International Journal of ChemTech Research
CODEN( USA): IJCRGG ISSN : 0974-4290
Vol.3, No.1, pp 136-142, Jan-Mar 2011

# Design, Synthesis and Biological Activities of Novel 4*H*-Pyrimido [2, 1-*b*] [1,3] Benzothiazole derivatives

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**Abstract :**The nucleus 9-Chloro-3-cyano-8-fluoro-4-imino-2-methylthio-4-*H* pyrimido [2, 1-*b*] benzothiazole and its 2-substituted derivatives were designed and their toxicity and pharmacological activities were studied with the help of software. The nontoxic compounds which are having Pa (Probable activity) value more than 0.3 & less then 0.5 were synthesized by reported procedure. All these compounds were screened for in vivo anti-inflammatory activity. Most of the tested compounds revealed significant anti-inflammatory activity, as compare to standard drug diclofenac sodium.

**Keywords** : Pyrimidobenzothiazole**,** PASS, Osiris Property Explorer, Anti Inflammatory Activity.

## INTRODUCTION:

Heterocyclic rings like pyrimidine, pyrazole, benzothiazole, benzoxazole and benzimidazole are effective pharmacophores. Fused heterocyclic compounds containing these important pharmacophores exhibits a wide spectrum of activities like anti-tumor [1], anti-inflammatory [2], anti-parkinsonism[3]. In view of the reported biological activities of this system, it was thought worthwhile to design and to synthesize the molecule with fused pyrimido benzothiazole[4] system and to study the toxicity and predicted biological activity with the help of software programs PASS[5-7] (**P**rediction of **A**ctivity **S**pectra for **S**ubstances) and Osiris Property Explorer [8] respectively. A survey of literature made it evident that very little work has been carried out on the synthesis of fused pyrimido benzothiazoles. Synthesis of pyrimido [2, 1-*b*] benzothiazole was reported by cumbersome method [9] which required presence of stream of nitrogen gas, and in which only 2 or 3 substituted compounds were synthesized.

The starting compound, 9-chloro-3-cyano-8-fluoro-4-imino-2-methylthio-4-*H* pyrimido [2, 1-*b*] benzothiazole (**3a**) was synthesized by the reaction of 6-chloro-7-fluoro benzothiazole(**1a**) with bis (methylthio) methylene malononitrile (**2a**) in presence of solvent DMF and anhydrous potassium carbonate[10] The 2-methylthio group of 9-chloro-3-cyano-8-fluoro-4-imino-2-methylthio-4-*H* pyrimido [2, 1-*b*] benzothiazole (**3a**) which is a best leaving group, was

further substituted by various nucleophiles such as aryl amines, heteryl amines, phenols and compounds containing active methylene group to get final compounds. The structures were assigned on the basis of elemental analysis , IR, NMR and Mass spectral data. Selected synthesized compounds were screened for in vivo anti-inflammatory activity at a dose of 100 mg/kg., by using reported procedure.

## EXPERIMENTAL:

**Synthesis of 9-Chloro-3-cyano-8-fluoro-4-imino-2-methylthio-4*H*-pyrimido[2, 1-*b*] [1, 3] benzothiazole (3a)**

A mixture of 2-amino-7-chloro-6-fluoro benzothiazole 2.02g (0.01mole) and bis(methylthio) methylene malononitrile 1.7g (0.01mol) was refluxed in the presence of 20-25ml of dimethyl formamide and a pinch of anhydrous potassium carbonate for 05 hrs. 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 1.31g of crystalline solid of compound (**3a**).

Yield: 65 %, m.p: 288$^0$C,IR: (KBr / cm$^{-1}$): 3291 cm$^{-1}$ (C=NH), 2886 (-$CH_3$), 2208cm$^{-1}$ (C≡N); $^1$H-NMR: (60 MHz, DMSO-$d_6$): δ 2.6 (s, 3H, $SCH_3$), δ 7.6-8.0 (d, 2H, Ar-H) 9.4 (s, 1H, -NH). EI-MS: (m/z: RA %): 326 ( $M^{+2}$ 33 %),324 (M‡ 100 %), $^{13}$C-NMR DMSO-$d_6$: δ : 12.89 ($C_1$, $CH_3$), 115.04 ($C_2$), 121.83 ($C_5$, Ar-C) , 122.49 ($C_6$-Ar-C) 125.87 ($C_3$), 127.37 ($C_7$, Ar-C) 130.86 ($C_8$, Ar-C), 135.4 ($C_9$, Ar-C), 152.56 ($C_{10}$, Ar-C), 157 ($C_4$, C=NH), 165 ($C_{11}$, C=N) 168 ($C_{12}$, CN) Elemental analysis: Calculated for $C_{12}H_6ClFN_4S_2$; C, 44.38; H, 1.86; N, 17.25; Found: C, 44.28; H, 1.74; N, 16.98.

