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Design and synthesis of N-substituted aminothiazole compounds as anti-inflammatory agents

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ABSTRACT

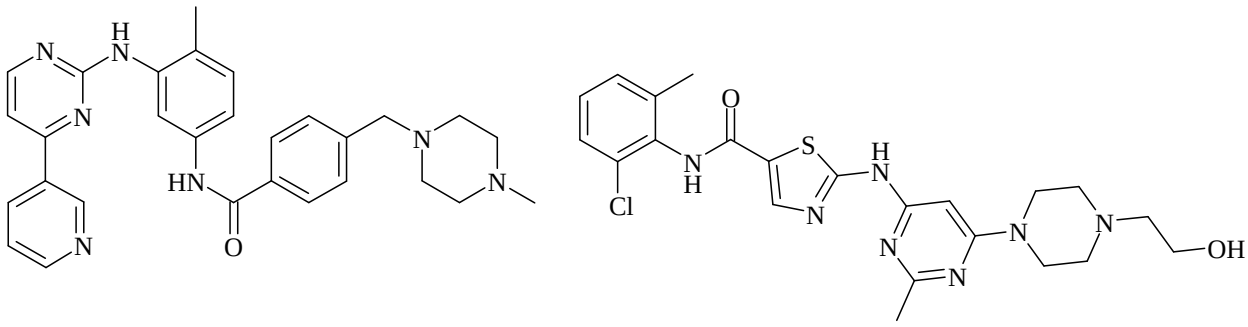
*A series of new N-(4-phenyl-1, 3-thiazol-2-yl) benzamides (**5a-o**) has been synthesized from 2-amino-4-substituted phenylthiazoles and substituted benzoyl chlorides. The structures of synthesized compounds were established based on spectral (FT IR, ^{1}H NMR, ESI Mass) analysis. The final fifteen compounds were screened for anti-inflammatory activity by following carrageenan induced rat paw edema method. Among the compounds screened, N-(4-phenyl-1, 3-thiazol-2-yl) 4-chlorobenzamide (**5c**) and N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl]-3-trifluro methylbenzamide (**5n**) were found to be more potent.*

Keywords: 2-amino-4-phenylthiazoles, benzamides, benzoyl chlorides, anti-inflammatory activity.

INTRODUCTION

Numerous drug molecules are known to possess amide group which grant one of the important hydrogen bond donor and acceptor properties and due to this amide-based molecules are considered to be suitable for drug research due to their biological compatibility. The occurrence of amide group in pharmaceuticals and biologically active compounds make it one of the most important links as observed in various natural and synthetic compounds like Piperine, Penicillin G, Aspirin, etc [1, 2]. The presence of amide group was observed in various anti-cancer agents like Paclitaxel, Docetaxel, Abraxane and few of newer receptor tyrosine kinase inhibitors like Imatinib, Dasatinib, etc possess amide group in structure **figure 1** [3].

As p38 kinase is one of the important target for next generation antiinflammatory agents, the second generation p38 kinase inhibitors consisting urea group were found to inhibit p38 kinase by binding the allosteric site in DFG out mode **figure 2** [4]. These urea derivatives were further modified into compounds which possess amide link, exemplified by 5-amino-2-carbonylthiophene derivatives, 1,3,5-triaminotriazine, naphthalene amide, etc **figure 3** [5].



