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SYNTHESIS OF CHALCONES, 1, 3-THIAZINES AND 1, 3-PYRIMIDINES DERIVATIVES AND THEIR BIOLOGICAL EVALUATION FOR ANTI-INFLAMMATORY, ANALGESIC AND ULCEROGENIC ACTIVITY

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ABSTRACT

Series of chalcones and 2-amino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl pyrimidine, 2-substituted guanidino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl-1, 3-thiazine, Schiff base of 2-amino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl pyrimidine, 2-[2"-(substituted) phenyl-4"-oxo-5"*H*-thiazol-3"-yl)-4-{2'-[2"'-(substituted)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl]-5'-substitued phenyl} mercapto-6-phenyl pyrimidine were synthesized and studied by IR, NMR and Mass spectroscopy. The new products showed anti-inflammatory, analgesic, and ulcerogenic activities comparable to that of indomethacin and acetylsalicylic acid, respectively.

Keywords: Pyrimidine, thiazine, chalcones, analgesic, anti--inflammatory, ulcerogenic activity.

INTRODUCTION

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1], anti-inflammatory[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalerial[6], anticancer[7], antiviral[8], antileishmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], immunomodulatory[13], inhabition of chemical mediators release[14], leukotriene B_4[15], tyrosinase[16] and aldose reductase[17] activites. Due to interesting activity of various substituted pyrimidines as biological agents[18, 19, 20] considerable attentions have focused on this class. The pharmaceutical importance of these compounds lies in the fact that they can be effectively used as analgesics, antiinflammatory, anticonvulsant, insecticidal, herbicidal, antitubercular, anticancer and antidiabetic agents. The ability of thiazine to exhibit antitubercular[21], antibacterial[22] and which is

inactivate HIV in biological fluids[23] and used as cannabinoid receptor agonists[24]. In the light of these interesting biological activities, it appeared of interest to synthesize some new amino/guanidino pyrimidines and thiazines derivatives. The constitution of the products has been supported by element analyses, physico-chemical tests, IR, NMR and Mass spectral data.

Experimental:

All the melting points were determined using open capillary tubes in scientific melting point apparatus and are uncorrected. IR spectra of the synthesized compounds were scanned using a Shimazdu-Fourier Transform Infrared Spectrophotometer-8300 and KBr press. NMR spectra of the synthesized compounds were recorded on JEOL spectrophotometers at 300 MHz. Mass spectra of the synthesized compounds were recorded on Shimazdu-GC-MS QP 5050A. Progress, purity of the reaction and the intermediates were analyzed using precoated TLC plate and using UV chamber. For column chromatography 60-200 mesh LR (Merck) silica gel was used. The biological activities were carried out at Department of Microbiology, K. C. College, Mumbai.

General method

1-(2'-amino-5'-substitued phenyl)mercapto-3-(substituted)phenyl-2-propen-1-one (**2**):

Substituted 2-amino thiophenol (**1**) (0.01 mol) was dissolved in 1, 4-dioxane (10 cm^3). To this solution cinnamoyl chloride (0.012 mol) in 1, 4-dioxane (25 cm^3) was added drop wise with constant stirring at 10-15°C under nitrogen atmosphere. After complete addition of cinnamoyl chloride, stirring was continued for one hour. After monitoring on TLC, the reaction mixture was then poured into ice cold water and filtered, washed with the 10% $NaHCO_3$ followed by water and recrystallized from ethyl acetate.

1-(2'-amino phenyl)mercapto-3-phenyl-2-propen-1-one (**2a**):

IR cm^{-1}: 3430 (NH_2), 1728 (C=O), 1630 (CH=CH); **PMR** (DMSO-d_6 , δ in ppm): 1.40 (s, 2H, NH_2), 6.50 (1H, d, J= 17.8 Hz, -CO-CH=), 6.84 (1H, d, J= 15.4 Hz, =CH-Ar), 7.02-7.67 (m, 9H, Ar-H); **CMR** (DMSO-d_6 , δ in ppm): 103.63 (CH), 121.85-139.45 (Ar C atoms), 145.09 (C=C-Ar), 166.92 (C=O); **m/z**: 256 $[M]^{+\bullet}$, 258, 167, 164, 150, 146, 129, 109, 104, 77, 74, 65.

1-(2'-amino-5'-methylphenyl)mercapto-3-phenyl-2-propen-1-one (**2b**):

IR cm^{-1}: 3432 (NH_2), 2951 (CH_3), 1735 (C=O), 1636 (CH=CH); **PMR** ($CDCl_3$, δ in ppm): 1.38 (s, 2H, NH_2), 2.26 (s, 3H, CH_3), 6.42 (1H, d, J= 17.9 Hz, -CO-CH=), 6.83 (1H, d, J= 15.6 Hz, =CH-Ar), 7.08-7.78 (m, 8H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 20.23 (CH_3), 107.14 (CH), 127.47-133.43 (Ar C atoms), 146.07 (C=C-Ar), 171.14 (C=O); **m/z**:

270 $[M]^{+\bullet}$, 257, 216, 192, 179, 166, 149. 134, 109, 91, 77, 69.

2-amino-4-(2'-amino-5'-substitued phenyl) mercapto -6- (substituted)phenyl pyrimidine (**3**):

An equimolar mixture of compound (**2**) and guanidine nitrate (0.01 mol) in EtOH was refluxed for 4-5 hours in presence of 40% NaOH (8 cm^3). The reaction was monitored by TLC. On cooling, crystals were obtained recrystallized from ethanol and identified as compound **3**.