**Synthesis of 2-Substituted Derivatives of 9-Chloro-3-Cyano--8-Fluoro-4-Imino-4*H*-Pyrimido [2, 1-*b*][1,3] Benzothiazole (3b-l): General Procedure.**

A mixture of (**3a**) (0.001 mol) and various aromatic amines / heteryl amines / phenols and compounds containing active methylene groups (0.001 mol ) in 10 ml of DMF and pinch of anhydrous potassium carbonate independently was refluxed for 6-7 hrs. The reaction mixture was cooled to room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallised from ethanol to give pure (3b to l). Mass spectra showed the molecular ion peak which corresponds to their respective molecular weight, $^1$H NMR spectra are also in agreement with the structures of the following compounds.

**9-Chloro-3-cyano-8-fluoro-4-imino-2- (*p*-toluidino) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3b)** Yield: 72%, m.p: 234$^0$C, IR: (KBr / cm$^{-1}$): 3288 cm$^{-1}$ (C=NH), 3111 cm$^{-1}$ (-NH), 2208cm$^{-1}$ (C≡N);$^1$H-NMR: (60 MHz, DMSO-$d_6$): δ 2.6, (s, 1H, Ar-$CH_3$), δ 7.6-8.7 (m, 6H, Ar-H), δ 9.7 (s, 1H, =NH), EI-MS: (m/z: RA %): 385 ($M^{+2}$ 7 %), 383 (M‡ 20 %)**.**Elemental analysis: Calculated for $C_{18}H_{11}ClFN_5S$; C, 56.33; H, 2.89; N, 18.25; found: C, 54.93; H, 2.80; N, 18.02;

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(4'- nitro anilino) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3c)** Yield: 68 %; m.p: 293$^0$C; IR: (KBr / cm$^{-1}$): 3361 cm$^{-1}$ (C=NH), 3286 cm$^{-1}$ (-NH), 2268 cm$^{-1}$ (C≡N); 1523 cm$^{-1}$ and 1479 cm$^{-1}$ -$NO_2$ asymmetric & symmetric stretching
EI-MS: (m/z: RA %): 416 ($M^{+2}$ 10 %), 414 (M‡ 40 %)
Elemental analysis: Calculated for $C_{17}H_8ClFN_6O_2S$; C, 49.23; H, 1.94; N, 20.26; Found:C, 49.40;H, 1.90; N,19.89.

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(4'- chloro anilino) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole(3d).**Yield: 69%,m.p., 252$^0$C, IR: (KBr / cm$^{-1}$): 3310 cm$^{-1}$ (C=NH), 2270cm$^{-1}$ (C≡N),
EI-MS: (m/z: RA %): 405 ($M^{+2}$ 27 %), 403 (M‡ 80 %),
Elemental analysis: Calculated for $C_{17}H_8Cl_2FN_5S$; C, 50.50; H, 1.99; N, 17.52; found: C, 49.50; H, 1.70; N, 17.30.

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(4'-nitro phenoxy) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3e).**Yield: 70 %, m.p: 212$^0$C, IR: (KBr / cm$^{-1}$): 3286 cm$^{-1}$ (C=NH), 2206cm$^{-1}$ (C≡N), 1523 cm$^{-1}$ and 1481 cm$^{-1}$ (Assymetric and symmetric stratching of -$NO_2$) 1180 cm$^{-1}$ and 1064 cm$^{-1}$ (Assymetric and Symmetric stratching of C-O-C), $^1$H-NMR: (60 MHz, DMSO-$d_6$): δ 7.6-8.4 (m, 6H Ar-H), δ 9.7 (s, 1H, -NH),EI-MS: (m/z: RA %): 416 ($M^{+2}$ 35 %), 414 (M‡100 %)
Elemental analysis: Calculated for $C_{17}H_7ClFN_5O_3S$; C, 49.11; H, 1.70; N, 16.50; found: C, 48.72; H, 1.64; N, 16.50.

