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A convenient one pot synthesis of 4-cyano-5-imino-3-methylthio-9-nitro-*2H*-1,2,4-triazipino[3,4-*b*] [1,3] benzothiazole and its 3-substituted derivatives

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ABSTRACT

3-Substituted derivatives ***[IV-a-d, V-a-d, VI-a-c and VII-a-c]*** *of 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-b] [1,3] benzothiazole have been prepared through One Step Multicomponent reaction by heating a mixture of 2-hydrazino-6-nitro benzothiazole* ***(I)*** *and bis methylthio methylene malononitrile* ***(II)*** *independently with aromatic amines / phenols / heterylamines / compounds containing active methylene group respectively in the presence of dimethyl formamide and catalytic amount of anhydrous potassium carbonate. All these newly synthesized compounds were screened for antibacterial activity.*

Key words: antibacterial activity, bis methylthio methylene malononitrile, 2-hydrazino-6-nitro benzothiazole , multicomponent reaction.

INTRODUCTION

Compounds containing thiazepines are well known for their varied biological activities [1-7] like analgesics, antihistamines, edrenolytics, neuroleptics and anti HIV. 1,4-Benzodiazepines [8-9] and thiazolotriazepines [10-11] and benzothiazolo triazepines [12] exhibit psychosedative, tranquilizing and CNS depressant activity. Z.Polivka et.al [13] reported 3-(4'-methyl piperazino) dibenzo (*b*,*f*) 1,2,4-triazolo (4,3-*d*)-1,4-thiazepine and its 6-chloro and 12-chloro derivatives as neurotropic and psychotropic agents. 4-H/CH_3 subtituted derivatives of dibenzo (*b*,*f*)-1,3-imidazolo(2,3-*d*) (1,4) diazepines/(1,4)oxazepines/(1,4)thiazepines are reported [14] to possess sedative and anticonvulsant (1,4-diazepines), anti-inflammatory and analgesics (1,4-oxazepines) and antiparkinsonism activities (1,4-thiazepines). An improved process for preparing 11-chloro dibenzo(*b*,*f*) (1,5) thiazepine has been reported by Joseph P.K. et.al [15] and G. Walther et.al [16] reported the synthesis of 4-substituted guanidine derivatives of dibenzo (*b, f*) (1, 5) oxazepines and dibenzo (*b, f*) (1,5) thiazepines which possess H_1-antihistaminic properties. Synthesis of 5-substitued of dibenzo (*b*,*f*) (1,4) thiazepines have been reported in the form of patent [17]. These compounds are useful as neuroleptic, antidepressants, neuroleptics and antischizophrenics. In our recent publications [18-21] we have outlined convenient synthesis of new fused heterocyclic systems like oxo pyimido benzothiazoles [18-19], pyrazolo pyrimido benzothiazoles [20] and benzothiazolo triazepines [21] and studied their biological activities. A survey of literature made it evident that very little work has been carried out on the preparation of fused benzothiazolo-1,2,4-triazepine system and moreover, reported methods are tedious and time consuming. In view of this, a more convenient route of multicomponent reaction was sought for the synthesis of compounds containing fused benzothiazolo triazepine system, 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole and its 3-substituted derivatives.

EXPERIMENTAL SECTION

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

Synthesis of 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzo thiazole. (III) A mixture of 2-hydrazino-6-nitro benzothiazole **(I)** [0.210 gm, 0.001 mole] and bis methylthio methylene malononitrile [0.170 gm, 0.001 mole] **(II)** was refluxed in the presence of 5 ml of dimethyl formamide and anhydrous potassium carbonate (0.2 gms) for five hours. The reaction mixture was cooled to room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from ethanol to get 0.215 gm of crystalline solid of **(III)**.

