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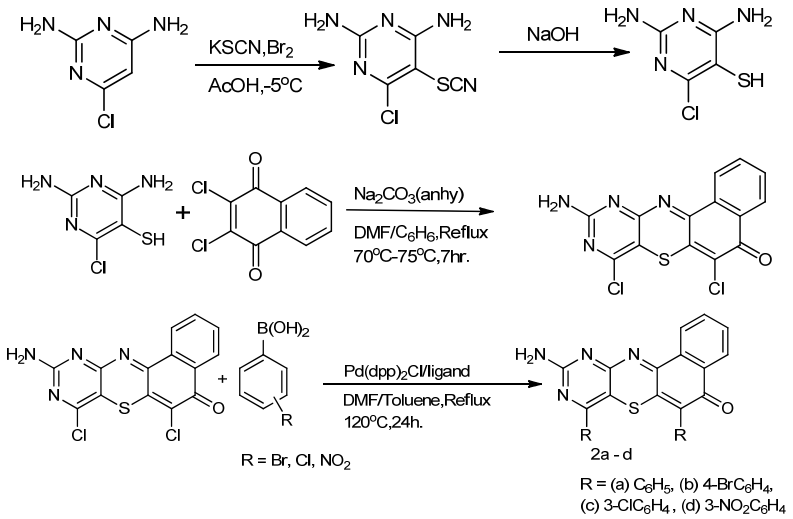
An Efficient Palladium Catalyzed Synthesis of Non-Linear 6, 8-Diaryl Diazaphenothiazinone Derivatives

Ayuk Eugene L[1]*; Nweke Cletus M[1], Agu Ifeoma S[2]

[1]Chemical Sciences Department, Faculty of Natural and Applied Sciences, Godfrey Okoye University, Ugwuomu-Nike, Enugu, Nigeria
[2]Department of Chemical Engineering, Institute of Management and Technology, Enugu, Nigeria

Abstract: *The synthesis of four new derivatives of 6,8-dichloro-10-amino-9,11-diazabenzo[a]phenothiazin-5-one, is reported in this article. One of the key intermediates 2,6-diamino-4-chloropyrimidin-3-thiol was obtained via the thiocyanation of 2,6-diamino-4-chloropyrimidine in the presence of bromine and acetic acid at -5^{o}C to give 2,6-diamino-4-chloro-3-thiocynatopyrimidine. This was then subjected to hydrolysis in the presence of 20% sodium hydroxide to furnish the intermediate. The condensation of 2,3-dichloro-1,4-naphthoquinone with 2,6-diamino-4-chloropyrimidin-3-thiol gave 6,8-dichloro-10-amino-9,11-diazabenzo[a]phenothiazin-5-one. This azaphenothiazinone was coupled with four arylboronic acids in the presence of diphenyl phosphinobutane palladium chloride, Pd (dppb)$_2$Cl (catalyst) and 1,4-bis-(2-hydroxy-3, 5-di-tert-butylbenzyl) piperazine (ligand) to furnish the four non-linear 6,8-diaryldiazaphenothiazine derivatives. The equations of reaction for the processes are shown below;*

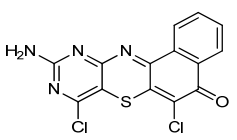


Keywords: *Catalyst, hydrolysis, thiocyanation, 6, 8-diaryldiazaphenothiazine6, 8-dichloro-10-amino-9, 11-diazabenzo[a]phenothiazin-5-one.*

1. INTRODUCTION

Phenothiazine derivatives are important constituents of drugs like antihistaminic, antihlemintic, neuropsycosis, antituberculotics, tranquilizers, antimalarian, antiparkinson, anticonvulsant, antiviral, anticancer, antibacterial, diuretics, sedatives, analgesics. [1]-[7] Some phenothiazine derivatives inhibit intracellular replication of viruses including human immunodeficiency viruses (HIV), others act as antitumor, anti-inflammatory, antifungal, antischizophrenic, andinodialators in congestive heart failure, as well as in treating migraine and other intractable headaches, and agitation in patients [8] [9].They have also found rising applications in material sciences as electrophoric sensors, photocopying inks and many other light sensitive materialsin photography [10]. Furthermore, some are used as dyes and pigments for textile and paint industries, antioxidants which increase the life-time of synthetic rubber, lubricating oils and other petroleum products in order to improve their durability as well as monomer stabilizers in the production of polymer products as well in drugs synthesis to prevent uncontrolled polymerization[11] and in the agricultural industry for the manufacturing of insecticides, herbicides and pesticides [12].