2-amino-4-(2'-aminophenyl)mercapto-6-phenyl pyrimidine (**3a**):

IR cm^{-1}: 3438, 3430 (NH_2), 1637, 1615 (C=N); **PMR** ($CDCl_3$, δ in ppm): 1.45 (s, 2H, NH_2), 2.60 (s, 2H, NH_2), 6.45 (s, 1H, CH), 7.08-7.83 (m, 9H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 107.02 (CH), 127.27-139.98 (Aromatic C atoms), 143.80 (C=C-Ar), 167.28 (N=C), 170.88 (S-C=N); **m/z**: 294 $[M]^{\bullet}$, 280, 261.5, 236, 203, 164, 133, 117, 102, 95, 77, 69.

2-amino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl pyrimidine (3**b**):

IR cm^{-1}: 3434, 3426 (NH_2), 2955 (CH_3), 1633, 1613 (C=N); **PMR** ($CDCl_3$, δ in ppm): 1.77 (s, 2H, NH_2), 2.01 (s, 3H, CH_3), 2.84 (s, 2H, NH_2), 6.42 (s, 1H, CH), 6.58-7.57 (m, 8H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.64 (CH_3), 106.41 (CH), 121.54-133.80 (Aromatic C atoms), 140.08 (C=C-Ar), 162.57 (N=C), 164.41 (S-C=N); **m/z**: 308 $[M]^{\bullet}$, 280, 193, 179, 149, 134, 91, 89, 77, 69.

2-substituted guanidino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl-1, 3-thiazine (**4**):

Compound (**2**) (0.01 mol), substituted amidinothiocarbamides (0.01 mol), 40% sodium hydroxide (3×2 cm^3, each 2 cm^3 at the interval of 1 h.) and C_2H_5OH (50 cm^3) were taken in round bottom flask. The reaction mixture was refluxed for 4-5 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was dumped onto crushed ice. The solid mass was obtained, filtered and washed several times with water. Purification was carried out by column chromatography (*n*-Hexane:Ethyl acetate; 9.5:0.5).

2-guanidino-4-(2'-aminophenyl)mercapto-6-phenyl-1, 3-thiazine (**4a**):

IR cm^{-1}: 3442, 3437 (NH_2), 3286 (NH), 1652-1621 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.59 (s, 2H, NH_2), 2.18 (s, 2H, NH_2), 6.42 (s, 1H, CH), 7.09-7.70 (m, 9H, Ar-H), 8.60 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 117.10 (H-C=C-Ar), 121.48-138.02 (Aromatic C atoms), 147.23 (C=C-Ar), 153.75 (C=NH), 163.23 (S-C=N), 167.11 (C=N); **m/z**: 353 $[M]^{\bullet}$, 296, 276, 228, 219, 151, 125, 93, 77.

2-(*N*-phenyl)guanidino-4-(2'-aminophenyl)mercapto-6-phenyl-1, 3-thiazine (**4b**):

IR cm $^{-1}$: 3449 (NH_2), 3290, 3285 (NH), 1657-1618 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.24 (s, 2H, NH_2), 5.05 (s, 1H, NH), 6.89 (s, 1H, CH), 7.24-8.00 (m, 14H, Ar-H), 8.99 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 117.98 (C=C-Ar), 121.44-137.80 (Aromatic C atoms), 142.13 (C=C-Ar), 153.46 (C=NH), 162.96 (S-C=N), 167.03 (C=N); **m/z**: 429 $[M]^{\bullet}$, 352, 303, 275, 218, 171, 124, 98, 82, 77.

2-[*N*-(4''-bromo)phenyl]guanidino-4-(2'-aminophenyl)mercapto-6-phenyl-1, 3-thiazine (**4d**):

IR cm $^{-1}$: 3454 (NH_2), 3295, 3289 (NH), 1654-1613 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.24 (s, 2H, NH_2), 5.06 (s, 1H, NH), 6.56 (s, 1H, CH), 7.14-8.01 (m, 13H, Ar-H), 8.67 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 117.73 (C=C-Ar), 120.88-137.49 (Aromatic C atoms), 144.63 (C=C-Ar), 153.23 (C=NH), 162.53 (S-C=N), 166.73 (C=N); **m/z**: 509, 507 $[M]^{\bullet}$, 430, 429, 350, 349, 275, 218, 124, 98, 82, 77.

2-guanidino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl-1, 3-thiazine (**4e**):

IR cm $^{-1}$: 3450, 3439 (NH_2), 3291 (NH), 2948 (CH_3), 1649-1621 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.20 (s, 2H, NH_2), 2.20 (s, 3H, CH_3), 2.42 (s, 2H, NH_2), 6.40 (s, 1H, CH), 7.24-7.91 (m, 8H, Ar-H), 8.02 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 21.51 (CH_3), 117.25 (C=C-Ar), 121.25-137.56 (Aromatic C atoms), 143.52 (C=C-Ar), 151.10 (C=NH), 152.01 (S-C=N), 166.17 (C=N); **m/z**: 367 $[M]^{\bullet}$, 310, 290, 233, 229, 219, 152, 138, 106, 91, 77.

2-(*N*-phenyl)guanidino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl-1, 3-thiazine (**4f**):

IR cm $^{-1}$: 3455 (NH_2), 3295, 3279 (NH), 2953 (CH_3), 1645-1618 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.40 (s, 2H, NH_2), 2.20 (s, 1H, CH_3), 5.91 (s, 1H, NH), 6.50 (s, 1H, CH), 7.24-8.01 (m, 13H, Ar-H), 8.67 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 23.46 (CH_3), 114.41 (H-C=C-Ar), 120.08-136.99 (Aromatic C atoms), 149.51 (C=C-Ar), 154.66 (C=NH), 160.83 (S-C=N), 166.09 (N-C=N); **m/z**: 443 $[M]^{\bullet}$, 366, 305, 289, 232, 228, 151, 138, 106, 94, 91, 77.