Yield: 64 % M.P: 274 ^{0}C, **IR:**(KBr/cm^{-1}): 3579 (=NH), 3500 (-NH), 2206 (CN), 1527 and 1338 (-NO_2), **^{1}H-NMR:** (DMSO) : δ 2.80 (s 3H SCH_3), δ 9.10 (s 1H -NH), δ 9.50 (s 1H =NH), δ 7.70 - 8.50 (m 3H Ar-H). **EI-MS:** (m/z:RA%): 333 (M+1). **^{13}C NMR** (DMSO) : δ 15 ($S\underline{C}H_3$), δ 61 (C_4), δ 115 (C-$\underline{C}$N), δ 117 (C_7, Ar-C), δ 118 (C_8 Ar-C), δ 126 (C_{10} Ar-C), δ 127 (C_{12} Ar-C), δ 138 (C_9 Ar-C), δ 153 (C_{13} Ar-C), δ 154 (C_{14}), δ 164 (C_5), δ 178 (C_3)**. Elemental analysis :** $C_{12}H_8N_6O_2S_2$, Calculated: (%) C 43.37, H 2.43, N 25.29, O 9.63, S 19.30 Found (%):C 43.33, H 2.41, N 25.22, O 9.60, S 19.25

General Method : Synthesis of 3-Substituted derivative of 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzo thiazole. (III)
A mixture of 2-hydrazino-6-nitro benzothiazole **(I)** [0.210 gm, 0.001 mole] and bis-methylthio methylene malononitrile **(II)** [0.170gm, 0.001mole] was refluxed in the presence of of dimethyl formamide (5ml) and a pinch of anhydrous potassium carbonate (0.2gm) was refluxed independently with one mole equivalent of aryl amines / phenols / heteryl amines and compounds containing active methylene group for six hours. The progress of reaction was monitored on TLC. After completion of reaction, the reaction mixture was cooled to room temperature and poured on ice cold water. The separated solid product was filtered, washed with water and recrystallized from ethanol to give respective products.

1) 4-Cyano-5-imino-3-(p-chloroanilino)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (IV-a) Yield: 74 %, M.P: 287 ^{0}C, **IR:**(KBr/cm^{-1}) : 3460 (=NH), 3303 (-NH), 2202 (CN), 1558 and 1342 (-NO_2). **^{1}H-NMR:** (DMSO): δ 4.30 (s 1H -NH), δ 6.70 to 7.00 (m 4H Ar-H), δ 7.20 (d 1H Ar-H), δ 7.40 (d 1H Ar-H), δ 7.65 (d 1H Ar-H), δ 8.05 (s 1H -NH) & δ 8.40 (s 1H =NH). **EI-MS:** (m/z:RA%) : 412 (M+1), **Elemental analysis :** $C_{17}H_{10}ClN_7O_2S$, Calculated: (%) C 49.58, H 2.45, Cl 8.61, N 23.81, O 7.77, S 7.79 Found (%) : C 49.53, H 2.41, Cl 8.55, N 23.77, O 7.74, S 7.72

02)4-Cyano-5-imino-3-(p-nitroanilino)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (IV-b)
Yield: 55 %, M.P : 271 ^{0}C, **IR:**(KBr/cm^{-1}) : 3420 (=NH), 3250 (-NH), 2210 (CN), 1522 & 1345 (-NO_2). **EI-MS:** (m/z:RA%): 423 (M+1). **Elemental analysis :** $C_{17}H_{10}N_8O_4S$, Calculated: (%) C 48.34, H 2.39, N 26.53, O 15.15, S 7.59 Found (%) : C 48.30, H 2.35, N 26.51, O 15.12, S 7.56

03) 4-Cyano-5-imino-3-(p-hydroxyanilino)-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole. (IV-c)
Yield: 68 %, M.P : 301 ^{0}C, **IR:** (KBr/cm^{-1}): 3460 (-OH), 3435 (=NH), 3224 (-NH), 2212 (CN), 1543 & 1340 (-NO_2). **EI-MS:** (m/z:RA%): 394 (M+1). **Elemental analysis:** $C_{17}H_{11}N_7O_3S$, Calculated: (%) C 51.90, H 2.82, N 24.92, O 12.20, S 8.15 Found (%) : C 51.85, H 2.80, N 24.81, O 12.15, S 8.12

04) 4-Cyano-5-imino-3-(p-toluidino)-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole. (IV-d)
Yield : 80 %, M.P : 288 ^{0}C, **IR:**(KBr/cm^{-1}) : 3452 (=NH), 3210 (-NH), 2215 (CN), 1555 & 1342 (-NO_2). **EI-MS:** (m/z:RA%) : 392 (M+1). **Elemental analysis:** $C_{18}H_{13}N_7O_2S$, Calculated: (%) C 55.23, H 3.35, N 25.05, O 8.18, S 8.19 Found (%) : C 55.20, H 3.31, N 25.02, O 8.11, S 8.13