Imatinib **Dasatinib**

Figure 1: Structures of kinase inhibitors as drugs containing amide linkage

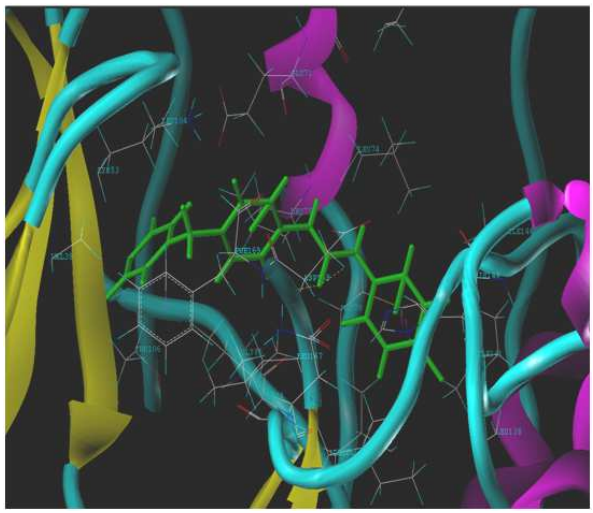


Figure 2: Binding pose of DFG out P38 kinase inhibitors

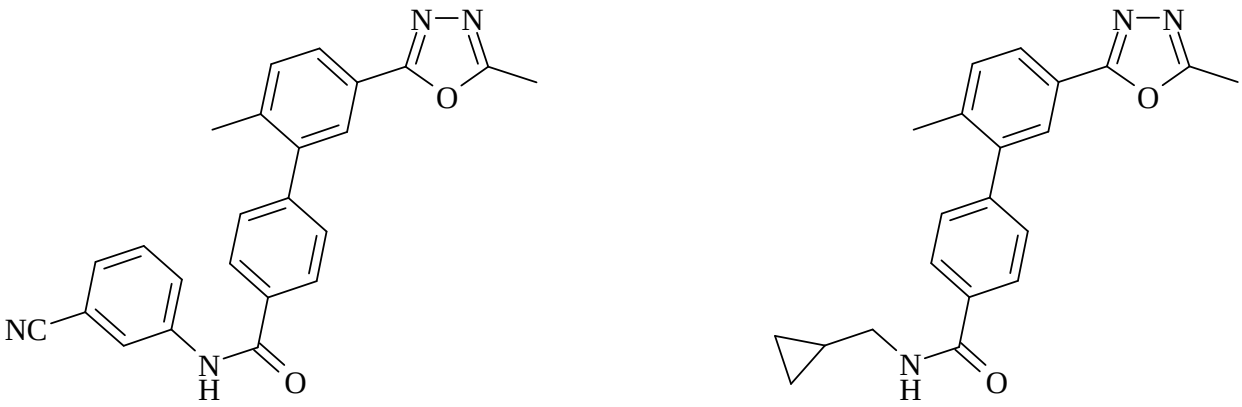


Figure 3: Amide p38 kinase inhibitors interact with DFG

Thiazole derivatives received sheer attention as bioactive moieties due to wide range of biological activities, some of the latest antiinflammatory agents reported with almost no gastric damage even at higher doses [6]. Recently, novel scaffolds with aminocarboxamide at 2nd position of thiazole nucleus were reported with potent antiinflammatory actvity [7, 8].

Our group is extensively engaged in the design and development of anti-inflammatory agents and some of the reported molecules also inhibited p38 kinase [9-12]. In our latest endeavor to develop newer antiinflammatory agents, we modified N, N' diaryl urea derivates into N, N'-substituted thiazolyl ureas and reported their antiinflammatory activity [13]. Now further modification of N'-substituted thiazolyl ureas has been intended here as depicted in **figure 4** and this communication reveals the synthesis, characterization and anti-inflammatory activity of N-(4-phenyl-1, 3-thiazol-2-yl) benzamides (**5a-o**).

