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Synthesis of 2-(N'-Substituted)Thiocarbamido-5-(N''-Substituted)-2,4-Dithiobiurato)-1,3 Benzothiazoles and Antimalarial Activity

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Abstract : Recently in this laboratory a somewhat convenient and green synthesis conventional method for a synthesis of 2-(N'-substituted)thiocarbamido-5-(N''-substituted)-2,4-dithiobiurato)-1,3-benzothiazoles were developed by an interactions of 5-substituted-thiocarbamido-2-aminobenzothiazole with various isothiocyanates in 60% acetone-ethanol medium on water bath. The synthesized compounds were characterized by spectral analysis and all compounds were screened for their antimalarial activates.
Keywords : Various isothiocyanates, 5-substitutedthiocarbamido-2-aminobenzothiazole and 60 % acetone-ethanol medium.

Introduction

Mono and di thiobiurets have been reported as bactericidal, fungicidal and herbicidal activities[1]. Analoges of 2,4-dithiobiuret have repelling property to birds, rodents, leporine animals and ruminants[2]. Effect of 1-allyl-2-thiobiuret on germinating pattern on wheat and cucumber seeds was studied successfully[3]. Chemosterilising activity of substituted-2,4-dithiobiurets in male house flies was reported [4-5]. Effective growth regulating property of different thiobiurets was studied[6]. Thiobiuret analogues had been reported as analgesic[7], anti-convulsant and hypnotic properties[8].Glycosylatedbiuret is used as glycoenzyme inhibitors[9]. Successive cyclisation of 2,4-dithiobiurate gave formation of five or six member heterocycles and showed medicinal, agricultural and pharmaceutical applications[10-14]. The synthesized heteroacycles are used as a best intermediated in the synthesis of thiadiazoles, dithiazoles, thiadizines, triazines, Hector's bases etc.

2,4-Dithiobiurates are used as drug and also showed biological applications and significances, hence many analogs of them are used in various medicinal, industrial, agricultural, biochemical sciences[15-16]. 1,2,4-Dithiazoles were obtained by an oxidative cyclisation of 2,4-dithiobiuret making use of bromine in chloroform[17], 1,3,5-dithiazines were synthesized from 2,4-dithiobiurets and isocyanodichlorides[18]and these 1,3,5-dithiazines gave directly 1,3,5-triazines by simple isomerization[19].

Considering all these facts, it was decided to study a synthesis of 2-(N'-substituted)thiocarbamido-5-(N''-substituted)-2,4-dithiobiurato-1,3-benzothiazoles (IIIa-g) by interacting 5-substitutedthiocarbamido-2-aminobenzothiazole (Ia) and various isothiocynates(IIa-g) in 60% acetone-ethanol medium **(Scheme-1).**