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(2'-methyl phenoxy) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (I3f).** Yield: 65 %, m.p: 202$^0$C, IR: (KBr / cm$^{-1}$): 3301 cm$^{-1}$ (C=NH), 2214cm$^{-1}$ (C≡N), EI-MS: (m/z: RA %):386 ($M^{+2}$ 30%); 384 (M‡ 90 %)**,** Elemental analysis: Calculated for $C_{18}H_{10}ClFN_4OS$; C, 56.18; H, 2.62; N, 14.56; found: C, 55.92; H, 2.12; N, 14.07.

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(2'-nitro phenoxy) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole(3g)**Yield: 71 %, m.p: 232$^0$C,IR: (KBr / cm$^{-1}$): 3286 cm$^{-1}$ (C=NH), 2206cm$^{-1}$ (C≡N), 1523 cm$^{-1}$ and 1481 cm$^{-1}$ ( Assymetric and Symmetric stratching of -$NO_2$) **,**EI-MS: (m/z: RA %):416 ($M^{+2}$ 10%); 414(M‡ 30 %) Elemental analysis: Calculated for

$C_{17}H_7ClFN_5O_3S$; C, 49.11; H, 1.70; N, 16.84; found: C, 48.81; H, 1.41; N, 16.75.

**9-Chloro-3-cyano-8-fluoro-4-imino-2– morpholino - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole(3h)**Yield: 62%, m.p: 224$^0$C, IR: (KBr / cm$^{-1}$): 3290cm$^{-1}$ (C=NH), 2194cm$^{-1}$ (C≡N), 1244 cm$^{-1}$ (OCH$_2$-) **,**$^1$H-NMR: (60 MHz, DMSO-d$_6$): δ 2.6 (t, 4H, 2 N-CH$_2$) δ 3.8 (t, 4H 2 O-CH$_2$), δ 7.9-8.2 (d,2H Ar-H), δ 9.7 (s, 1H, -NH), EI-MS: (m/z: RA %): 365 (M$^{+\,2}$ 33 %), 363 (M‡ 100 %) **,** Elemental analysis: Calculated for $C_{15}H_{11}ClFN_5OS$; C, 49.52; H, 3.05; N, 19.25; found: C, 49.21; H, 2.81; N, 18.80.

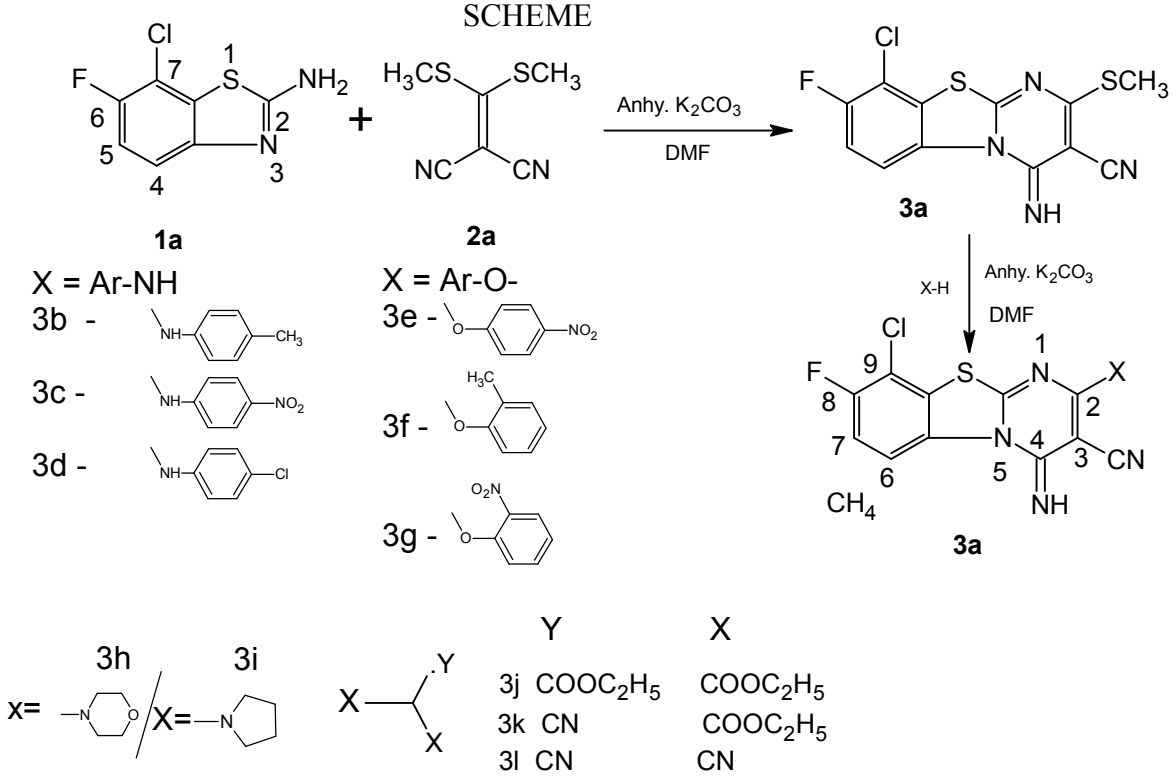
**9-Chloro-3-cyano-8-fluoro-4-imino-2-pyrrolidino - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole(3i)** Yield: 65%, m.p: 242$^0$C, IR: (KBr / cm$^{-1}$): 3290 cm$^{-1}$ (C=NH) 2196 cm$^{-1}$ (C≡N), EI-MS: (m/z: RA %): 349 (M$^{+\,2}$ 20 %), 347 (M‡60 %), Elemental analysis: Calculated for $C_{15}H_{11}ClFN_5S$; C, 51.80; H, 3.19; N, 20.14; found: C, 51.50; H, 2.70; N, 9.90.