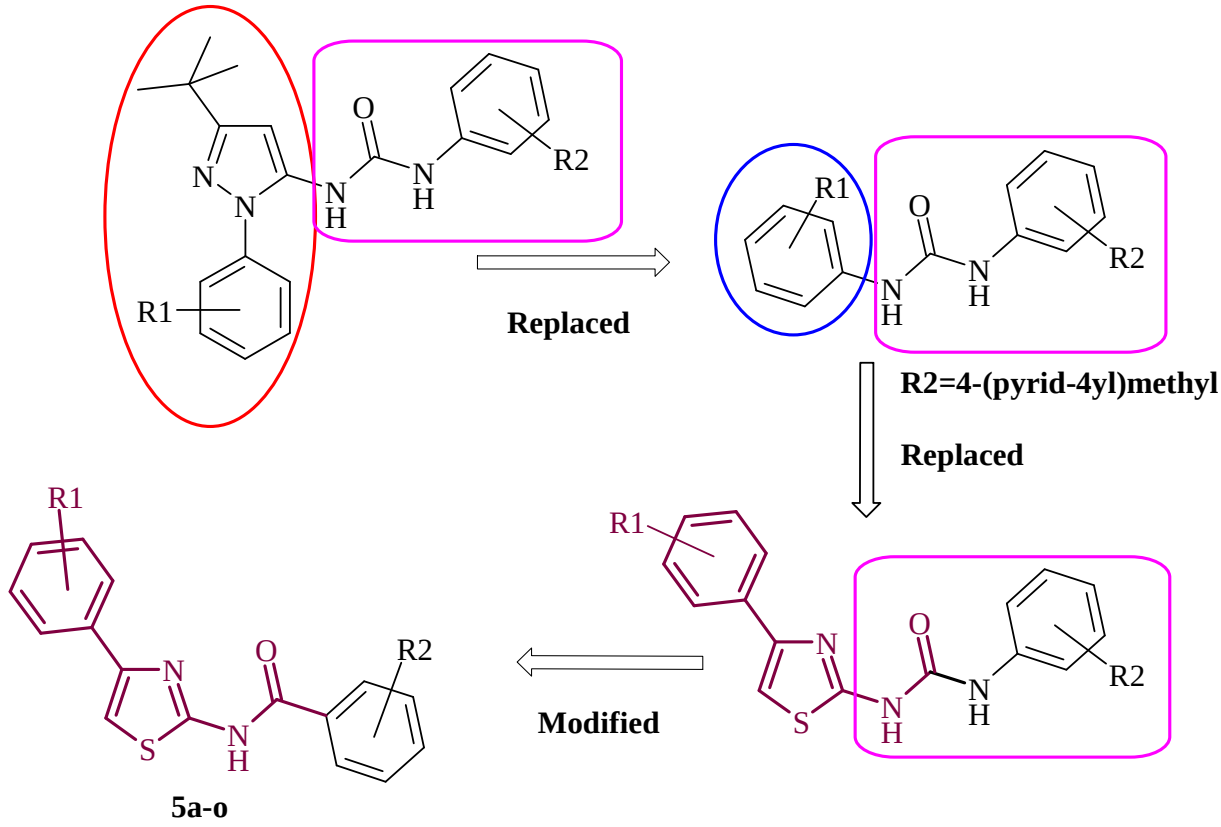


Figure 4: Design of newer thiazolamides as antiinflammatory agents

MATERIALS AND METHODS

Experimental

All the chemicals were purchased from M/s Sigma Aldrich, S. D Fine and all chemicals solvents were purchased from local vendors and are purified before being used. Pre-coated silica gel F254 (Merck) plates were employed for thin layer chromatography and column chromatography was performed using silica gel 60-120 mesh.

Albino rats of either sex weighing between 150-200 g were used during the study. They were purchased from a local vendor i.e., Sri Sai Enterprises, HYD. The study had permission from the Animal Ethical Committee. All the animals were fasted overnight and allowed water. Anti-Inflammatory activity of synthesized compounds was determined by carrageenan induced rat hind paw edema method.

Melting points were recorded in open glass capillaries using **Polmon** melting point apparatus and are uncorrected. Infrared spectra were recorded on **Bruker** FT IR spectrophotometer by KBr / ATR. Mass spectra obtained on **VG-7070H** mass spectrometer. ^{1}HNMR spectra were recorded at 300 MHz on a **Bruker Avance** NMR spectrometer in $CDCl_3$ (δ 7.26) or DMSO- d_6 (δ 2.49).

General procedure for the synthesis of 2-amino-4-(substituted) phenylthiazole (3a-c)
Substituted amino phenylthiazoles were synthesized by adding the mixture of thiourea (0.2 mol) and iodine (0.1 mol) to substituted acetophenone (0.1 mol) and heated on water bath with occasional stirring for 8 h [14]. The crude product thus obtained was dissolved in hot water, filtered to remove the sulphone and 2-amino-4-phenylthiazoles (**3a-c**) were precipitated by addition of ammonia. The product was purified by recrystallization from ethanol to get pure **3a-c**.

Synthesis of N-(4-phenyl-1, 3-thiazol-2-yl)-benzamide (5a-o)
2-amino-4-(substituted) phenylthiazoles **3a-c** (1 mmol) and substituted benzoyl chlorides **4a-e** (1.2 mmol) was dissolved in dimethyl formamide or dichloromethane by stirring and diisopropyl ethylamine (1 mL) was added drop wise to the above solution with continuous stirring at room temperature. The reaction was monitored over TLC, upon completion; the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate; solvent was removed under reduced pressure to afford crude final product **5a-o** and purified over silica gel using 30% ethyl acetate in hexane as eluent to get **5a-o**.

Carrageenan Induced Rat hind Paw Edema
Anti-Inflammatory activity of synthesized compounds was determined by carrageenan induced rat hind paw edema method. The drugs were prepared as a suspension by triturating with 1% tween 80. The suspension of test compounds (10 mg/kg) were administered orally in the 15 treated groups and after 30 minutes, inflammation was induced by injecting 0.1 mL of 1% carrageenan solution in the intraplantar region. The standard group received 10 mg/kg of Diclofenac, test group received 10 mg/kg of synthesized compounds and the control group received 1% w/v of tween 80. The percentage inhibition of inflammation after 4 hour was calculated using following formula [15, 16].

$$\% \text{ Inhibition of edema} = (1\text{-Et/Em}) \times 100$$

Where Et represents the average value of the edema in mL in treated groups in 1– 4 h after carrageenan injection, while Em represents the average value of the edema in mL in control group in 1 – 4 hours after carrageenan injection.

Characterization of synthesized compounds
4-phenyl - 1, 3-thiazole - 2-amine (3a):
Yield: 93%, m.p.: 140-143 ºC, **FT IR (KBr):** 3414.00 cm^{-1} (NH Assym. str), 3397.11 cm^{-1} (NH Sym. str), 3105.22 cm^{-1} (CH Ar. str), 1407.50 cm^{-1} (C=C Str) ; **^{1}H NMR (DMSO) (ppm):** 4.0 (bs, 2H, NH_2), 6.74 (s, 1H, thiazole C_4-H), 7.34-7.45 (m, 3H, Ar-H), 7.78 (d, 2H, Ar-H); **ESI-MS** (m/z): 177.2 $[M+H]^+$.

4-(3-chlorophenyl)-1, 3-thiazol-2-amine (3b):
Yield: 90%, m.p.: 146-148 ºC, **FT IR (KBr):** 3440.00 (NH_2 Anti Sym. Str), 3358.13 cm^{-1} (NH_2 Sym. Str), 3028.55 cm^{-1} (CH Ar. str), 1608 cm^{-1} (NH-Bnd) 1512.30 cm^{-1} (C=C Str) **; ^{1}H NMR (DMSO) (ppm):** 3.8 (bs, 2H, NH_2), 6.84 (s, 1H, thiazole C_4), 7.45-7.52 (t, 1H, C'_5 aromatic), 7.78-7.81 (d, 1H, C'_6 aromatic), 7.87-7.88 (d, 1H, C'_4 aromatic), 7.91-7.98 (s, 1H, C'_2 aromatic); **ESI-MS** (m/z): 211.7 $[M+H]^+$.