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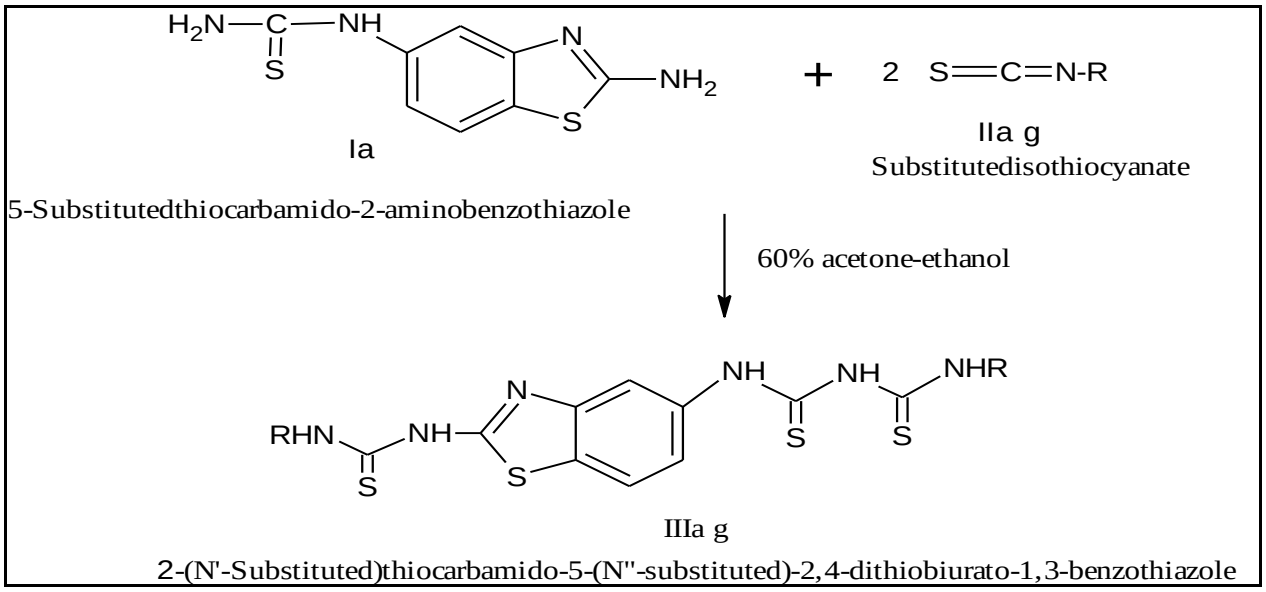

where, R= -ethyl, -tert-butyl, -phenyl,-*p*-chlorophenyl, *o*-tolyl, *m*-tolyl, *p*-tolyl.

(Scheme-I)

Materials and Method

AR grade Merck and Sigma chemicals were used for synthesis. Melting points of all synthesized compounds were recorded in open glass capillaries with a SGW X-4 digital apparatus and were uncorrected. Carbon and hydrogen estimation were carried out on Carlo-Ebra-1106 analyzer while of Nitrogen Colman-N-analyzer-29 and sulphur estimations were carried out by Carius method. IR spectra were recorded on Perkin Elmer spectrometer in the range 4000-400 cm^{-1} in KBr pellets. PMR and C^{13}spectra were recorded on BruckerAvance II- 400 NMR spectrometer with TMS as an internal standard using $CDCl_3$ and DMSO-d_6 as a solvent. Purity of the compounds were checked on silica gel -G plates by TLC with layer thickness of 3mm by using dioxane as solvent. Mass spectra were recorded on WATERS,Q-TOF micromass(ESI-MS).

Synthesis of 2-(N'-ethyl)thiocarbamido-5-(N"-ethyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIa)

In 100 ml round bottom flask a reaction mixture of 5-substitutedthiocarbamido-2-aminobenzothiazole (Ia) and ethylisothiocyanate (IIa) in 1:2 molar proportions was refluxed in 60% acetone-ethanol medium for 4 hours on water bath, brownish yellow crystals were separated out, filtered and dried at room conditions. Recrystallised from aqueous ethanol, Completion of reaction was monitoring by TLC. Yield 84%,m.pt.-226^{o}C.

Similarly, 5-substituted-thiocarbamido-2-aminobenzothiazole (Ia) interacted with *t*-butylisothiocyanate(IIb), phenylisothiocyanate (IIc), *p*-chlorophenylisothiocyanate (IId), *o*-tolylisothiocyanate (IIe), *m*-tolylisothiocyanate (IIf), *p*-tolylisothiocyanate (IIg) to isolate 2-(N'-*t*-butyl)-thiocarbamido-5-(N"-*t*-butyl)-2,4-dithiobiurato-1,3-benzothiazole(IIIb),2-(N'-phenyl) thiocarbamido-5-(N"-phenyl)-2,4-dithiobiurato-1,3-benzothiazole(IIIc), 2-(N'-*p*-chlorophenyl) thiocarbamido-5-(N"-*p*-chlorophenyl)-2,4-dithiobiurato-1,3-benzothiazole (IIId), 2-(N'-*o*-tolyl)thiocarbamido-5-(N"-*o*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIe), 2-(N'-*m*-tolyl)-thiocarbamido]-5-(N"-*m*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIf), 2-(N'-*p*-tolyl)thio-carbamido-5-(N'-*p*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIg) respectively by above mentioned method and enlisted in **Table No. I.**