Recently,the used of transition metals as catalysts in the synthesis of phenothiazine derivatives has open a new chapter in the synthesis of these very important heterocyclic compounds[13]-[15]. We have earlier reported the synthesis of 6-aryl non-linear derivatives of monoazaphenothiazinones in our previous works using palladium complex catalysis [16] [17]. In furtherance of the above, this time we present another research work on the synthesis of four new 6,8-diaryl derivatives (**2a-d**) of 6,8-dichlorol-10-amino-9,11-diazabenzo[a]phenothiazin-5-one **1** via palladium complex catalysis with arylboronic acids.



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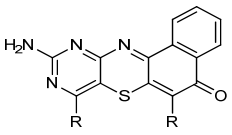


2a - d

R = (a) C_6H_5, (b)C_6H_4Br
(c) C_6H_4Cl, (d) $C_6H_4NO_2$

2. MATERIALS AND METHODS

Most of the reagents used were sourced locally from commercial chemical shops and were obtained in sealed containers and were used without further purification.The melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. The UV-Vis spectra were recorded in DMF on a UV-2500PC series V2.30 spectrum version at NARICT, Zaria, Nigeria, using matched 1 cm quartz cells. Absorption maxima are given in nanometer (nm) while the numbers in parenthesis are ε-values. Infrared Spectral data were obtained on FTIR-8400S (Fourier Transform Infrared Spectrophotometer), NARICT in Zaria, Nigeria using KBr disc and absorptions are given per centimeter (cm^{-1}). Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) were determined using Varian mercury 200 BB spectrometer atObafemiAwolowo University Ile-Ife, Nigeria. (Chemical Shifts are reported on δ scale relative to tetramethylsilane (TMS) as an internal standard).Chemical shifts are reported in (δ-ppm) scale. The analytical samples were obtained by recrystallization from benzene.

2.1. Diamino-4-chloro-3-thiocyanatopyrimidine 4

2,6-Diamino-4-Chloropyrimidine3 (25g, 0.2mol) was placed in a 250ml three neck reaction flask containing precooled acetic acid (150ml) at 0°C equipped with a mechanical stirrer and a quick-fit thermometer. This was followed by the addition potassium thiocyanate (50g, 0.5mole). The mixture was stirred for 30minutes in an ice-salt bath at a temperature between -5°C to 0°C. After stirring for 30 minutes, bromine (4ml) in precooled acetic acid (50ml) was added to the mixture intermittently for 2hrs. The temperature of the mixture was maintained between -5°C and 0°C. The slurry became golden yellow as the addition of bromine progressed. After adding the bromine solution for 2hrs, the yellow slurry was stirred for additional 4hrs at 0°C and finally stirred for 10hrs at room temperature and left to stand overnight.

Boiled water (200ml) was added to the deep yellow solution and filtered hot. The residue was discarded and the filtrate cooled to temperature of 0°C after which it was neutralized with concentrated ammonia to a PH of 7.0. The temperature was maintained below 20°C throughout the period of neutralization. The yellow product formed from the neutralized solution was filtered by suction and more products were obtained by cooling in a freezer at 0°C for several days. The filtrate was exposed to air for drying and then recrystallized from acetone. This gives 2,6-Diamino-4-chloro-3-thiocyanatopyrimidine4 (15.5g), m.p>200°C

