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Eco-Friendly Synthesis and Antimicrobial Activity of N-[7-(5-Substitutedimino-3-Amino)-1,2,4-Dithiazo-4-Yl]-N,N-Diethyl-Pentane-1,4-Diamine

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ABSTRACT

Heteroacyclic and Heterocyclic containing drugs showed remarkable and noticeable drug absorption, transmission and drug effects; hence they created their own identity and importance in pharmaceutical, medicinal, agricultural and drug sciences. Benzonido and pyridino, dithiazolo, quinolino and alkylamino heterocycles showed important applications in industrial, pharmaceutical, medicinal and drug chemistry. Considering all these facts into consideration recently in this laboratory interaction of N-(7-chloroquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine **(1)** was carried out with thiourea **(2)** in ethanol medium to isolate N-(7-thiocarbamidoquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamines **(3).** N-(7-thiocarbamido quinoline-4-yl)-N,N-diethyl-pentane-1,4-diamines on further interactions with various isothiocynates **(4)** in acetone-ethanol medium produces N-[7-(1- substituted) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine **(5)** which were successfully oxidatively cyclised into N-[7-(5-substitutedimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine **(6)** these reactions are hither to unknown. The justification and identification of the structure of these newly synthesized compounds had been established on the basis of chemical characterization, elemental analysis and through spectral data.

Keywords: Substituted isothiocynates, N-(7-substitutedthiocarbamidoquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamines, Green synthesis, bromine, acetone, ethanol and carbon tetrachloride.

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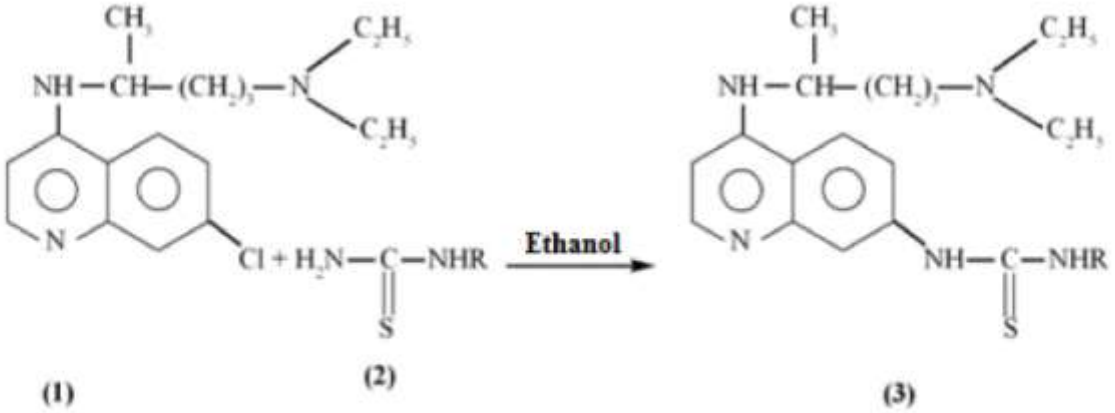
INTRODUCTION

Recently in this laboratory, the synthetic applications of cyanoguanidine had been briefly explored.[1] As evident from the structure of the 1-pyridino,1-(4-thiocarbamido)-dimethyl propanamine, it was observed that there are various reactive sites in this molecule for the reactions. This molecule possesses –SH, and -NH_2 important reactive sites for the reactions. As a wider programmee of this laboratory in the synthesis of nitrogen, nitrogen and sulphur containing heteroacycles and heterocycles. The interactions of cyanoguanidine with various thioureas and alkyl or aryl isothiocyanates have been investigated in sufficient details.[2-5] Some of these compounds showed remarkable pharmaceutical and biological activities.[6] The synthesized heteroacycles are used as a best intermediate[7-8] in the synthesis of thiadiazoles, dithiazoles, thiadizines, triazines, Hector's bases etc.

An exhaustive literature survey on substitutedthiobiureto, pyridino, dithiaozoyl and bezonido nucleus containing drugs created their own identity in medicinal and pharmaceutical sciences. Hence taking all these things into considerations interaction of N-(7-chloroquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine (1) with thiourea (2) in ethanol medium was investigated to synthesize N-(7-thiocarbamidoquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine (3). **(Scheme-1).** N-(7-Thiocarbamidoquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine was then interacted with alkyl or aryl isothiocynates (4) in acetone-ethanol medium to isolate yet new series of N-[7-(1- substituted) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine(5). **(Scheme-2).**