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(α-diethyl malonyl ) -4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3j)** Yield: 71%, m.p: 268$^0$C, IR: (KBr / cm$^{-1}$): 3298 cm$^{-1}$ (C=NH), 2208cm$^{-1}$ (C≡N), 1735 cm$^{-1}$ (C=O),$^1$H-NMR**:** (60 MHz, DMSO-d$_6$)**:** δ 2.4(t, 6H,2 CH$_3$ ), δ 3.8(q, 4H, 2CH$_2$ ),δ 7.8-8.0 (d,2H Ar-H), δ 9.7 (s, 1H, -NH), EI-MS: (m/z: RA %): 438 (M$^{+\,2}$ 23 %), 436 (M‡ 70 **%**)
Elemental analysis: Calculated for $C_{18}H_{14}ClFN_4O_4S$; C, 49.49; H, 3.23; N, 12.83; found: C, 49.30; H, 3.20; N, 12.75.

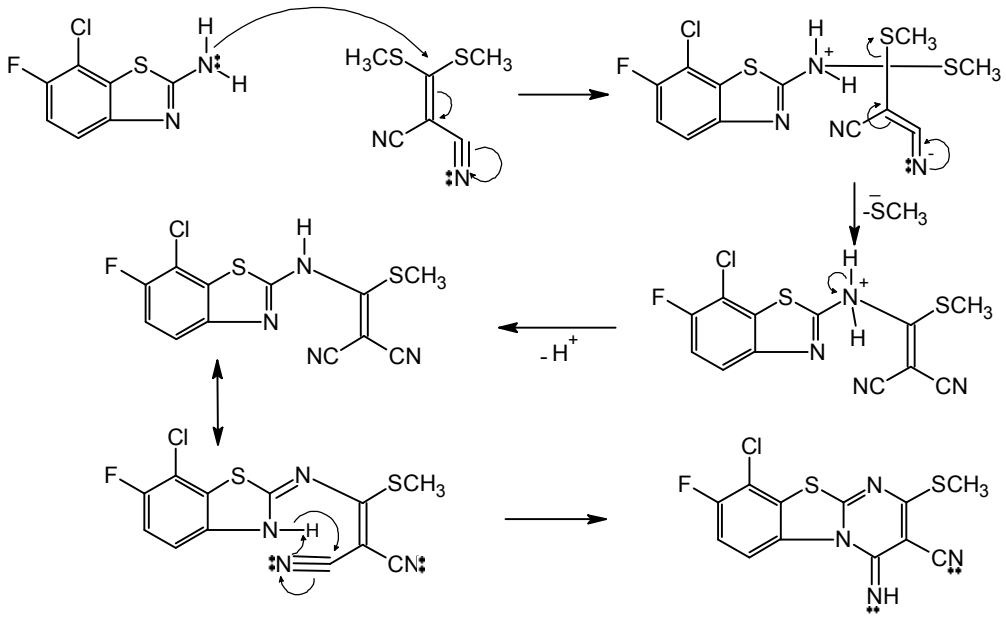
**9-Chloro-3-cyano-8-fluoro-4-imino-2-(α-ethyl cyano acetyl) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3k)** Yield: 65%, m.p: 238$^0$C,IR: (KBr / cm$^{-1}$): 3327 cm$^{-1}$ (C=NH) 2208cm$^{-1}$ (C≡N), 1744 cm$^{-1}$ (CO), EI-MS: (m/z: RA %): 240 (M$^{+\,2}$ 10 %), 238 (M‡ 30 %)
Elemental analysis: Calculated for $C_{16}H_9ClFN_6O_2S$; C, 49.30; H, 2. 33; N, 17.97; found: C, 48.91; H, 1.93; N, 17.82