Table No. I

Sr. No.	2-(N'-**Substituted)**thiocarbamido-5-(N"-substituted)-2,4-dithiobiurato-1,3-benzothiazole (IIIb-g)	**Yield (%)**	**m.p.** °C
1.	*2-(N'-**tert-Butyl)***----------benzothiazole (IIIb)	86	173
2.	*2-(N'-**phenyl)***----------benzothiazole(IIIc)	95	247
3.	*2-(N'-**p-Chlorophenyl)***----------benzothiazole(IIId)	88	201
4.	*2-(N'-**o-Tolyl)***----------benzothiazole (IIIe)	92	262
5.	*2-(N'-**m-Tolyl)***----------benzothiazole (IIIf)	84	168
6.	*2-(N'-**p-Tolyl)***----------benzothiazole (IIIg)	86	219

Antimalarial activity:

All the synthesized compounds were evaluated in vitro antimalarial activity against Plasmodium *falciparum* strain. Acoording to microassay protocol of Rieckmann et al[20] was carried out in 96 well microtitre plates with minor modifications.The cultures of the strain were maintained in medium RPMI 1640 medium supplemented with 25mM HEPES,1% D-glucose,0.23% sodium bicarbonate and 10% heat inactivated human serum. For antimalarial testing, the asynchronous parasites of Plasmodium *falciparum* was synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay,an initial ring stage parasitaemia of 1.2 to 1.5% at 3% haematocrit in a total volume of 200 µL of medium RPMI-1640 was uniformly maintained with 50% RBCs (O^{+ve}). A stock solution of (1mg/mL) of test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µL volume were added to the test wells so as to obtain final concentration ranging between 0.4µg/mL to 100 µg/mL in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37°C in a candle jar. After 36 to 40 hrs incubation, blood smears from each well were prepared and stained with 3 % Giemsa stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozites and schizonts in presence of different concentration of test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentration.

Results and Discussion

Spectral data of all the synthesized compounds (IIIa-g) are given below,

Spectral Characterization:

2-(N'-ethyl)thiocarbamido-5-(N"-ethyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIa): Brownish yellow crystalline solid, M.F. $C_{14}H_{18}N_6S_4$, Yield 84%, M.P. 226° C; **Elemental analysis: Found(Calculated)**C:41.30(42.21), H:04.03(04.52), N:20.21 (21.10), S:31.25(32.16)^{1}H NMR (400 MHz,DMSO-d_6): NH protons at δ 9.8026-9.4717 ppm, Ar-H protons at δ7.7572-7.0562 ppm, -NH protons at δ 3.5385 ppm, CH_2 protons at δ 2.5486-2.5403,CH_3 protons at δ1.1625-1.0974., ^{13}C: C=S carbon at δ 183.76 ppm, Ar-C carbon at δ 140.87-120.72 ppmCH_2 carbon at δ79.02-78.36,CH_3 carbon at δ40.09-38.63 ppm.IR (KBr,cm^{-1}): 3414 N-H stretching., 2972 C-H stretching.,1734 N=C-N stretching., 1616 C=C stretching., 1541 N-C=S stretching., 1149 C-N stretching;MS (ESI) (m/z) :398.3$(M)^+$, 355, 327, 252.