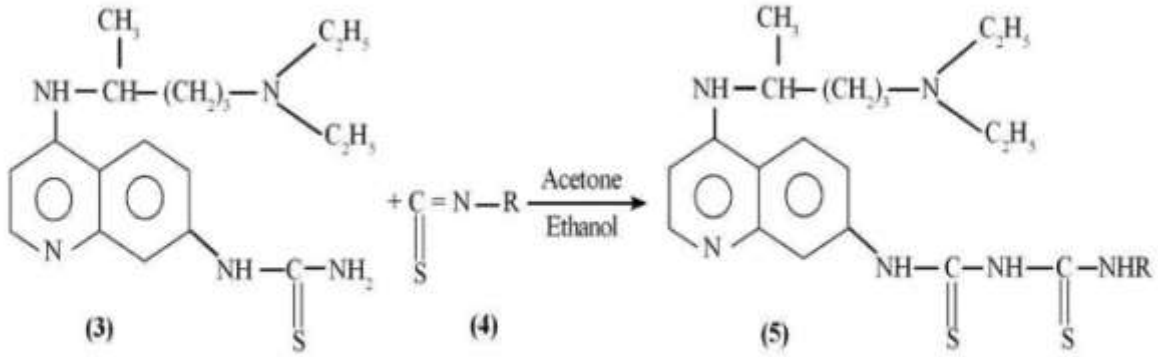
We developed the new route for this synthesis, in which the time span of the reactions decreases which maintain the green chemistry parameters and we used 80% acetone-ethanol mixture, as a medium in which the percentage of acetone is only 20% which help one green chemistry parameter. At the same time yield of product is also increased by maintaining purity of products. N-[7-(1-Substituted)-2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine on further oxidatively cyclisation with bromine in carbon tetrachloride gave N-[7-(5-substitutedimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine **(6). (Scheme-3)** These reactions are hither to unknown. The justification and identification of the structure of these newly synthesized compounds had been established on the basis of chemical characterization, elemental analysis and through spectral data.



(1) (2) (3)

Where R = -H, -phenyl, -methyl, -ethyl, -allyl

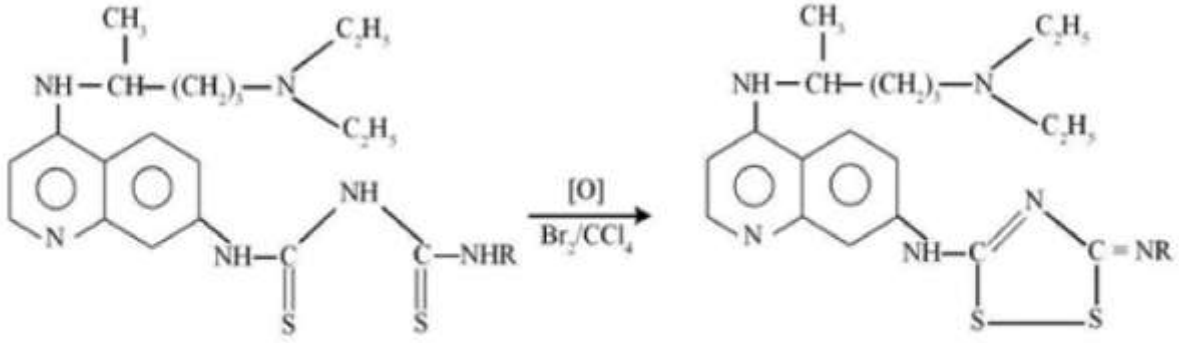
Scheme-I



(3) (4) (5)

Where R = -phenyl, -p-Cl-phenyl, -methyl, -ethyl, t-butyl

Scheme-II



(5) (6)

Where R = -phenyl, -p-Cl-phenyl, -methyl,-ethyl, t-butyl

Scheme-III

MATERIALS AND METHOD

The melting point of the all synthesized compounds was recorded using hot Paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra 1106 analyzer. Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Perkin Elmer Spectrometer in range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Brucker Ac 300 F Spectrometer with TMS as internal standard using $CDCl_3$ and DMSO–d_6 as solvent. The purity of compound was checked on silica Gel-G Pellets by TLC with layer thickness of 0.3 mm. All chemicals used were of AR-grade.

N-(7-Thiocarbamidoquinoline-4-yl)-N, N-diethyl-pentane-1,4-diamines (3a):-

A mixture of N-(7-chloroquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine **(1)** (0.1M), thiourea **(2)** and ethanol (40ml) was refluxed on boiling water bath for 3 hrs. During boiling suspended N-(7-chloroquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamine went into the solution and the new product was found to be gradually separated out ,which on basification with dilute ammonium hydroxide afforded white crystals. It was filtered in hot conditions and recrystallized with aqueous ethanol to obtained **(3a),** yield 69 %, melting point 193^0 C.

Properties:-

It is white , crystalline solid having melting point 193 ^{0}C. It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution. It formed picrate, melting point 119 ^{0} C.