2.2. 2,6-Diamino-4-chloropyrimidin-3-thiol 5

2,6-Diamino-4-chloro-3-thiocyanatopyrimidine4 (10g, 0.5mole) was placed in a 250ml reaction flask equipped with a reflux condenser. 20% solution of sodium hydroxide (100ml) was added and the mixture refluxed on a sand bath until all the ammonia gas cease to evolve. The solution was cooled to 0°C after which it was neutralized with acetic acid in an ice-salt bath ensuring that the temperature did not exceed 10°C. A massive orange precipitate was formed; and was allowed to stay for 24hrs in fridge before it was filtered and re-crystallized from benzene and dried in a desiccators to give 2,6-diamino-4-chloropyimidin-3-thiol (7.5g)a pale yellow crystalline product. Melting point >250°C. UV-Vis absorptions are λmax (Acetone), 363.50nm (ε 1.329), 350.50nm (ε 1.9765), 207.50nm (ε 1.1701). IR (KBr): 3390.97cm^{-1} N-H stretching, 2935cm^{-1}(C-H), 1577cm^{-1} C=N stretching, 1425cm^{-1} C=C stretching 798.58cm^{-1} C-Cl bending, 635.57cm^{-1} C-S bending.

2.3. 10-Amino-6,8-chloro-9,11-diazabenzo[a]phenothiazin-5-one1

A mixture of 2,6-diamino-4-chloropyimidin-3-thiol (4g, 0.023mole) and anhydrous sodium carbonate (5g, 0.05mole), benzene(40ml) mixed with DMF (4ml) were charged into a three neck reaction flask equipped with a magnetic stirring bar and a reflux condenser. The mixture was stirred while heating on a water bath at70-75 °C for 45minutes. 2,3-dichloro-1,4-naphthoquinone 6(4.5g, 0.02mole) was added and the entire mixture was refluxed with continuous stirring for 7hrs at temperature of 75-80°C. The color of the reaction mixture changed from bright yellow to brown and then to reddish brown and finally to intense red as the reaction progressed. No further color change was observed 4hours after the addition of the compound 2,3-dichloro-1,4-naphthoquinone. At the end of 7hrs, benzene was distilled off and the slurry poured into crushed ice and stirred to dissolve the inorganic materials. It was filtered and dried to give a reddish powder which was recrystallized from benzene to give 10-amino-6,8-chloro-9,11-diazabenzo[a]phenothiazine-5-oneas the product, melting at 180°C, yield: 86.12%. UV-Vis absorptions are λmax (Acetone), 502nm (ε 2.6140), 280.50nm (ε 1.5411), 240nm (ε 1.4606). IR (KBr): 3964.81cm^{-1} N-H stretching, 2932cm^{-1} C-H aromatic stretching, 1670cm^{-1} C=O stretching, 1566.25cm^{-1} C=N stretching, 1543.23cm^{-1} C=C stretching 804.34cm^{-1} C-Cl bending, 804cm^{-1} of aromatic. ^{1}H-NMR (Acetone): δ7.96-7.73 (4H, m) corresponding to aromatics protons, δ 3.23-3.39 (2H, s) due to the NH_2. ^{13}C-NMR (Acetone): δ181.7 (C=O), δ 151.2 (C=N), 133.9(C=C), δ 43.7 (C-C).

2.4. General Method used for the Synthesis of the 6,8-diaryl Derivatives of Compound 1

In a 250ml two-necked round bottom flask, diphenylphosphinobutane palladium chloride, Pd(dppb)2Cl (0.005mmol) 1,4-bis-(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine (0.005mmol) and mixture of DMF and toluene (10ml) (2:3) were placed and stirred for 5minutes using a short magnetic bar without heating. Thereafter,10-amino-6,8-chloro-9,11-diazabenzo[a]phenothiazin-5-one,(1.047mmol), arylboronic acids (0.75mmol) respectively, and potassium carbonate (0.11mmol) were added and the mixtures refluxed for 24h. The courses of the reactions were monitored with TLC analysis. At the end of the reactions, the mixtures were poured into glass petri dishes to evaporate the solvents completely and the residues were allowed todry. The dried residues were treated with water (10ml), filtered and then extracted with acetone (10ml) to obtain theproducts which were later recrystallized from acetone to obtain the different derivatives.

