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RESEARCH ARTICLE

Synthesis Characterization and Pharmacological Evaluation of Some Novel Trisubstituted Thiazole Derivatives

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ABSTRACT

Sets of trisubstituted thiazoles ***(AR-11a-AR-53a)*** were synthesized by reaction of substituted N-(morpholino/methoxyphenylpiperazin/methylpiperazine-1-yl-4-thiazol-5-carbonyl) benzamide **(3)** with (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-one), respectively. The (**3**) were synthesized by nucleophilic addition of benzoyl isothiocyanate /substituted benzoyl isothiocyanate and morpholino/methoxyphenylpiperazin/methylpiperazine-1-yl-4-thiazol-5-carbonyl in equimolar quantity at reflux temperature. The selected synthesized compounds from ***(AR-11a-AR-53a)*** were screened for their *in vivo* anti-inflammatory activity in carrageen in-induced rat hind paw oedema model at three graded doses employed at 10, 20 and 40 mg/kg body weight using Diclofenac sodium (10 mg/kg, 75 %) and ibuprofen (20 mg/kg, 74%) drug while other compounds were screened at single grad dose of 20 mg/kg. Among all the tested compounds ***AR-21a, AR-31a, AR-12a and AR-42a*** showed maximum anti-inflammatory activity of 70**%** protection at 20 mg/kg and 56% protection at 40 mg/kg to inflamed paw, while other compounds showed Moderate to less protection at 10 mg/kg, 20 mg/kg & 40 mg/kg to inflamed paw.

KEYWORDS

Thiazoles, Nitroimidazole, Inflammation, Anti-Inflammatory Activity

INTRODUCTION

Inflammation is one of the important processes involved in the defense of an organism and it may be a normal and essential response to any noxious stimulus that threatens the host and may diverge from a localized to a generalized response, involving the whole organism.[1,2] The stimulus may be external as with a burn, chemical irritation or mechanical trauma; or internal such as neoplasms, viruses or bacteria. Inflammation is the result of concentrated participation of a large number of vasoactive, chemolactic and proliferative factors at different stages and each type of stimulus provokes a characteristic prototype of response that represents a relatively minor variation on a theme. At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia) and pain.[3]

Inflammatory bowel disease is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. Number of mediators such as prostaglandins, cytokines and reactive oxygen species are proposed to be involved in the pathogenesis of the diseases.[4,5]

Multi-drug treatment of inflammatory conditions associated with microbial infections poses a

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unique problem especially for patients with impaired liver or kidney functions. Therefore from the pharmacoeconomic and patient compliance points of view, the monotherapy with a drug having both anti-inflammatory and antimicrobial activities is highly desirable.[6]

Many attempts have been made to find a cure for inflammatory diseases and as a result, many non-steroidal anti-inflammatory drugs such as phenylbutazone, oxyphenbutazone, diclofenac, ibuprofen, fenoprofen, indomethacin, benoxaprofen, benorylate, caprofen, tiopinac, ketoprofen and sulindac etc. are available in the market. These are more prevalent on chronic use and sometimes so severe that they can be fatal. This is an ugly facet of these invaluable therapeutic agents. This had geared the search for new and effective therapeutic agent, which could be used in the treatment of inflammation and pain.[7]

Various substituted thiazole have recently received attention of their diverse pharmacological properties, these includes anti-cancer, anti-inflammatory, anti-infective, anti-diabetic, anti-HIV, anti-viral, anti-fungal, anti-oxidant, anesthetics, antibacterial, hypoglycemic, anticonvulsant activities.[8,9,10]

Rajan S. Giri. *et al*.[11] reported a series of 2-(2,4-di substituted-thiazole-5- yl)-3-aryl-3H-quinaz oline-4-one derivatives and evaluated for their inhibitory activity towards transcription factors TNFk B and AP-1 mediated transcriptional activation in a cell line based *in vitro* assay and for their anti-inflammatory activity in *in vivo* model of acute inflammation. Sherif Rostom AF *et al.*[12] synthesized antipyrine moieties attached to poly substituted thiazole and 2, 5-disubstituted-1, 3, 4-thiadiazole through various linkages and evaluated for their anti-inflammatory activity using the formalin-induced paw edema and the turpentine oil-induced granuloma pouch bioassays. Jagabandhu Das *et al*.[13] reported a series of structurally novel aminothiazole based small molecule inhibitors of Itk, some compound identified as a potent and selective Itk inhibitor which reported to reduce lung inflammation in a mouse model of ovalbumin induced allergy/asthma. Taterao M. Potewar *et al*.[14] were also reported a highly efficient and rapid synthesis of 2-amino-4-arylthiazoles and 2-methyl-4-arylthiazole from a bromoketone and thiourea / thioamide was described using room temperature ionic liquid at ambient conditions. This methodology is successfully applied for a practical synthesis of an antiinflammatory agent, Fanetizole.