Elemental analysis:- C [(found 67.4%) calculated 68.96]**, H** [(found 7.17%) calculated 7.58% **], N [(**found 16.1%) calculated 16.19], **S**[(found 6.72%) calculated 7.35]**.**

IR Spectra:-

The IR spectra was carried out in KBr pellets and The important absorption can be correlated as (cm^{-1}) 3435.6 (N-H stretching), [C-H(Ar)] stretching 3150.5, 1638.1 (C-N stretching), 1523.6 (=C=NH imino), 1199.7 (C-N stretching), 991.9 (N=C=S).

NMR Spectra:-

The spectrum was carried out in $CDCl_3$ and DMSO-d_6 .This spectrum distinctly displayed the signals due to Ar-H, protons at δ7.9525-7.9543 ppm, Ar-NH protons at δ 5.0417-5.0483 ppm, pyridino-NH at δ 4.2911-4.4564 ppm, $–CH_2$ protons at 3.3386-3.8638 ppm., $–CH_3$ protons at 1.2538ppm.

N-[7-(1- Phenyl) -2, 4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine (5a) :

A mixture of N-(7-thiocarbamidoquinoline-4-yl)-N, N-diethyl-pentane-1,4-diamines **(3a)** (0.05M) and phenylisothiocyanate **(4a)** (0.05m) was refluxed on water bath in acetone-ethanol

(15 ml) medium for 3 hrs in round bottom flask. It was filtered in hot conditions. The resultant filtrate on distillation gave **(5a),** yield 75% m.p.184^{0}C.

Examination of Product:

It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution.

Elemental Analysis :- C

[(Found 62.85%) calculated 63.15%], **H**[(found 5.95%) calculated 6.88%], **N**[(found 16.14%) calculated 17.00%], **S**[(found 11.28%) calculated 12.95%]

IR Spectrum: -

The IR spectrum was carried out in KBr pellets. The important absorption can be correlated as (cm^{-1}):- 3268.6 (N-H-Stretching), 3057.3 (Ar C-H-stretching), 2239.3(C=N stretching), 2935.0 (C-N-stretching), 1073.0 (C-S-stretching).

NMR Spectrum :-

The spectrum was carried out in $CDCl_3$ and DMSO-d_6. This spectrum distinctly displayed the signals due to Ar-H, protons at δ7.1-7.5 ppm., Ar-NH protons at δ 6.9 ppm, pyridino-NH at δ 4.29-4.45 ppm., $-CH_2$ protons at 3.7 ppm. , $-CH_3$ protons at 2.3-1.4ppm

This reaction was studied in various solvents and percent ratio of solvents for improving the yield and purity of the products as well as to maintain green chemistry parameters. The results are depicted in **Table. 1**

Table 1 Medium is used for the synthesis

Sr. No.	Solvent used	Quantity (ml)	Time Span (hours)	Yield (%)
1	Water	50	No reaction	- -
2	Acetone	50	4	52
3	Ethanol*****	50	4	57
4	Methanol	50	5	42
5	Isopropanol	50	8	35
6	Benzene	No reaction	--	--
7	Dioxane	50	10	20
8	Acetone-ethanol (20%)	30	7	60
9	Acetone-ethanol (40%)	30	5	65
10	Acetone-ethanol (60%)	30	4	71
11	**Acetone-ethanol (80%)**	**20**	**3**	**75**

This medium is used for the synthesis of all compounds (**5b-5e**).

Similarly, N-[7-(1-p-Cl-phenyl) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine (5b), N-[7-(1-methyl) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine (5c), N-[7-(1-ethyl) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine (5d), N-[7-(1-allyl) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine (5e) were synthesized by interacting N-(7-

thiocarbamidoquinoline-4-yl)-N,N-diethyl-pentane-1,4-diamines (3) with p-chlorophenylisothiocyanate (4b) methylisothiocyanate (4c) ethylisothiocyanate (4d) and tert-butylisothiocyanate (4e) by above mentioned method and enlisted in **Table 2**.

Table 2 Yield of compounds

Sr. No.	N-[7-(1- **substituted)** -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine	**Yield %**	**M.P. ^{0}C**
5b	.(1-p-Cl-phenyl)	64	146
5c	(1-methyl)	63	182
5d	.(1-ethyl)	70	171
5e	(1-tert-butyl)	54	157

N-[7-(5-Phenylimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine(6a):-

In china dish paste of N-[7-(1- phenyl) -2,4-dithiobiureto)-4-yl]-N,N-diethyl-pentane-1,4-diamine **(5a)** (0.5 M) was made in carbon tetrachloride, to it 10% bromine in carbon tetrachloride was added till the reaction mixture persist the colour of bromine. The reaction mixture was kept for 3 hrs at room conditions dark yellowish crystals were obtained yield 75% m.p.151^{0}C.