2-[*N*-(4''-methoxy)phenyl]guanidino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl-1, 3-thiazine (**4g**):

IR cm $^{-1}$: 3449 (NH_2), 3289, 3281 (NH), 2949 (CH_3), 1650-1613 (3×C=N); **PMR** ($CDCl_3$, δ in ppm): 1.23 (s, 2H, NH_2), 2.25 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 5.02 (s, 1H, NH), 6.42 (s, 1H, CH), 6.82-7.78 (m, 12H, Ar-H), 8.87 (s, 1H, =NH); **CMR** ($CDCl_3$, δ in ppm): 20.66 (CH_3), 64.22 (OCH_3), 117.51 (H-C=C-Ar), 122.23-134.42 (Aromatic C atoms), 146.45 (C=C-Ar), 155.01 (C=NH), 161.61 (S-C=N), 167.15 (N-C=N); **m/z**: 473 $[M]^{\bullet}$, 442, 396, 365, 308, 288, 227, 150, 138, 106, 93, 91, 77.

Schiff base of 2-amino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl pyrimidine (5):

A mixture of compound **3** (5 mmol), substituted aromatic aldehyde (10 mmol) and acetic acid (0.5 mL) was refluxed in toluene for 3 h using a deanstark apparatus and the water formed was removed azeiotropically. The progress of the reaction was checked by TLC using hexane:ethyl acetate (4:1) as an eluent. After completion of the reaction, solvent was removed by distillation to give solid. Thus solid obtained was washed with ice-cold water and recrystallized from ethyl alcohol to give pure compound **5**.

2-(*N*-benzylidene)-4-(2'-*N*-benzylidene phenyl)mercapto-6-phenyl pyrimidine (**5a**):

IR cm^{-1}: 1639-1612 (C=N); **PMR** ($CDCl_3$, δ in ppm): 6.45 (s, 1H, CH), 8.09 (s, 1H, HC=N pyrimidine), 8.39 (s, 1H, CH), 7.00-7.92 (m, 19H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 110.23 (CH), 122.60-138.54 (Aromatic C atoms), 147.64 (C=C-Ar), 160.16 (N=C), 161.32 (N=C), 168.84 (N=C), 173.55 (S-C=N); **m/z**: 470 $[M]^{\bullet}$, 393, 213, 180, 156, 128, 112, 77.

2-(*N*-4"-hydroxybenzylidene)-4-(2'-*N*-4"'-hydroxy benzylidene phenyl)mercapto-6-phenyl pyrimidine (**5b**):

IR cm^{-1}: 1640-1610 (C=N); **PMR** ($CDCl_3$, δ in ppm): 5.08 (s, broad peak, 2H, 2×OH), 6.47 (s, 1H, CH), 8.10 (s, 1H, HC=N pyrimidine), 8.37 (s, 1H, CH), 7.06-7.86 (m, 17H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 110.56 (CH), 120.96-137.78 (Aromatic C atoms), 148.06 (C=C-Ar), 160.76 (N=C), 161.46 (N=C), 168.35 (N=C), 172.84 (S-C=N); **m/z**: 502 $[M]^{\bullet}$, 468, 406, 375, 289, 198, 167, 133, 114, 76.

2-(*N*-4"-methoxybenzylidene)-4-(2'-*N*-4"'-methoxybenzylidene phenyl)mercapto-6-phenyl pyrimidine (**5c**):

IR cm^{-1}: 1638-1611 (C=N); **PMR** ($CDCl_3$, δ in ppm): 3.74 (S, 6H, 2×OCH_3), 6.46 (s, 1H, CH), 8.10 (s, 1H, HC=N pyrimidine), 8.40 (s, 1H, CH), 6.94-7.88 (m, 17H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 55.96 (2×OCH_3), 109.89 (CH), 121.56-139.21 (Aromatic C atoms), 147.05 (C=C-Ar), 160.79 (N=C), 161.65 (N=C), 167.34 (N=C), 173.91 (S-C=N); **m/z**: 530 $[M]^{\bullet}$, 499, 468, 375, 289, 198, 167, 133, 114, 76.

2-(*N*-benzylidene)-4-(2'-*N*-benzylidene-5'-methylphenyl)mercapto-6-phenyl pyrimidine (**5e**):

IR cm^{-1}: 1639-1610 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.29 (s, 3H, CH_3), 6.46 (s, 1H, CH), 8.10 (s, 1H, HC=N pyrimidine), 8.40 (s, 1H, CH), 7.00-7.89 (m, 18H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.56 (CH_3), 110.32 (CH), 122.56-139.13 (Aromatic C atoms), 147.09 (C=C-Ar), 160.65 (N=C), 161.79 (N=C), 169.75 (N=C), 173.34 (S-C=N); **m/z**: 484 $[M]^{\bullet}$, 407, 227, 194, 170, 142, 126, 91, 77.

2-(*N*-4"-hydroxybenzylidene)-4-(2'-*N*-4"'-hydroxybenzylidene-5'-methylphenyl)mercapto-6-phenyl pyrimidine (**5f**):

IR cm^{-1}: 1641-1612 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.28 (s, 3H, CH_3), 5.10 (s, broad peak, 2H, 2×OH), 6.45 (s, 1H, CH), 8.08 (s, 1H, HC=N pyrimidine), 8.38 (s, 1H, CH), 7.05-7.97 (m, 16H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.42 (CH_3), 109.69 (CH), 122.42-138.06 (Aromatic C atoms), 148.13 (C=C-Ar), 161.01 (N=C), 161.47 (N=C), 168.31 (N=C), 174.08 (S-C=N); **m/z**: 516 $[M]^{\bullet}$, 482, 405, 231, 203, 112, 91, 77.