05) 4-Cyano-5-imino-3-(4'-nitrophenoxy)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (V-a)
Yield : 66 %, M. P : 265 ^{0}C, **IR:**(KBr/cm^{-1}) : 3390 (=NH), 3124 (-NH), 2204 (CN), 1515 & 1334 (-NO_2), 1116 (-C-O-C- stretching). **^{1}H-NMR:** (DMSO): δ 6.70 (s 1H -NH), δ 7.00 (t 4H Ar-H), δ 7.50 (d 2H Ar-H), δ 7.80 (d 1H Ar-H), δ 8.80 (s 1H =NH). **EI-MS:** (m/z:RA%) : 424 (M+1). **Elemental analysis :** $C_{17}H_9N_7O_5S$, Calculated: (%) C 48.23, H 2.14, N 23.16, O 18.90, S 7.57 Found (%) : C 48.20, H 2.11, N 23.12, O 18.85, S 7.53

06) 4-Cyano-5-imino-3-(4'-carboxylicphenoxy)-9-nitro-2H-1,2,4-triazipino[3,4-*b*] [1,3] benzothiazole. (V-b)
Yield : 57 %, M. P : 285 ^{0}C, **IR:**(KBr/cm^{-1}) : 3507 (-OH), 3450 (=NH), 3222 (-NH), 2210 (CN), 1620 (C=O), 1542 & 1345 (-NO_2), 1085 (-C-O-C- stretching). **EI-MS:** (m/z:RA%) : 423 (M+1). **Elemental analysis :** $C_{18}H_{10}N_6O_5S$, Calculated: (%) C 51.19, H 2.39, N 19.90, O 18.94, S 7.59 Found (%) : C 51.15, H 2.31, N 19.88, O 18.92, S 7.54

07) 4-Cyano-5-imino-3-(phenoxy)-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole. (V-c)
Yield : 52 %, M. P : 252 ^{0}C, **IR:** (KBr/cm^{-1}) : 3425 (=NH), 3210 (-NH), 2215 (CN), 1542 & 1345 (-NO_2), 1077 (-C-O-C- stretching). **EI-MS:** (m/z:RA%) : 379 (M+1). **Elemental analysis:** $C_{17}H_{10}N_6O_3S$, Calculated: (%) C 53.96, H 2.66, N 22.21, O 12.69, S 8.47 Found (%) : C 53.91, H 2.60, N 22.15, O 12.55, S 8.44

08) 4-Cyano-5-imino-3-(4'-methylphenoxy)-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole. (V-d)
Yield : 67 %, M. P : 290 ^{0}C, **IR:**(KBr/cm^{-1}) : 3420 (=NH), 3208 (-NH), 2210 (CN), 1545 & 1352 (-NO_2), 1082 (-C-O-C- stretching). **EI-MS:** (m/z:RA%) : 393 (M+1), **Elemental analysis :** $C_{18}H_{12}N_6O_3S$, Calculated: (%) C 55.10, H 3.08, N 21.42, O 12.23, S 8.17 Found (%) : C 55.06, H 3.02, N 21.37, O 12.20, S 8.11

09) 4-Cyano-5-imino-3-(malononitrile)-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole. (VI-a)
Yield : 55 %, M. P : 322 ^{0}C, **IR:** (KBr/cm^{-1}) : 3442 (=NH), 3182 (-NH), 2204 (CN), 1519 & 1338 (-NO_2). **^{1}H-NMR :** (DMSO): δ 4.30 (s 1H CH), δ 6.80 (s 1H -NH), δ 7.30 (d 1H Ar-H), δ 7.80 (d 1H Ar-H), δ 8.00 (d 1H Ar-H) & δ 8.50 (s 1H =NH). **EI-MS:** (m/z:RA%) : 351 (M+1). **Elemental analysis :** $C_{14}H_6N_8O_2S$, Calculated: (%) C 48.00, H 1.73, N 31.99, O 9.13, S 9.15 Found (%) : C 47.90, H 1.71, N 31.96, O 9.10, S 9.12

