Synthesis and anti-inflammatory activity evaluation of some sulfonamide and amidine derivatives of 4-aryl-3-(2 or 4-picolyl)-2-imino-4-thiazolines

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Condensation of 2- and 4-picolylaminehydrochloride 2a,b with (un) substituted phenacylthiocyanate 1a-d gives 4-aryl-3-(2- or 4-picolyl)-2-imino-4-thiazolines 3a-h in moderate yields. Sulfonamide derivatives 4a-h have been synthesized by condensation of 4-aryl-3-(2- or 4-picolyl)-2-imino-4-thiazolines 3a-h with methanesulfonyl chloride in good yields. Condensation of 2-cyanopyridine with thiazolines 3a, 3e and of 4-cyanopyridine with 3a, c, e and h gives amidine derivatives 5a, b and 6a-d respectively. Thiazoline derivatives 3a-h, sulfonamide derivatives 4a-h and amidine derivatives 5a, b; 6a-d are characterized by IR, 1H NMR, GC-MS spectral data and elemental analysis. Anti-inflammatory activity evaluation of 3a-h, 4a-d, g-h, 5a, b and 6a-c using carrageenan induced paw oedema assay at 50 mg/kg p.o. has been carried out and compound 6a exhibited anti-inflammatory activity comparable to standard drug ibuprofen.

Keywords: Thiazoline, sulfonamide, amidine, anti-inflammatory

Inflammatory diseases such as arthritis, asthma, allergy, multiple sclerosis, etc. are very common from which human beings suffer most. For the treatment of these diseases various anti-inflammatory drugs such as ibuprofen, aspirin, indomethacin, dichlofenac, nimesulide, celecoxib and rofecoxib, etc. are prescribed and used1,2. Various side effects such as gastrointestinal bleeding, ulceration and heart failure are associated with long-term use of the above said drugs3,4. Search of potent compounds which can be developed as safer anti-inflammatory drugs is a major challenge to the researchers working in this area. 3,4-Diaryl-2-imino-4-thiazoline derivatives exhibiting anti-inflammatory activity is reported in literature5-9. Sulfonamide derivatives exhibiting anti-inflammatory10-12, antiviral13, anticancer12,13 and HIV protease inhibiting activities12 are well documented in literature. Amidine derivatives exhibiting a wide variety of biological activities such as anti-inflammatory14,15, antimicrobial16,17, antifungal18, antibacterial19, antimalarial20 and anticancer21,22 are well documented in literature. In continuation of the efforts in search of potent molecules possessing anti-inflammatory activity several new 4-aryl-3-(2- or 4-picolyl)-2-imino-4-thiazoline sulfonamide and amidine derivatives have been synthesized and screened for anti-inflammatory activity which are reported in this paper.

Results and Discussion

Chemistry

Equimolar ratio of 2-picolylamine hydrochloride 2a (Scheme I) and phenacyl thiocyanate 1a (Scheme I) on condensation gave 4-phenyl-3-(pyridine-2ylmethyl)thiazol-2(3H)imine 3a (Scheme I) in 47% yield. Spectral data of 3a fully support the structure assigned to it. Similarly, condensation of 1b-d with 2a,b yielded thiazoline derivatives 3b-h in moderate yields. Spectral and analytical data of 3b-h is in complete agreement with structures assigned to them. 4-Phenyl-3-(pyridine-2ylmethyl)thiazol-2(3H)imine 3a (Scheme I) on condensation with methansulfonyl chloride gave N-(4-phenyl-3-(pyridine-2ylmethyl)-thiazol-2(3H)-ylidene)methanesulfonamide 4a (Scheme I) in 81% yield. Spectral and analytical data of 4a fully support the structure assigned to it. Similarly, other sulfonamide derivatives 4b-h (Scheme I) were synthesized in good yields. Spectral and analytical data of 4b-h is in complete agreement with the structures assigned to 4b-h. Condensation of 4-phenyl-3-(pyridine-2ylmethyl)thiazol-2(3H)imine 3a (Scheme I) with 2-cyanopyridine by refluxing in methanol for 12 hr and then purifying the crude product by column chromatography over silica gel gave pure amidine derivative i.e. N-(4-phenyl-3-
(pyridine-2-ylmethyl)thiazol-2(3H)-ylidene)picolaniminidine 5a (Scheme I) in moderate yield. Spectral and analytical data of 5a fully support the structure assigned to it.

