMRT technique for keeping the doses within the permitted level for the organs at risk. □

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OCCURRENCE OF MICROPLASTICS IN SURFACE SEDIMENTS OF BEACHES IN LAGOS, NIGERIA

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and Akudo Ugochi Akandu^[a]

Keywords: Microplastics, plastic debris, coastal environment, sediments, Nigeria, beach.

This study investigated the occurrence and abundance of microplastics in surface sediments from five beaches in Lagos State, Nigeria. The beaches are Alpha, Oniru, Eleko and Lekki. Microplastics were taken from the sediments by floatation method. The number of microplastics in 50 g of dry sediment were counted with a photo microscope and results were as follows: Eleko (170 ± 21 items), Lekki (141 ± 36 items), Alpha (133 ± 16 items), and Oniru (121 ± 38 items). Fragments dominated among the microplastics found in the beaches while three polymers; polypropylene (PP), polyethylene (PE) and polystyrene (PS) were identified using Fourier transform infrared spectroscopy (FTIR). This study serves as baseline for further investigations on the occurrence of microplastics in the Nigerian coastal environment.

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INTRODUCTION

Plastic debris is ubiquitous in all ecosystems and it presently has the attention of environmental scientists and policy makers.^{1,2} They disintegrate into smaller particles in the environment and when the particles reach a size below 5 mm, they are called microplastics.

Microplastics are plastics particles lower than 5 mm in any one dimension.^{3,4} In most cases, they are only discernable to the eye with the use of microscopy.⁵ However, most authors define microplastics as plastics particles whose longest diameter is <5 mm.⁶ The presence of small plastic fragments in the marine environment was first highlighted in the 1970s and renewed interest in microplastics over the past decade has shown that these contaminants are widespread and ubiquitous in the marine environment with the potential to cause harm to biota.⁷⁻⁹

Microplastics are of two types; primary and secondary microplastics. Plastics manufactured to be of microscopic size are defined as primary microplastics. Primary microplastics are used in facial-cleansers, cosmetics, personal cleansing and house-hold products.^{4,10} Secondary microplastics occur when larger pieces of plastics break down into smaller pieces as a result of photochemical, mechanical and biological processes.^{11,12} Microplastic sources in the environment include waste water treatment plants (WWTPs), biosolid application, storm water overflow, incidental releases such as tire wear, release from industrial products or processes, and atmospheric deposition.^{3,13,14}

Microplastics accumulated in the marine environment are carriers of many pollutants which can affect the development of organisms. The risks to organisms include physiological injuries, blockage of digestive tract, alteration of feeding and reproductive activities and decreased immune response.¹⁵⁻¹⁷ They sorb persistent organic pollutants such as PCBs, DDT, PAHs and organochlorine pesticides.¹⁸⁻²¹ They have the potential to be ingested by marine biota and may be transferred to higher food chain.^{7,22-25} Microplastics are like other classes of chemical contaminants such as pesticides, trace metals and flame retardants and should be handled as such rather than simply a single compound.²⁶

The ubiquitous nature of microplastics and its ability to break into smaller particles even into nano levels makes it a major concern for the environment. This is further heightened by the ability of these microplastics to move through the food chain.²⁵ Occurrence of microplastics in aquatic environment has been studied by several workers.²⁷⁻³³ However, there has been paucity of data on microplastic occurrence in Africa especially West Africa. This study is the first attempt to quantify microplastics in the Nigerian coastal environment. The aim, therefore, was to quantify microplastic abundance and identify the nature of microplastics in surface sediments from four beaches along the West African coast in Lagos State, Nigeria.

EXPERIMENTAL

Sampling sites

Table 1. Sampling stations and geographical coordinates.

Sample/Beach Designation	Beach Name	Coordinates
A	Alpha	N6.4225 E3.5236
B	Oniru	N6.4398 E3.4306
C	Eleko	N6.4403 E3.8472
D	Lekki	N6.2518 E3.4432

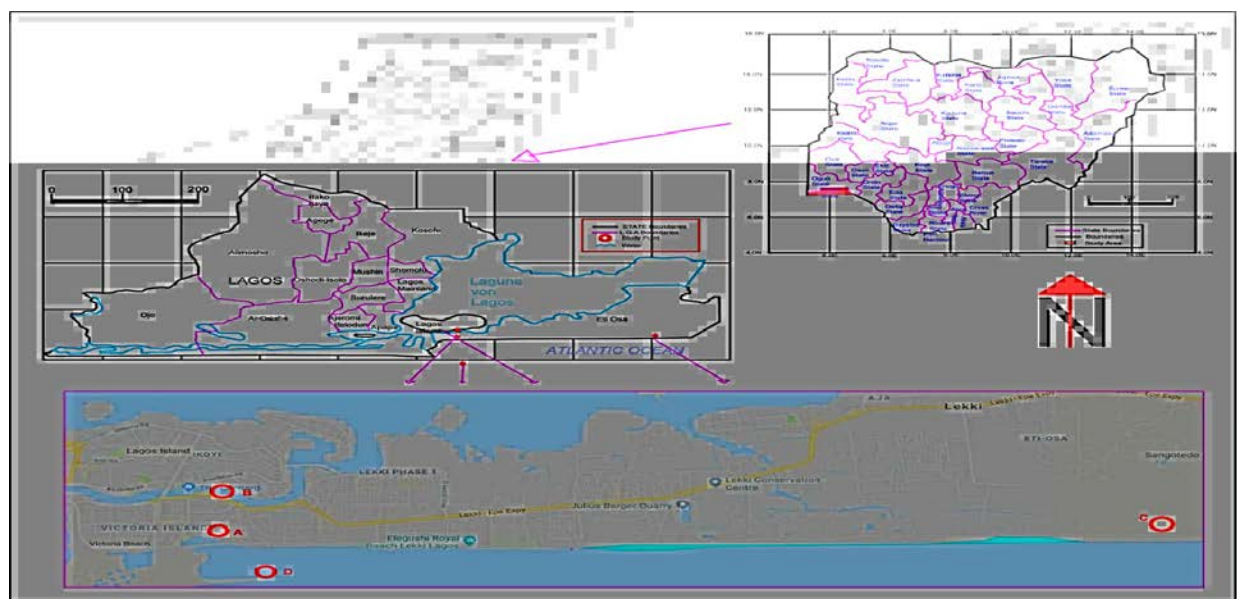


Figure 1. Geographical location of the study area showing the four sampling sites.