10) 4-Cyano-5-imino-3-(α-ethylacetoacetyl)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (VI-b)
Yield : 65 %, M. P : 285 ^{0}C, **IR:** (KBr/cm^{-1}) : 3410 (=NH), 3212 (-NH), 2220 (CN), 1617 (C=O), 1541 & 1350 (-NO_2). **EI-MS:** (m/z:RA%) : 415 (M+1). **Elemental analysis :** $C_{17}H_{14}N_6O_5S$, Calculated: (%) C 49.27, H 3.41, N 20.28, O 19.30, S 7.74 Found (%) : C 49.23, H 3.35, N 20.21, O 19.25, S 7.70

11)4-Cyano-5-imino-3-(α-acetylacetone)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (VI-c) Yield : 57 %, M. P : 277 ^{0}C, **IR:** (KBr/cm^{-1}) : 3430 (=NH), 3221 (-NH), 2205 (CN), 1615 (C=O), 1540 & 1355 (-NO_2). **EI-MS:** (m/z:RA%) : 385 (M+1), **Elemental analysis :** $C_{16}H_{12}N_6O_4S$, Calculated: (%) C 50.00, H 3.15, N 21.86, O 16.65, S 8.34 Found (%) : C 49.92, H 3.11, N 21.80, O 16.63, S 8.30

12) 4-Cyano-5-imino-3-(piperizino)-9-nitro-2H-1,2,4-triazipino[3,4-*b*][1,3] benzothiazole. (VII-a)
Yield : 60 %, M. P : 262 ^{0}C, **IR:** (KBr/cm^{-1}) : 3456 (=NH), 3221 (NH), 2194 (CN), 1541 & 1338 (-NO_2). **^{1}H-NMR:** (DMSO): δ 2.20 (s 1H NH), δ 2.40 to 3.00 (m 8H -CH_2), δ 6.40 to 7.00 (m 3H Ar-H), δ 8.20 (s 1H -NNH) & δ 8.70 (s 1H =NH). **EI-MS:** (m/z:RA%) : 371 (M+1). **Elemental analysis :** $C_{15}H_{14}N_8O_2S$, Calculated: (%) C 48.64, H 3.81, N 30.25, O 8.64, S 8.66 Found (%) : C 48.60, H 3.75, N 30.21, O 8.62, S 8.60

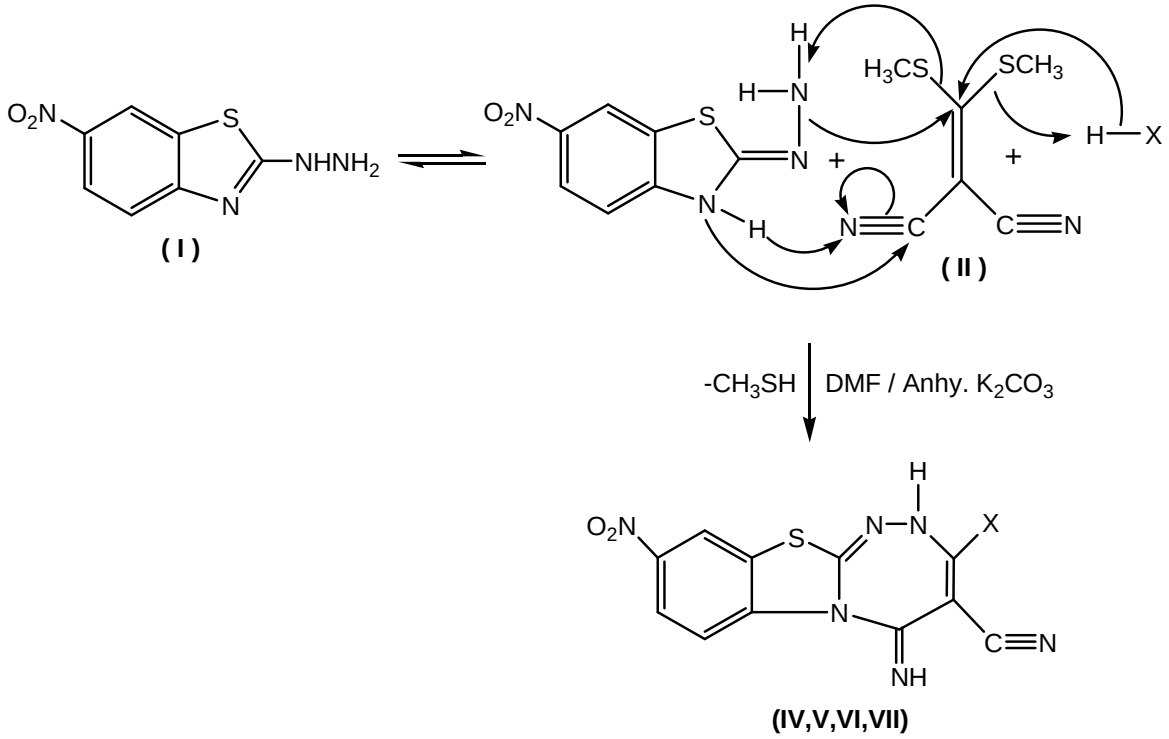
13) 4-Cyano-5-imino-3-(marpholino)-9-nitro-2H-1,2,4-triazipino[3,4-*b*] [1,3] benzothiazole. (VII-b)
Yield : 64 %, M. P: 271 ^{0}C, **IR:** (KBr/cm^{-1}) : 3422 (=NH), 3235 (-NH), 2208 (CN), 1542 & 1334 (- NO_2), 1045 (C-O-C). **EI-MS:** (m/z:RA%) : 372 (M+1). **Elemental analysis :** $C_{15}H_{13}N_7O_3S$, Calculated: (%) C 48.51, H 3.53, N 26.40, O 12.92, S 8.63 Found (%) : C 48.45, H 3.50, N 26.37, O 12.88, S 8.61

