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SYNTHESIS OF NEW DIAZA ANGULAR AND TETRAAZA COMPLEX PHENOTHIAZINE RINGS

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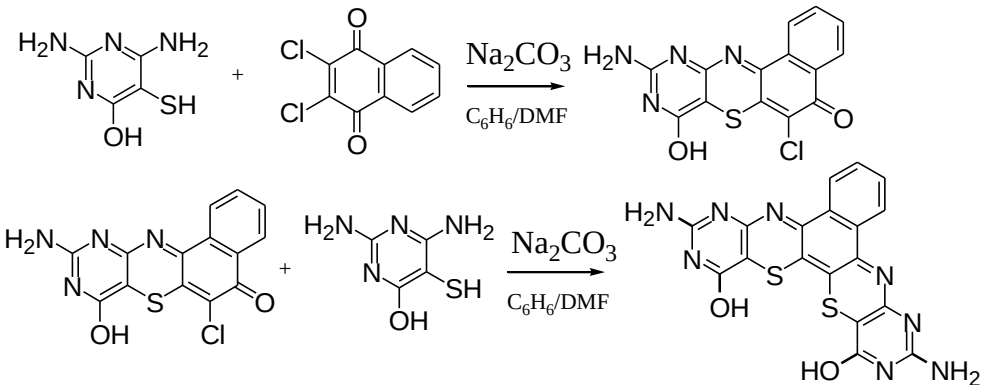
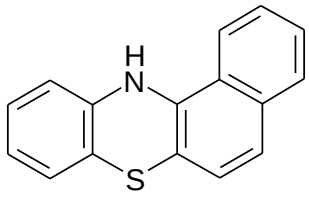
Abstract
New diaza angular and tetraaza complex phenothiazine rings are synthesized and characterized. Alkaline hydrolysis of 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine in 20% sodium hydroxide solution and neutralization with acetic acid gave 2,4-diamino-6-hydroxyprimidine-5-thiol (7). Base catalyzed (anhydrous sodium carbonate) condensation of this compound with 2,3-dichloro-1,4-naphthoquinone in yielded the diaza heterocycle 10-amino-5-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one(9). Further condensation of (9) with another molecule of (7) in the presence of anhydrous sodium carbonate gave the tetraaza heterocycle identified as 7,14-diamino-9,12-dihydroxy-6,8,13,15-tetraazabenzo[a][1,4]benzothiazino[3,2-c]pheno thiazine, a deep red solid. The intense colour, high molar absorptivity of the new heterocycles and the ease re-oxidation of the reduced leuco-bases by atmospheric air (O_2) makes them suitable as vat dyes.
Keywords: 2,4-diamino-6-hydroxypyrimidine-5-thiol, 2,3-dichloro-1,4-naphthoquinone, anhydrous sodium carbonate, hydrolysis, condensation.

Graphical abstract:



1. INTRODUCTION

The usefulness of phenothiazine compound and its derivatives in drug, textile, agriculture and other related industries has long been recognized. In medicine they are used as antitussive and antitumor agents, anticonvulsants, tranquilizers, antipsychotic and antimalarial agents[1] and in the treatment of prion diseases[2] to mention but a few. In textile, paint and plastic industries, they are used as dyes and pigments[3] and in agricultural industries as insecticides and nematodicides[4]. In petroleum industries, they are found useful as antioxidants in lubricants and fuels[5]. Angular phenothiazine ring of the type **(1)** [6] have been known for more than a century now. Although the mono-, di- and tri-aza complex phenothiazine **(2)** [7] and phenoxazine rings **(3)** [8] have also been reported, apparently there has been no report on the tetraaza analogues. We wish to report the successful synthesis of the first tetraaza analogues of complex phenothiazine.



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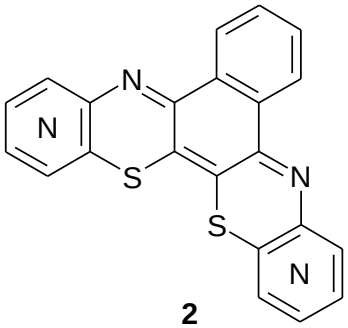

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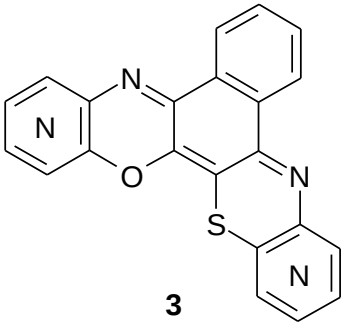

