Research Article

Multicomponent Synthesis and Pharmacological Screening of 3-Cyano -4-Imino -2- Methylthio -8- Nitro -4H- Pyrimido [2,1-*b*] [1,3] Benzothiazole and its 2-Substituted Derivatives

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ABSTRACT

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, we report multicomponent synthesis of novel fused heterocyclic compound, 3-cyano-4-imino-2-methylthio-8-nitro -4H- pyrimido [2,1-*b*] [1,3] benzothiazole and its 2-substituted derivatives.

2-Substituted derivatives of 3-cyano-4-imino-2-methylthio -8- nitro -4H- pyrimido [2,1-*b*] [1,3] benzothiazole have been prepared through One Step Multicomponent reaction by heating a mixture of 2-amino -6- nitro benzothiazole and bis methylthio methylene malononitrile 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 characterized by IR, NMR, Mass spectroscopy and all the compounds were screened for antibacterial activity.

Keywords: 2-amino-6-nitro benzothiazole, antibacterial activity, bis methylthio methylene malononitrile, DMF, multicomponent reaction, potassium carbonate, pyrimido benzothiazole

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INTRODUCTION

A survey of literature reveals that very little work has been carried out on synthesis of fused pyrimido benzothiazole exhibits activities like anti-allergic [1-4], antiparkinsonium [1], herbicidal [2], antiviral [3], phosphodiesterase inhibition [4], antiparasitic activity[5], anti-inflammatory [6], fungicidal [7], antitumor [8] and pharmacophore activity[9-11]. Wade James J. *et.al.* [1] reported synthesis and anti-allergic activity of some acidic derivatives of 4H-pyrimido [2,1-*b*]benzazol-4-ones. Vishnuji Ram [2] reported the preparation of benzothiazolo [3,2-*a*]pyrimidine-3-carbonitrile. These compounds were screened for Leishmanicidal and Herbicidal activities and few of them exhibited significant activity.

Pyrimido [2,1-*b*] benzothiazole and its 8-substitued derivatives were synthesized by Nair Mohan D.*et.al*[3]**.** These derivatives were found to have antiviral activity. 5-(4-Oxo-4H-pyrimido [2,1-*b*] benzothiazolo)–tetrazole possessing antiallergic activity, reported by Covington Robert R. *et.al*. [4]. Synthesis of 7,8-disubstituted-4-oxo-3-(4H-pyrimido [2,1-*b*] benzothiazole) carboxylic acids and esters has been reported by Alaimo Robert J. [5] These compounds were examined for antiparasitic activity. M.F.G. Stevens et.al. [12-15] reported the compounds containing benzothiazole possess antitumor activity against renal, ovarian and breast cancer cell line.

In view of these taking into consideration the importance of biological activities and

various application of pyrimidines, oxo-pyrimidines, imino-pyrimidines[16-23] amino and imino benzothiazoles, synthesis of such condensed system has attracted much attention in recent years. In this note, we report one pot multicomponent synthesis of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*][1,3]benzothia-zole and its 2-substituted derivatives.

MATERIALS AND METHODS

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 3-Cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole.

A mixture of 2-amino-6-nitrobenzothiazole **(I)** [0.195gm, 0.001 mole] and bismethylthio methylene malononitrile **(A)** [0.170gm, 0.001mol] was refluxed in the presence of 5 ml of dimethyl formamide and a pinch of anhydrous potassium carbonate (0.2gm) for six hours. The progress of reaction was monitored by TLC. After completion of reaction, 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 DMF-ethanol mixture to give crystalline solid (0.22 gm)

Yield = 69 %, Melting Point : 252^{0}C

IR: (KBr / cm^{-1}): 3300 (=NH), 3100 (Ar-H), 2210 (-C≡N), 1620 (C=N), 1350 & 1520 (-NO_2)

^{1}H-NMR: (DMSO) **:** δ 2.5 (s 3H SCH_3), δ 6.70 (d 1H Ar-H), δ 7.80 (d 1H Ar-H), δ 8.40 (d 1H Ar-H), δ 9.05 (s 1H =NH)