2.5. 10- Amino-6,8-diphenyl-9,11-diazabenzo[a]phenothiazin-5-one(2a)

Yield (0.34g, 88.2%).Melting point >500°C, UV/Vis λmax (ε): 503 (2.615)nm, 281(1.5421)nm, 261(1.4616)nm, IR(KBr), 3864cm^{-1} (N-H), 2942cm^{-1}, 1674cm^{-1} (C=O), 1568cm^{-1}, 1558 (C=N, C=C) 1235cm^{-1}(C-S),1080cm^{-1}.MS: *m/z* (relative intensity), mol.wt. = 432.5, 431.1(100.0%), 433.11(28.3%), 434.10(5.0%). ^{1}H-NMR DMSO-d6:δ7.96 (s,10H of 6 & 8-phenyl substituents), δ 7.73 (m,4H,Ar), 3.22 (2-NH_2); ^{13}C-NMR (DMSO-d6) δ:176.7 (C=O), 152.2 (C=N), 135.7 (C=C), 44.7 (C-C). Elemental analysis;C=72.20, H=3.77, N=12.95, O=3.70, S=7.41, molecular formula ($C_{26}H_{16}N_4OS$).

2.6. 10-Amino-6,8-(di-4-bromophenyl)-9,11-diazabenzo[a]phenothiazine-5one (2b)

Yield (0.35g, 79.3%) m.p>500°C, UV–Visλmax 502(ε=2.6140) nm, 280(ε=1.5411)nm, 260(ε=1.4606)nm. IR (KBr), 3964.81cm^{-1}(N-H stretching), 2932cm^{-1}(C –H stretching),1670cm^{-1}(C=O), 1566.25, 1559cm-1(C=N, C=C),1212cm^{-1}(C-S) 805cm^{-1}(C-Br).^{1}H-NMR (DMSO-d6) δ 7.76 (s,8H of 6 & 8-phenyl substituents), δ 7.73 (m,4H,Ar), 3.33 (2-NH_2); ^{13}C-NMR (DMSO-d6) δ:181.7 (C=O), 151.2 (C=N), 134.7(C=C), 43.7 (C-C).MS: *m/z* (relative intensity), mol. Wt. = 590.29, 589.92(100.0%), 591.92(52.4%), 587.2(50.2%).Elemental analysis; C=52.90;H = 2.39;Br = 27.07;N = 9.49; O = 2.71; S = 5.43, molecular formula ($C_{26}H_{14}Br_2N_4OS$).

2.7. 10- Amino-6,8-(di-3-chlorophenyl)-9,11-diazabenzo[a]phenothiazin-5-one(2c)

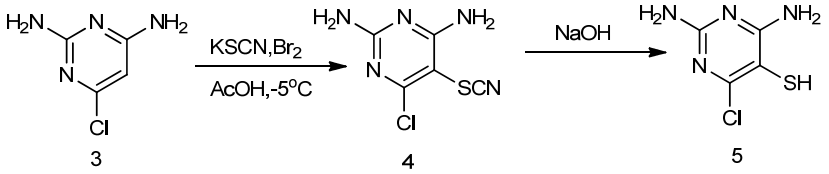
Yield (0.38g, 78.9%), m.p. >500°C, UV/Vis λmax (ε): 501 (2.593)nm, 283(1.5423)nm, nm, 263(1.4636)nm, IR(KBr);3764.81cm^{-1}(N-H stretching), 2942cm^{-1}(C –H stretching),1675cm^{-1}(C=O), 1564.25, 1549cm^{-1}(C=N, C=C), 1224cm^{-1}(C-S),756cm^{-1}(C-Cl).^{1}H-NMR (DMSO-d6) δ 7.86 (s,8H of 6 & 8-phenyl substituents), δ 7.73 (m,4H,Ar), 3.22 (2-NH_2); ^{13}C-NMR (DMSO-d6) δ:180.6 (C=O), 151.2 (C=N), 135.7(C=C), 45.7 (C-C). MS: *m/z* (relative intensity); mol. Wt.=501.39, 500.03(100.0%), 502.02(68.5%), 501.03(29.1%).Elemental analysis; C=26.28, H=2.81, Cl=14.14, N=11.7, O=3.19, S=6.40, molecular formula ($C_{26}H_{14}Cl_2N_4OS$)

2.8. 10-Amino-6, 8-(di-3-nitrophenyl)-9,11-diazabenzo[a]phenothiazine-5-one (2d)