2-(*N*-4"-chlorobenzylidene)-4-(2'-*N*-4"'-chlorobenzylidene-5'-methylphenyl)mercapto-6-phenyl pyrimidine (**5h**):

IR cm^{-1}: 1638-1610 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.29 (s, 3H, CH_3), 6.46 (s, 1H, CH), 8.09 (s, 1H, HC=N pyrimidine), 8.40 (s, 1H, CH), 7.04-7.92 (m, 16H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.45 (CH_3), 109.84 (CH), 121.79-139.65 (Aromatic C atoms), 148.11 (C=C-Ar), 160.76 (N=C), 161.42 (N=C), 168.26 (N=C), 173.48 (S-C=N); **m/z**: 554, 552 $[M]^{\bullet}$, 477, 475, 440, 288, 234, 123, 111, 91, 76.

2-[2"-(substituted)phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-(substituted)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}-5'-substitued phenyl]mercapto-6-phenyl pyrimidine (**6**):

A mixture of compound **5** (5 mmol), thioglycolic acid (12 mmol) in *N*, *N*-dimethylformamide (40 mL) with a pinch of anhydrous ZnCl2, was refluxed for 6 h, the progress of the reaction was checked by TLC using hexane-ethyl acetate (9:1) as an eluent. The reaction mixture was cooled to room temperature and then poured into crushed ice. It was set-aside at room temperature overnight. The solid thus separated was filtered, washed several times with water, and purified by column chromatography on silica-gel with hexane-ethyl acetate (8.5:1.5) as eluent to afford pure compound **6**.

2-[2"-phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}phenyl] mercapto-6-phenyl pyrimidine (**6a**):

IR cm^{-1}: 1722 (C=O), 1636, 1618 (C=N); **PMR** ($CDCl_3$, δ in ppm): 3.33 (s, 2H, CH_2), 3.38 (s, 2H, CH_2), 5.86 (s, 2H, 2×CH), 6.47 (s, 1H, CH), 6.94-7.68 (m, 19H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 32.65 (2×CH_2:thiazole), 65.29 (2×CH:thiazole), 107.16 (CH), 123.64-139.45 (Aromatic C atoms), 143.80 (C=C-Ar), 168.34 (N=C), 172.37 (S-C=N), 175.49 (2×C=O); **m/z**: 618 $[M]^{\bullet}$, 541, 420, 387, 299, 222, 164, 134, 77.

2-[2"-(*p*-hydroxy)phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-(*p*-hydroxy)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}phenyl]mercapto-6-phenyl pyrimidine (**6b**):

IR cm^{-1}: 1720 (C=O), 1637, 1618 (C=N); **PMR** ($CDCl_3$, δ in ppm): 3.34 (s, 2H, CH_2), 3.40 (s, 2H, CH_2), 5.12 (s, broad peak, 2H, 2×OH), 5.80 (s, 2H, 2×CH), 6.43 (s, 1H, CH), 7.12-7.85 (m, 17H,

Ar-H); **CMR** ($CDCl_3$, δ in ppm): 33.87 (2×CH_2:thiazole), 66.05 (2×CH:thiazole), 109.19 (CH), 122.45-138.73 (Aromatic C atoms), 143.16 (C=C-Ar), 169.16 (N=C), 171.94 (S-C=N), 176.72 (2×C=O); **m/z**: 650 [M]•, 616, 573, 539, 419, 360, 301, 217, 140, 77.

2-[2"-(*p*-methoxy)phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-(*p*-methoxy)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}phenyl]mercapto-6-phenyl pyrimidine (**6c**):

IR cm^{-1}: 1721 (C=O), 1635, 1620 (C=N); **PMR** ($CDCl_3$, δ in ppm): 3.30 (s, 2H, CH_2), 3.35 (s, 2H, CH_2), 3.79 (s, 6H, 2×OCH_3), 5.85 (s, 2H, 2×CH), 6.49 (s, 1H, CH), 7.08-7.91 (m, 17H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 32.78 (2×CH_2:thiazole), 55.17 (2×OCH_3), 65.67 (2×CH:thiazole), 108.56 (CH), 121.85-139.58 (Aromatic C atoms), 144.02 (C=C-Ar), 168.75 (N=C), 172.97 (S-C=N), 176.19 (2×C=O); **m/z**: 678 [M]•, 616, 601, 570, 539, 465, 391, 273, 213, 136, 76.

2-[2"-phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}-5'-methylphenyl]mercapto-6-phenyl pyrimidine (**6e**):

IR cm^{-1}: 1720 (C=O), 1636, 1618 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.27 (s, 3H, CH_3), 3.30 (s, 2H, CH_2), 3.41 (s, 2H, CH_2), 5.75 (s, 2H, 2×CH), 6.44 (s, 1H, CH), 7.15-7.86 (m, 19H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.54 (CH_3), 31.95 (2×CH_2:thiazole), 65.68 (2×CH:thiazole), 107.19 (CH), 120.43-138.16 (Aromatic C atoms), 144.85 (C=C-Ar), 169.12 (N=C), 172.77 (S-C=N), 175.43 (2×C=O); **m/z**: 632 [M]•, 555, 478, 401, 342, 283, 223, 146, 91, 77.

2-[2"-(*p*-hydroxy)phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-(*p*-hydroxy)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}-5'-methylphenyl]mercapto-6-phenyl pyrimidine (**6f**):

IR cm^{-1}: 1722 (C=O), 1636, 1618 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.28 (s, 3H, CH_3), 3.31 (s, 2H, CH_2), 3.39 (s, 2H, CH_2), 5.18 (s, broad peak, 2H, 2×OH), 5.90 (s, 2H, 2×CH), 6.49 (s, 1H, CH), 7.06-7.73 (m, 17H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 19.65 (CH_3), 32.98 (2×CH_2:thiazole), 65.43 (2×CH:thiazole), 108.72 (CH), 123.25-139.38 (Aromatic C atoms), 143.38 (C=C-Ar), 168.83 (N=C), 171.31 (S-C=N), 175.73 (2×C=O); **m/z**: 664 [M]•, 647, 630, 587, 553, 476, 399, 340, 281, 221, 144, 91, 77.