MS: (m/z : RA %): = 318.3 (M+1)

^{13}C-NMR in DMSO : δ12.89 (C_1-CH_3), δ86.7 (C_2), δ167.5 (C_3, C-CN), δ140.6 (C_4, C=NH), δ118.9 (C_5, Ar-C), δ120.7 (C_6, Ar-C), δ122.6 (C_7, Ar-C), δ144.7 (C_8, C-NO_2), δ125.5 (C_9, Ar-C), δ152.3 (C_{10}), δ162.3 (C_{11}, C=N), δ114.7 (C_{12}, CN)

Elemental analysis: $C_{12}H_7N_5O_2S_2$, Calculated: (%) C 45.42, H 2.22, N 22.07, O 10.08, S 20.21 Found (%):C 45.40, H 2.20, N 22.05, O10.05, S 20.19

General Method

Synthesis of 2-Substituted derivative of 3-Cyano-4-imino-2-methylthio-8-nitro-4H- pyrimido[2,1-*b*][1,3]benzothiazole.

A mixture of 2-amino-6-nitro benzothiazole **(I)** [0.195gm, 0.001mole] and bismethylthio methylene malaononitrile **(A)** [0.170gm, 0.001mol] was refluxed in the presence of of dimethyl formamide (5 ml) and a pinch of anhydrous potassium carbonate (0.2 gm) 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 product.

1) 3-Cyano-4-imino-2-(p-chloroanilino)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-a)

Yield: 66 % , m.p. : 243 ^{0}C

IR: (KBr / cm^{-1}): 3444 (=NH), 3382 (N-H), 3112 (Ar-H), 2202 (-C≡N), 1620 (C=N), 1338 & 1515 (-NO_2)

^{1}H-NMR : (DMSO) : δ 4.00 (s 1H N-H), δ 6.60 (d 1H Ar-H), δ 6.70 (d 1H Ar-H), δ 6.90 (d 1H Ar-H), δ 7.20 (d 1H Ar-H), δ 7.35(d 1H Ar-H), δ 8.40(d 1H Ar-H), δ 8.70 (d 1H Ar-H), δ 8.90 (s 1H =NH)

MS: (m/z : RA %): = 397 (M+1)

Elemental analysis: $C_{17}H_9ClN_6O_2S$, Calculated: (%) C 51.46, H 2.29, Cl 8.93, N 21.18, O 8.06, S 8.08 Found (%) : C 51.41, H 2.27, Cl 8.90, N 21.16, O 8.02, S 8.01

2) 3-Cyano-4-imino-2-(p-nitroanilino)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-b)

Yield: 59 %, m.p. : 271 ^{0}C

IR: (KBr / cm^{-1}): 3450 (=NH), 3100 (Ar-H), 2208 (-CN), 1622 (C=N), 1340 & 1520 (-NO_2) **^{1}H-NMR :** (DMSO) : δ 4.30 (s 1H N-H), δ 6.50 (d 1H Ar-H), δ 7.30 (d 2H Ar-H), δ 7.50 (d 2H Ar-H), δ 7.95 (d 2H Ar-H), δ 8.65 (s 1H =NH)

MS: (m/z : RA %): = 408 (M+1)
Elemental analysis : $C_{17}H_9N_7O_4S$, Calculated: (%) C 50.12, H 2.23, N 24.07, O 15.71, S 7.87 Found (%) : C 50.10, H 2.20, N 24.05, O 15.68, S 7.82

3) 3-Cyano-4-imino-2-(p hydroxy-anilino)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-c)

Yield: 53 %, m.p.: 265 ^{0}C
IR: (KBr / cm^{-1}): 3550 (O-H), 3440 (=NH), 3110 (Ar-H), 2212 (-C≡N), 1615 (C=N), 1345 & 1517 (-NO_2)
^{1}H-NMR : (DMSO) : δ 4.12 (s 1H N-H), δ 4.5 (s 1H -OH), δ 6.50 (d 2H Ar-H), δ 6.60 (d 2H Ar-H), δ 6.75 (d 1H Ar-H), δ 7.85 (d 1H Ar-H), δ 8.10 (d 1H Ar-H), δ 8.85 (s 1H =NH)
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 2.64, N 22.17, O 12.65, S 8.45