4-(4-chlorophenyl)-1, 3-thiazol-2-amine (3c):
Yield: 78%, m.p.: 149-151 ºC, **FT IR (KBr):** 3440.00 (NH_2 Anti Sym. Str), 3345.13 cm^{-1} (NH_2 Sym. Str), 3041.65 cm^{-1} (CH Ar. str), 1520.30 cm^{-1} (C=C Str), 1422.25 cm^{-1} (C-N)**; ^{1}H NMR (DMSO) (ppm):** 4.22 (bs, 2H, NH_2), 6.91 (s, 1H, thiazole C_4), 7.67 (d *J=8.9 Hz*, 2H, $C'_{3,5}$), 7.8 (d *J=9.2 Hz*, 2H, $C'_{2,6}$); **ESI-MS** (m/z): 210.7 $[M+H]^+$.

N-(4-phenyl -1, 3-thiazol-2-yl)-benzamide (5a):
Yield: 64%, m.p.: 175-180 ºC, **FT IR (KBr):** 3344 cm^{-1} (NH str), 2929.92 cm^{-1} (CH Ar. str), 1659 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.71 (s, 1H, thiazole C_4), 7.26-7.34 (m, 3H, $C'_{3,4,5}$), 7.48-7.56 (m, 3H, $C''_{3,4,5}$), 7.66 (d *J=10.2 Hz*, 2H, $C'_{2,6}$), 8.02 (d *J=9.4 Hz*, 2H, $C''_{2,6}$), 8.7 (bs, 1H, NH); **ESI-MS** (m/z): 281 $[M+H]^+$.

N-(4-phenyl-1, 3-thiazol-2-yl) 4-fluorobenzamide (5b):
Yield: 61%, m.p.: 192-198 ºC, **FT IR (KBr):** 3345 cm^{-1} (NH str), 2952.65 cm^{-1} (CH Ar. str), 1705 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.75 (s, 1H, thiazole C_4), 7.33-7.40 (m, 3H, $C'_{3,4,5}$), 7.57 (d *J=8.8 Hz*, 2H, $C'_{2,6}$), 7.88 (d *J= 8.3 Hz*, 2H, $C''_{3,5}$), 8.19 (d *J= 8.9 Hz*, 2H, $C''_{2,6}$), 8.82 (bs, 1H, NH); **ESI-MS** (m/z): 299 $[M+H]^+$.

N-(4-phenyl-1, 3-thiazol-2-yl) 4-chlorobenzamide (5c):
Yield: 53%, m.p.: 190-194 ºC, **FT IR (KBr):** 3340 cm^{-1} (NH str), 2989.69 cm^{-1} (CH Ar. str), 1722 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.92 (s, 1H, thiazole C_4), 7.20-7.28 (m, 3H, $C'_{3,4,5}$), 7.45-7.53 (d *J= 7.8 Hz*, 2H, $C'_{2,6}$), 7.72 (d *J= 7.6 Hz*, 2H, $C''_{3,5}$), 8.1 (d *J= 9.0 Hz*, 2H, $C''_{2,6}$), 8.66 (bs, 1H, NH); **ESI-MS** (m/z): 316 $[M+H]^+$.

N-(4-phenyl-1, 3-thiazol-2-yl) 3-trifluoromethyl benzamide (5d):
Yield: 62%, m.p.: 228-230 ºC, **FT IR (KBr):** 3367 cm^{-1} (NH str), 2944.99 cm^{-1} (CH Ar. str), 1683 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.53 (s, 1H, thiazole C_4), 7.12-7.27 (t, 3H, $C'_{3,4,5}$), 7.44-7.57 (m, 3H, $C'_{2,6}$, C''_5), 7.6 (d *J= 10.1 Hz*, 1H, C''_4), 8.16 (d *J= 10.8 Hz*, 1H, C''_6), 8.3 (s, 1H, C''_2), 8.37 (bs, 1H, NH); **ESI-MS** (m/z): 349 $[M+H]^+$.

N-(4-phenyl-1, 3-thiazol-2-yl) 3-nitrobenzamide (5e):
Yield: 68%, m.p.: 180-185 ºC, **FT IR (KBr):** 3358 cm^{-1} (NH str), 2947.89 cm^{-1} (CH Ar. str), 1671 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.58 (s, 1H, thiazole C_4), 7.2-7.28 (t, 3H, $C'_{3,4,5}$), 7.52-7.6 (m, 3H, $C'_{2,6}$, C''_5), 8.06 (d *J= 9.4 Hz*, 1H, C''_6), 8.33 (d *J= 12.3 Hz*, 1H, C''_4), 8.52 (s, 1H, C''_2), 9.01 (bs, 1H, NH); **ESI-MS** (m/z): 326 $[M+H]^+$.