2-[2"-(*p*-chloro)phenyl-4"-oxo-5"*H*-thiazol-3"-yl]-4-[2'-{2"'-(*p*-chloro)phenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl}-5'-methylphenyl]mercapto-6-phenyl pyrimidine (**6h**):

IR cm^{-1}: 1720 (C=O), 1635, 1619 (C=N); **PMR** ($CDCl_3$, δ in ppm): 2.29 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 3.37 (s, 2H, CH_2), 5.80 (s, 2H, 2×CH), 6.46 (s, 1H, CH), 7.14-7.83 (m, 17H, Ar-H); **CMR** ($CDCl_3$, δ in ppm): 18.97 (CH_3), 32.23 (2×CH_2:thiazole), 65.88 (2×CH:thiazole), 108.16 (CH), 122.09-139.67 (Aromatic C atoms), 143.10 (C=C-Ar), 167.72 (N=C), 172.96 (S-C=N), 176.35 (2×C=O); **m/z**: 702, 700 [M]•, 667, 665, 632,

630, 625, 623, 553, 476, 399, 340, 281, 221, 137, 91, 77.

Pharmacological Screening

Animals

Both sexes of Swiss albino mice (25–30 g) were used in analgesic activity testing and adult female Sprague-Dawley rats (150–180 g) were used in anti-inflammatory and ulcerogenic testing. International principle and local regulations concerning the care of used laboratory animals was taken into account [27]. The animals had free access to standard commercial diet and water *ad libitum* and were kept in rooms maintained at 22 ± 1 °C with a 12 h light/dark cycle.

Anti-inflammatory activity

The method adopted resembles essentially that described by Winter *et al*.[28]. Tween- -80 (10%, *V/V*) was selected as vehicle to suspend the standard drug and test compounds. The rats were starved for 18 h prior to the experiment. The animals were weighed, marked for identification and divided into 14 groups, each containing 6 animals. Edema was induced in the left hind paw of all rats by subcutaneous injection of 0.1 mL of 1% (*m/V*) aqueous carrageenean into their footpads. The 1st group was kept as control and was given 1.0 mL of the vehicle. The 2nd to 13th groups were orally administered an aqueous suspension of the synthesized compounds (15 mg kg–1 body mass) 1 hour before carrageenean injection. The last group (standard) was administered indomethacin in a dose of 10 mg kg–1 body mass, orally as suspension in 10% Tween 80[29]. The paw volume of each rat was measured with a mercury plethysmometer, before carrageenean injection and then hourly for 4 hours post administration of the suspension of synthesized compound in 10% Tween 80.

Analgesic activity

The compounds **2a, b**, **3a, b**, **4a-h** were selected for investigating their analgesic activity in acetic acid induced writhing response in mice, following the method [30]. Eighty four mice were divided into 14 groups (six in each) and starved for 16 h. The 1st group which served as control was orally given distilled water in an appropriate volume. The 2nd to 13th groups received the aqueous suspension of synthesized compounds orally (15 mg kg–1 body mass). The last group received acetylsalicylic acid orally in a dose of 100 mg kg–1 body mass. After 30 minutes, each mouse was administerated 0.7% of an aqueous solution of acetic acid (10 mL kg–1 body mass) and the mice were then placed in transparent boxes for observation. The number of writhes was counted for 20 min after acetic acid injection. The number of writhes in each treated group was compared to that of the control group. The number of writhings was

recorded and the percentage protection was calculated.

Ulcerogenicity

Ulceration in rats was induced as described by *Goel et al.*[31]. Rats were divided into 14 groups, of six animals each. The control group of animals was administered only 10% (*V/V*) Tween 80 suspension intraperitonially. One group was administered acetylsalicylic acid intraperitoneally in a dose of 200 mg kg–1 once daily for 3 days. The remaining groups of animals were administered test compounds intraperitoneally in a dose of 20 mg kg–1. On the fourth day, pylorus was ligated as per the method of Shay *et al.*[32]; animals were fasted for 36 h before the pylorus ligation procedure. Four hours after the ligation, animals were sacrificed. The stomach was removed and opened along the greater curvature. Ulcer index was determined by the method[33] and is given in Table 4.

Table 1 Physical data & elemental analysis of newly synthesized compounds

Comd	R_1	R_2	Ar	m. p.	Yield	M. F. / M. W.	Elemental Analysis (Calculated/ Found)		
				°C	%		C	H	N
2a	H	-	-	184-188	88	$C_{15}H_{13}NOS$/255	70.56	5.13	5.49
							70.76	5.28	5.61
2b	CH_3	-	-	176-178	82	$C_{16}H_{15}NOS$/269	71.34	5.61	5.20
							71.81	5.82	5.54
3a	H	-	-	110-114	63	$C_{16}H_{14}N_4S$/294	65.28	4.79	19.03
							65.47	4.95	19.25
3b	CH_3	-	-	132-134	65	$C_{17}H_{16}N_4S$/308	66.21	5.23	18.17
							66.58	5.46	18.54
4a	H	H	-	106-110	72	$C_{17}H_{15}N_5S_2$/353	57.77	4.28	19.81
							58.04	4.71	19.19
4b	H	C_6H_5	-	172-175	69	$C_{23}H_{19}N_5S_2$/429	64.31	4.46	16.30
							64.88	4.84	16.75
4c	H	*p*-OCH_3-C_6H_4	-	98-100	73	$C_{24}H_{21}N_5OS_2$/459	62.72	4.61	15.24
							63.08	4.84	15.65
4d	H	*p*-Br-C_6H_4	-	164-167	71	$C_{23}H_{18}BrN_5S_2$/508	54.33	3.57	13.77
							54.69	3.74	13.92
4e	CH_3	H	-	185-188	68	$C_{18}H_{17}N_5S_2$/367	58.83	4.66	19.06
							59.12	4.81	19.28
4f	CH_3	C_6H_5	-	189-191	71	$C_{24}H_{21}N_5S_2$/443	64.98	4.77	15.79
							65.25	4.93	15.98
4g	CH_3	*p*-OCH_3-C_6H_4	-	128-131	74	$C_{25}H_{23}N_5OS_2$/473	63.40	4.89	14.79
							63.89	5.06	14.98
4h	CH_3	*p*-Br-C_6H_4	-	124-128	72	$C_{24}H_{20}BrN_5S_2$/522	55.17	3.86	13.40
							55.56	3.98	13.78
5a	H	-	C_6H_5	178-181	74	$C_{30}H_{22}N_4S$/470	76.57	4.71	19.91
							76.82	4.92	20.13
5b	H	-	*p*-OH-C_6H_4	175-179	72	$C_{30}H_{22}N_4O_2S$/502	71.69	4.41	11.15