Sang Geon Kim *et al.*[15] were also prepared the derivatives of thiazoles, including thiazole, benzothiazole and benzothiadiazole as intermediates in the production of a number of therapeutic agents. Benzothiazole derivatives exhibit analgesic and anti-inflammatory activities, possibly through the mechanism of 5-1ipoxygenase and thromboxane synthetase inhibition. Other benzothiazole compounds have gastric antisecretory activity or an anthelmintic effect. Shaohua Chang *et al*.[16] designed a new series of 2-substitute d thiazole carboxamides were identified as potent pain inhibitors against all three isoforms of Akt (Akt1, Akt2 and Akt3) by systematic optimization of weak screening hit N -(1-amino-3-phenylpropan-2-yl)-2-phenylthi-azole-5-carboxamide. The inhibitors might serve as lead compounds for further development of novel effective anticancer agents.

Moreover Jin-Hun Park *et al*.[17] designed a series of new imidazo [2, 1- b] thiazole derivatives and *in vitro* antiproliferative activities against A375P human melanoma cell line and NCI-60 cell line panel were tested. Some compounds showed superior potency against A375P to sorafenib. Cristina Mariana *et al.*[18] designed and reported series of novel acyl-hydrazones bearing 2-aryl-thiazole moiety by the condensation between derivatives of 4-[2-(4 -methyl-2phenyl-thiazole-5-yl)-2-oxo-ethoxy]-benzaldehyde and 2, 3 or 4-(2-aryl-thiazol-4-ylmethoxy)-benzaldehyde, respectively and different carboxylic acid hydrazides. These compounds were tested *in vivo* for their anti-inflammatory activity, in an acute experimental inflammation.

Prakash K *et al.*[19] synthesized series of novel 4-aryl/chloroalkyl-2-(2, 3, 5-trichlorophenyl)-1, 3-thiazoles by condensing 2, 3, 5-

trichlorobenzenecarbothioamide with phenacyl bromide/dichloroacetone. 2, 3, 5-trichlorobenzaldehyde thiosemicarbazone on treatment with phenacyl bromide afforded 4-aryl-2-(2, 3, 5-trichlorophenylidenehydrazino)-1, 3-thiazoles in good yield. These compounds were also screened for their antibacterial and antifungal activities.

Based on through envisaged and importance the emergence of challenging diseases associated with inflammatory conditions leads to development of novel series of substituted thiazole compound. Development was made taking into account of recent approaches in synthesis of thiazole containing drug proposed to act as excellent agent with multiple pharmacological response.

MATERIAL AND METHODS

Chemistry

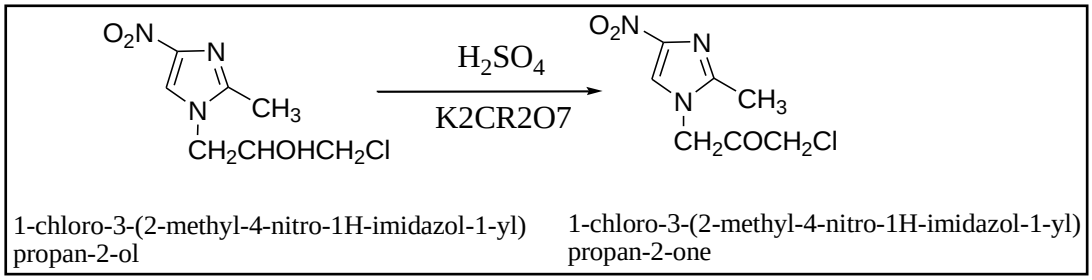
All reagents and solvents were used as obtained from the supplier or recrystallized/ redistilled as necessary. Thin layer chromatography was performed on microscopic slides coated with silica gel G and and toluene: methanol as a mobile phase. The spots were visualized by normal TLC and exposure to iodine vapour. Melting points were recorded on open capillary melting point apparatus and were uncorrected. IR spectra were recorded in KBr on SHIMADZU Fourier Transform Infrared 8400 S spectrophotometer. Mass spectra were recorded on Electron impact (EI) on a Jeol JMS-D-300 spectrometer with the ionization potential of 70 eV. Nuclear Magnetic Resonance spectra (^{1}H NMR) were recorded in DMSO-d6 on Bruker advance at 400 MHz using Tetramethyl silane (TMS) as internal standard and the chemical shift (δ) were reported in parts per million (ppm). Elemental analysis data were determined using a Carlo-Erba 1108 instrument or Elementar's Vario EL III micro-analyzer.