4) 3-Cyano-4-imino-2-(*p*-toluidino)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-d)

Yield : 64 % , m.p. : 221 ^{0}C
IR: (KBr / cm^{-1}): 3450 (=NH), 3120 (Ar-H), 2210 (-C≡N), 1620 (C=N), 1342 & 1515 (-NO_2)
^{1}H-NMR : (DMSO) : δ 2.35 (s 3H Ar-CH_3), δ 4.10 (s 1H NH), δ 6.55 (d 2H Ar-H), δ 6.70 (d 1H Ar-H), δ 7.10 (d 2H Ar-H), δ 7.80 (d 1H Ar-H), δ 8.20 (d 1H Ar-H), δ 8.70 (s 1H =NH) **MS: (m/z : RA %):** = 377 (M+1)
Elemental analysis: $C_{18}H_{12}N_6O_2S$, Calculated: (%) C 57.44, H 3.21, N 22.33, O 8.50, S 8.52 Found (%) : C 57.42, H 3.17, N 22.31, O 8.47, S 8.50

5) 3-Cyano-4-imino-2-(4'-nitrophenoxy) -8-nitro-4H-pyrimido[2,1-*b*][1,3] benzo-thiazole (II-e)

Yield: 51 %, m.p.: 310 ^{0}C
IR: (KBr / cm^{-1}): 3440 (=NH), 3105 (Ar-H), 2205 (-C≡N), 1625 (C=N), 1340 & 1520 (-NO_2), 1067 (-C-O-C-)
^{1}H-NMR : (DMSO) : δ 6.60 (d 1H Ar-H), δ 7.10 (d 2H Ar-H), δ 7.80 (d 1H Ar-H), δ 7.95 (d 1H Ar-H), δ 8.25 (d 2H Ar-H), δ 8.95 (s 1H =NH)
MS: (m/z : RA %): = 409 (M+1)
Elemental analysis: $C_{17}H_8N_6O_5S$, Calculated: (%) C 50.00, H 1.97, N 20.58, O 19.59, S 7.85 Found (%) : C 49.95, H 1.95, N 20.55, O 19.55, S 7.80

6) 3-Cyano-4-imino-2-(4'-carboxy-licphenoxy)-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (II-f)

Yield : 56 % , m.p. : 234 ^{0}C
IR: (KBr / cm^{-1}): 3510 (-OH), 3417 (=NH), 3112 (Ar-H), 2202 (-C≡N), 1338 & 1515 (NO_2), 1060 (-C-O-C) , 1620 (C=O)
^{1}H-NMR : (DMSO) : δ 6.60 (d 1H Ar-H), δ 7.15 (d 2H Ar-H), δ 7.90 (d 1H Ar-H), δ 8.10 (d 1H Ar-H), δ 8.40 (d 2H Ar-H), δ 8.70 (s 1H =NH), δ 10.50 (s 1H -COOH)
MS: (m/z : RA %): = 408 (M+1)
Elemental analysis: $C_{18}H_9N_5O_5S$, Calculated: (%) C 53.07, H 2.23, N 17.19, O 19.64,S 7.87 Found (%) : C 53.05, H 2.21, N 17.15, O 19.60, S 7.85

7) 3-Cyano-4-imino-2-(phenoxy)-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzo-thiazole(II-g)

Yield: 61 % , m.p. : 258 ^{0}C
IR: (KBr / cm^{-1}): 3400 (=NH), 3110 (Ar-H), 2210 (-C≡N), 1335 & 1520 (-NO_2), 1070 (-C-O-C)
^{1}H-NMR : (DMSO) : δ 6.40 - 9.10 (m 8H Ar-H), δ 9.50 (s 1H =NH)
MS: (m/z : RA %): = 364 (M+1)
Elemental analysis: $C_{17}H_9N_5O_3S$, Calculated: (%) C 56.19, H 2.50, N 19.27, O 13.21, S 8.82 Found (%) : C 56.17, H 2.45, N 19.25, O 13.19, S 8.80