**9-Chloro-3-cyano-8-fluoro-4-imino-2-(α-Malono nitrilyl) - 4*H*-pyrimido [2, 1-*b*] [1, 3] benzothiazole (3l)** Yield: 52%, m.p: 252$^0$C, IR: (KBr / cm$^{-1}$): 3450 cm$^{-1}$ (C=NH) 2281cm$^{-1}$ (C≡N),
EI-MS: (m/z: RA %):344 (M$^{+\,2}$ 15 %), 342 (M‡ 45 %), Elemental analysis: Calculated for $C_{14}H_4ClFN_6S$; C, 49. 06; H, 1.18; N, 24.52; found: C, 48.90; H, 1.01; N, 24.22.

SCHEME



**MECHANISM OF REACTION**



**BIOLOGICAL ACTIVITY:**

**Anti-inflammatory activity using carrageenan induced hind paw edema method in rats** [11]

**Animals** –Wister rats (150-200g) and Mice (20-25g) of either sex were housed under standard laboratory conditions, maintained on a natural light and dark cycle and had free access to food and water. Animals were acclimatized to laboratory conditions before the experimentation. All experiments were carried out between 09.00 and 15.00 hrs. The experimental protocol was approved by the **Institutional Ethics Committee** (MES's College of Pharmacy, Sonai. Dist. Newasa, (MS) India. Pin. 414105.) and conducted according to the Indian National Academic Guidelines for the use and care of experimental animals.

**Drug:** Diclofenac sodium. (Navkatan Pharma Pvt. Ltd. Aurangabad, India.)

**Acute Toxicity Studies:** Healthy young mice of either sex, starved overnight were divided into groups (n=6) and were orally feed with increasing doses i.e. 100, 200, 500, 3000, and 5000 mg/kg of each of the selected compounds. These did not produce any evident sign of toxicity and any mortality in mice when observed up to 14 days after administration

**Method:** The anti-inflammatory screening was done by employing the carrageenan induced rat paw edema method described by Randall and Baruth [12,13] by modification of mercury displacement method. The animals were divided into groups each (n=6) and were starved overnight. On the next day, each group independently received control, standard drug; diclofenac [14](100mg/kg) and the selected compounds as shown in Table I. The compounds selected for this screening were given to the animals in the same volume. The suspension was prepared in Tween-80 (1%) and water. Thirty minutes later, the rats were challenged by a subcutaneous injection of 0.1ml of 1 % w/v carrageenan into the plantar side of left hind paw. The paw was marked with ink at the level of the lateral malleolus so that every time the paw is dipped into the column of mercury up to the fixed mark to ensure constant paw volume.

Paw volume was measured plethysmographically immediately after injection, again after 30mins, 60mins, 90mins, 120mins, 180mins, 6hrs and 24hrs after challenge of irritant.

**Evaluation:** The increase of paw volume after the mentioned time intervals was calculated as percentage compared with the volume measured immediately after injection of the irritant for each animal using the following formula [15].

% inhibition = 100 - (Vt /Vc) X 100

Where, Vt = average volume of paw edema in treatment group.

Vc = average volume of paw edema in control group.