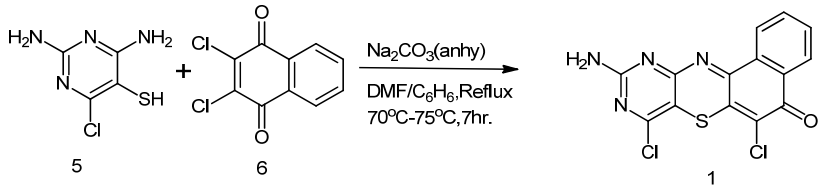
Yield (0.39g, 76.9%),m.p >500°C,UV/Vis λmax (ε): 500 (2.585)nm, 284(1.561)nm, 259(1.4229)nm, IR(KBr)3664.81cm^{-1}(N-H stretching), 2940cm^{-1}(C–H stretching),1670cm^{-1}(C=O), 1554.25, 1539cm^{-1}(C=N, C=C),1243cm^{-1}(C-S),756cm^{-1}(C-NO2).^{1}H-NMR (DMSO-d6) δ 7.86 (s,8H of 6 & 8-phenyl substituents), δ 7.73 (m,4H,Ar), 3.26 (2-NH_2); ^{13}C-NMR (DMSO-d6) δ:180.6 (C=O), 151.2 (C=N), 135.7(C=C), 45.7 (C-C). MS: *m/z* (relative intensity); mol. wt. = 522.49, 522.07(100.0%), 523.08(28.5%), 524.08(5.8%). Elemental analysis; C=59.77, H=2.70, N=16.08, O=15.31, S=6.14, molecular formula ($C_{26}H_4N6O5S$).

3. RESULTS AND DISCUSIONS

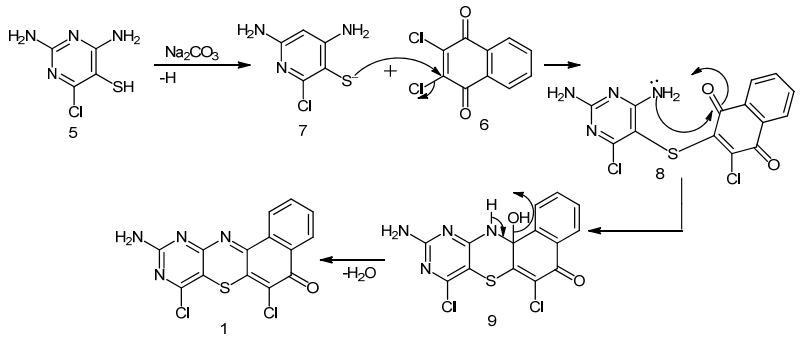
2,6-Diamino-4-chloropyrimidine3 was subjected tothiocyanationto give 2,6-diamino-4-chloro-3-thiocyanatopyrimidine 4 which was hydrolyzed by refluxing with 20% sodium hydroxide, followed by neutralization with acetic acid to furnish 2,6- diamino-4-chloropyrimidine -5-thiol 5 in a good yield as shown in the scheme below [18-19];



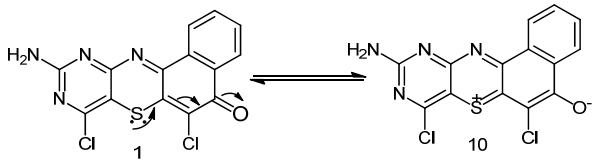
The synthesis of 10-amino-6,8-chloro-9,11-diazabenzo[a]phenothiazine-5-one 1 was achieved by the condensation of the key intermediate 2,6-diamino-4-chloropyrimidin-3-thiol 7 with 2,3-dichloro-1,4-naphthoquinone 6 in a mixture of benzene/DMF in the presence of anhydrous sodium carbonate at 70-75◦C for 9hrs [18] [19].