The beaches (Alpha, Oniru, Eleko and Lekki) used for this study are located in Lagos State, southwestern Nigeria. (Table1, Figure 1). They are bound by the Atlantic Ocean and serve as “fun spots” for tourists and fun seekers. Sediment samples were collected with a steel spoon along the littoral zones of each beach. Surface sediments (1-5 cm) were randomly collected with a stainless-steel spoon and a 20 × 20 cm wooden quadrant. In each beach, samples were randomly collected from three different points and thoroughly mixed to form a single composite sample. Samples were transferred to an aluminum foil, properly sealed and transported to the laboratory. Samples were collected in March 2018.

Sample Preparation and Processing

The sediment samples were dried at 50 °C for 48 h and sieved through a 5 mm mesh. Density floatation method was used to extract microplastics from the sediment.^{30,32} Triplicate 50 g dried sediment of each sample was weighed into a glass beaker and 200 ml NaCl solution (300 g/L) was added to the samples. The mixture was stirred for two min, properly covered with aluminum foil and kept for 24 hours. The supernatant containing microplastics was then filtered with vacuum pump. The filtrate was discarded while the residue which contained microplastics was dried in the oven at 50 °C for 24 h and stored in glass Petri dishes.

Enumeration and identification

Materials were examined with photo microscope (Olympus CX31RTSF) equipped with Olympus E330-ADU1.2X6K1338 camera at 40x magnification. Photographs of suspected particles were directly taken on the filters. Natural debris was separated from particles suspected to be microplastics during visual inspection according to the criteria enumerated by other workers.³³⁻³⁶ Selected suspected particles were further identified with

FTIR (Buck Scientific M530 USA). Spectra were in transmittance mode and ranged from 500 to 4000 cm⁻¹. Polymer types were identified by matching the wavelength data with those obtained from literatures. Laboratory materials used for sample preparation and extraction were rinsed with double distilled water and all liquids were filtered before use. Samples were covered when not in use and filters were carefully examined to prevent contamination by air-borne particles. Blank extraction was also run without the samples to ensure non-contamination.

RESULTS AND DISCUSSION

Abundance

Microplastics were found in the triplicate samples from all sampling stations (Figure 2). This implies that Nigerian beaches are not immune to microplastic pollution and accumulation.

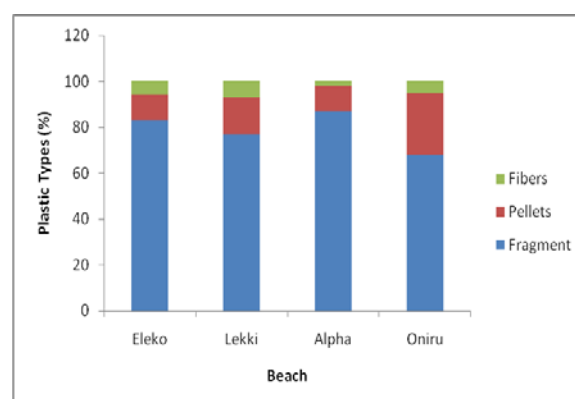


Figure 2. Abundance of microplastic types in the sediment samples.

Concentrations of microplastics in 50 g of dry sediment were in the following order: Eleko beach (170 ± 21 items), Lekki beach (141 ± 36 items), Alpha beach (133 ± 16 items) and Oniru (121 ± 38 items). Eleko beach had the highest number of microplastics while Oniru beach had the least number of microplastics. Oniru beach, apart from being a private beach does not allow the use of plastic materials. It

is one of the beaches in Nigeria that has become conscious of the potential environmental risk of microplastics. It is usually ambiguous to ascertain the sources of microplastics in beach sediments. This is because plastics in beach sediments have long residence time and are highly fragmented under high UV irradiation, high temperature and physical abrasion by waves.³⁷