							71.85	4.67	11.36
5c	H	-	*p*-OCH_3-C_6H_4	168-172	70	$C_{32}H_{26}N_4O_2S$/530	72.43	4.94	10.56
							72.69	5.17	10.74
5d	H	-	*p*-Cl-C_6H_4	153-156	71	$C_{30}H_{20}Cl_2N_4S$/538	66.79	3.74	13.14
							66.96	3.90	13.31
5e	CH_3	-	C_6H_5	175-177	73	$C_{31}H_{24}N_4S$/484	76.83	4.99	11.56
							77.05	5.18	11.71
5f	CH_3	-	*p*-OH-C_6H_4	165-169	75	$C_{31}H_{24}N_4O_2S$/516	72.07	4.68	10.85
							72.29	4.86	11.02
5g	CH_3	-	*p*-OCH_3-C_6H_4	156-159	71	$C_{33}H_{28}N_4O_2S$/544	72.77	5.18	10.29
							72.89	5.31	10.52
5h	CH_3	-	*p*-Cl-C_6H_4	161-163	70	$C_{31}H_{22}Cl_2N_4S$/552	67.27	4.01	12.81
							67.45	4.20	12.96
6a	H	-	C_6H_5	148-152	73	$C_{34}H_{26}N_4O_2S_3$/618	65.99	4.21	9.05
							66.19	4.45	9.24
6b	H	-	*p*-OH-C_6H_4	136-139	69	$C_{34}H_{26}N_4O_4S_3$/650	62.75	4.03	8.61
							62.93	4.26	8.82
6c	H	-	*p*-OCH_3-C_6H_4	142-144	70	$C_{36}H_{30}N_4O_4S_3$/678	63.69	4.45	8.25
							63.91	4.55	8.47
6d	H	-	*p*-Cl-C_6H_4	138-140	72	$C_{34}H_{24}Cl_2N_4O_2S_3$/ 686	59.38	3.52	8.15
							59.56	3.70	8.36
6e	CH_3	-	C_6H_5	147-150	70	$C_{35}H_{28}N_4O_2S_3$/632	66.43	4.46	8.85
6f	CH_3	-	*p*-OH-C_6H_4	143-145	69	$C_{35}H_{28}N_4O_4S_3$/664	63.23	4.25	8.43
							63.42	4.47	8.60
6g	CH_3	-	*p*-OCH_3-C_6H_4	155-158	71	$C_{37}H_{32}N_4O_4S_3$/692	64.14	4.66	8.09
							64.30	4.89	8.26
6h	CH_3	-	*p*-Cl-C_6H_4	149-151	70	$C_{35}H_{26}Cl_2N_4O_2S_3$/ 700	59.91	3.73	7.98
							60.10	3.90	8.16

Table 2. Percent anti-inflammatory activity of test compounds[a, b, c]

Compd.	1 hour Edema rate (%)	Pot. (%)	2 hours Edema rate (%)	Pot. (%)	3 hours Edema rate (%)	Pot. (%)	4 hours Edema rate (%)	Pot. (%)
Control	34.8 ± 3.1[f]	0	53.0 ± 1.9[f]	0	82.0 ± 3.3[f]	0	91.6 ± 4.5[f]	0
2a	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.9)	51	74.6 ± 3.3[e,f] (18.6)	40
2b	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.9)	51	74.5 ± 3.3[e,f] (18.6)	40
3a	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
3b	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
4a	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9e,f (21.8)	51	74.5 ± 3.3[e,f] (18.6)	40
4b	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
4c	31.1 ± 1.8[f] (10.5)	15	52.5 ± 1.9[f] (0.9)	2	81.7 ± 4.1[f] (0.1)	0	90.9 ± 3.0 (0.8)	2
4d	24.2 ± 0.9[e,f] (30.5)	54	41.9 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.8)	51	74.5 ± 3.3[e,f] (18.6)	40
4e	25.7 ± 1.2[f] (25.9)	46	40.9 ± 3.1[e,f] (22.8)	39	62.3 ± 4.2[e,f] (23.9)	56	71.6 ± 3.3[e,f] (21.8)	47
4f	25.7 ± 1.2[f] (25.9)	46	40.9 ± 3.1[e,f] (1.2)	39	62.3 ± 4.2[e,f] (23.9)	56	71.6 ± 3.3[e,f] (21.8)	47
4g	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f]	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	21
4h	31.1 ± 1.8[f] (10.5)	15	52.5 ± 1.9[f] (0.9)	2	81.7 ± 4.1[f] (0.1)	0	90.9 ± 3.0 (0.8)	2
Indomethacin	15.0 ± 0.9[e] (56.9)	100	22.2 ± 0.8[e] (58.2)	100	47.0 ± 5.0[e] (42.6)	100	49.1 ± 2.7[e] (46.4)	100

[a] Vehicle: 1 mL 10% (*V/V*) Tween-80. Dose: 15 mg kg–1 b.m. test compound and 10 mg kg–1 b.m. of indomethacin.
[b] Values represent the mean ± SEM ($n = 6$).
[c] Each value in parentheses indicates the percentage inhibition rate.
[d] The potency (pot.) was calculated compared to the reference drug indomethacin.
[e] Significantly different from control (Dunnett's test): $p < 0.05$.
[f] Significantly different from indomethacin (Dunnett's test): $p < 0.05$.