Similarly, 5b and 6a-d were synthesized (Scheme I), structures assigned to 5b and 6a-d are fully supported by correct spectral and analytical data.

**Biological activity**

Anti-inflammatory activity\(^{23}\) evaluation of 3a-h, 4a-d, g-h, 5a,b and 6a-d was carried out using carrageenan induced paw oedema assay and results are summarized in Table I. Compounds 5g and 6a exhibited anti-inflammatory activity 34.7% and 37% comparable to ibuprofen which exhibited 39% activity at 50 mg/kg po.

**Experimental Section**

Melting points (m.p.) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT spectrometer. \(^1\)H NMR spectra were recorded on a Bruker WH-500 spectrometer at ca 5-15% (w/v) solution in DMSO-	extsubscript{d}6 (TMS as internal standard) GC-MS was recorded on
General procedure for synthesis of various substituted 4-phenyl-3-(2 or 4 picoly)-2-imino-4-thiazolines, 3a-h

4-Phenyl-3-(pyridine-2ylmethyl)thiazol-2(3H)imine, 3a

Phenacyl thioacetal 1a (Scheme I) (0.177 g, 1 mmole) was taken in 15 mL absolute methanol and to it was added (0.144 g, 1 mmole) 2-picolyaminonitrile 2a (Scheme I). Reaction contents were heated under reflux for 24 hr. Solvent was removed under reduced pressure and the crude product so obtained was dissolved in hot water. The hot aqueous solution was cooled to RT and then basified with aqueous solution of sodium hydroxide. A low melting solid product precipitated out. This crude product was filtered, washed with water and then dissolved in diethyl ether. This ether solution was dried over anhydrous sodium sulphate and then the solvent was removed under reduced pressure to give a low melting product which was kept under high vacuum for 10 min to give pure product 3a. (0.125 g) 47% yield. Semisolid; IR (KBr): 3481 (NH), 1642 (>C=N-), 1620 (C=O) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 4.87 (s, 2H, CH₂), 6.08 (s, 1H, >C=CH-), 7.06-7.08 (d, 1H, Ar), 7.20-7.22 (dd, 1H, Ar), 7.31-7.38 (m, 5H, Ar), 7.69-7.73 (m, 1H, Ar), 7.85 (bs, 1H, NH exch.), 8.43-8.44 (d, 1H, Ar); GC-MS: m/z 267 (M⁺, 35%), 266 (M⁺-1, 36%). Anal. Calcd for C₁₇H₁₃N₃S: C, 67.41; H, 4.86; N, 15.73; S, 11.98. Found: C, 67.01; H, 4.73; N, 15.55; S, 12.05%.

Similarly, condensation of 1b-d with 2a and 1a-d with 2b yielded 3b-h.

3-(Pyridine-2ylmethyl)-4-p-tolylthiazol-2(3H)imine, 3b

Solvent of purification; diethyl ether; Yield: 51%. Semisolid; IR(KBr): 3464 (NH), 1638 (C=O), 1617 (C=O) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 2.27 (s, 3H, CH₃), 4.85 (s, 2H, CH₂), 6.02 (s, 1H, >C=CH-), 7.06-7.07 (d, 1H, Ar) 7.14-7.23 (m, 5H, Ar), 7.70-774 (m, 1H, Ar), 8.44-8.45 (dd, 1H, Ar); GC-MS: m/z 281 (M⁺, 42%), 280 (M⁺-1, 37%). Anal. Calcd for C₁₉H₁₃N₃S: C, 68.32; H, 5.33; N, 14.94; S, 11.38. Found: C, 68.26; H, 5.54; N, 15.15; S, 11.68%.