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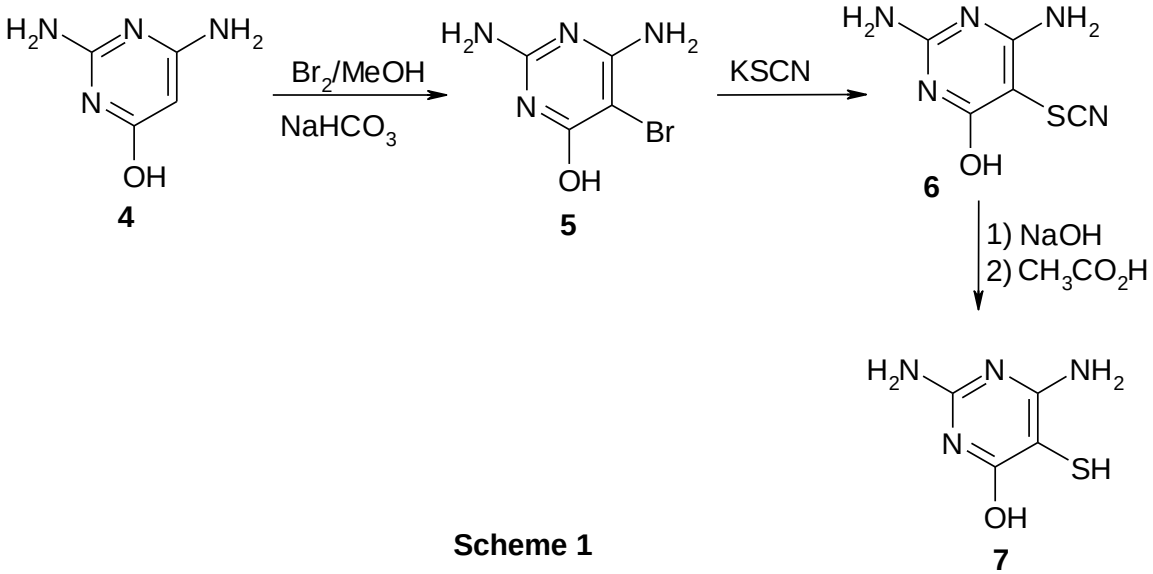
2. RESULTS AND DISCUSSION

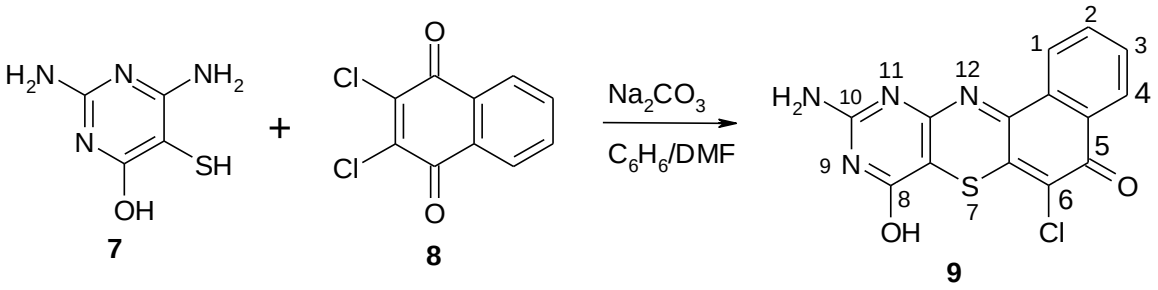
2,4-diamino-6-hydroxypyrimidine **(4)** was treated with bromine in methanolic solution in the presence of sodium bicarbonate to give 2,4-diamino-5-bromo-6-hydroxypyrimidine **(5).** Compound **5** was further converted to 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine **(6)** with a solution of potassium thiocyanate**.** Refluxing of compound **6** in 20% sodium hydroxide solution for 12 h. followed by neutralization with acetic acid gave a product identified as 2,4-diamino-6-hydroxyprimidine-5-thiol **(7)** in good yield**.**

The UV spectrum of compound **7** showed maxima absorption band at 338 which is consistent with the pyrimidine structure. Thus, IR spectrum of **7** revealed bands at 3435 cm^{-1}br. (NH); 1575, 1502 cm^{-1}(C=C, C=N). ^{1}H-NMR spectrum of **7** in (DMSO-d_6) exhibited signals at δ 4.10 assigned to ($2NH_2$), δ 2.90 corresponding to (SH) and δ 5.10 due to (OH) whereas ^{13}C-NMR spectrum in ($CDCl_3$) gave further support of the compound exhibiting signals at ppm: 160.514 (C-OH), 157.264 (2C-NH_2), 120.810 (C-SH) respectively (scheme 1).