8) 3-Cyano-4-imino-2-(4'-methylpheno-xy)-8-nitro-4H-pyrimido [2,1-*b*] [1,3] benzothiazole (II-h)

Yield: 74 % , m.p. : 277 ^{0}C
IR: (KBr / cm^{-1}): 3450 (=NH), 3112 (Ar-H), 2202 (-C≡N),1342 & 1515 (-NO_2), 1071 (-C-O-C)
^{1}H-NMR : (60 MHz, DMSO) : δ 2.50 (s 3H –CH_3), δ 6.50 (d 1H Ar-H), δ 6.70 (d 2H Ar-H), δ 7.10 (d 2H Ar-H), δ 8.10 (d 1H Ar-H), δ 8.30 (d 1H Ar-H), δ 8.90 (s 1H =NH)
MS: (m/z : RA %): = 378 (M+1)
Elemental analysis: $C_{18}H_{11}N_5O_3S$, Calculated: (%) C 57.29, H 2.94, N 18.56, O 12.72, S 8.50 Found (%) : C 57.27, H 2.90, N 18.52, O 12.70, S 8.45

9) 3-Cyano-4-imino-2-(malononitrile)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-i)

Yield: 58 %, m.p.: 273 ^{0}C
IR: (KBr / cm^{-1}): 3440 (=NH), 3111 (Ar-H), 2205 (-C≡N), 1340 & 1510 (-NO_2)
^{1}H-NMR : (DMSO): δ 4.20 (s 1H CH), δ 6.90

(d 1H Ar-H), 7.60 (d 1H Ar-H), 8.15 (d 1H Ar-H), δ 8.65 (s 1H =NH)
MS: (m/z : RA %): = 336 (M+1)
Elemental analysis : $C_{14}H_5N_7O_2S$, Calculated: (%) C 50.15, H 1.50, N 29.24, O 9.54, S 9.56 Found (%) : C 50.10, H 1.45, N 29.20, O 9.50, S 9.51

10) 3-Cyano-4-imino-2-(α-ethylaceto-acetyl)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-j)

Yield: 57 %, m.p. : 262 ^{0}C
IR: (KBr / cm^{-1}): 3440 (=NH), 3112 (Ar-H), 2881 (C-H), 2202 (-C≡N), 1620 (C=O), 1338 & 1515 (-NO_2)
^{1}H-NMR : (DMSO) : δ 1.50 (t 3H -CH_3), δ 2.10 (s 3H -CH_3), δ 3.95 (s 1H -CH), δ 4.20 (q 2H -CH_2), δ 6.60 (d 1H Ar-H), δ 7.80 (d 1H Ar-H), δ 7.95 (d 1H Ar-H), δ 8.60 (s 1H =NH)
MS: (m/z : RA %): = 400 (M+1)
Elemental analysis : $C_{17}H_{13}N_5O_5S$, Calculated: (%) C 51.12, H 3.28, N 17.54, O 20.03, S 8.03 Found (%) : C 51.08, H 3.25, N 17.50, O 20.01, S 8.01

11) 3-Cyano-4-imino-2-(α-acetylaceto-ne)-8-nitro-4H-pyrimido[2,1-*b*][1,3] benzothiazole (II-k)

Yield: 89 % , m.p. : 281 ^{0}C
IR: (KBr / cm^{-1}): 3442 (=NH), 3110 (Ar-H), 2890 (C-H), 2205 (-C≡N), 1625 (C=O), 1340 & 1517 (-NO_2)
^{1}H-NMR : (DMSO) : δ 2.10 (s 6H -CH_3), δ 3.95 (s 1H -CH), δ 6.65 (d 1H Ar-H), δ 7.85 (d 1H Ar-H), δ 8.10 (d 1H Ar-H), δ 8.80 (s 1H =NH)
MS: (m/z : RA %): = 370 (M+1)
Elemental analysis : $C_{16}H_{11}N_5O_4S$, Calculated: (%) C 52.03, H 3.00, N 18.96. O 17.33, S 8.68 Found (%) : C 52.01, H 2.95, N 18.92. O 17.30, S 8.65