4-(4-Methoxyphenyl)-3-(pyridine-2ylmethyl)thiazol-2(3H)imine, 3c

Solvent of purification; diethyl ether; Yield: 24%. Semisolid; IR(KBr): 3448 (NH), 1638 (C=O), 1617 (C=O) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 3.76 (s, 3H, OCH₃), 4.85 (s, 2H, CH₂), 5.99 (s, 1H, >C=CH-), 6.89-6.91 (q, 2H, Ar) 7.04-7.08 (t, 2H, Ar), 7.21-7.26 (m, 2H, Ar), 7.70-7.74 (m, 1H, Ar), 8.44-8.45 (t, 1H, Ar); GC-MS: m/z 297 (M⁺, 19%), 296 (M⁺-1, 13%). Anal. Calcd for C₁₆H₁₃N₃S: C, 64.64; H, 5.05; N, 14.14; S, 10.77. Found: C, 64.21; H, 5.28; N, 14.54; S, 10.55%.

4-(4-Chlorophenyl)-3-(pyridine-2ylmethyl)thiazol-2(3H)imine, 3d

Solvent of purification; diethyl ether; Yield: 25%. Semisolid; IR(KBr): 3481 (NH), 1620 (C=O), 1617 and 1490 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 4.87 (s, 2H, CH₂), 6.12 (s, 1H, >C=CH-), 7.08-7.12 (d, 1H, Ar) 7.21-7.23 (m, 1H, Ar), 7.35-7.38 (m, 2H, Ar), 7.40-7.43 (m, 2H, Ar), 7.69-7.73 (m, 1H, Ar), 8.43-8.44 (m, 1H, Ar); GC-MS: m/z 303 (M⁺ Cl⁻, 9%), 301 (M⁺ Cl⁻, 24%). Anal. Calcd for C₁₇H₁₂N₃Cl: C, 59.70; H, 3.98; N, 13.97; S, 10.61. Found: C, 60.18; H, 4.20; N, 14.32; S, 10.26%.

4-Phenyl-3-(pyridine-4ylmethyl)thiazol-2(3H)imine, 3e

Solvent of purification; diethyl ether; Yield: 36%. Semisolid; IR(KBr): 3421 (NH), 1593 (C=O), 1416 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 4.85 (s, 2H, CH₂), 6.12 (s, 1H, >C=CH-), 7.00-7.01 (d, 2H, Ar), 7.25-7.27 (dd, 2H, Ar), 7.35-7.41 (m, 3H, Ar), 7.97 (s, 1H, NH exch.), 8.43-8.44 (d, 2H, Ar); GC-MS: m/z 267 (M⁺, 17%), 266 (M⁺-1, 33%). Anal. Calcd for C₁₇H₁₃N₃S: C, 67.41; H, 4.86; N, 15.73; S, 11.98. Found: C, 67.76; H, 5.01; N, 15.43; S, 11.66%.

3-(Pyridine-4ylmethyl)-4-p-tolylthiazol-2(3H)imine, 3f

Solvent of purification; diethyl ether; Yield: 42%. Semisolid; IR(KBr): 3436 (NH), 1601 (C=O), 1576 and 1511 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 2.51 (s, 3H, CH₃), 4.85 (s, 2H, CH₂), 6.18 (s, 1H, >C=CH-), 7.01-7.02 (d, 2H, Ar), 7.28-7.30 (dd, 2H, Ar), 7.43-7.44 (q, 2H, Ar), 8.44-8.45 (q, 2H, Ar);
GC-MS: $m/z$ 281 (M+, 8%), 280 (M+ - 1, 16%). Anal. Caled for C$_{16}$H$_{13}$N$_2$S: C, 68.32; H, 5.33; N, 14.94; S, 11.38. Found: C, 68.45; H, 5.64; N, 15.05; S, 11.45%.

4-(4-Methoxyphenyl)-3-(pyridine-4-ylmethyl)thiazol-2(3H)imine, 3g

Solvent of purification: diethyl ether; Yield: 37%. Semisolid; IR(KBr): 3440 (NH), 1666 (C=N), 1605 and 1507 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 3.77 (s, 3H, OCH$_3$), 4.82 (s, 2H, CH$_2$), 6.03 (s, 1H, C=CH-), 6.91-6.93 (d, 2H, Ar) 7.00-7.04 (m, 2H, Ar), 7.18-7.20 (d, 2H, Ar), 8.44-8.46 (dd, 2H, Ar); GC-MS: $m/z$ 297 (M$^+$, 52%), 296 (M$^+$-1, 77%). Anal. Caled for C$_{16}$H$_{12}$N$_2$O$_{2}$S: C, 64.64; H, 5.05; N, 14.14; S, 10.77. Found: C, 64.40; H, 5.32; N, 14.38; S, 10.37%.