Examination of Product:

It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution.

Elemental Analysis:- C

[(Found 61.35%) calculated 63.41%], **H** [(found 5.95%) calculated 6.50%], **N** [(found 16.6%) calculated 17.07%], **S** [(found 12.28%) calculated 13.00%]

IR Spectrum: -

The IR spectrum was carried out in KBr pellets. The important absorption can be correlated as (cm^{-1}):- 3410.1 (N-H-Stretching), 3024.3 (Ar C-H-stretching), 1511.9(C=N stretching), 1442.9 (C-S-stretching).

NMR Spectrum :-

The PMR spectrum was carried out in $CDCl_3$ and DMSO–d_6. This spectrum distinctly displayed signals due to Ar-H protons at δ 7.4-7.1 ppm, Ar-NH protons at δ 5.8 ppm, aliphatic NH-proton at δ 3.7-3.8 ppm.

Similarly,N-[7-(5-p-Cl-phenylimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine (6b), N-[7-(5-p-Cl-methylimino-3-amino)-1,2,4-dithiazo-4-yl]-N, N-diethyl-pentane-1,4-diamine (6c), N-[7-(5-p-Cl-ethylimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine (6d), N-[7-(5-p-Cl-t-butylimino-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine (6e), were synthesized by oxidative cyclization of 1-pyridino,1-[4(1-p-

chlorophenyl)-2,4-dithiobiureto]phenyl-dimethyl propanamine(5b), 1-pyridino,1-[4(1-methyl)-2,4-dithiobiureto]phenyl-dimethyl propanamine.(5c), 1-pyridino,1-[4(1-ethyl)-2,4-dithiobiureto]phenyl-dimethylpropanamine.(5d), and 1-pyridino,1-[4(1-tert-butyl)-2,4-dithiobiureto]phenyl-dimethylpropanamine.(5e) respectively by above mentioned method and enlisted in **Table. 2 and 3**

Table 3 Yield of compounds

Sr.No.	N-[7-**(5-substitutedimino**-3-amino)-1,2,4-dithiazo-4-yl]-N,N-diethyl-pentane-1,4-diamine	**Yield %**	**M.P. ^{0}C**
6b	(5-p-Cl-phenylimino)	84	202
6c	(5-methylimino.)	81	172
6d	(5-ethylimino)	72	152
6e	(5-tert-butylimino)	79	144

Table.4 Antimicrobial activities

Comp. No	**S.*typhi* (mm)**	**E.*coli* (mm)**	**S. *abony* (mm)**	**P.*aeruginosa* (mm)**	**B. *subtilis* (mm)**	**A. *niger* (mm)**	**C. *albicans* (mm)**
6b	1.3	1.2	1.3	0.9	0.5	0.6	0.2
6c	1.9	1.5	1.6	1.3	1.3	0.3	0.3
6d	1.3	1.3	1.6	0.9	0.7	0.3	0.2
6e	1.5	1.0	0.9	0.7	0.8	0.1	0.4

ANTIMICROBIAL ACTIVITIES

The antimicrobial and antifungal activities of this compounds were screened by using cup-plate agar diffusion method in DMF, using standard Co-Trimazin 25 µg/ml against gram positive and gram negative bacteria such as E. *coli*, S. *typhi*, S. *abony*, P. *aeruginosa*, and B. *subtilis*. While all compounds were also screened for their antifungal activities by using standard Greseofulvin (10µg/ml) against A. *niger* and C. *albicans*.

Cup-plate method :-

A medium used throughout the experiment was HI-Media (India make) having composition of Pepton- 5gm/lit., NaCl -5gm/lit, Yeast extract -1.5gm/lit, Agar powder -20gm/lit, pH - 7.4 ± 0.1. The medium for antibacterial and antifungal activities were prepared [N-agar for bacterial and Sabourands dextrose agar for fungi] by dissolving 26 gms of ingredients in one liter of distilled water and sterilized in autoclave at 121^{0}C at 15 Ibs/inch pressure in an autoclave for 154 minutes. Then microbes were inoculated with requisite quantity to the medium at temperature 40-50^{0}C and immediately poured the inoculate medium in to sterilized petridishes to give a depth of 3-4 mm of uniform thickness. After solidification the well or holes were prepared by well borer. The dimethylformamide solution of the compound was added in sufficient amount to fill the well. Then it was kept at room temperature for 4 h, as a pre-incubation and then plates of

bacteria were inoculated for 18-24 hrs, at 36-38^{0}C and all plates fungi were inoculated 48 hrs at 20-25 ^{0}C. After the period of inoculation, zones of inhibition were recorded around the wells. The results are depicted in **Table.4**

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