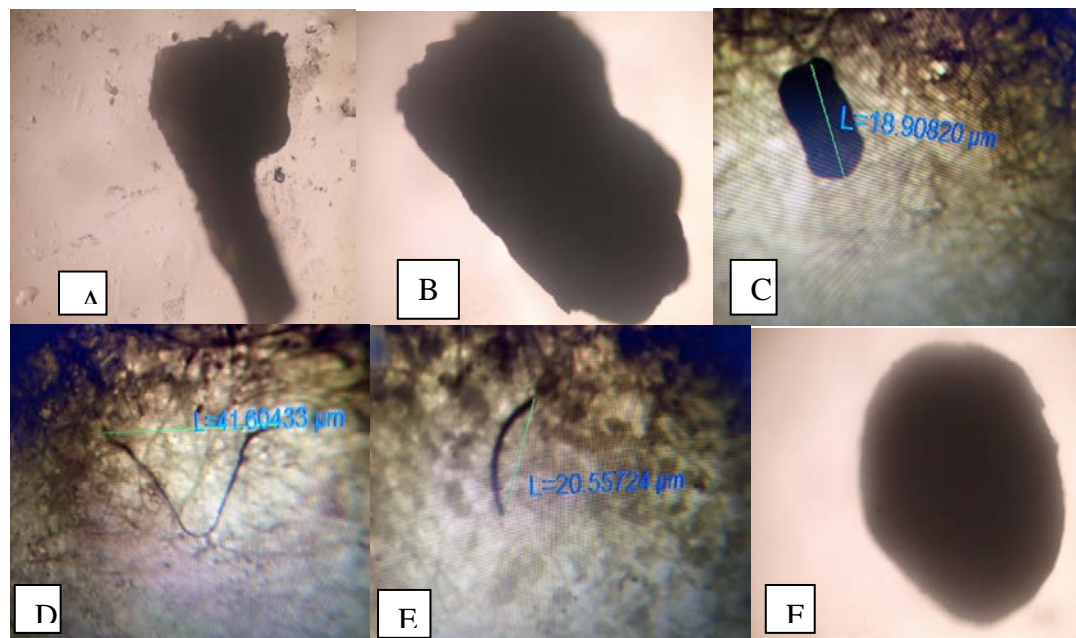


Figure 3. Types of Microplastics identified in the samples A-C; Fragment D-E; Fiber F; Pellet.

These microplastics may be washed ashore from the ocean³⁸ or may be from fragmentation of larger plastics littered on the shore as a result of photochemical, mechanical and biological processes.^{11,12} No particular pattern was observed in the abundance of microplastics in the sediments except that fragments dominated in all samples followed by pellets and then fibers. (Figure 2 and 3). This similarity in the nature of microplastics from all these sites indicates the uniformity of their likely sources. The higher number of fragments suggests the breakdown of larger plastic items into secondary microplastics as the most significant source of microplastics in the beaches. It is difficult to compare microplastics abundance in different countries and regions due to different sampling and analysis protocols such as solutions used for density floatation, enumeration and identification methods, pretreatment temperature and lack of standardized normalization units.^{1,3,21,28} However, the result of this study confirms the ubiquitous nature of microplastics in the Atlantic as reported in other studies from different regions and locations.^{14, 39-43} It is also possible that microplastics in these sediments were underestimated because only microplastics with density $<1.2 \text{ g/cm}^3$ could be extracted with the solution used for density floatation.^{35,44,45}

Composition

The results of FTIR analysis of some of the samples confirmed the presence of polyethylene (PP), polypropylene

(PP), and polystyrene (PS) when compared with other wavelength data in literature.^{28,31,46} Polystyrene was dominant among microplastics selected for FTIR analysis while the only two fibers analysed presented as polypropylene. Four pellets were found to be polyethylene. Polystyrene is used in rigid food service containers such as disposable cups and plates (popularly known as “takeaways” in Nigeria) and for building insulation. It is more susceptible to outdoor weathering than the other polymers identified in this study,⁴⁷ apparently, one of the reasons it dominates among microplastics selected for FTIR analysis; the other reason being poor management of wastes generated by eateries on these beaches. Polyethylene is commonly used in plastic wrappings and bags, drainpipes, bottles, and garbage bins while polypropylene is used in manufacturing disposable bottles, piping systems, and automotive components.^{28,33,48} Polypropylene fibers are used in ropes, fishing nets and diapers.³³

CONCLUSION

Microplastics largely dominated by fragments were found in sediments of the four beaches used for this study. Polymers identified include polyethylene (PE), polypropylene (PP) and polystyrene (PS). The result of this study serves as baseline information on the occurrence, abundance and nature of microplastics in the Nigerian coastal environment.

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TETRASUBSTITUTED (4-CHLOROPHENOXY)- AND (2,4,5-TRICHLOROPHENOXY)PHTHALOCYANINE METAL(II) COMPLEXES AND THEIR SULPHONATED DERIVATIVES: SYNTHESIS AND PROPERTIES

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Keywords: 4-Nitrophthalonitrile; phthalocyanine; synthesis; sulfonation; electronic absorption spectra.

By template condensation of 4-(4-chlorophenoxy)- and 4-(2,4,5-trichlorophenoxy)phthalonitriles with cobalt(II), copper(II) and zinc(II) acetates, the corresponding metal(II) phthalocyaninates were synthesized, and some of their sulfonic acid derivatives were also isolated after sulphonation reactions. The spectroscopic characteristics and some physicochemical properties of the synthesized compounds were also given.

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INTRODUCTION

In modern chemistry, phthalocyanine derivatives have a great interest in the creation of novel functional materials.¹⁻³ Due to modification of metal complexing agent within the macrocycle or introduction of various peripheral substituents, it is possible to fine-tune the properties of the compound obtained and, correspondingly, of the material or devices based on them.⁴⁻⁶

Among the substituted phthalocyanines, aryloxy substituted were found to be antioxidants, substances exhibiting photoelectric and antimicrobial properties, photosensitizers for the photodynamic therapy of cancer, and catalysts for desulfurization, are very promising materials. The presence of aryloxy-substituents in the phthalocyanine ring allows good solubility in organic solvents, which facilitates the process of isolation and purification of the target products.

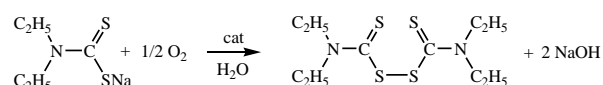
The literature presents data on phenoxy-substituted zinc phthalocyaninates containing halogen atom substituents (F, Cl, Br) as photosensitizers^{7,8} and it was shown that the introduction of halogen atoms into the phthalocyanine molecule leads to an increase in their activity. In addition, aryloxy-substituted phthalocyanines containing halogen atoms are promising for use as an information storage devices⁹⁻¹⁰ and sensors.¹¹⁻¹²

Based on the foregoing, the aim of this work was to the synthesis of tetra(4-chlorophenoxy) and tetra(2,4,5-trichlorophenoxy)phthalocyaninates of copper(II), cobalt(II) or zinc(II) and sulfonic acids based on them, as well as to study of their properties.