The IR and ^{13}CNMR spectra of compound showed absorption bands at 1670cm^{-1} and δ 181.7, which indicate the presence the carbonyl group observed in the spectra of compound These revelations are consistent with the assigned structures of the above compounds. The scheme below shows the mechanism of compound 1, thus;

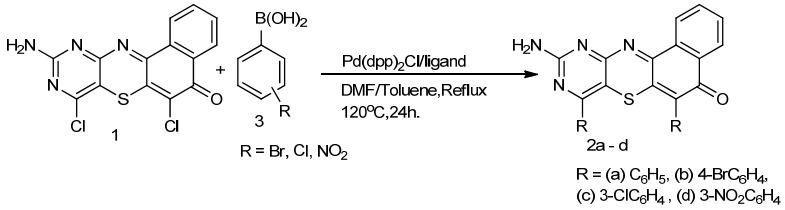


The first step in the mechanism of the above reaction is the abstraction of a proton from the mercapto group of the thiol by the base. The mercapto ion 7 which is formed from the lost proton from the thiol 5 mounts a nucleophilic attack on the halogen atom of the naphthoquinone6 to form the sulphide8. The sulphide cyclizes by the nucleophilic attack of the amino group of the thiolon the carbon of the carbonyl group of compound 6 followed by the loss of water to give compound 1 [19] [20]. The absorption band of the compound in the UV-Visible region are as follows λmax (Acetone), 240nm (ε 3.037), 280.50nm (ε 3.741), 502nm (ε 1.242) these are consistent with the observed color of the compound. In the infrared spectrum, there was a lowering of the carbonyl [C=O] absorption from the expected 1700cm^{-1} to 1670cm^{-1}. This is attributed to the contribution of the ionic resonance which increases the [C=O] bond length with the attendant decrease in the vibration frequency of absorption as shown below [20] [22];



The absorption band at 1566cm^{-1} is due to C=N of pyrimidine is consistence with the assigned structure. In proton magnetic resonance spectrum δ 3.23-3.39 is due to the amine proton NH2, while δ 7.73-7.96 is due to 4-H attached to benzene (C-1, C-2, C-3, C-4), these are consistent with the assigned structure. In ^{13}C-NMR the peak at δ181.7 is due to the carbonyl carbon.

The 6,8-diaryl derivatives of the above compound were produced via the Suzuki-Miyaura cross-coupling reaction of 10-amino-6,8-chloro-9,11-diazabenzo[a]phenothiazine-5-one1 with four arylboronic acids in the presence of diphenylphosphinobutane palladium chloride, Pd(dppb)2Cl (catalyst) and 1,4-bis-(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine (ligand) as shown in the scheme below [23];



The mechanism of the above process is shown below [23];

(i) The oxidative addition of an organic halide to the Pd(0)-species to form Pd(11) (organopalladium halide complex) (R–M–X) which is the rate determine step in the catalytic process.

(ii) Exchange of the anion attached to the palladium for the anion of the base (metathesis).

(iii) Transmetallation between Pd (11)and the alkyl borate complex (R–M–R).

(iv)Reductive elimination to form c-csigma bond and the regeneration of the Pd (0)

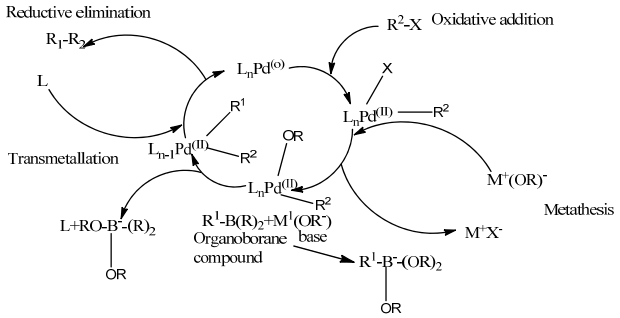


Table1. *Spectra data of compounds*

Compound	UV-Vis (EtOH)λ_{max}(nm)	IR(KBr) νmax(cm^{-1})	1HNMR (DMSO)δ	13CNMR (DMSO) δ	MASS SPEC (*M/Z* ,% INTENSITY)
1	502.00 (2.6140) 280.53)1.4606) 240.00 (2.5411)	3964.81(N-H) 2932.32(C-H) 1670.41(C=O) 1566.25(C=N) 1426.25 (C=C) 1128.24(C-S) 710.79(C-Cl)	7.90(m,2H) 7.70(m,2H) 3.39(s,1H 3.22(s,1H)	181.7 (C=O), 151.2(C=N). 134.7(C=C) 44.3(C-C)	
2a	503.00(2.615) 281(1.5421) 261(1.4616)	3864(N-H), 2942(C-H) 1674(C=O), 1568 (C=N) 1558 (C=C) 1235(C-S),	7.96(s,10H) 7.73(m,4H) 3.23 (d,2H)	δ:176.7(C=O), 152.2(C=N), 135.7(C=C), 44.7 (C-C).	431.1(100.0%), 433.11(28.3%), 434.10(5.0%).
2b	502(2.6140) 280(1.5411)	3964.81(N-H) 2932(C–H)	7.96(s,8H) 7.73(m,4H)	181.7 (C=O), 151.2(C=N),	589.92(100.0%), 591.92(52.4%),