N-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl] benzamide (5f):
Yield: 71%, m.p.: 196-198ºC, **FT IR (KBr):** 3351cm^{-1} (NH str), 3081.26 cm^{-1} (CH Ar. str), 1672 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.29 (s, 1H, thiazole C_4), 7.35-7.43 (t, 3H, $C''_{3,4,5}$), 7.52 (d *J= 8.4 Hz*, 2H, $C'_{3,5}$), 7.66 (d *J= 9.1 Hz*, 2H, $C'_{2,6}$), 7.93 (d *J= 11.3 Hz*, 2H, $C''_{2,6}$), 8.38 (bs, 1H, NH); **ESI-MS** (m/z): 315 $[M+H]^+$.

N-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl] -4-fluorobenzamide (5g):
Yield: 73%, m.p.: 186-189ºC, **FT IR** (KBr): 3385cm^{-1} (NH str), 2936.65 cm^{-1} (CH Ar. str), 1689 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.66 (s, 1H, thiazole C_4), 7.42 (d *J= 9.3 Hz*, 2H, $C'_{3,5}$), 7.61 (d *J= 8.4 Hz*, 2H, $C'_{2,6}$), 7.72 (d *J= 8.8 Hz*, 2H, $C''_{3,5}$), 8.05 (d *J= 10.6 Hz*, 2H, $C''_{2,6}$), 9.0 (s, 1H, NH); ESI-MS (m/z): 333 [M+H]+.

N-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl] -4-chlorobenzamide (5h):
Yield: 63%, m.p.: 205-207ºC, **FT IR (KBr):** 3354cm^{-1} (NH str), 2989.65 cm^{-1} (CH Ar. str), 1657 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.45 (s, 1H, thiazole C_4), 7.36 (d *J= 9.9 Hz*, 2H, $C'_{3,5}$), 7.5 (d *J= 9.2 Hz*, 2H, $C'_{2,6}$), 7.67 (d *J= 9.1 Hz*, 2H, $C''_{3,5}$), 7.96 (d *J= 10.0 Hz*, 2H, $C''_{2,6}$), 8.7 (s, 1H, NH); **ESI-MS** (m/z): 348 $[M+H]^+$.

N-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl]-3-trifluromethylbenzamide (5i):
Yield: 72%, m.p.: 184-187ºC, **FT IR (KBr):** 3372cm^{-1} (NH str), 2961.65 cm^{-1} (CH Ar. str), 1664 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.71 (s, 1H, thiazole C_4), 7.29 (d *J= 9.1 Hz*, 2H, $C'_{3,5}$), 7.58 (d *J= 10.6 Hz*, 2H, $C'_{2,6}$), 7.66-7.72 (t, 1H, C''_5), 7.9 (d *J= 9.2 Hz*, 1H, C''_4), 8.05 (d *J= 8.6 Hz*, 1H, C''_6), 8.4 (s, 1H, C''_2), 9.3 (bs, 1H, NH); **ESI-MS** (m/z): 383 $[M+H]^+$.

N-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl]-3-nitrobenzamide (5j):
Yield: 70%, m.p.: 210-214ºC, **FT IR (KBr):** 3327cm^{-1} (NH str), 2956.89 cm^{-1} (CH Ar. str), 1656 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.83 (s, 1H, thiazole C_4), 7.35 (d *J= 9.9 Hz*, 2H, $C'_{3,5}$), 7.5 (d *J= 9.2 Hz*, 2H, $C'_{2,6}$), 7.6 (t, 1H, C''_5), 8.13 (d *J= 10.3 Hz*, 1H, C''_6), 8.44 (d *J= 10.4 Hz*, 1H, C''_4), 8.6 (s, 1H, C''_2), 9.86 (bs, 1H, NH); **ESI-MS** (m/z): 360 $[M+H]^+$.

N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl] benzamide (5k):
Yield: 66%, m.p.: 181-183 ºC, **FT IR (KBr):** 3365cm^{-1} (NH str), 2996.65 cm^{-1} (CH Ar. str), 1715 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.47 (s, 1H, thiazole C_4), 7.4-7.46 (t, 1H, C'_5), 7.55-7.64 (m, 3H, $C''_{3,4,5}$), 7.73 (d *J= 8.4 Hz*, 1H, C'_6), 7.86 (d *J= 9.3 Hz*, 1H, C'_4), 7.98 (s, 1H, C'_2), 8.01 (d *J= 11.1Hz*, 2H, $C''_{2,6}$), 9.10 (bs, 1H, NH); **ESI-MS** (m/z): 315 $[M+H]^+$.