4-(4-Chlorophenyl)-3-(pyridine-4-ylmethyl)thiazol-2(3H)imine, 3h

Solvent of purification: diethyl ether; Yield: 41%. Semisolid; IR (KBr): 3419 (NH), 1630 (C=H), 1593 and 1482 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 4.83 (s, 2H, CH$_2$), 6.07 (s, 1H, C=CH-), 7.01-7.02 (d, 2H, Ar) 7.14-7.19 (m, 4H,Ar), 8.43-8.45 (dd, 2H, Ar); GC-MS: $m/z$ 303 (M$^+$ Cl$_{37}$ 10%), 301 (M$^+$ Cl$_{35}$ 27%), 300 (M$^+$-1 24%). Anal. Caled for C$_{15}$H$_{12}$N$_2$S: C, 59.70; H, 3.98; N, 13.97; S, 10.61. Found: C, 60.03; H, 3.86; N, 13.66; S, 10.45%.

General procedure for synthesis of methane sulfonamide derivatives

N-(4-Phenyl-3-(pyridine-2-ylmethyl)thiazol-2(3H)-ylidene)methane sulfonamide 4a

4-Phenyl-3-(pyridine-2-ylmethyl)thiazol-2(3H)imine (3a) 0.267 g (1 mmole) was taken in dry THF (20 mL) and to it was added anhydrous K$_2$CO$_3$ (2 g). Reaction contents were stirred at RT for 30 min. Methanesulfonyl chloride (0.17 mL, 1.5 mmole) was added to this reaction-mixture and it was allowed to stir further for 1 hr. Reaction contents were filtered and the solvent from filtrate was removed under vacuum. The solid residue left behind was washed with saturated solution of sodium bicarbonate (5 mL). Solid, so obtained was filtered, washed with water and air dried to give crude product, which was purified by recrystallization from methanol to give pure product 4a. Solvent of crystallization: MeOH; Yield: 0.279 g (81%); m.p. 152°C; IR (KBr): 1594 (C=N), 1498 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.77 (s, 3H, CH$_3$), 5.14 (s, 2H, CH$_2$), 6.93 (s, 1H, >C=CH-), 7.11-7.13 (d, 1H, Ar), 7.25-7.27 (t, 1H, Ar), 7.39-7.44 (m, 5H, Ar), 7.71-7.74 (t, 1H, Ar), 8.46-8.47 (d, 1H, Ar); GC-MS does not show M$^+$ ion peak but gave M$^+$SO$_2$ peak at $m/z$ 281 (3%); 268 (M$^+$- C$_8$H$_5$, 74%). Anal. Caled for C$_{16}$H$_{14}$N$_2$O$_2$S: C, 55.65; H, 4.34; N, 12.17; S, 18.55. Found: C, 55.42; H, 4.63; N, 12.44; S, 18.25%.

Similarly, methanesulfonamide derivatives 4b-h were synthesized.

N-(3-(Pyridine-2-ylmethyl)-4-p-tolylthiazol-2(3H)-ylidene) methane sulfonamide, 4b

Solvent of crystallization: MeOH; Yield: 78%; m.p. 132°C; IR (KBr): 1650 (C=N), 1559 and 1501 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.31 (s, 3H, CH$_3$), 2.76 (s, 3H, CH$_3$), 5.12 (s, 2H, CH$_2$), 6.87 (s, 1H, >C=CH), 7.11-7.13 (d, 1H, Ar), 7.20-7.22 (d, 2H, Ar), 7.25-7.28 (t, 3H, Ar), 7.72-7.75 (dt, 1H, Ar), 8.46-8.47 (d, 1H, Ar); GC-MS does not show M$^+$ ion peak but gave $m/z$ 281 (M$^+$-C$_9$H$_7$N, 10%). Anal. Caled for C$_{17}$H$_{15}$N$_2$O$_2$S: C, 56.82; H, 4.73; N, 11.69; S, 17.82. Found: C, 57.04; H, 4.56; N, 11.63; S, 17.55%.