14) 4-Cyano-5-imino-3-(piperidino)-9-nitro-2H-1,2,4-triazipino[3,4-*b*] [1,3] benzothiazole. (VII-c)
Yield : 70 %, M. P: 285 ^{0}C, **IR:** (KBr/cm^{-1}) : 3380 (=NH), 3210 (-NH), 2215 (CN), 1540 & 1345 (- NO_2). **EI-MS:** (m/z:RA%) : 370 (M+1). **Elemental analysis :** $C_{16}H_{15}N_7O_2S$, Calculated: (%) C 52.02, H 4.09, N 26.54, O 8.66, S 8.68 Found (%) : C 51.91, H 4.03, N 26.50, O 8.62, S 8.65

Chemistry :
Multicomponent reactions which are one pot reactions constitute an especially attractive recent synthetic strategy since they provide easy and rapid access to large number of organic compounds with diverse substitution

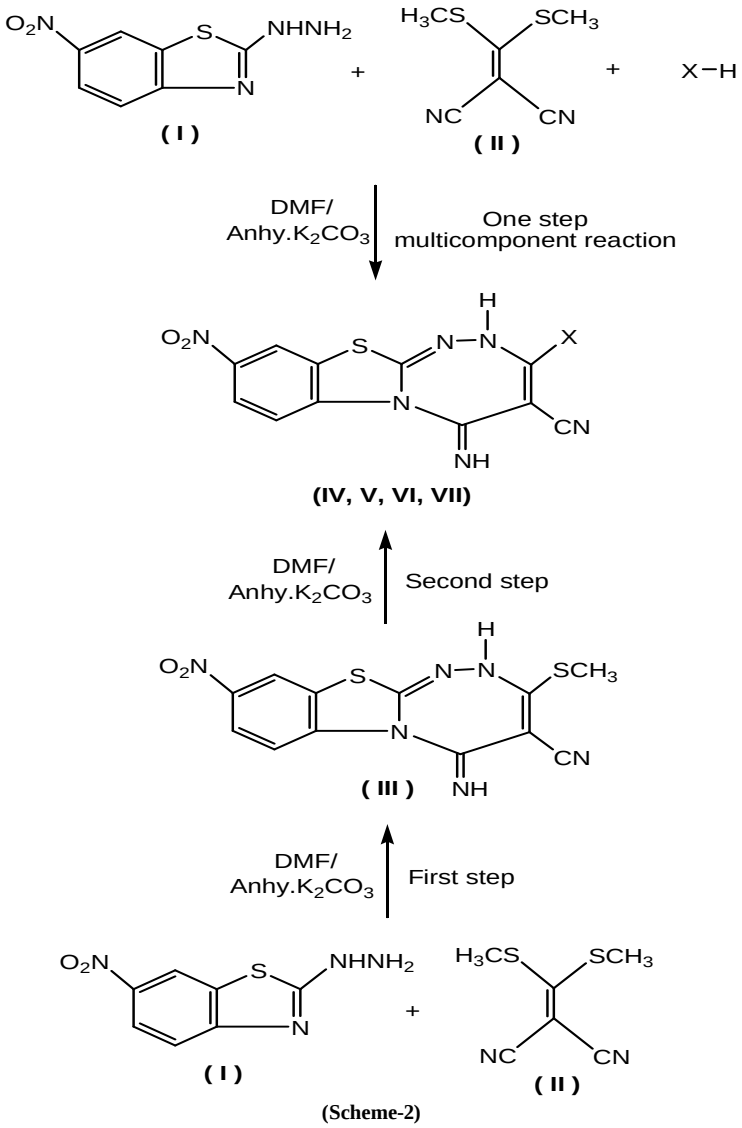
pattern.Hence in the present work, we report one step multicomponent synthesis of 3-substituted derivatives of 4-Cyano -5-imino -3-methylthio-9-nitro-2H -1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole **(IV,V,VI,VII).**