Table 3. Peripheral analgesic activity[a]

Compd.	No. of writhes in 20 min	Protection (%)
Control	48.0 ± 2.2[d]	0
2a	23.2 ± 1.4[c]	52
2b	31.0 ± 1.6[c,d]	35
3a	30.2 ± 1.7[c,a]	37
3b	31.0 ± 1.6[c,d]	35
4a	41.3 ± 2.4[d]	14
4b	45.2 ± 1.8[d]	6
4c	31.3 ± 2.5[c,d]	35
4d	19.6 ± 0.5[c]	59
4e	19.0 ± 1.2[c]	60
4f	19.6 ± 0.5[c]	59
4g	45.8 ± 2.9[d]	5
4h	45.8 ± 2.9[d]	5
Acetylsalicylic acid	22.6 ± 2.0[c]	53

[a] Vehicle: 1 mL of distilled water. Dose: 15 mg kg–1 b.m. of test compound and 100 mg kg–1 b.m. of acetylsalicylic acid. [b] Values represent the mean ± SEM (n = 6). [c] Significantly different from control (Dunnett's test): $p < 0.05$. [d] Significantly different from acetylsalicylic (Dunnett's test): $p < 0.05$.

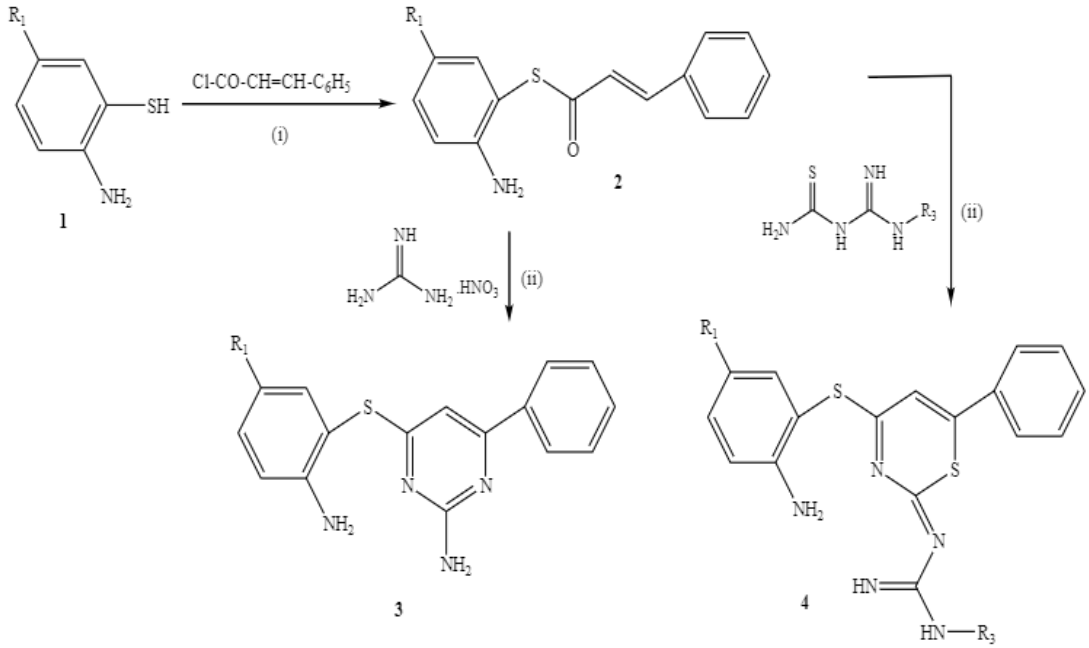
Table 4. Ulcerogenicity index

Compd.	Ulcer idex
Control	0.9 ± 0.1[c]
2a	1.1 ± 0.3[d]
2b	0.9 ± 0.3[c]
3a	1.2 ± 0.3[d]
3b	0.7 ± 0.2[c]
4a	1.1 ± 0.2[d]
4b	0.8 ± 0.2[c]
4c	0.9 ± 0.2[c]
4d	1.1 ± 0.2[d]
4e	1.1 ± 0.2[d]
4f	0.9 ± 0.3[c]
4g	0.9 ± 0.2[c]
4h	1.1 ± 0.3
Acetylsalicylic acid	1.7 ± 0.4[d]

[a] Vehicle: 1 mL of 10% (*V/V*) of Tween-80. Dose: 20 mg kg–1 b.m. of test compound and 200 mg kg–1 b.m. of acetylsalicylic acid.
[b] Each value represents the mean ± SEM (n = 6).
Significantly different from acetylsalicylic acid: [c] $p < 0.05$, [d] $p < 0.01$.