12) 3-Cyano-4-imino-2-piperizino-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzo-thiazole(II-m)

Yield : 51 % , m.p. : 219 ^{0}C
IR: (KBr / cm^{-1}): 3429 (=NH), 3278 (-NH), 3112 (Ar-H), 2202 (-C≡N), 1625 (C=N), 1338 & 1515 (-NO_2)
^{1}H-NMR : (DMSO) : δ 2.10 (s 1H NH), δ 2.6 - 2.8 (m 8H -CH_2), δ 6.70 (d 1H Ar-H), δ 7.90 (d 1H Ar-H), δ 8.10 (d 1H Ar-H), δ 8.60 (s 1H =NH)
MS: (m/z : RA %): = 356 (M+1)
Elemental analysis : $C_{15}H_{13}N_7O_2S$, Calculated: (%) C 50.70, H 3.69, N 27.59, O 9.00, S 9.02 Found (%) : C 50.62, H 3.62, N 27.55, O 8.92, S 9.00

13) 3-Cyano-4-imino-2-marpholino-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzo-thiazole(II-n)

Yield : 49 % , m.p. : 269 ^{0}C
IR: (KBr / cm^{-1}): 3435 (=NH), 3110 (Ar-H), 2210 (-C≡N), 1622 (C=N), 1340 & 1515 (-NO_2), 1010 cm^{-1}(C-O-C)
^{1}H-NMR : (DMSO) : δ 2.90 (m 4H N-CH_2), δ 3.80 (m 4H O-CH_2), δ 6.55 (d 1H Ar-H), δ 7.80 (d 1H Ar-H), δ 8.00 (d 1H Ar-H), δ 8.60 (s 1H =NH)
MS: (m/z : RA %): = 357 (M+1)
Elemental analysis: $C_{15}H_{12}N_6O_3S$, Calculated: (%) C 50.56, H 3.39, N 23.58, O 13.47, S 9.00 Found (%) : C 50.48, H 3.32, N 23.51, O 13.45, S 8.92

14) 3-Cyano-4-imino-2-piperidino-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzo-thiazole(II-o)