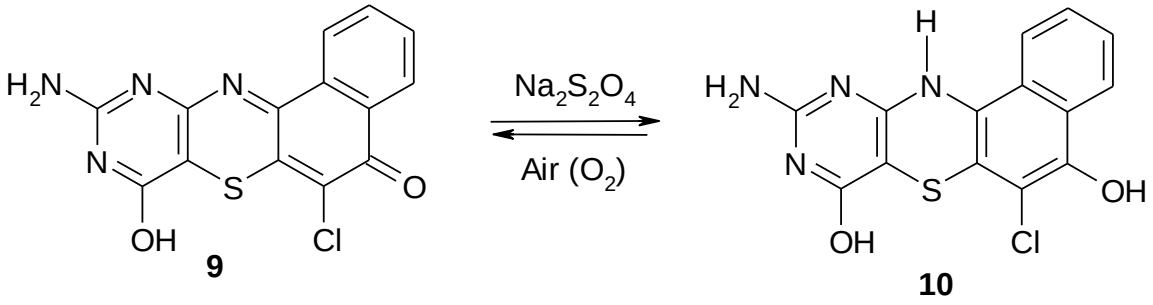
Scheme 1

2,4-diamino-6-hydroxypyrimidine-5-thiol **7** readily coupled with 2,3-dichloro-1,4-naphthoquinone **(8)** under reflux for 6 h. in the presence of anhydrous sodium carbonate to give 10-amino-6-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one **(9)** as reddish solid after recrystallization from aqueous acetone. Compound **9** gave uv-visible maxima absorption band at 421 nm. The elemental analysis agrees with the molecular formular $C_{14}H_7N_4ClO_2S$. The infrared spectrum gave bands at 3430, 3303 cm^{-1} (NH), 1661 cm^{-1} (C=O), 1594 cm^{-1} (C=C, C=N). Thus, ^{1}H-NMR gave signals at δ: 7.50-7.90 (4H, m) corresponding to the aromatic protons, 5.15 (H, s) assigned to the OH group and 3.90 (2H, s) due to the NH_2. ^{13}C-NMR gave further evidence of the structure exhibiting signal at 183.014 ppm corresponding to C=O (scheme 2).