Synthesis of novel (1-chloro-3-(2-methyl-4-nitro1h-imidazole-1-yl) propane-2-on)[20]

20 g (0.09 mol) of (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-ol) and 14 g (0.045mol) of potassium dichromate were placed in conical flask. To the reaction flask sulfuric acid was added dropwise at reduced temperature (15-20 °C). Once the mixture turned greenish to greenish black, stirring was started for 20 hour. The reaction container was removed and reaction mixture was transferred in to 200 mL of water. Reaction mixture was set aside for five days to obtained solid crystals of oxidized form (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-ol). Filtered& washed with water & dried at 60-70 °C in an oven. The yield of solid was obtained 5 g. The melting point was recorded 151-152 °C.[21] Percentage Yield: 46 %, Melting point: 122 °C TLC: Toluene: Methanol (8.5: 1.5 Rf Value: 7.6)

General Method for Synthesis of Compounds (*AR-11a-AR-53a)*

As shown in Scheme II, isothiocyanate (***2***) were obtained by stirring ammonium thiocyanate (0.1379 mol) in 100 mL acetone at room temperature with benzoyl chloride/substituted benzoyl chloride (0.1263 mol) for 15-25 minutes followed by refluxing the reaction mixture for 15 min. Substituted N- (Morpholino/4-methoxy-phenylpiperazinyl/N-methylpiperazinyl-4-thioyl) benzamide (***3***) were synthesized by



1-chloro-3-(2-methyl-4-nitro-1H-imidazol-1-yl) propan-2-ol

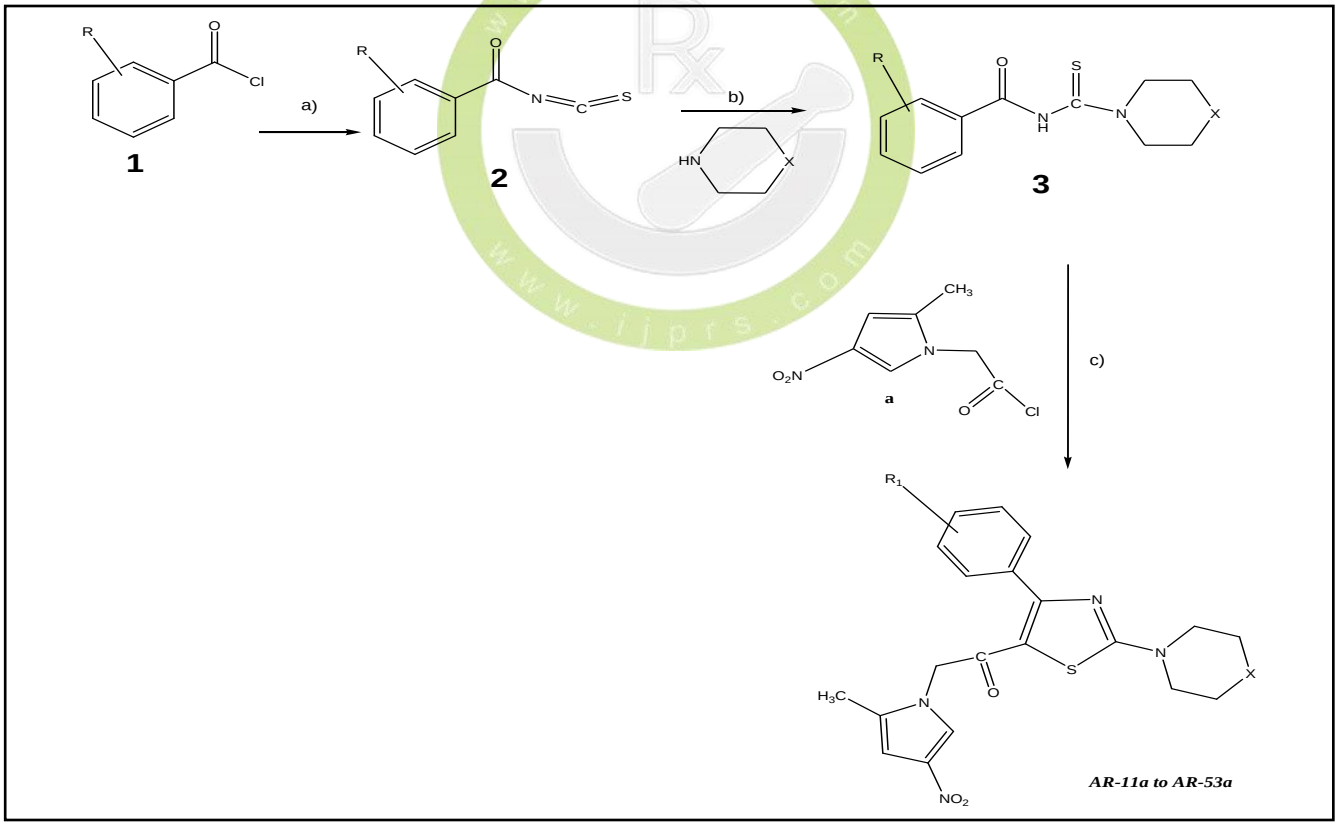
1-chloro-3-(2-methyl-4-nitro-1H-imidazol-1-yl) propan-2-one