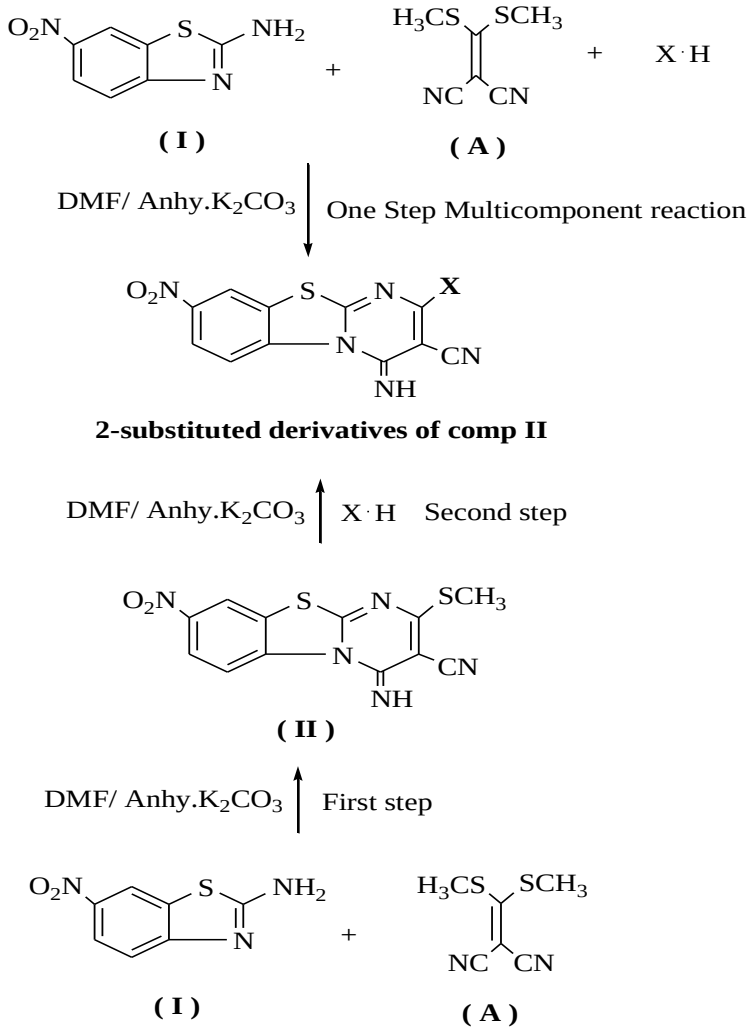
Yield : 60 % , m.p. : 235 ^{0}C
IR: (KBr / cm^{-1}): 3430 (=NH), 3110 (Ar-H), 2205 (-C≡N), 1625 (C=N), 1340 & 1520 (-NO_2) **^{1}H-NMR :** (DMSO) : δ 1.60 (m 6H -CH_2), δ 2.80 (m 4H N-CH_2), δ 6.60 (d 1H Ar-H), δ 7.70 (d 1H Ar-H), δ 8.40 (d 1H Ar-H), δ 8.90 (s 1H =NH)
MS: (m/z : RA %): = 355 (M+1)
Elemental analysis: $C_{16}H_{14}N_6O_2S$, Calculated: (%) C 54.23, H 3.98, N 23.71, O 9.03, S 9.05 Found (%) : C 54.20, H 3.92, N 23.65, O 9.00, S 9.01

RESULTS AND DISCUSSION

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. In present work, we report multicomponent synthesis of novel fused heterocyclic compound, 3-cyano-4-imino-2- methylthio-8-nitro-4H-pyrimido [2,1-*b*][1,3]benzothiazole **(II)** and its 2-substituted derivatives **(IIa to IIo)**.

Accordingly, a mixture of 2-Amino-6-nitro benzothiazole (I) and bis methylthio methylene malononitrile (A) 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 2-substituted derivatives.

Authentication of 2-substituted derivatives obtained by above multicomponent reaction was done by isolating them in two steps. In first step, the required compound 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole **(II)** was prepared by heating 2-amino-6-nitro benzothiazole **(I)** with bis methylthio methylene malononitrile in DMF and anhydrous K_2CO_3. **(Scheme 1)**