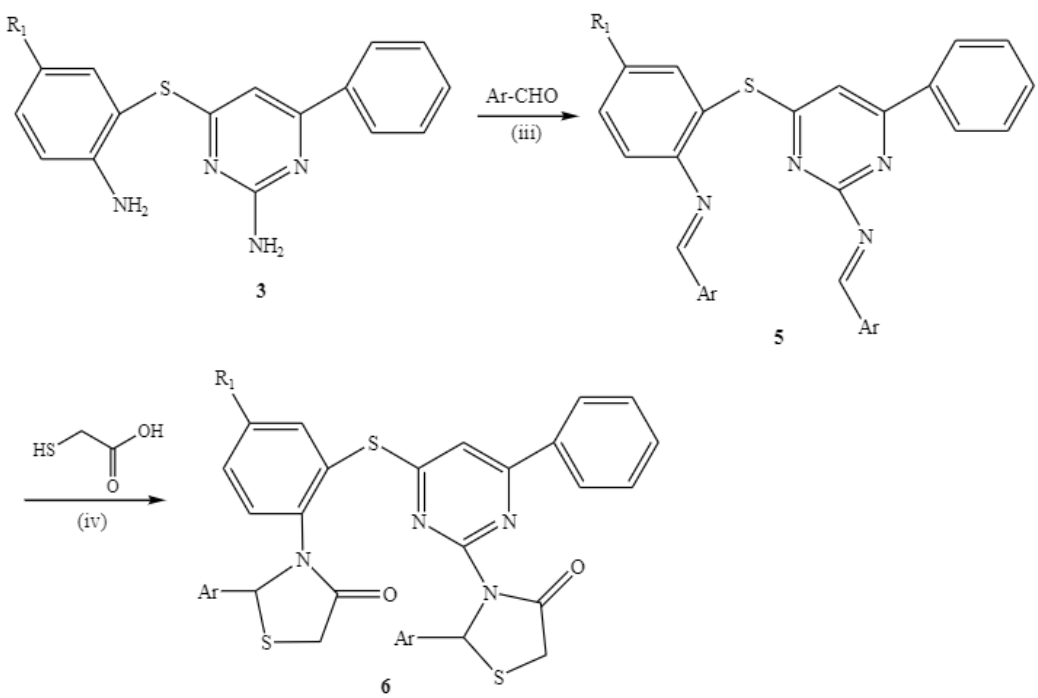
Result and Discussion:

Cinnamoyl chloride was reacted with 2-amino thiophenol (**1**) in 1, 4-dioxane at low temperature to obtained chalcone (**2**), which was further condensed with guanidine nitrate and substituted amidinothiocarbamides in presence of catalytic amount of NaOH and ethanol as solvent at reflux for 4-5 hours to obtain amino/ guanidino pyrimidines (**3**) and thiazines (**4**) derivative respectively. The synthetic sequences leading to the formation of targeted compounds are depicted in **Scheme I**. The compound **3** on reaction with substituted aromatic benzaldehyde in the presence of acetic acid at reflux for 3-4 h, furnished the corresponding **5** in 74% yield. Compounds Schiff base of 2-amino-4-(2'-amino-5'-substitued phenyl)mercapto-6-phenyl pyrimidine (**5**) when reacted with thioglycolic acid in the presence of $ZnCl_2$ in DMF at reflux temperature for 6 h, afforded the 2-(2"-substituted phenyl-4"-oxo-5"*H*-thiazol-3"-yl)-4-[2'-(2"'-substitutedphenyl-4"'-oxo-5"'*H*-thiazol-3"'-yl)-5'-substituedphenyl] mercapto-6-phenyl pyrimidine (**6**) in 71% yield (**Scheme II**). The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and MS spectral data. The physical constant and elemental analyses of all synthesized compounds are incorporated in Table 1. The anti-inflammatory activity data (Table 2) indicated that all the test compounds protected rats from carrageen an induced inflammation. Compounds **2a**, **2b**, **4a**, **4d**, **4e** and **4f** protected rats by 36 to 56% from inflammation while the other tested compounds showed lower anti-inflamatory activity in comparison to indomethacin. This means that the chalcones and 1,3-thiazine possess good anti-inflammatory activity. The results of analgesic activity indicate that all the test compounds exhibited high activity (Table 3). 1-(2'-amino phenyl)mercapto-3-phenyl-2-propen-1-one **2a** showed high activity comparable to that of acetylsalicylic acid. The other compounds showed moderate activity. Also, **2**-[*N*-(4''-bromo)phenyl]guanidino-4-(2'-aminophenyl) mercapto-6-phenyl-1, 3-thiazine **4d** and other thiazine derivatives **4e**, **4f** were found to be the most active analgesic agents, even more potent than acetylsalicylic acid. The ulcer index of the test compounds (Table 4) reveals that all compounds showed a mild ulcer index as compared to acetylsalicylic acid.



Reagents and condition: (i) 1, 4-dioxane, 10-15°C (ii) 40% NaOH, Ethanol, Reflux, 4-5 h

Scheme I



Reagents and condition: (iii) AcOH, reflux, 3-4 h (iv) DMF, $ZnCl_2$, reflux, 6 h

Scheme II

Conclusion

New compounds, 1-(2'-amino phenyl)mercapto-3-phenyl-2-propen-1-one **2a**, 1-(2'-amino-5'-methylphenyl)mercapto-3-phenyl-2-propen-1-one **2b**, 2-guanidino-4-(2'-aminophenyl)mercapto-6-phenyl-1, 3-thiazine **4a**, 2-[*N*-(4''-bromo)phenyl]guanidino-4-(2'-aminophenyl) mercapto-6-phenyl-1, 3-thiazine (**4d**), 2-guanidino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl-1, 3-thiazine (**4e**) and 2-(*N*-phenyl)guanidino-4-(2'-amino-5'-methylphenyl)mercapto-6-phenyl-1, 3-thiazine (**4f**) showed moderate anti-inflammatory activity. However, **2a, b** and **4a, b** and **4e** and compounds **4d**, **4e** and **4f** showed good to excellent analgesic activity.

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