EXPERIMENTAL

Elemental analysis of the synthesized compounds was carried out on a CHNS-O-Flash-EA 1112 analyzer. Before elemental analysis, the samples of the studied compounds were subjected to heat treatment at 110 °C for 2 hours. Electronic absorption spectra were recorded on a HITACHI-2001 spectrophotometer in organic solvents, in water, and sulfuric acid at room temperature in the wavelength range of 350-900 nm. IR spectra were recorded on an Avatar 360 FT-IR ESP spectrometer in the region of 400–4000 cm⁻¹ in a potassium bromide matrix and thin films (chloroform). MALDI-TOF mass spectra were obtained on a Shimadzu Biotech Axima Confidence mass spectrometer in positive ion mode as a matrix 2,5-dihydroxybenzoic acid was used. Samples were prepared by dissolving the compounds in chloroform (10⁻⁴-10⁻⁵ mol L⁻¹), then mixed in a 1:1 ratio (v/v) with a solution of the matrix (30 mg mL⁻¹) in THF.

The catalytic activity of cobalt phthalocyanines was measured by a known method¹³⁻¹⁴ using the oxidation reaction of sodium N,N-diethyldithiocarbamate. The process proceeds according to Scheme 1.



Scheme 1. Oxidation of sodium N, N-diethyldithiocarbamate.

General synthetic process of 4-(4-chlorophenoxy)- and 4-(2,4,5-trichlorophenoxy)phthalonitriles

4-Nitrophthalonitrile (1.73 g, 0.01 mol) and 0.01 mol of the corresponding substituted phenol were dissolved in 30 mL of DMF. A solution of 2.76 g (0.02 mol) of K_2CO_3 in 5 mL of water was added to the resulting solution and stirred at 100 °C for 3 h. The precipitate obtained was filtered off, washed with water to pH 7 and dried in air at 70-80 °C. (Scheme 2).

4-(4-Chlorophenoxy)phthalonitrile (2)

Yield: 2.05 g (80.7 %). FT-IR: 2229 ($C\equiv N$), 1278 (Ar-O-Ar), 1085 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{14}H_7ClN_2O$: C 66.03, H 2.77, N 11.00. Found: C 65.98, H 2.79, N 10.97.

4-(2,4,5-Trichlorophenoxy)phthalonitrile (3)

Yield: 2.43 g (75 %). FT-IR: 2231 ($C\equiv N$), 1250 (Ar-O-Ar), 1088 (C-Cl) cm^{-1} . 1H NMR ($CDCl_3$) δ = 7.81 (d, 1H, H^3 , J_{HH} 10.89 Hz), 7.69 (s, 1H, H^4), 7.33 (s, 1H, H^1), 7.29-7.28 (m, 1H, H^2), 7.24-7.22 (m, 1H, H^5). MALDI-TOF: m/z = 362 $[M+K]^+$. Anal. Calcd. for $C_{14}H_5Cl_3N_2O$: C 51.97; H 1.56; N 8.66. Found: C 51.89; H 1.60; N 8.64.

Synthesis of tetra(4-chlorophenoxy)phthalocyanine metal complexes

A thoroughly ground mixture of 1 mmol of the corresponding substituted phthalonitrile (**2** or **3**) and 0.3 mmol of the acetate of the corresponding metal was heated at 185-190 °C until it solidified. The resulting complexes were reprecipitated from concentrated sulfuric acid on ice. The precipitate was filtered off and washed with water to pH 7, then dried. The final purification was performed by column chromatography on silica gel M60 using chloroform as eluent.

Tetra(4-chlorophenoxy)phthalocyaninatocobalt(II) (4a)

Yield: 0.21 g (78.1 %). MALDI-TOF: m/z = 1077 $[M]^+$. FT-IR: 1249 (Ar-O-Ar), 1080 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{56}H_{28}Cl_4CoN_8O_4$: C 62.42; H 2.62; N 10.40. Found: C 62.40; H 2.70; N 10.38.

Tetra(4-chlorophenoxy)phthalocyaninatocopper(II) (4b)

Yield: 0.19 g (70.3 %). MALDI-TOF: m/z = 1082 $[M]^+$. FT-IR: 1248 (Ar-O-Ar), 1081 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{56}H_{28}Cl_4CuN_8O_4$: C 62.15; H 2.61; N 10.35. Found: C 62.11; H 2.65; N 10.30.

Tetra(4-chlorophenoxy)phthalocyaninatozinc(II) (4c)

Yield: 0.20 g (74.1 %). MALDI-TOF: m/z = 1084 $[M]^+$. FT-IR: 1246 (Ar-O-Ar), 1080 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{56}H_{28}Cl_4ZnN_8O_4$: C 62.04; H 2.60; N 10.34. Found: C 61.99; H 2.62; N 10.31.

Tetra(2,4,5-trichlorophenoxy)phthalocyaninatocobalt(II) (5a)

Yield: 0.22 g (65.0 %). MALDI-TOF: m/z = 1352 $[M-H]^+$. FT-IR: 1246 (Ar-O-Ar), 1080 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{56}H_{20}Cl_{12}CoN_8O_4$: C 49.71; H 1.49; N 8.28. Found: C 49.69; H 1.51; N 8.26.