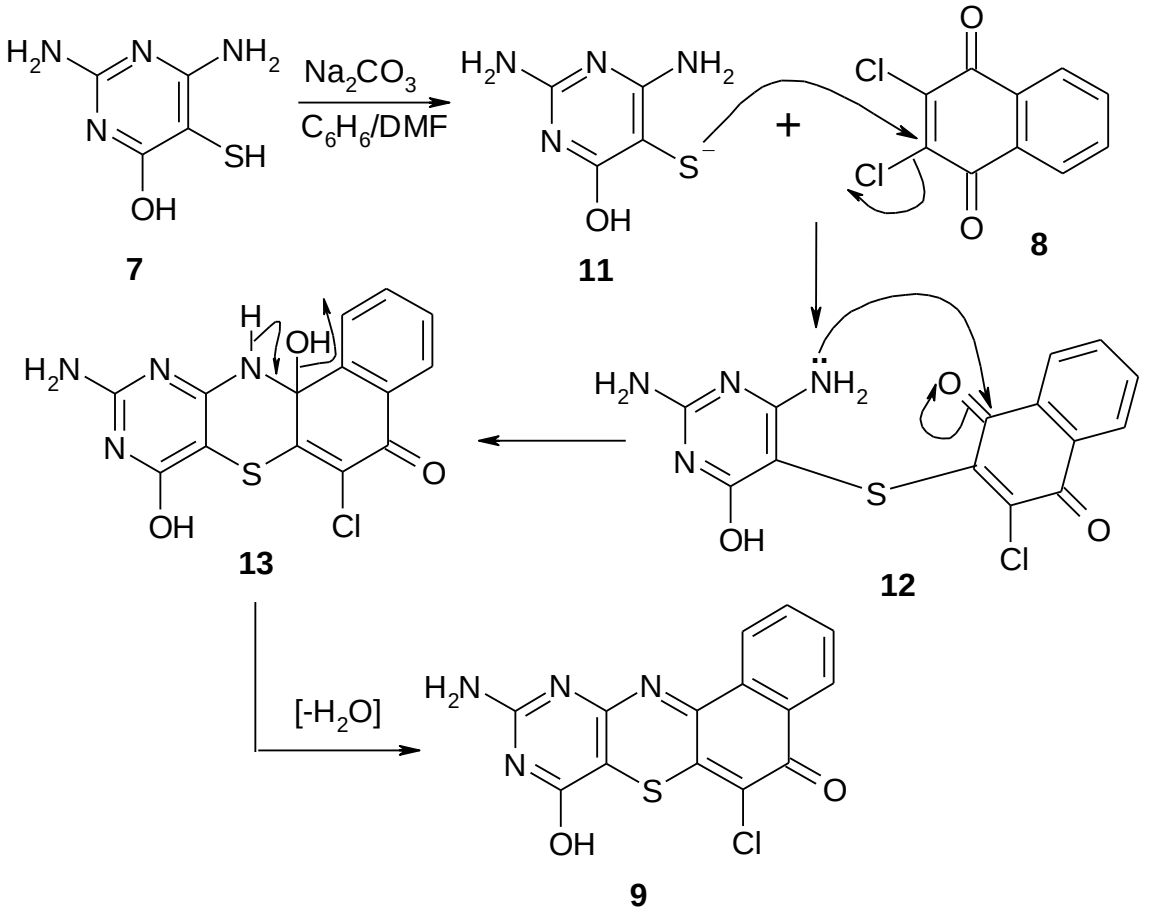


(Scheme 2)

Reduction of **9** with sodium dithionite led to the loss of the reddish colouration due to the formation of the unstable dihydro leuco-base **(10)** which reverted in the presence of atmospheric oxygen to the iminoquinone compound **9.**



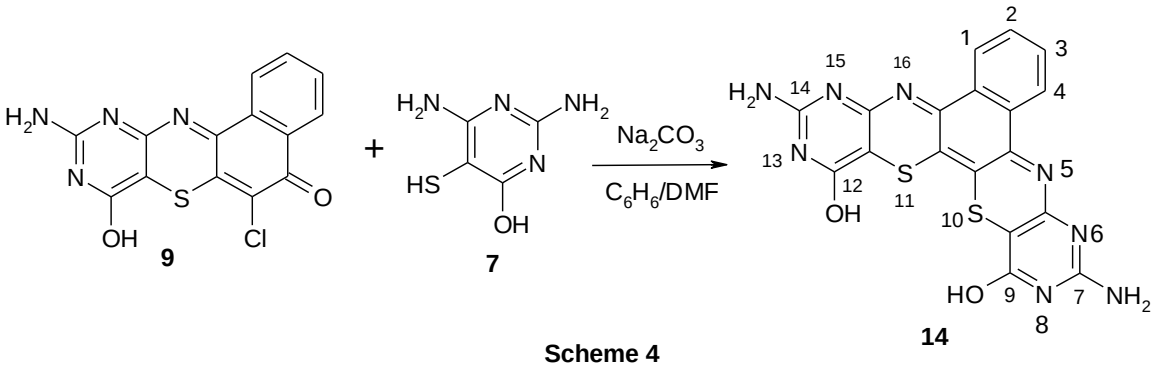
Compound **9** is likely formed by an initial nucleophilic attack by thiol ion **11** on the 2- or 3-position of the dichloronapthoquinone **8** which is resulted in the loss of one of the halogen atoms and the formation of the diaryl sulphide **12**. Cyclisation takes place by internal condensation of the amino group with the carbonyl in **12** resulting in elimination of water molecule and the formation of the angular diaza compound 10-amino-6-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one **(9)** scheme 3.