These observations are depicted in Tables 1 and 2. The difference of average values between treated animals and control groups was calculated for each time interval and the results were statistically evaluated by employing one way ANOVA followed by Dunnet test [16].

**Table1. Mean edema volume of compounds.**

| Co. No. | 30min. | 60min. | 90min. | 120min. | 180min. | 6h. | 24h. |
|---|---|---|---|---|---|---|---|
| Control 1% Tween 80 | 0..47±0.08** | 00.57±0.08** | 0.6±0.11** | 0.65±0.12** | 0.8±0.7** | 0.82±0.08** | 0.75±0.27** |
| Diclofenac Sod. | 0.25±0.11** | 0.22±0.12** | 0.20±0.11** | 0.18±0.08** | 0.15±0.06** | 0.10±0.07** | 0.05±0.08** |
| I3 a | 0.32±0.08** | 0.31±0.14** | 0.30±0.09** | 0.28±0.12** | 0.28±0.11** | 0.24±0.13** | 0.20±0.11** |
| I3c | 0.38±0.09** | 0.34±0.08** | 0.31±0.14** | 0.29±0.10** | 0.23±0.10** | 0.20±0.04** | 0.17±0.09** |
| I3d | 0.44±0.05* | 0.50±0.08* | 0.54±0.09* | 0.56±0.08* | 0.58±0.06* | 0.62±0.10* | 0.65±0.15* |
| I3f | 0.37±0.09** | 0.35±0.12** | 0.34±0.11** | 0.33±0.12** | 0.32±0.08** | 0.28±0.14** | 0.25±0.15** |
| I3g | 0.38±0.09** | 0.33±0.12** | 0.32±0.04** | 0.30±0.12** | 0.29±0.07** | 0.27±0.13** | 0.27±0.11** |
| I3j | 0.36±0.09** | 0.32±0.10** | 0.31±0.03** | 0.26±0.07** | 0.24±0.08** | 0.18±0.07** | 0.14±0.04** |
| I3k | 0.39±0.05** | 0.38±0.06** | 0.37±0.04** | 0.36±0.08** | 0.36±0.07** | 0.40±0.07** | 0.44±0.09** |
| I3l | 0.35±0.12** | 0.31±0.08** | 0.30±0.06** | 0.27±0.05** | 0.26±0.10** | 0.22±0.08** | 0.18±0.08** |

The figure indicates mean edema volume ± S. D. of respective group of animals. (n=6). The results were statistically evaluated by employing one way ANOVA followed by Dunnett test.
** P < 0.01, * P < 0.05

**Table2. % Edema Inhibition of Compounds**

| Compound No. | %edema inhibition at 30min. | %edema inhibition at 60min. | %edema inhibition at 90min. | %edema inhibition at 120min. | %edema inhibition at 180min. | %edema inhibition at 6h. | %edema inhibition at 24h. |
|---|---|---|---|---|---|---|---|
| Diclofenac Sodium | 46.80 | 61.40 | 66.66 | 72.30 | **81.25** | 87.80 | 93.33 |
| 3a | 31.91 | 45.61 | 50.00 | 56.92 | **65.00** | 70.73 | 77.33 |
| 3c | 19.14 | 40.35 | 48.33 | 55.38 | **71.25** | 75.60 | 77.33 |
| 3d | 6.38 | 12.28 | 10.00 | 13.84 | **27.5** | 24.39 | 13.33 |
| 3f | 21.27 | 38.59 | 43.33 | 49.23 | **60.00** | 65.85 | 66.66 |
| 3g | 19.14 | 42.10 | 46.66 | 53.84 | **63.75** | 67.07 | 70.66 |
| 3j | 23.40 | 43.85 | 49.16 | 60.00 | **70.00** | 78.04 | 81.33 |
| 3k | 17.02 | 33.33 | 38.33 | 44.61 | **55.00** | 51.21 | 41.33 |
| 3l | 25.53 | 45.61 | 50.00 | 58.46 | **67.50** | 73.17 | 76.00 |