	260(1.4606)	1670(C=O), 1566.25 (C=N, 1559 (C=C), 1252(C-S) 805(C-Br).	3.23(2NH2)	134.7(C=C), 43.7 (C-C).	587.2(50.2%).
2c	501 (2.593) 283(1.5423) 263(1.4636)	3764.81(N-H) 2942(C–H) 1675(C=O), 1564(C=N, 1549C=C), 1224(C-S), 756(C-Cl).	7.86(s,8H) 7.73(m,4H,) 3.22(d,2H)	180.6(C=O), 191.2(C=N), 135.7(C=C), 45.7(C-C).	500.03(100.0%), 502.02(68.5%), 501.03(29.1%).
2d	500 (2.585) 284(1.561) 259(1.4229)	3664(N-H), 2940(C-H), 1670(C=O), 1554.(C=N) 1539(C=C), 1243(C-S), 756(C-NO_2).	7.86 (s,8H), 7.73(m,4H) 3.26 (d,2H)	180.6(C=O), 191.2(C=N), 135.7(C=C), 44.5 (C-C).	522.07(100.0%), 523.08(28.5%), 524.08(5.8%).

Table. *Physical and analytical data of compounds*

Compound	Melting point(oC)	Color	% yield	Elemental analysis Calculated	Molecular Weight(g)	Molecular formula
1	180	Red	86.1	C = 48.15, H = 1.73,Cl = 20.37 N = 16.04, S = 4.58, O = 9.19	349.19	$C_{14}H_6Cl_2N_4OS$
2a	>450	Reddish-brown	88.2	C=72.20;H=3.77;N=12.95, O=3.70, S=7.41	432.50	$C_{26}H_{16}N_4OS$
2b	>450	Reddish-brown	79.3	C=52.90;H=2.39; Br=27.07;N=9.49;O=2.71;S=5.43	590.29	$C_{26}H_{14}Br_2N_4OS$
2c	>450	Reddish	78.9	C=26.28;H=2.81;Cl=14.14, N=11.7;O=3.19;S=6.40,	501.39	$C_{26}H_{14}Cl_2N_4OS$
2d	>500	Reddish	76.9	C=59.77;H=2.70;N=16.08, O=15.31;S=6.14,	522.49	$C_{26}H_4N_6O_5S$

4. CONCLUSIONS

The synthesis of phenothiazine derivatives discussed above was carried out using simple commercially available starting materials. The methods employed are straight forward and stereo-selective products were obtained.These newly synthesized compounds have promising and interesting applicability in pharmaceutical, textile, petroleum, agricultural industries etc.

The intense colours of these compounds suggest that they could be used as dyes. Studies on their dyeing and antimicrobial potentials are ongoing in our laboratory.

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AUTHORS' BIOGRAPHY

Ayuk Eugene L. , is a lecturer in the Department of Chemical Sciences, Faculty of Natural and Applied Sciences, Godfrey Okoye University, Enugu, Nigeria. He obtained a Bachelor of Science degree in Chemistry from Benue State University, Makurdi in 2002 and a Master of Science degree with specialization in Organic Chemistry from University of Nigeria, Nsukka in 2012. He is presently pursing his doctorate degree in Organic Chemistry at University of Nigeria, Nsukka.

Nweke Cletus M. , is a young chemist with passion for education. He is a graduate of Godfrey Okoye University, Enugu and he holds a Bachelor of Science degree in Chemistry.

Agu Ifeoma S. , obtained a Higher National Diploma in Chemical Engineering from Institute of Management and Technology, Enugu. She is a young lady that has interest in academic work and research.Top of Form