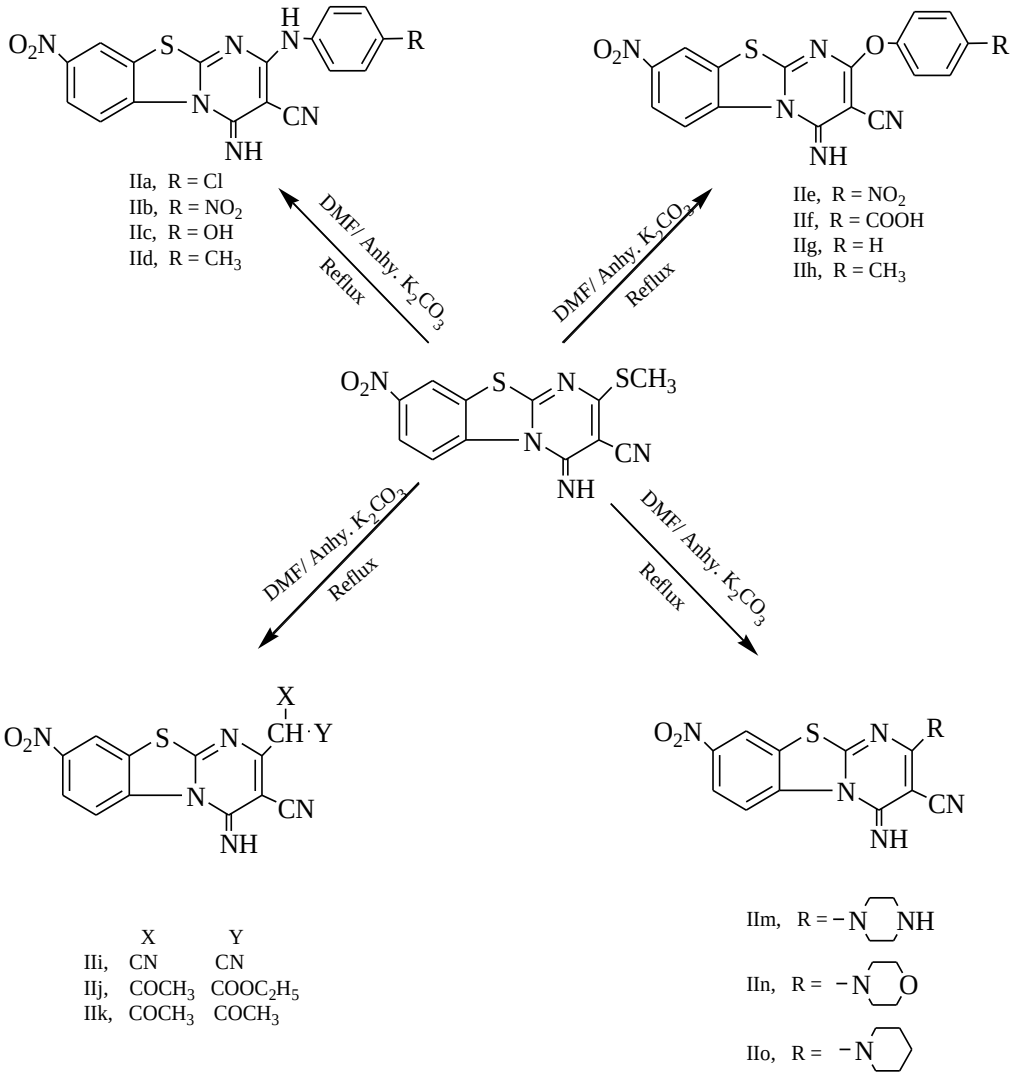
Where, X – H = Substituted aryl amines / phenols / heteryl amines and compounds containing active methylene group.

(Scheme 1)

In second step, compound- II was heated independently under similar experimental condition with aryl amines / phenols / heteryl amines and compounds containing active methylene group to get respective 2-substituted derivatives. (**Scheme 2**)**.**

Biological Activity:

All newly synthesized 2-substituted derivatives **(IIa-o)** were evaluated in-vitro for antibacterial activity against gram positive and gram negative bacterial strain such as *Bacillus subtilis, Bacillus Megatenium***,** *Escherichia coli* and *Pseudomonas aureginosa* atconcentration 100µ/ml by disc diffusion method[24] by using DMSO as solvent control and nutrient agar was employed as culture media. After 24h of incubation at 37^0C, the zones of inhibition were measured in mm. The activity was compared with known antibiotic Streptomycin and the data was represented in (**Table 1**).



(Scheme 2)

Table 1: Antibacterial activity of 2-substituted derivatives (IIa-o)

Sample code	*Zone of inhibition (diameter in mm)			
	B. subtilis 100µ/ml	*B. Megatenium* 100µ/ml	*E. coli* 100µ/ml	*P. aureginosa* 100µ/ml
IIa	11	15	07	10
IIb	22	27	19	20
IIc	14	17	19	21
IId	21	23	17	20
IIe	23	22	19	20
IIf	17	19	16	19
IIg	26	25	18	21
IIh	17	11	20	17
IIi	21	22	21	25
IIj	22	24	19	21
IIk	13	09	19	16
Streptomycin	31	35	28	27
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.

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 IIb. IId, IIe, IIg, IIi and IIj 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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