Tetra(2,4,5-trichlorophenoxy)phthalocyaninatocopper(II) (5b)

Yield: 0.21 g (61.9 %). 1HNMR ($CDCl_3$) δ = 7.80 (d, 1H, H^3 , J_{HH} 8.70 Hz), 7.69 (s, 1H, H^4), 7.33 (s, 1H, H^1), 7.29-7.28 (m, 1H, H^2), 7.22 (dd, 1H, H^5 $^2J_{HH}$ 8.70, $^3J_{HH}$ 2.6 Hz). MALDI-TOF: m/z = 1358 $[M+H]^+$, 1374 $[M+Na]^+$. FT-IR: 1244 (Ar-O-Ar), 1084 (C-Cl) cm^{-1} . Anal. Calcd. for $C_{56}H_{20}Cl_{12}CuN_8O_4$: C 49.54; H 1.48; N 8.25. Found: C 49.52; H 1.51; N 8.23.

Tetra(2,4,5-trichlorophenoxy)phthalocyaninatozinc(II) (5c)

Yield: 0.24 g (74 %). FT-IR: 1246 (Ar-O-Ar), 1080 (C-Cl) cm^{-1} . MALDI-TOF: m/z = 1359 $[M]^+$. Anal. Calcd. for $C_{56}H_{20}Cl_{12}ZnN_8O_4$: C 49.43; H 1.32; N 8.23. Found: C 49.39; H 1.40; N 8.20.

Synthesis of sulfonic acid derivatives of tetra(4-chlorophenoxy) and tetra(2,4,5-trichlorophenoxy)phthalocyaninatometal(II) complexes

Sulfonic acid derivatives were synthesized by the interaction of 0.1 mmol of the corresponding phthalocyanine metal complex and 15 mL of 26 % oleum at 70 °C for 2 h and 10 h for chlorophenoxy- and trichlorophenoxy-derivatives, respectively. The reaction mixture was poured into the mixture of ice and NaCl. The precipitate was filtered off, washed with cc. HCl and dried in air. The desired product was extracted with water and the water was removed from the solution by evaporation. The final purification step was carried out by column chromatography on silica gel M 60, DMS was selected as eluent.

Tetra(2,3,5,6-tetrasulfo-4-chlorophenoxy)phthalocyaninatocopper(II) (6b)

Yield: 0.13 g (56.5 %). 1HNMR δ = 7.34 (s, H^3 , 4H), 7.23 (s, H^1 , 4H), 7.13 (s, H^2 , 4H). FT-IR (KBr): 1249 (Ar-O-Ar), 1167, 1042 (S=O), 1086 (C-Cl), 1069 (C-S) cm^{-1} .

Tetra(2,3,5,6-tetrasulfo-4-chlorophenoxy)phthalocyaninatozinc(II) (6c)

Yield: 0.14 g (60.9 %). FT-IR (KBr): 1248 (Ar-O-Ar), 1160, 1048 (S=O), 1081 (C-Cl), 1069 (C-S) cm^{-1} .

Tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyaninatocobalt(II) (7a)

Yield: 0.14 g (70.3 %). FT-IR (KBr): 1240 (Ar-O-Ar), 1045 (C-Cl), 1167, 1042 (S=O), 1069 (C-S) cm^{-1} .

Tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyaninato-copper(II) (7b)

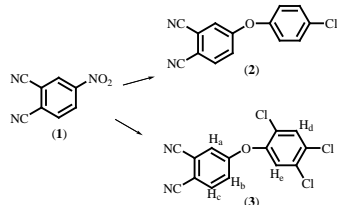
Yield: 0.15 g (75.3 %). $^1\text{H NMR}$ δ = 7.23 (s, H3, 4H), 7.13 (s, H1, 4H), 7.03 (s, H2; 4H). FT-IR (KBr): 1249 (Ar-O-Ar), 1123, 1052 (S=O), 1082 (C-Cl), 1069 (C-S) cm^{-1} .

Tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyaninato-zinc(II) (7c)

Yield: 0.14 g (70.0 %). FT-IR (KBr): 1248 (Ar-O-Ar), 1120, 1048 (S=O), 1083 (C-Cl), 1067 (C-S) cm^{-1} .

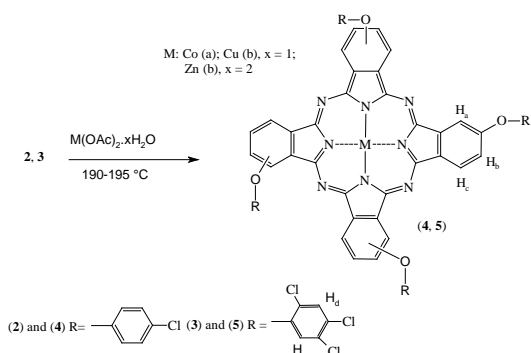
RESULTS AND DISCUSSION

For the synthesis of the target phthalocyanines in the first stage, the initial 4-chlorophenoxy- (**2**)¹⁵ and 4-(2,4,5-trichlorophenoxy)phthalonitriles (**3**) were obtained by means of the interaction of 4-nitrophthalonitrile (**1**) and the corresponding phenols (Scheme 2) in DMF in the presence of potassium carbonate.



Scheme 2. Synthesis of substituted phthalonitriles.

Next, the synthesis of phthalocyanines by the “nitrile” method was carried out by fusing phthalonitriles (**2**, **3**) with acetates of copper, cobalt and zinc at 180–200 °C until the reaction mixture solidified (Scheme 3).