N-(4-(4-Methoxyphenyl)-3-(pyridine-2-ylmethyl)thiazol-2(3H)-ylidene)methane sulfonamide, 4c

Solvent of crystallization: MeOH; Yield: 75%; m.p. 155°C; IR (KBr): 1651 (C=N), 1613 and 1558 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.75 (s, 3H, CH$_3$), 3.85(s, 3H, OCH$_3$), 5.12 (s, 2H, CH$_2$), 6.88 (s, 1H, >C=CH), 6.94-6.96 (m, 2H, Ar), 7.12-7.14 (d, 1H, Ar),7.26-7.29 (m, 1H, Ar), 7.31-7.33 (q, 2H, Ar), 7.73-7.76 (m, 1H, Ar), 8.468-8.477 (t, 1H, Ar); GC-MS does not show M$^+$ ion peak but gave $m/z$ 283 (M$^+$-C$_9$H$_7$N, 3%). Anal. Caled for C$_{17}$H$_{17}$N$_2$O$_2$S: C, 54.40; H, 4.53; N, 11.20; S, 17.06. Found: C, 54.25; H, 4.91; N, 11.46; S, 17.29%.

N-(4-(4-Chlorophenyl)-3-(pyridine-2-ylmethyl)thiazol-2(3H)-ylidene)methane sulfonamide, 4d

Solvent of crystallization: MeOH; Yield: 83%; m.p. 130°C; IR (KBr): 1592 (C=N), 1492 (Ar) cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.77 (s, 3H, CH$_3$), 5.14 (s, 2H, CH$_2$), 6.96 (s, 1H, >C=CH-), 7.14-7.16 (d, 1H, Ar), 7.25-7.27 (t, 1H, Ar), 7.42-7.49 (m, 4H, Ar),7.71-7.73 (t, 1H, Ar), 8.45-8.46 (d, 1H, Ar); GC-MS does not show M$^+$ ion peak but gave $m/z$ 283 (M$^+$ Cl$_{37}$, C$_{10}$H$_7$N, 20%). Anal. Caled for C$_{17}$H$_{14}$N$_2$O$_2$S: C, 50.59; H, 3.69; N, 11.06; S, 16.86. Found: C, 51.04; H, 3.48; N, 11.47; S, 16.63%.
N-(4-Phenyl-3-(pyridine-4-ylmethyl)thiazol-2(3H)-ylidene)methanesulfonamide, 4e

Solvent of crystallization: MeOH; Yield: 72%; m.p. 140°C; IR(KBr): 1600 (C=N), 1560 and 1500 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 2.89 (s, 3H, CH₃), 5.10 (s, 2H, CH₂), 6.94-6.95 (d, 2H, Ar), 6.99 (s, 1H, =C=CH⁻), 7.29-7.309 (dd, 2H, Ar) 7.40-7.46 (m, 3H,Ar), 8.460-8.472 (dd, 2H, Ar); GC-MS does not show M⁺ ion peak but gave m/z 268 (M⁺- C₅H₃, 19%). Anal. Calcd for C₁₈H₁₅N₂O₂S₂C₁: C, 50.59; H, 3.69; N, 11.06; S, 16.86. Found: C, 50.24; H, 3.85; N, 11.02; S, 16.55%.