Accordingly, a mixture of 2-hydrazino-6-nitro benzothiazole **(I)** and bis methylthio methylene malononitrile **(II)** was refluxed in dimethyl formamide and anhydrous K_2CO_3 independently with aryl amines / phenols / heteryl amines and compounds containing active methylene group to isolate respective 3-substituted derivatives **(IV,V,VI,VII). (Scheme-1)**



(Scheme-1)

Authentication of 3-substituted derivatives **(IV,V,VI,VII)** obtained by above multicomponent reactions was done by isolating the same compounds from the reaction of aryl amines/phenols/ heteryl amines/compounds containing active methylene group with 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole **(III)** under similar experimental conditions **(Scheme-2)**.

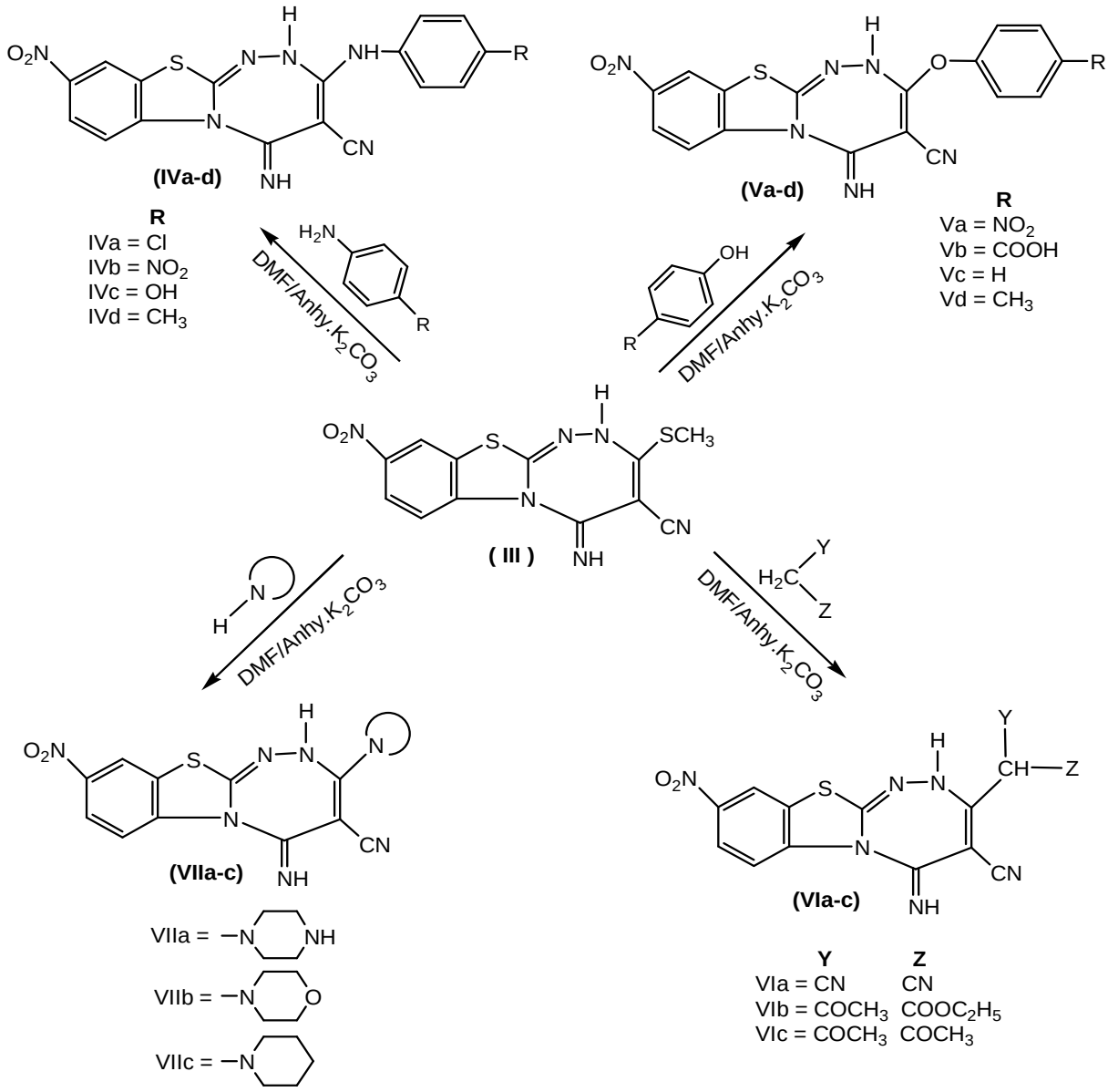


(Scheme-2)

Where, X – H = Substituted aryl amines / phenols / heteryl amines and compounds containing active methylene group.

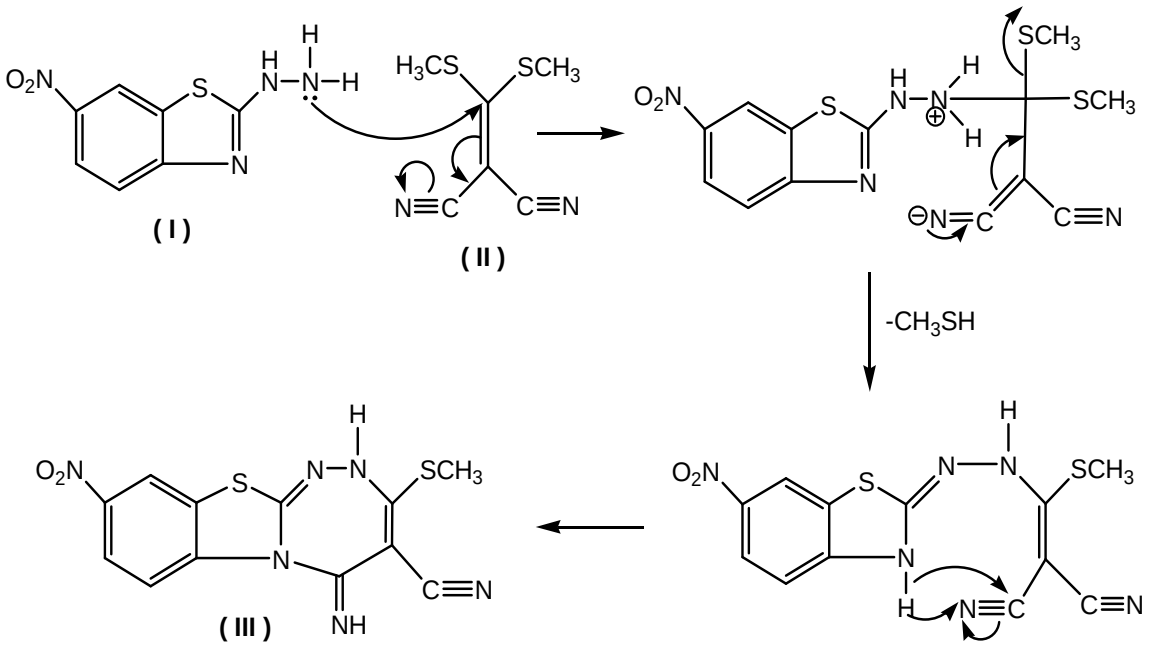
RESULTS AND DISCUSSION

4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*][1,3]benzothiazole **(III)** was heated independently under similar experimental condition with aryl amines / phenols / heteryl amines and compounds containing active methylene group to get respective 3-substituted derivatives **(IV-a-d, V-a-d, VI-a-c, VII-a-c)**. **(Scheme-3)**



(Scheme-3)

The mechanism of formation of compound **III** can be adduced as follows. **(Scheme-4)**.