Scheme 3

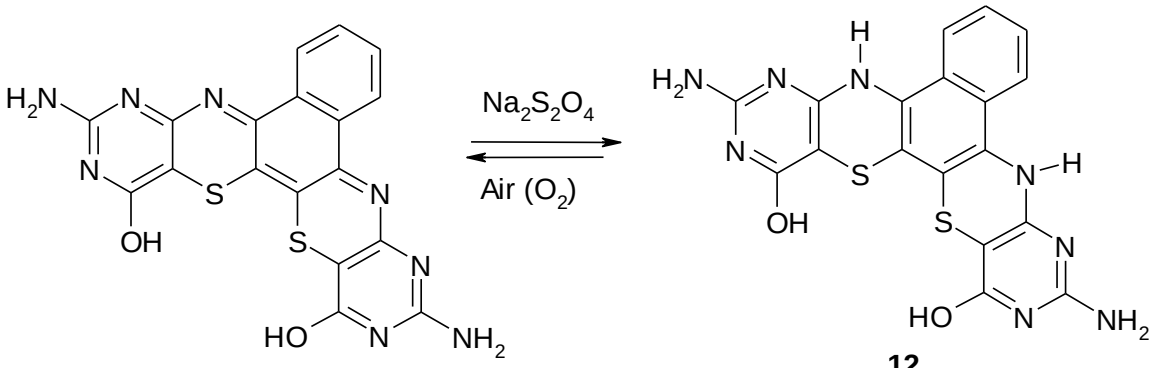
Since compound **9** still contains reactive halogen and carbonyl groups, further condensation with a another molecule of 2,4-diamino-6-hydroxypyrimidine-5-thiol gave the complex tetraaza heterocycle characterized as 7,14-diamino-9,12-dihydroxy-6,8,13,15-tetraazabenzo[a][1,4]benzothiazino[3,2-c]phenothiazine **(14).** Compound **14** is a deep-red solid m.p. > 360^{o}C. Elemental analysis is in agreement with the molecular formula $C_{18}H_{10}N_8O_2S_2$. ^{1}H-NMR spectrum gave signals at δ 7.60-8.00 multiplet corresponding to the aromatic protons, 5.10 singlet due to 2OH protons and 4.10 singlet assigned to $2NH_2$ groups. ^{13}C-NMR spectrum provided further evidence for the assigned structure, it showed the absence of C=O signal.

The Uv-visible absorption maxima band shifts from 421 in compound **9** to 530 nm in compound **14** was in commensurate with **14** having extended conjugation. The infrared spectrum gave bands at 3454 cm^{-1} (NH), 3095 cm^{-1} (C=C-H), 1605, 1502 cm^{-1} (aromatic C=C, C=N) (scheme 4).