Scheme I: Synthesis of (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on) Reagents and conditions: a) Stirred for 20 hr (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-ol) $K_2cr_2O_7$, H_2SO_4

nucleophilic addition of benzoyl isothiocyanate /substituted benzoyl isothiocyanate and morpholine/4-methoxyphenylpiperazine/4-methylpiperazine in equimolar quantity at reflux temperature. The compounds (***AR-11a-AR-53a***) were synthesized as per procedure reported by Reji *et al*[21.] In brief the 1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on ***(a)*** was added in equimolar quantity to a solution of adduct (substituted N-(Morpholino/4-methoxy-phenylpiperazinyl/N-methylpiperazinyl-4-thioyl) benzamide ***(3)*** in 10 mL acetonitrile. The reaction mixture was heated on a water bath at 100^0C for 5 hr. The reaction mixture was cool and filtered. To the filtrate a pinch of sodium bicarbonate was added. Yellow precipitates thus obtained were filtered, wash with water, air dried and purified by recrystallization corresponding to the (***AR-11a-AR-53a***) and was characterized as per the analytical data.[22,23,24]

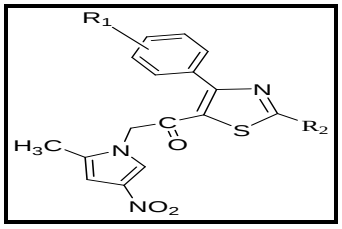
AR-11a: 2-(2-methyl-4-nitro-1H-imidazol-1-yl)-1-(2-morpholino-4-phenylthiazol-5-yl) ethanone

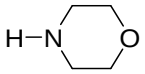
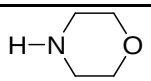
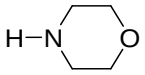
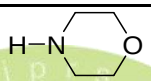
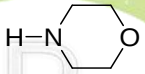
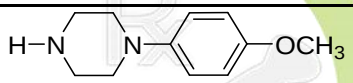
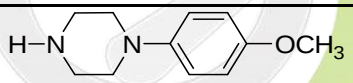
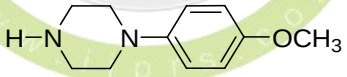
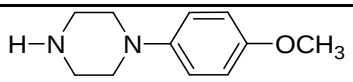
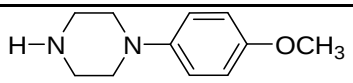
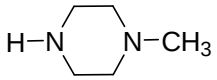
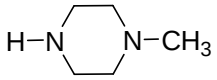
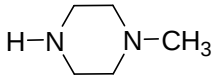
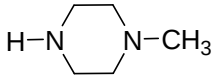
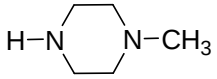
IR (KBr,Cm[1]): 3150 (aromatic stretching), 2820 (-CH_3 stretching), 1626 (C=O stretching), 1444 (C=C stretching, aromatic), 1392 (NO_2-stretching), 1305 (N-C of aromatic), 908 (-C=C out of plane for benzene), 1120 (C-O-C stretching of morpholine).,[1]H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.4 (t, 4H, morpholine N-CH_2), 3.3-3.6 (t, 4H, morpholine O-CH_2), 2.42 (s, 3H proton at 2[nd] position of nitroimidazole –CH_3) 4.8 (s, 2H, –CH_2-C=O), 7.2-7.5-8 (m, 5H, aromatic proton at 4[th] position), 7.6 (s, 1H, aromatic proton at 5[th] position of nitroimidazole), MS: m/z., 413.20, 414 (M+1) Anal for $C_{19}H_{19}N_5O_4S$: Calculated C, 55.19; H, 4.63; N, 16.44 Found: C, 54.15; H, 4.43; N, 16.74;