(Scheme-4)

Biological Activity :

All newly synthesized 3-substituted derivatives **(IV-a-d, V-a-d, VI-a-c, VII-a-c)** were evaluated in-vitro for antibacterial activity against gram positive and gram negative bacterial strain such as *Bacillus Megatenium* and *Escherichia coli* at concentration 100µ/ml by disc diffusion method by using DMSO as solvent control and nutrient agar was employed as culture media. After 24h of incubation at 37^0C, the zone of inhibition were measured in mm. The activity was compared with known antibiotic Streptomycin and the data was represented in **Table-1** and comparative representation shown in **Figure-1.**

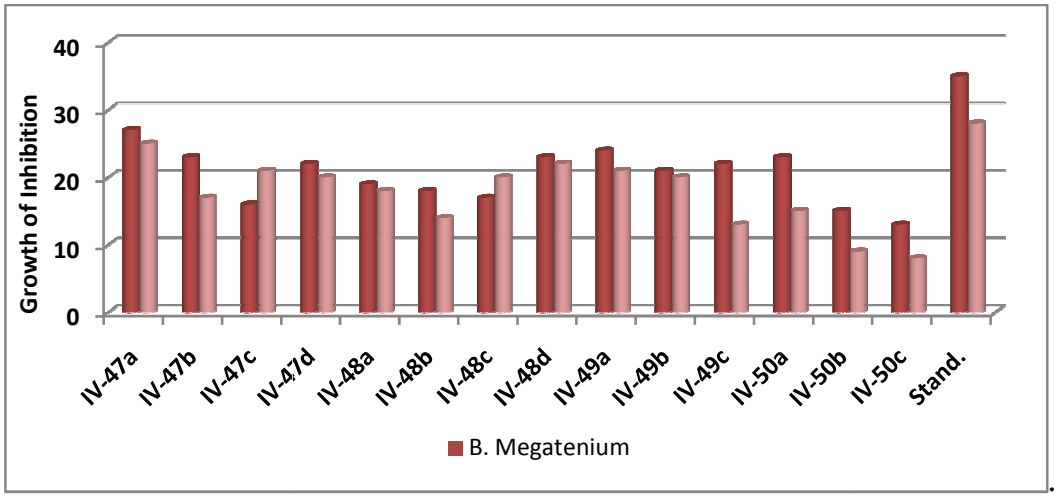
Table 1 : Antibacterial activity of 3-substituted derivatives (IV-a-d, V-a-d, VI-a-c, VII-a-c) of 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*][1,3]benzothiazole (III)

Sample code	*Zone of inhibition (diameter in mm)	
	B. Megatenium	***E. coli***
	100µ/ml	**100µ/ml**
IV-a	27	25
IV-b	23	17
IV-c	16	21
IV-d	22	20
V-a	19	18
V-b	18	14
V-c	17	20
V-d	23	22
VI-a	24	21
VI-b	21	20
VI-c	22	13
VII-a	23	15
VII-b	15	09
VII-c	13	08
Streptomycin	35	28
DMSO	-	-

**Each value is an average of three independent determinations ± Standard deviation.*

Note : *'-' denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity,18-20 mm and above good activity.*

Figure- 01
Antibacterial Activity shown by Graphical representation of 3-substituted derivatives of 4-Cyano-5-imino-3-methylthio-9-nitro-2H-1,2,4-triazipino [3,4-*b*] [1,3] benzothiazole (III) by Disc Diffusion Method



CONCLUSION

In conclusion a facile multicomponent and one pot synthesis has been developed for the title compounds using readily available starting materials. All the 14 newly synthesized compounds were screened for antibacterial activity studies at a concentration of 100µ/ml using DMSO as a control and Streptomycin used asstandard against gram positive and gram negative bacteria. The data in the **Table 1** indicates that among the synthesized compounds Iva, IV-b, IV-d, V-a, V-d, VI-a, VI-b, and VII-a compounds was found to possess a broad spectrum activity. However, the activities of the tested compounds are much less than those of standard antibacterial agents used.

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