**Table 3. Toxicity Risk Assessment, Predicted Anti-Inflammatory Activities and Observed% edema inhibitionof Scheme.**

| **Co. No.** | **Muta genic** | **Tumorigenic** | **Irritant** | **Reproducti ve affective** | **Pa. value predicted by PASS for Anti-inflammatory Activity** | **Observed% edema inhibition** |
|---|---|---|---|---|---|---|
| **3a** | NT | NT | T | NT | 0.642 | 65.00 |
| **3b** | T | NT | NT | NT | 0.359 | NS |
| **3c** | NT | NT | NT | NT | 0.472 | 71.25 |
| **3d** | NT | NT | NT | NT | 0.431 | 27.5 |
| **3e** | T | NT | NT | NT | 0.462 | NS |
| **3f** | NT | NT | NT | NT | 0.421 | 60.00 |
| **3g** | NT | NT | NT | NT | 0.458 | 63.75 |
| **3h** | NT | NT | NT | T | 0.384 | NS |
| **3i** | T | NT | T | NT | 0.384 | NS |
| **3j** | NT | NT | T | NT | 0.492 | 70.00 |
| **3k** | NT | NT | NT | NT | 0.341 | 55.00 |
| **3l** | NT | NT | NT | NT | 0.482 | 67.50 |

***Pa** = Probable activity, **T** = Having Toxicity, NT = No Toxicity, NS = Not selected for screening.

**RESULTS:**

The9-chloro-3-cyano-8-fluoro-4-imino-2 (methylthio) -4-*H* pyrimido [2, 1-*b*] benzothiazole(**3a**) was synthesized by the condensation of 2-amino-6-chloro-7-fluoro benzothiazole with bis (methylthio) methylene malanonitrile The yield was found to be 65 %., The compound (**3a**) on condensation independently with various aromatic amines, heteryl amines, phenols and compounds containing active methylene groups to yield derivatives (**3b to l**). The yield was found in the range of 65 – 75 %.

Compound 3b, 3e and 3l have shown mutagenicity and I3h, have shown tumorigenicity, so these compounds were not screened for anti inflammatory activity; at the same all the compounds shown the **Pa** values more than 0.3 and less than 0.5 were selected for screening of anti inflammatory activity, to find the new chemical entity.

Before proceeding for evaluation of biological activity the compounds were tested for acute toxicity in mice. The selected compound not showed the mortality even at the dose of 5000mg/ kg b.w. p.o. The selected synthesized compounds were evaluated for their anti-inflammatory activity at 100 mg/kg of dose, by using hind paw edema method in rats**.** Diclofenac sodium was selected as standard drug. It was found that the all compounds exhibit marked anti-inflammatory activity. Thus result confirmed the significant anti-inflammatory activity of all compounds

Compound 3c, 3j & 3l of showed edema inhibition 71.25% , 70.00% & 67.50 %respectively, were found to be most potent as compare to remaining compounds and exhibit potent anti-inflammatory activity as compare to diclofenac sodium at 3hr.after treatment.

**DISCUSSION:**

In general; the reactions proceeded smoothly and the spectral data suggests that the expected products were obtained. It was possible to predict the biological activity spectrum of all the synthesized compounds by the use of computer program PASS and also to study their toxicity by employing toxicity risk assessment through Osiris property explorer via Internet. In the latter study, all the compounds were evaluated for the presence of various toxicity parameters like mutagenicity, tumorigenicity, reproductive affective effects and irritation. Only those compounds which are devoid of any of these toxic effects and at the same time, also exhibiting the predicted anti inflammatory activity **Pa** < 0.5 > 0.3 were selected independently for anti inflammatory activity screening. In acute toxicity selected compound (3a) even at 5000 mg/kg body weight did not showed any mortality this shows wide margin of the therapeutic index for the compounds

Table no.3 depicts a comparative data of the predicted activities by PASS and pharmacological screened activity of the selected compounds. Thus, from Table**,** it is observed that nearly all the compounds exhibit good activities. Also, there is a marked co ordination between the predicted and actually screened activities except compound 3d.

**ACKNOWLEDGEMENT:**

We express sincere gratitude to Dr N.V. Kalyankar. Principal, Yashwant Mahavidyalaya, Nanded. For providing laboratory facilities, we express sincere thanks to Principal MES;s College of Pharmacy Sonai, for providing animal experimental facilities.

Authors thanks to IICT Hyderabad, for providing NMR & Mass Spectra, Garaware Research Center, Pune University Pune for providing IR Spectra and National toxicology center, Pune for providing Animals for Pharmacological Activity.

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