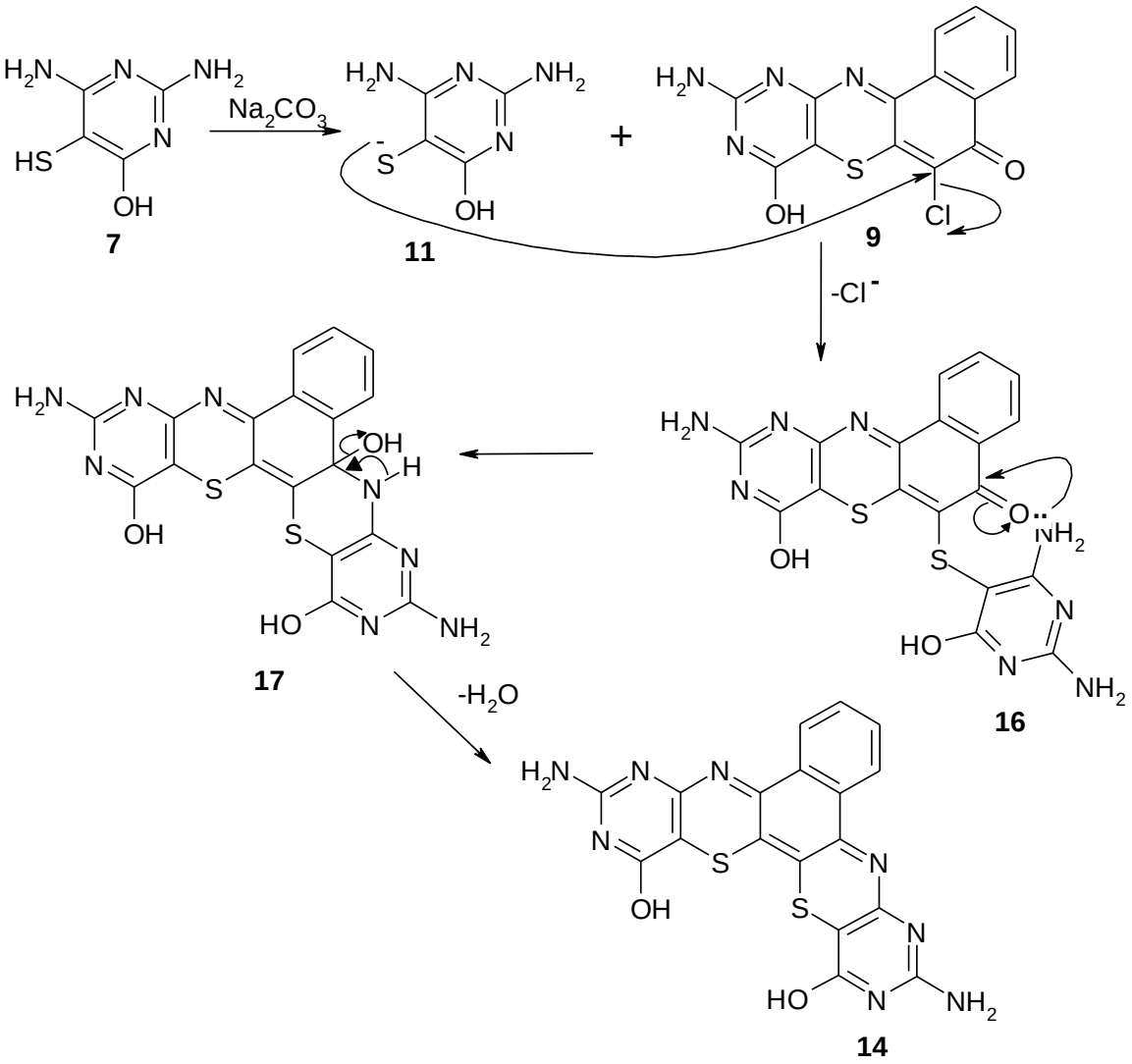
Scheme 4

When compound **14** was treated with sodium dithionite, it gave colour discharged unstable leuco-base **(15)** which reverted in the presence of atmospheric oxygen to dehydro compound **14**. This property makes compound **14** applicable as a vat dye.



11 **12**

Compound **14** is probably formed by initial nucleophilic attach by the thio-pyrimidine ion **(11)** on compound **9** by displacing the reactive halogen group to form a diaryl sulphide intermediate **(16).** Condensation of the amino and the carbonyl groups of **16** and the loss of water molecule gave the new heterocycle 7,14-diamino-9,12-dihydroxy-6,8,13,15-tetraazabenzo[a][1,4]benzothiazino[3,2-c]phenothiazine **(14)** (Scheme 5).



Scheme 5

3. 0. EXPERIMENTAL

The reagents were sourced commercially: benzene product of BDH chemicals England; acetone and methanol products of sigma-Aldrich. DMF is product of Kermel chemicals. 2,4-diamino-6-hydroxypyrimidine and 2,3-dichloro-1,4-naphthoquinone were products of Aldrich chemicals. Melting points were determined using electrothermal melting point apparatus in open capillaries and are uncorrected. Ultraviolet and visible spectra were recorded on Unicon-Uv 2102 PC spectrometer using matched 1cm quartz cells; absorption maxima are given in nanometers (nm), the figures in parenthesis are the molar absorptivity coefficient (ε) values. Infrared spectra were recorded on Buck 504 spectrometer using KBr discs. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) were determined using Varian mercury 200 BB spectrometer; chemical shifts are reported in (δ-ppm) scale. Products were purified by column chromatography on aluminium oxide 90 (Merck, 70-230 mesh) using employing benzene-chloroform as eluent before recrystallization Elemental analysis was obtained using Heraous CHN-O rapid analyzer

3.1. 5-Bromo-2, 4-diamino-6-hydroxypyrimidine (5)

2, 4-Diamino-6-hydroxypyrimidine monohydrate **(4)** (4.0 g, 30 mmole) was placed in a reaction flask containing 50% of methanol (50 ml). Sodium bicarbonate (8.0 g) was later added. Bromine (5 ml) was added from a dropping funnel for a period of 40 min with constant stirring. After 20 min of further stirring, additional sodium bicarbonate (5.0 g) was added and the entire mixture stirred for a period of 2 h. The slurry was kept overnight and

the product collected by filtration after adding water to dissolve the inorganic material. It was recrystallized from water after treatment with activated charcoal to give 5-bromo-2,4-diamino-6-hydroxypyrimidine **(5)** (5.0 g, 70% yield) as white crystals m.p. 267^{o}C dec.; as described by Okafor.[9]