2-(N'-tert-butyl)thiocarbamido-5-(N"-tert-butyl)-2,4-dithiobiurato-1,3-benzothiazole(IIIb): Dark brown crystalline solid, M.F. $C_{18}H_{26}N_6S_4$, Yield 86%, M.P. 173° C; **Elemental analysis: Found(Calculated)**C:61.03(47.78), H:04.67(05.86), N:18.58 (18.58), S:27.31(28.31)^{1}H NMR (400 MHz,DMSO-d_6): NH protons at δ 9.6047-8.0555 ppm, Ar-H protons at δ6.6167-6.3910 ppm, -NHprotons at δ 3.4605ppm,CH_3protons at δ1.3808-1.2457.,^{13}C: C=S carbon at δ 184.72 ppm, Ar-C carbon at δ 142.67-122.80 ppm, CH_2 carbon at δ78.22-77.16, CH_3 carbon at δ39.25 ppm.IR (KBr,cm^{-1}): 3429 N-H stretching., 3151C-H stretching.,1750 N=C-N stretching., 1639 C=C stretching., 1478 N-C=S stretching., 1092 C-N stretching;MS (ESI) (m/z) : 454.50 $(M)^+$, 288, 229.18.

2-(N'-phenyl)thiocarbamido-5-(N"-phenyl)-2,4-dithiobiurato-1,3-benzothiazole(IIIc): Pale yellow crystalline solid, M.F. $C_{22}H_{18}N_6S_4$, Yield 95%, M.P. 247° C; **Elemental analysis:**

Found(Calculated)C:52.41(53.44), H:03.20(03.64), N:16.56 (17.00), S:24.21(25.91)^{1}H NMR (400 MHz,DMSO-d_6): NH protons flanked in thioamido and benzothiazole ring at δ 9.0109 ppm, NH protons flanked in thioamido and phenyl ring at δ8.0516 ppm,Ar-H protons of benzothiazole ring at δ7.7403-7.7024 ppm,Ar-H protons at δ7.6976-7.0233 ppm ., ^{13}C: C=S carbon at δ 183.90 ppm, Ar-C carbon at δ 140.57-120.79 ppm. .IR (KBr,cm^{-1}): 3412 N-H stretching., 3155 C-H stretching.,1751 N=C-N stretching., 1577 C=C stretching., 1425 N-C=S stretching., 1199 C-N stretching.,;MS (ESI) (m/z) :494(M)$^+$, 403, 300, 268.

2-(N'-*p*-chlorophenyl)thiocarbamido-5-(N"-*p*-chlorophenyl)-2,4-dithiobiurato-1,3-benzothiazole (IIId): Brown yellow crystalline solid, M.F. $C_{22}H_{16}N_6S_4Cl_2$, Yield 88%, M.P. 201^o C; **Elemental analysis: Found(Calculated)**C:46.32(47.14), H:03.24(03.41), N:15.00 (15.00), S:21.65(22.85),Cl:11.35(12.50)^{1}H NMR (400 MHz,DMSO-d_6): NH protons flanked in thioamido and benzothiazole ring at δ10.8250 ppm, NH protons flanked in thioamido and phenyl ring at δ9.5973 ppm,Ar-H protons of benzothiazole ring at δ7.9515-7.1054 ppm, Ar-H proton at δ6.9520-6.4599 ppm., ^{13}C:C=S carbon at δ 185.76 ppm, Ar-C carbon at δ 144.45-119.72 ppm.IR (KBr,cm^{-1}): 3370 N-H stretching., 3143 C-H stretching.,1681 N=C-N stretching., 1608 C=C stretching., 1487 N-C=S stretching., 1097 C-N stretching;MS (ESI) (m/z) :529(M)$^+$, 418, 253.

2-(N'-*o*-tolyl)thiocarbamido-5-(N"-*o*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole(IIIe): yellow crystalline solid, M.F. $C_{24}H_{22}N_6S_4$, Yield 92%, M.P. 262^o C; **Elemental analysis: Found(Calculated)**C:54.21(55.38), H:03.11(03.84), N:16.15 (16.15), S:24.61(24.61)^{1}H NMR (400 MHz,DMSO-d_6): NH protons at δ 9.9261 ppm, NH protons flanked in thioamido and phenyl ring at δ8.7891 ppm., Ar-H protons of benzothiazole ring at δ7.9686-7.0080 ppm, Ar-H protons at δ6.9888-6.3602 ppm,CH_3 protons at δ1.2489 ppm., ^{13}C: C=S carbon at δ 180.76 ppm, Ar-C carbon at δ 139.87-118.82 ppm, CH_3 carbon at δ39.25-37.69 ppm.IR (KBr,cm^{-1}): 3429 N-H stretching., 3152 C-H stretching.,1574 N=C-N stretching., 1640 C=C stretching., 1505 N-C=S stretching., 1089 C-N stretching;MS (ESI) (m/z) :513(M)$^+$, 312, 288, 760.