N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl] -4-fluorobenzamide (5l):
Yield: 58 %, m.p.: 208-212 ºC, **FT IR (KBr):** 3375cm^{-1} (NH str), 2981.56 cm^{-1} (CH Ar. str), 1658 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.64 (s, 1H, thiazole C_4), 7.34-7.42 (t, 1H, C'_5), 7.66-7.8 (m, 3H, C'_6, $C''_{3,5}$), 7.9 (d *J= 9.9 Hz*, 1H, C'_4), 8.05 (s, 1H, C'_2), 8.17 (d *J= 10.1 Hz*, 2H, $C''_{2,6}$), 9.11 (bs, 1H, NH); **ESI-MS** (m/z): 333 $[M+H]^+$.

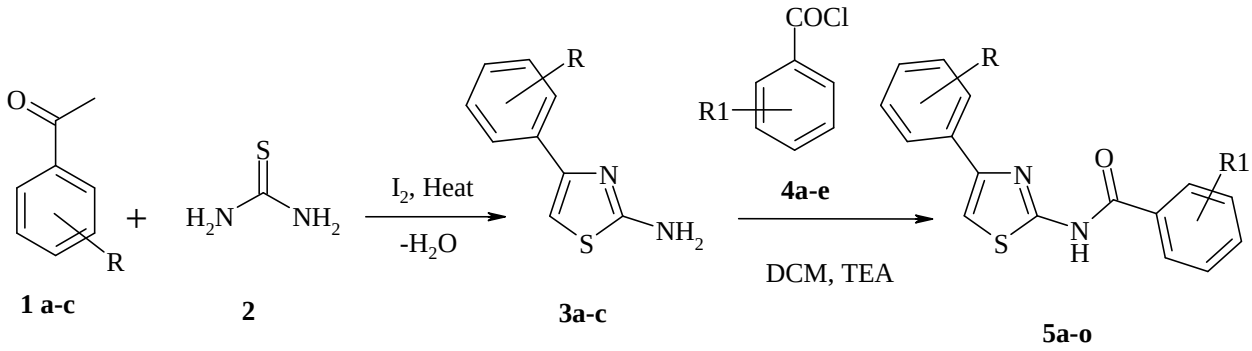
N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl] -4-chlorobenzamide (5m):
Yield: 69 %, m.p.: 201-203 ºC, **FT IR (KBr):** 3381cm^{-1} (NH str), 2963.56 cm^{-1} (CH Ar. str), 1676 cm^{-1} (C=O), 1207.12 cm^{-1} (C-N); **^{1}H NMR (DMSO) (ppm):** 6.72 (s, 1H, thiazole C_4), 7.28-7.36 (t, 1H, C'_5), 7.58-7.71 (m, 3H,

C′$_{6,}$ C″$_{3, 5}$), 7.82 (d *J= 7.9 Hz*, 1H, C′$_4$), 7.98 (s, 1H, C′$_2$), 8.06 (d *J= 11.6 Hz*, 2H, C″$_{2, 6}$), 8.9 (bs, 1H, NH); **ESI-MS** (m/z): 349 $[M+H]^+$.

N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl]-3-trifluromethylbenzamide (5n):
Yield: 59 %, m.p.: 233-236 ºC, **FT IR (KBr):** 3313cm^{-1} (NH str), 2975.56 cm^{-1} (CH Ar. str), 1652 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.52 (s, 1H, thiazole C$_4$), 7.31-7.39 (m, 1H, C′$_5$), 7.6-7.74 (m, 3H, C′$_{4, 6,}$ C″$_5$), 7.85-8.1 (m, 3H, C′$_{2,}$ C″$_{4, 6}$), 8.3 (d *J= 8.6 Hz*, 1H, C″$_2$), 8.95 (bs, 1H, NH); **ESI-MS** (m/z): 383 $[M+H]^+$.

N-[4-(3-chlorophenyl)-1, 3-thiazol-2-yl]-3-nitrobenzamide (5o):
Yield: 62 %, m.p.: 196-198 ºC, **FT IR (KBr):** 3366cm^{-1} (NH str), 2998.56 cm^{-1} (CH Ar. str), 1695 cm^{-1} (C=O); **^{1}H NMR (DMSO) (ppm):** 6.53 (s, 1H, thiazole C$_4$), 7.34-7.4 (m, 1H, C′$_5$), 7.5-7.64 (m, 2H, C′$_{6,}$ C″$_5$), 7.8-8.2 (m, 3H, C′$_{2, 4,}$ C″$_6$), 8.36 (d *J=9.4 Hz*, 1H, C″$_4$), 8. 6 (d *J=9.9 Hz*, 1H, C″$_2$), 9.2 (bs, 1H, NH); **ESI-MS** (m/z): 360 $[M+H]^+$.