3.2. 2,4-Diamino-6-hydroxy-5-thiocyanatopyrimidine (6)

5-Bromo-2, 4-diamino-6-hydroxypymidine (**5**) (4.8 g 26 mmole) was placed in a 3-necked flask containing boiled water (240 ml). The mixture was boiled until the solid dissolved. Potassium thiocyanate (6.0 g, 58 mmole) in water (25 ml) was then added and the entire solution was refluxed for 2 h. At the end of the refluxing period, the mixture was cooled, filtered and the residue recrystallized from acetone after treatment with activated charcoal to give 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine **(6)** m.p. > 300^{o}C; as described previously.[9]

3.3. 2,4-Diamino-6-hydroxypyrimidine-5-thiol (7)

2,4-Diamino-6-hydroxy-5-thiocyanatopyrimidine **(6)** (5.0 g, 27 mmole) was placed in a 250 ml reaction flask equipped with reflux condenser. Sodium hydroxide (20 g, 54 mmole) in water (60 ml) was added and the mixture refluxed in a sand bath for 24 h until ammonia gas ceased to evolve. At the end of the reaction period, a little amount of activated carbon was added and the mixture boiled for additional 20 min and then filtered. The filtrate was allowed to cool and later neutralized with ethanoic acid in an ice bath ensuring that the temperature did not exceed 10^{o}C. A massive orange precipitate was formed; it was filtered and later recrystallized from acetone and dried in a desicator to give 2,4-diamino-6-hydroxypyrimidine-5-thiol **(7)** as pale yellow crystals; (4.0 g, 82%); m.p. > 300^{o}C; (lit. m.p. > 300^{o}C).[9]

Uv-V (MeOH) λ_{max} (nm) (ε): 237 (11,540), 275 (20,615), 338 (8,465). IR (KBr): ν_{max} 3435 cm^{-1} (2NH), 1502 (C=C, C=N), 791, 760 and 651 cm^{-1}.). ^{1}H-NMR in (DMSO-d_6): δ 4.10 (s, 2NH$_2$), δ 2.90 (s, SH) and δ 5.10 (s, OH) ^{13}C-NMR ($CDCl_3$) ppm 160.514 (C-OH), 157.264 (2C-NH$_2$), 120.810 (C-SH).

3.4. 10-Amino-6-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one (9)

A mixture of 2,4-Diamino-6-hydroxypyrimidine-5-thiol **(7)** (2.0 g, 12 mmole) and anhydrous sodium carbonate (2.6 g, 25 mmole) was placed in a 250 ml reaction flask equipped with magnetic stirrer, thermometer and reflux condenser. A solution of benzene (100 ml) and DMF (10 ml) was added and the mixture refluxed for 45 min for dissolution. 2,3-Dichloro-1,4-naphthoquinone (2.6 g, 12 mmole) was later added and the entire mixture was refluxed with continuous stirring for 6 h at 75-80^{o}C. At the end of the reflux period, benzene solvent was distilled off and the slurry poured into water and stirred to dissolve the inorganic materials. It was cooled, filtered, dried and subjected to column chromatography on aluminum oxide using benzene-chloroform (1:1) as eluent. The first yellow band eluted was the unreacted 1,4-naphthoquinone. The second reddish band was collected and recrystallized from acetone after treatment with activated carbon to yield 10-amino-6-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one **(8)** as reddish solid mp. > 330^{o}C; (3.46 g, 71%)

Uv-V (MeOH) λ_{max} (nm) (ε): 213 (21,014), 260 (19,153), 421 (17,008). IR (KBr): ν_{max} 3430, 3303, 3189, 2924, 1661, 1594, 1440, 1378, 1211, 1101, 1023, 938, 848, 728 and 650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.50-7.90 (4H, m, Ar-H), 5.10 (H, s), 3.90 (2H, s), ^{13}C-NMR ($CDCl_3$) (ppm): 183.539 (C=O), 170.477 (1C), 164.191 (1C), 161.904 (1C), 157.183 (1C), 141.814, 135.539, 134.544, 132.127, 130.702, 129.292, 127.875, 123.458, 121.041(9C).