General procedure for synthesis of amidine derivatives (5a,b; 6a-d) N-(4-Phenyl-3-(pyridine-2-ylmethyl)thiazol-2(3H)-ylidene)picolinamidine, 5a

4-Phenyl-3-(pyridine-2-ylmethyl)thiazol-2(3H)imine (3a) 0.267 g (1 mmole) was dissolved in absolute methanol (20 mL) and to it was added 2-cyanopyridine 0.104 g (1 mmole). The resulting solution was heated under reflux for 12 hr. Solvent was removed under reduced pressure to give crude product which was purified by column chromatography over silica gel (elution with pet ether:CHCl₃, 5:5) to give pure product 5a. Yield: 0.133 g (36%). Semisolid; IR (KBr): 3437 (NH), 1597 (C=N), 1560 and 1478 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 5.57 (s, 2H, CH₂), 7.13 (s, 1H, >C=CH⁻), 7.19-7.24 (m, 2H, Ar) 7.41-7.49 (m, 6H,Ar), 7.67-7.72 (m, 1H, Ar), 7.85-7.88 (m, 1H, Ar), 8.08-8.10 (d, 1H, Ar), 8.42-8.43 (d, 1H, Ar), 8.66-8.67 (d, 1H, Ar); GC-MS: m/z 371 (M⁺, 2%), 370 (M⁺-1, 8%). Anal. Calcd for C₁₇H₁₇N₃S: C, 67.92; H, 4.58; N, 18.86; S, 8.62. Found: C, 67.53: H, 4.18; N, 19.15; S, 8.45%.

Similarly, condensation of 3e with 2-cyanopyridine and 3a,c,e,h, with 4-cyanopyridine gave 5b and 6a-d respectively.

N-(4-(4-Methoxyphenyl)-3-(pyridine-4-ylmethyl)-thiazol-2(3H)-ylidene)methanesulfonamide, 4g

Solvent of crystallization: MeOH; Yield: 79%; m.p. 160°C; IR (KBr): 1601 (C=N), 1490 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 2.87 (s, 3H, CH₂), 3.77 (s, 3H, OCH₃), 5.08 (s, 2H, CH₂), 6.91 (s, 1H, >C=CH⁻), 6.96-6.98 (t, 4H, Ar), 7.25-7.27 (t, 2H, Ar), 8.47-8.48 (d, 2H, Ar); GC-MS: m/z 375 (M⁺, 43%), 296 (M⁺-SO₂CH₃, 100%). Anal. Calcd for C₁₇H₁₄N₂O₂S: C, 54.40; H, 4.53; N, 11.20; S, 17.06. Found: C, 54.65; H, 4.33; N, 11.46; S, 17.48%.

N-(4-(4-Chlorophenyl)-3-(pyridine-4-ylmethyl)thiazol-2(3H)-ylidene)methane sulfonamide, 4h

Solvent of crystallization: MeOH; Yield: 71%; m.p. 105°C; IR (KBr): 1600 (>C=–N), 1510 and 1415 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 2.89 (s, 3H, CH₃), 5.10 (s, 2H, CH₂), 6.96-6.97 (d, 2H, Ar), 7.03 (s, 1H, >C=CH⁻), 7.36-7.38 (m, 2H, Ar), 7.49-7.51 (q, 2H, Ar), 8.466-8.478 (q, 2H, Ar); GC-MS does not show M⁺ ion peak but gave peaks at m/z 303(M⁺ Cl⁻³⁷, C₅H₅N, 24%), 302 (M⁺ Cl⁻³⁷SO₂CH₃, 49%), 301 (M⁺ Cl⁻³⁷SO₂CH₂N, 63%), 300 (M⁺ Cl⁻²⁹SO₂CH₃, 100%). Anal. Calcd for C₁₆H₁₄Cl₂N₂O₂S₂Cl: C, 50.59; H, 3.69; N, 11.06; S, 16.86. Found: C, 50.24; H, 3.85; N, 11.02; S, 16.55%.

N-(4-Phenyl-3-(pyridine-4-ylmethyl)thiazol-2(3H)-ylidene)sonicotinamidine, 6a

Solvent of crystallization: MeOH; Yield: 31%; m.p. 150°C; IR (KBr): 3427 (NH), 1640 (>C=–N), 1592, 1540 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 5.56 (s, 2H, CH₂), 7.19 (s, 1H, >C=CH⁻), 7.23-7.28 (m, 2H, Ar) 7.44-7.52 (m, 5H,Ar), 7.72-7.75 (d, 1H, Ar), 7.88-7.89 (d, 2H, Ar), 8.44-8.45 (d, 1H, Ar),
8.68-8.69 (d, 2H, Ar); GC-MS: m/z 371 (M⁺, 3%). Anal. Calcd for C₂H₄N₂S: C, 67.92; H, 4.58; N, 18.86; S, 8.62. Found: C, 67.23; H, 4.85; N, 19.11; S, 8.45%.