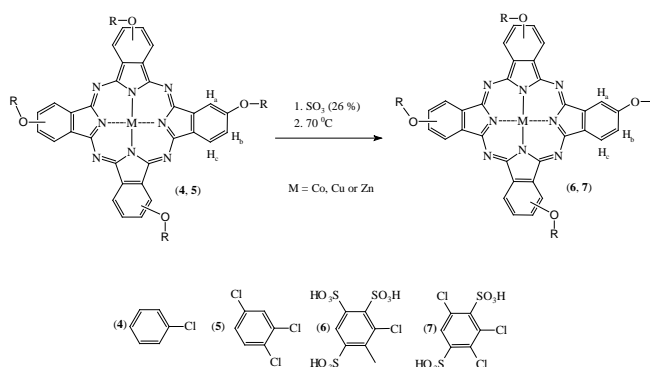
Scheme 3. Synthesis of metal complexes of phthalocyanines

The synthesized complexes were reprecipitated from concentrated sulfuric acid. The final purification was carried out by column chromatography on silica gel M60 using chloroform as eluent.

The composition and structure of the obtained compounds were established using data from MALDI-TOF spectrometry, $^1\text{H NMR}$, IR and electron spectroscopy.

In the FT-IR spectra of the synthesized phthalocyanines (**4–5a,b**), there are no absorption bands in the region of 2228–2231 cm^{-1} , corresponding to stretching vibrations of the nitrile group, which indicates the absence of the initial phthalonitrile as an impurity. Absorption bands characteristic of compounds of the phthalocyanine series are observed.¹⁶ In addition, there are bands in the region of 1244–1246 cm^{-1} (C-O-C) and the region of 1080–1084 cm^{-1} (C-Hal).^{17–18}

To obtain water-soluble complexes, sulfonation of the above-described phthalocyanines (**4b,c**, **5a–c**) was carried out. Chlorosulfonic acid did not lead to expected products; therefore, oleum was used for the sulfonation reactions (Scheme 4).



Scheme 4. Sulfonation of phthalocyanine complexes.

Sulfonation reactions were carried out with 26 % oleum with constant stirring and a temperature of 70 °C for 2 h and 10 h, for complexes **4** and **5**, respectively. At the end of the reaction, the sulfonated mass was poured into a mixture of ice and sodium chloride, the precipitate formed was filtered off, washed with concentrated hydrochloric acid, then dried in the air, the target product was extracted with water, which was then evaporated. The final purification was carried out by column chromatography on silica gel M60. The eluent was DMF. The composition and structure of the obtained compounds were determined using $^1\text{H NMR}$, IR, and electron spectroscopy.

The number and position of sulfonic acid groups in the phthalocyaninatozinc(II) complexes were studied by $^1\text{H NMR}$ spectroscopy (Figure 1). The NMR spectra of sulfonic acid complexes (**6b**, **7b**) showed proton signals as triplets at 7.03, 7.13 or 7.23 ppm and 7.13, 7.23 or 7.34 ppm for **7b** and **6b**, respectively. These signals relate to the protons in positions 2, 1 and 3 of the phthalocyanine nuclei. Since only these protons could be detected by $^1\text{H NMR}$, the chlorophenyl rings are completely substituted with sulphonic acid groups, namely two and four sulfonic acid groups were introduced into the compounds **6b** and **7b**, respectively. It is noted that upon the introduction of new sulfonic acid groups into the phthalocyanine molecule, the signals of the ring protons are shifted into a weaker field, which is associated with the effect of the strong electron-acceptor sulfonic acid substituents.

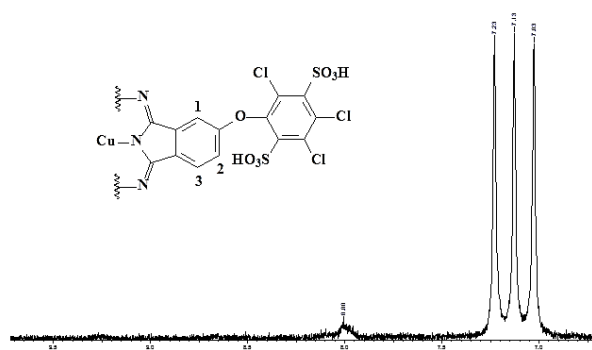


Figure 1. ^1H NMR spectrum of tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyaninatocopper(II) (**7b**)

In the FT-IR spectra of the obtained sulphonated phthalocyanine complexes (**6-7**), the bands characteristic of phthalocyanine compounds, as well as of C-O-C and C-Hal bonds could be observed without important changes. In addition, bands appear in the regions $1210\text{--}1150\text{ cm}^{-1}$ and $1060\text{--}1030\text{ cm}^{-1}$, characteristic of modes of sulfonic acid groups¹⁹ appeared. It was also noted that FT-IR spectra of sulfonic acids are more diffuse compared to the initial ones, as was previously noted for phthalocyanines sulfonic acids.²⁰⁻²¹

The solubility in the synthesized phthalocyanines (**4-7**) in organic solvents or aqueous-alkaline solutions allowed us to study their spectral characteristics. So, electronic absorbance spectra of all synthesized complexes are characterized by intense absorption in the wavelength region of $660\text{--}680\text{ nm}$, caused by the $\pi\text{--}\pi^*$ electronic transition in the main conjugation circuit of the phthalocyanine ring. The position of the absorption bands is shown in Table 1.

Table 1. The position of the UV-VIS absorption bands of synthesized phthalocyanines.