Analysis: Calculated for $C_{14}H_7N_4ClO_2S$: (%) C, 50.83; H. 2.13; N, 16.94; Cl, 10.72, S, 9.69; (Found: C, 50.86; H, 2.18; N, 16.96; Cl, 10.73; S, 9.67).

3.5. 7,14-Diamino-9,12-dihydroxy-6,9,13,15-tetraazabenzo[a][1,4]benzothiazino[3,2-c]phenothiazine (12)

2,4-Diamino-6-hydroxypyrimidine-5-thiol **(7)** (1.50 g, 9 mmole) and anhydrous sodium carbonate (2.0 g, 18 mmole) were placed in 250 ml 3-necked reaction flask equipped with magnetic stirrer, thermometer and reflux condenser. A solution of benzene (100 ml) and DMF (15 ml) was added and the mixture boiled for 45 min. 10-Amino-6-chloro-8-hydroxybenzo[a]-9,11-diazaphenothiazin-5-one **(8)** (3.0 g, 9 mmole) was later added and the entire mixture refluxed in water bath with continuous stirring for 10 h. At the end of the reaction period, the benzene solvent was distilled off and slurry added to water (600 ml), heated to near boiling, filtered, dried and subjected to column chromatography on aluminum oxide using benzene-chloroform and later recrystallized twice from aqueous acetone after treatment with activated carbon to give 7,14-diamino-9,12-dihydroxy-6,8,13,15-tetraazabenzo[a][1,4]benzothiazino[3,2-c]phenothiazine **(12)** as deep-red solid; mp. > 360^{o}C, (2.80 g, 62.22%)

Uv-V (MeOH) λ_{max} (nm) (ε): 275 (25,814), 293 (26,040), 311 (26,040), 317 (26,040), 347 (12,941), 383 (15,797), 455 (15,847), 500 (17,542), 512 (17,854), 530 (15,823). IR (KBr): ν_{max} 3454, 3095, 2919, 2852, 2645, 1605, 1502, 1380, 1192, 1107, 1005, 842, 794, 794 and 746 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.60-8.00 (4H, m, Ar-H), 5.10 (2H, s, 2OH), 4.10 (4H, s, $2NH_2$). ^{13}C-NMR ($CDCl_3$) (ppm): 173.629(2C), 164.146(2C), 160.376(2C), 156.117(2C), 133.379(2C), 131.600(2C), 129.777(2C), 127.048(2C), 122.545(2C),
Analysis: Calculated for $C_{18}H_{10}N_8O_2S_2$: (%): C, 49.76, H, 2.32, N, 25.79, S, 14.76.
(Found: (%): C, 49.80, H, 2.31, N, 25.78, S, 14.77).

3.6. Reduction of the dyes

Each of the new compounds (0.5 g) was boiled with dimethylformamide until dissolution was observed. Sodium dithionite (1.0 g) was added and the mixture heated for 2 h at 170^0C, during which time the dyes lost their colour and became reduced to the leuco-base. A piece of white material was dipped inside the solution and the colour was noted. On exposure of the soaked material to the atmospheric oxygen for drying, the reduced dyes became re-oxidized to the starting dyes resulting in the regeneration of the original colour of the dyes.

Conclusion

The new compounds were applied on white textile materials (cotton, nylon, polyester and silk). The dyed materials were tested for some properties; fastness to sunlight and ironing, resistant to washing away with detergent, dilute alkalis and acids etc and they were found to be good.

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REFERENCES

1. Kalkanidis, M.; Klonis, N.; Tilley, L.; Deady, L.W. (2002), Biochem. Pharmacol, , 63 (5), 833.
2. Korth, L. H. (2001), National Academy of Science USA. 98, (17)**,** 9836-9841.
3. Okafor, C. O. Okerelu, I. O.; Okeke, S. I.; **(**1986), Dyes and pigments, , 8, 11-24.
4. Mitchell, S. C. (1982), Drug Metabolism Rev., 13**,** 319-343.
5. Murphy, C. M. Rarner, H.; Smith, N. L.; (1950), Ind. Eng. Chem.**,** 42, 2479.
6. Okafor, C. O. (1986)**,** Dyes and Pigments, 7, 249.
7. Okafor, C. O. Okoro, U. C.; (1988), Dyes and Pigments, **,** 9, 427-422.
8. Okafor, C. O. (1988), Tetrahedron 44, 1187-1194
9. Okafor, C. O. (1980)**,** Studies in the Heterocyclic Series XVIII**,** 17, 1587-1591.

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