N-(4-(4-Methoxyphenyl)-3-(pyridine-2-ylmethyl)-thiazol-2(3H)-ylidene)isonicotinamidine, 6a

Solvent of crystallization: MeOH; Yield: 34%; m.p. 155°C; IR (KBr): 3433 (NH), 1597 (>C=N-), 3210 (OH), 1544 and 1478 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆); δ 5.55 (s, 2H, CH₂), 7.00-7.01 (d, 2H, Ar), 7.39-7.40 (d, 2H, Ar), 7.47-7.51 (m, 5H, Ar); GC-MS: m/z 405 (M⁺, 1%). Anal. Calcd for C₂H₄N₂S: C, 67.83; H, 4.73; N, 17.45; S, 7.98. Found: C, 65.54; H, 4.45; N, 17.86; S, 8.20%.

N-(4-Phenyl-3-(pyridine-4-ylmethyl)thiazol-2(3H)-ylidene)isonicotinamidine, 6c

Solvent of crystallization: MeOH; Yield: 34%; m.p. 166°C; IR (KBr): 3419 (NH), 1601 (>C=N-), 1544 and 1478 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆); δ 5.55 (s, 2H, CH₂), 6.99-7.00 (d, 2H, Ar), 7.26 (s, 1H, >C=CH-), 7.42-7.51 (m, 5H, Ar) 7.93-7.94 (d, 2H, Ar), 8.44-8.45 (d, 2H, Ar), 8.70-8.71 (d, 2H, Ar); GC-MS: m/z 371 (M⁺, 6%). Anal. Calcd for C₂H₄N₂S: C, 67.92; H, 4.58; N, 18.86; S, 8.62. Found: C, 67.68; H, 4.23; N, 19.15; S, 8.44%.

N-(4-Chlorophenyl-3-(pyridine-4-ylmethyl)thiazol-2(3H)-ylidene)isonicotinamidine, 6d

Solvent of crystallization: MeOH; Yield: 35%; m.p. 198°C; IR (KBr): 3440 (NH), 1599 (>C=N-), 1540 and 1470 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆); δ 5.55 (s, 2H, CH₂), 7.00-7.01 (d, 2H, Ar), 7.29 (s, 1H, >C=CH-), 7.42-7.46 (d, 2H, Ar), 7.53-7.55 (d, 2H, Ar), 7.93-7.94 (dd, 2H, Ar), 8.44-8.46 (dd, 2H, Ar), 8.70-8.71 (dd, 2H, Ar); GC-MS: m/z 401 (M⁺, 1%). Anal. Calcd for C₂H₄N₂S: C, 64.14; H, 3.94; N, 17.26; S, 7.89. Found: C, 62.45; H, 4.05; N, 17.15; S, 7.81%.

Anti-inflammatory activity

Paw oedema inhibition test was used on albino rats of Charles Foster by adopting the method of Winter et al. Groups of five animals of both sexes (body weight 120-160 g), excluding pregnant females, were given a dose of test compound. After 30 min, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1-3 hr later. The mean increase of paw volume at each interval was compared with that of control group (five rats treated with carrageenan but not with test compound) at the same intervals and percent inhibition value calculated by the formula given below.

% Anti-inflammatory activity = \[1 - \frac{D_a}{D_c}\] × 100

Dₐ and Dₐ are paw volumes of oedema in tested and control groups, respectively. Compounds 3a-h, 4a-d, g-h; 5a,b and 6a-c were screened for anti-inflammatory activity and results are summarized in Table 1.

Conclusion

A number of 4-aryl-3(2 or 4-picolyl)-2-imino-4-thiazoline 3a-h derivatives have been synthesized and then converted to corresponding sulfonamide 4a-h and amidine 5a,b and 6a-d derivatives. All these compounds were screened for anti-inflammatory activity. Compound 6a exhibited anti-inflammatory activity comparable to the standard drug ibuprofen.

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