No.	M	λ_{max} , nm			
		CHCl_3	DMF	H_2SO_4	H_2O
4a	Co	670	665	838	-
4b	Cu	681	676	860	-
4c	Zn	681	680	851	-
5a	Co	667	662	815	-
5b	Cu	678	621,	838	-
5c	Zn	677	678	831	-
6a	Cu	-	695	779	641, 682
6b	Zn	-	708	810	658, 698
7a	Co	-	685	759	673
7b	Cu	-	711	785	676
7c	Zn	-	714	792,81	718

Analyzing the effect of the nature of the substituent for complexes (**4-5**) soluble in organic solvents on the position of the Q-band, it was noted that the presence of additional chlorine atoms (**5a-c**) in the substituent leads to the hypsochromic shift of the main band compared to monochloro-substituted complexes (**4a-b**) (Table 1). The nature of the solvent also has an influence on the shape of the spectra for all complexes except zinc. Thus, a change in polar aprotic DMF to weakly polar aprotic chloroform leads to a bathochromic shift of the Q-band (Table 1).

It was noted that the position of the Q-band of cobalt complexes (**4a-7a**) both in chloroform and in DMF is shifted relative to the corresponding copper and zinc phthalocyanines (Table 1).

In the transition from organic solvents to concentrated sulfuric acid, a strong shift of the absorption bands to the long-wavelength region is observed due to protonation of the macro ring by the meso nitrogen atoms, the smallest shift observed for metal(II) tetra(2,4,5-trichlorophenoxy)-phthalocyanines (Table 1). Depending on the nature of the metal, the position of the main band of the synthesized phthalocyanine complexes in concd. H_2SO_4 has a bathochromic shift in the following order $\text{Co} < \text{Zn} < \text{Cu}$ (Figure 2, Table 1).

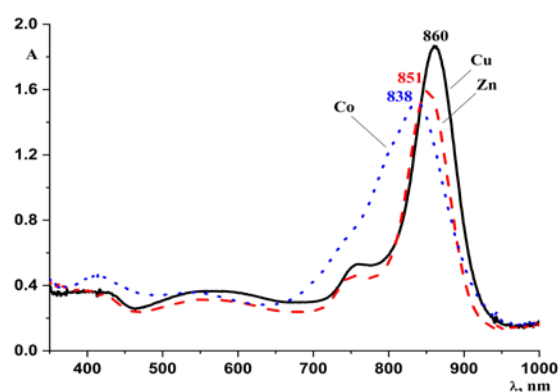


Figure 2. Electronic absorption spectra phthalocyanines **4a-c** in sulfuric acid.

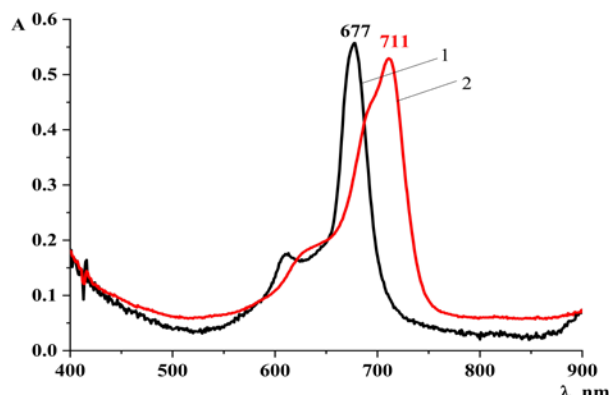


Figure 3. UV-vis spectra in DMF: 1 - copper phthalocyanine (**5b**), 2 – copper phthalocyanine (**7b**) complexes

The introduction of sulfonic acid groups into the molecules leads to a change in the spectra compared to the spectra of initial phthalocyanine derivatives. Thus, in DMF, the spectral curves become more diffuse, which indicates an increase in the tendency to the association in solutions (Figure 3). A bathochromic shift of the Q absorption band in DMF with respect to the corresponding non-sulfonated phthalocyanines was also noted (Table 1), with the most significant shift recorded for tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyanines (Figure 3, Table 1).

The nature of metal in sulfonic acid derivatives has a strong influence on the absorption spectra in DMF. The bathochromic shift of absorption bands is observed in the following order: Co < Cu < Zn (Figure 4, Table 1). Thus, the presence of sulfonic acid groups in the substituents leads to an increase in the influence of the nature of the metal on the position of the Q-band.

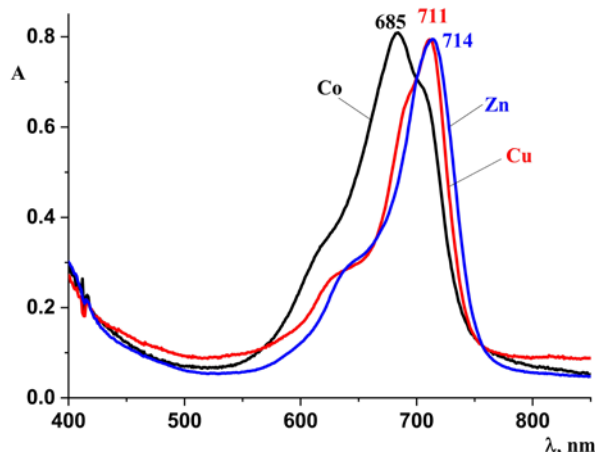


Figure 4. Electronic absorption spectra of tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyanines (7) in DMF.

The spectral curves obtained for these complexes change on the transition from DMF to water. The absorption bands become more diffuse, and the hypsochromic shift is noted relative to those recorded in DMF, which indicates an increase in the tendency to associative processes. It was shown that the presence of three chlorine atoms in the compounds 7 prevents the association compared with monohalogenated derivatives 6 (Figure 5).