RESULTS AND DISCUSSION



SCHEME 1: Scheme involved in the synthesis of thiazolamides 5a-o

3.1 Chemistry

The synthetic route of the thiazole amide derivatives is outlined in **Scheme. 1**. Acetophenone was heated with thiourea in presence of iodine to obtain 2-amino-4-(substituted) phenylthiazole (**3a-c**). Continuous stirring at room temperature of compound (**3a-c**) with substituted benzoyl chlorides (**4a-e)** in dimethyl formamide and diisopropyl ethylamine afforded N-(4-phenyl-1, 3-thiazol-2-yl)-benzamide (**5a-o**) in good yields, which were purified by passing through silica gel using 20% v/v ethyl acetate in hexane as eluent. The physical properties of the synthesized compounds are listed in the **Table 1**. The structure of the synthesized compounds was confirmed by FT IR, Mass and ^{1}H NMR spectral analysis. FT IR spectrum of compound **3a-c** (KBr) showed absorption bands at ~3400.00 cm^{-1}, ~ 3350 cm^{-1} accounting for asymmetric stretching and symmetric primary amine stretching respectively. Band for CH aromatic stretching appeared in the range of 3100-3000 cm^{-1} and stretching for C=C observed at ~1600 cm^{-1}. ^{1}H NMR spectrum of compound **3a-c** confirmed the formation of 2-aminothiazole, all the aromatic protons of 4-phenyl group resonated in the range of δ 7.34-7.78 as exemplified by **3a** in which a doublet at δ 7.78, triplets at δ 7.34 and δ 7.45 were found. C$_4$ proton of thiazole was observed little downfield at δ 6.74 and a broad singlet at δ 4.0 resultant of NH resonance. The molecular ion peak [m/z] at 177.2 in mass spectrum of compound **3a** found to be in conformity with the molecular formula of the assigned structure. Reaction of compound **3a-c** with benzoyl chlorides **4a-e** led to formation of N-(4-phenyl-1, 3-thiazol-2-yl)-benzamide derivative **5a-o**. The FT IR spectrum of **5a** showed an absorption frequency at 3383 cm^{-1} due to the stretching of amide group. A band at 1659 cm^{-1} observed which could be due to carbonyl stretching of amide group. ^{1}H NMR of compound **5a** also confirmed the formation of amide by the appearance of NH peak at down field values at δ 8.7 as broad singlet. Protons of phenyl group resonated in the range of δ 7.30-8.16. The molecular ion peak [m/z] at 281 in mass spectrum of compound **5a** found to be in conformity with the molecular formula of the assigned structure.

3.2 Biological activity

All the compounds were subjected to anti-inflammatory activity by paw edema method using Diclofenac sodium as standard. All the fifteen synthesized thiazole benzamide derivatives **5a-o** showed promising anti-inflammation activities, as represented in **Table 2** and the results were compared against blank and standard drug.

Table 1: Physical properties of N-(4-phenyl-1, 3-thiazol-2-yl)-benzamide

Comp. No	Mol.For.	Mol.Wt.	Yield (%)	m.p. (°C)	Rf	cLogP
5a	$C_{16}H_{12}N_2OS$	280.34	64	175-180	0.48	3.98
5b	$C_{16}H_{11}FN_2OS$	298.33	61	192-198	0.48	4.15
5c	$C_{16}H_{11}ClN_2OS$	314.79	53	190-194	0.49	4.72
5d	$C_{17}H_{11}F_3N_2OS$	348.34	62	228-230	0.51	4.94
5e	$C_{16}H_{11}N_3O_3S$	325.34	68	180-185	0.53	3.83
5f	$C_{16}H_{11}ClNOS$	314.03	66	181-183	0.54	4.70
5g	$C_{16}H_{10}ClFN_2OS$	332.72	58	220-224	0.52	4.87
5h	$C_{16}H_{10}Cl_2N_2OS$	347.99	69	201-203	0.51	5.44
5i	$C_{17}H_{10}ClF_3N_2OS$	382.02	59	233-236	0.55	5.66
5j	$C_{16}H_{10}ClN_3O_3S$	359.7	64	196-198	0.46	4.55
5k	$C_{16}H_{11}ClN_2OS$	314.80	71	196-198	0.63	4.70
5l	$C_{16}H_{10}ClFN_2OS$	332.78	73	186-189	0.68	4.87
5m	$C_{16}H_{10}Cl_2N_2OS$	347.23	63	205-207	0.69	5.44
5n	$C_{17}H_{10}ClF_3N_2OS$	382.79	72	184-187	0.49	5.66
5o	$C_{16}H_{10}ClN_3O_3S$	359.01	70	210-214	0.62	4.55

All the compounds exhibited increase in anti-inflammatory activity from 1st hour till 3rd hour after carrageenan administration, ten compounds showed decrease in activity in 4th hour where as six compounds demonstrated further increase in anti-inflammatory activity even in the 4th hour. Six compounds displayed greater than 50% paw edema protection in the 3rd hour and six compounds in the 4th hour of the study.

The unsubstituted compound **5a** (R and R_1=H) possessed encouraging anti-inflammatory activity and peak activity was observed in the 4th hour. Substitution by 4F, 4Cl and $3CF_3$ at R_1 decreased the activity in the 1st and 2nd hour and significant increase in the activity was noticed in the 3rd hour for **5c** and **5d**. Compound **5e** demonstrated better activity in first and second hour and decreased activity in 3rd and 4th hour as compared to **5a**.