2-(N'-*m*-tolyl)thiocarbamido-5-(N"-*m*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIf): Ivory crystalline solid, M.F. $C_{24}H_{22}N_6S_4$, Yield 84%, M.P. 168^o C; **Elemental analysis: Found(Calculated)**C:54.21(55.38), H:03.11(03.84), N:16.15 (16.15), S:24.61(24.61)^{1}H NMR (400 MHz,DMSO-d_6): NH protons at δ10.0847-9.8343 ppm, NH protons flanked in thioamido and phenyl ring at δ8.1204 ppm, Ar-H protons of benzothiazole ring at δ7.9548-7.4093 ppm,Ar-H protons at δ6.7323-6.1267., CH_3 proton at δ1.9112 ppm., ^{13}C: C=S carbon at δ 184.77 ppm, Ar-C carbon at δ 138.62-119.43 ppm ,CH_3 carbon at δ39.15-37.31 ppm.IR (KBr,cm^{-1}): 3383 N-H stretching., 3049 C-H stretching.,1596 N=C-N stretching., 1636 C=C stretching., 1497 N-C=S stretching., 1033 C-N stretching;MS (ESI) (m/z) :513(M)$^+$, 314, 290, 76.

2-(N'-*p*-tolyl)thiocarbamido-5-(N"-*p*-tolyl)-2,4-dithiobiurato-1,3-benzothiazole (IIIg): Dark yellow crystalline solid, M.F. $C_{24}H_{22}N_6S_4$, Yield 86%, M.P. 219^o C; **Elemental analysis: Found(Calculated)**C:54.21(55.38), H:0.311(03.84), N:16.15 (16.15), S:24.61(24.61)^{1}H NMR (400 MHz,DMSO-d_6): NH protonsat δ10.5663 ppm,NH protons flanked in thioamido and phenyl ring at δ9.8049-8.2144 ppm, Ar-H protons of benzothiazole ring at δ7.8125-7.0865 ppm, Ar-H proton at 6.9969-6.8951 ppm ,CH_3protons at δ1.8437 ppm., ^{13}C: to C=S carbon at δ 181.16 ppm, Ar-C carbon at δ 137.85-119.70., ppmCH_3 carbon at δ39.09-36.23 ppm.IR (KBr,cm^{-1}): 3375 N-H stretching., 3182 C-H stretching.,1661 N=C-N stretching., 1627 C=C stretching., 1467 N-C=S Stretching., 1075 C-N Stretching;MS (ESI) (m/z) :513.10(M)$^+$.

Antimalarial activity:

The newly synthesized compound **(IIIa-IIIg)** were evaluted for thierantimalarial activity against plasmodium *falciparum* by MIC method . Chloroqunine was used as standard drug to compare the antimalarial activity .Compound **(IIIb)**and **(IIId)** was superior over the activity of standard drug Chloroqunine.

Compound code	**Chloroqunine**	**IIIa**	**IIIb**	**IIIc**	**IIId**	**IIIe**	**IIIf**	**IIIg**
MIC µg/ml	0.050	1.21	0.073	0.17	0.091	0.21	0.19	0.15

Where MIC (minimal inhibition concentration)

Conclusion :

The present work reports the synthesis of novel compounds reaction scheme **(IIIa-g)** are verified and confirmed by making use of several chemicals tests. Spectral data analysis of the synthesized compound**(IIIa-g)**also support and confirm the desired product moieties . Compound (**IIIb)** and (**IIId)** superior over the activity of standard antimalarial agents.

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