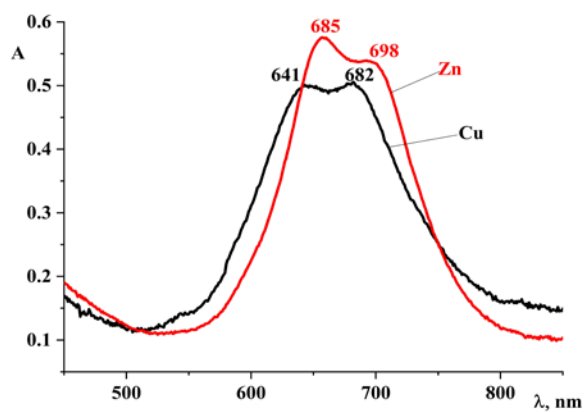


Figure 5. UV-VIS of tetra(2,3,5,6-tetrasulfo-4-chlorophenoxy)phthalocyanine complexes (6) in DMF.

It is important to note that cobalt complexes are the least prone to the association, which is due to the higher coordinating ability of cobalt (Figure 6). Cobalt phthalocyanine complexes in aprotic solvents form complexes with the solvent molecules as ligands, and intermolecular interactions²² also complicate the spectral characteristics.

Change DMF and water to concentrated sulfuric acid, both the phthalocyanine sulfonic acid derivatives (6-7) and the non-sulfonated phthalocyanine complexes (4-5), show a bathochromic shift for all absorption bands. These are smaller in the case of 6 and 7 compounds than the values for the appropriate initial phthalocyanines (4-5) (Table 1).

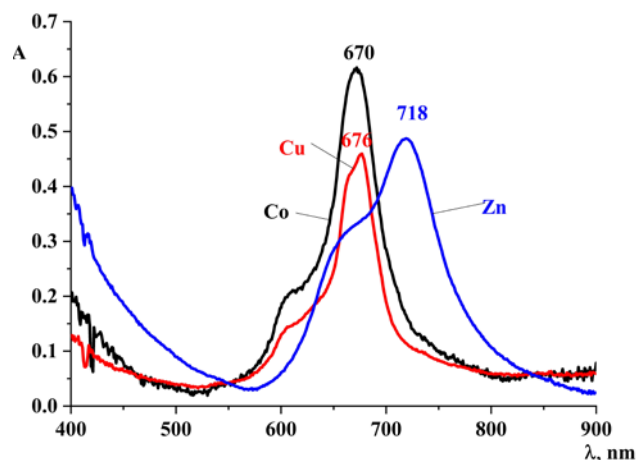


Figure 6. Electronic absorption spectra of tetra(3,6-disulfo-2,4,5-trichlorophenoxy)phthalocyanines (7) in water.

It can be observed due to steric difficulties associated with bulky substituents and, as a consequence, a decrease in the degree of protonation nitrogen meso-atoms of the macroring (Figure 7).

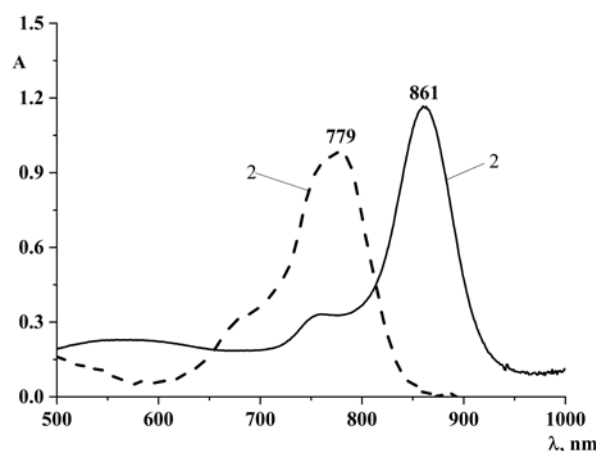


Figure 7. UV-VIS spectra 4b (1) and 6b (2) complexes in concentrated sulfuric acid

The nature of the metal also influences the position of the Q-band in concentrated sulfuric acid. It was noted that, as in DMF, a bathochromic displacement is observed in the following order: Co < Cu < Zn (Table 1).

As it is well known,²³⁻²⁴ cobalt complexes of phthalocyanines are widely used as catalysts for oxidation of mercaptans and hydrogen sulfide in petrochemical processes. These catalysts allow the oxidation process to be carried out under mild conditions, which prevents further oxidation of the disulfide and leads to a significant increase in the quality of the product.

In this regard, the catalytic activity of tetra(2,4,5-trichloro-3,6-disulfophenoxy)phthalocyaninatocobalt(II) (**7a**) was studied in the oxidation of sodium N,N-diethyldithiocarbamate to Thiuram E (Scheme 4). Thiuram E is a crucial component for obtaining drugs for the treatment of chronic alcoholism.²⁵⁻²⁶ It was shown that tetra(2,4,5-trichloro-3,6-disulfophenoxy)cobalt(II) (**7a**) is an active catalyst, the oxidation rate constant of sodium diethyldithiocarbamate at a catalyst $6 \cdot 10^{-5}$ mol L⁻¹ and substrate 0.00203 mol·L⁻¹ concentration at pH = 7.6 was found to be $41.97 \cdot 10^{-3}$ L·mol⁻¹·s⁻¹.

CONCLUSIONS

Complexes of substituted phthalocyanines with cobalt, zinc, and copper-containing 4-chlorophenoxy and 2,3,5-trichlorophenoxy-substituents, as well as their completely sulfonated analogs were prepared. The structure of the synthesized compounds was confirmed by IR and NMR spectroscopy and mass spectrometric methods.

UV-VIS spectra of the synthesized complexes were studied in various solvents, the positions of the absorption maxima depending on the nature of the solvent were determined. The conditions for the existence of complexes in aggregated and monomeric forms were also determined.

A study on the catalytic properties of the tetra(2,4,5-trichloro-3,6-disulfophenoxy)cobalt(II) was carried out in the oxidation of sodium diethyldithiocarbamate into Thiuram E.

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