Table 2: Anti-inflammatory activity of 5a-o

S. No	R	R_1	% Inhibition at different intervals (hrs)			
			1	2	3	4
5a	H	H	24.3*	32*	49.9**	51.9**
5b	H	4F	23.4*	28.4*	45.5**	41.2*
5c	H	4Cl	20.6*	26.5*	53.2**	51.5**
5d	H	$3CF_3$	21.8*	25.3*	51.7**	49.9**
5e	H	$3NO_2$	28.4*	33.2*	42.6**	39.6*
5f	4Cl	H	22.6*	28.6*	45.5**	39.2*
5g	4Cl	4F	25.2*	27.6*	39.2*	35.6*
5h	4Cl	4Cl	24.6*	31.2*	51.2**	50.3**
5i	4Cl	$3CF_3$	29.6*	32.6*	52.2**	51.5**
5j	4Cl	$3NO_2$	23.2*	30.8*	48.6**	49.8**
5k	3Cl	H	21.6*	29.6*	47.5**	42.2**
5l	3Cl	4F	22.9*	39.8**	46.8**	41.9**
5m	3Cl	4Cl	23.4*	37.2**	52.1**	50.2**
5n	3Cl	$3CF_3$	21.5*	33.7*	56. 0***	55.7***
5o	3Cl	$3NO_2$	26.8*	30.5*	37.5**	38.3**
Standard			25.9*	32.4*	50.6**	59.7***

*Results expressed in mean ±SEM. (n=6). ANOVA follo wed by Dunnett's test. ***p<0.001, ** p<0.01, *p<0.05 when compared to control group.*

Substitution at R by 4Cl or 3Cl always reduced the activity in the first hour. Compounds **5g**, **5h** and **5i** exhibited enhanced activity in the first hour and compound **5j** along with **5f** showed reversal in activity in the same period when compared with unsubstituted compound **5a**. In the second hour, compound **5f, 5g** and **5j** found to possess inferior activity while compound **5h** and **5i** found to be with superior activity. Compounds **5f**, **5g** and **5h** have shown decreased activity in the third hour where as compounds **5i** and **5j** have demonstrated enhanced activity and the same profile as mentioned earlier could be observed in the fourth hour. The unsubstituted compound in this series **5f** displayed protection of rat paw swelling by 22.6% with a gradual increase in activity and the peak activity was observed in the third hour with 45.5% activity. Substitution at R_1 by various groups increased the activity in the first hour of carrageenan challenge. $3CF_3$ bearing compound **5i** was found to possess highest activity among all the synthesized compounds in the first hour. In the second hour, a marginal decrease in the anti-inflammatory activity

was observed among all **5f-5j** compounds, however a reversal in the activity profile was observed in third hour as compared to second hour activity data. All the four compounds in this series except **5g** showed increased activity as compared to **5f** and for **5g**, **5h** and **5i** the peak activity was observed in this study hour.

For the compounds bearing 3Cl group at R (**5k-5o**), substitution of 3Cl group has imparted mixed effects as compared to unsubstituted compounds (R=H, **5a-5e**). Only **5m** demonstrated enhanced activity as compared to **5c** in the first hour, surprisingly **5l**, **5m** and **5n** have found to show better activity over **5b**, **5c** and **5d** respectively in the second hour. Compounds **5l** and **5n** possessed better activity in third and fourth hour as compared to **5b** and **5d** and rest other compounds exhibited decreased activity when compared to respective compounds with R=H. Overall, substitution with CF_3 has enhanced the activity in all study compounds except **5n** indicating electron withdrawing groups may affect activity positively however this could be partially supported by NO_2 group.

CONCLUSION

In conclusion, fifteen 4-phenyl-1, 3-thiazol-2-yl-benzamide have been synthesized and characterized. These compounds were designed by modification of our reported urea derivatives containing a thiazole group. All the compounds have been subjected to anti-inflammatory activity in carrageenan induced rat paw edema model. Several compounds showed increase in activity trend from 1st hour and peak activity was observed in the 3rd hour for maximum compounds and few compounds exhibited peak activity in the 4th hour. One compound **5n** demonstrated 56.0% anti-inflammatory activity in the 3rd hour and found to be potent among all the compounds in the test dose. These compounds could be further modified to improve and to afford still potent molecules and those could be tested against p38 kinase in order to ascertain the mechanism of anti-inflammatory activity.

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LIST OF ABBREVIATIONS
Bnd = Bending
bs = Broad singlet
$CDCl_3$ = Chloroform (Deuteriated)
°C = Degree Centigrade
d = Doublet
DCM = Dichloromethane
DFG = Aspartate-phenylalanine-glycine
DMF = Dimethyl formamide
DMSO = Dimethyl sulfoxide
ED_{50} = Effective dose in 50% of species tested
h = Hour
IR = Infra red
^1H NMR = Proton nuclear magnetic resonance
LD_{50} = Lethal dose in 50% of species tested
m = Multiplet
m.p = Melting point
M.Wt = Molecular weight
min = Minutes
mL = Milli litres
mm = Millimetres
Mol = Moles
R_f = Retention factors
s = Singlet
spp = Species
str = Stretching
t = Triplet
TLC = Thin layer chromatography
µg = Microgram

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