Scheme II: Synthesis of 3-(4-(substituted) phenyl-2-morpholine/methoxyphenylpiperazin/methyl-piperazine -1-yl-4-thiazol-5-carbonyl). Reagents and conditions: a) NH4SCN, acetone, reflux 15-25 min; b) reflux for 20 min, pour reaction mixture to crushed ice; c) acetonitrile, stir at 100°C for 5 h, pour to crush

Table 1: Physicochemical properties of synthesized compound



Compound	R_1	R_2	Melting Point	Rf Value	% Yield
AR-11-a	Benzoyl chloride		178-180	0.63	62%
AR-21-a	*p*-Chlorobenzoyl chloride		196-196	0.64	58%
AR-31-a	*o*-Chlorobenzoyl chloride		152-154	0.64	71%
AR-41-a	*m*-Chlorobenzoyl chloride		154-158	0.64	62%
AR-51-a	Furoyl chloride		218-220	0.69	68%
AR-12-a	Benzoyl chloride		208-210	0.54	49%
AR-22-a	*p*-Chlorobenzoyl chloride		170-172	0.56	48%
AR-32-a	*o*-Chlorobenzoyl chloride		177-179	0.55	64%
AR-42-a	*m*-Chlorobenzoyl chloride		172-174	0.57	60%
AR-52-a	Furoyl chloride		196-198	0.62	82%
AR-13-a	Benzoyl chloride		156-158	0.63	55%
AR-23-a	*p*-Chlorobenzoyl chloride		154-156	0.62	61%
AR-33-a	*o*-Chlorobenzoyl chloride		162-163	0.58	55%
AR-43-a	*m*-Chlorobenzoyl chloride		168-170	0.64	70%
AR-53-a	Furoyl chloride		158-160	0.49	61%

AR-21a: 1-(4-(4-chlorophenyl)-2-morpholino-thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^1): 3130 (aromatic stretching), 2880 (-CH_3 stretching), 1660 (C=O stretching), 1510-1461 (C=C stretching, aromatic), 1450-1392 (NO_2- stretching), 1308 (N-C of aromatic), 827-914 (-C=C out of plane for mono substituted benzene), 1119 (C-O-C stretching of morpholine), 670 (-C-Cl Bending)^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.47 (t, 4H, morpholine N-CH_2), 3.45-3.76 (t, 4H, morpholine O-CH_2) 3.32 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.40 (s, 2H, –CH_2-C=O), 7.35-7.59 (m, 4H, aromatic proton at 4th position), 8.1 (s, 1H, aromatic proton at 5th position of nitroimidazole) MS: m/z., 447, 448 (M+1)., Anal for $C_{19}H_{18}ClN_5O_4S$: Calculated: C, 50.95; H, 4.05; N, 15.64; Found: C, 50.65; H, 4.15; N, 14.65

AR-31a: 1-(4-(2-chlorophenyl)-2-morpholino-thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^1): 3137 (aromatic stretching), 2890 (-CH_3 stretching), 1640 (C=O stretching), 1531-1446 (C=C stretching, aromatic), 1494-1392 (NO_2- stretching), 1308 (N-C of aromatic), 907(-C=C out of plane for mono substituted benzene), 1144-1120 (C-O-C stretching of morpholine), 650 (-C-Cl Bending)^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.29-2.56 (t, 4H, morpholine N-CH_2), 3.45-3.76 (t, 4H, morpholine O-CH_2), 3.32 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.42 (s, 2H, –CH_2-C=O), 7.32-7.39 (m, 4H, aromatic proton at 4th position), 7.98 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 447.08.20, 448 (M+1)., Anal for $C_{19}H_{18}ClN_5O_4S$: Calculated C, 50.95; H, 4.05; Cl, 7.92; N, 15.64; Found: C, 50.55; H, 4.05; N, 15.44.

AR-41a: 1-(4-(3-chlorophenyl)-2-morpholino-thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^1): 3204 (aromatic stretching), 2904 (-CH_3 stretching), 1704 (C=O stretching), 1530-1463 (C=C stretching, aromatic), 1469 (NO_2-stretching), 1342-1290 (N-C of aromatic), 836 (-C=C out of plane for mono substituted benzene), 1112 (C-O-C stretching of morpholine), 668 (-C-Cl Bending) ^{1}H NMR:(400 MHz, DMSO-d6)δ (ppm): 2.46 (t, 4H, morpholine N-CH_2), 3.45-3.76 (t, 4H, morpholine O-CH_2), 3.32 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.40 (s, 2H, –CH_2-C=O), 7.36-7.99 (m, 4H, aromatic proton at 4th position), 8.02 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 447.08, 448 (M+1)., Anal for $C_{19}H_{18}ClN_5O_4S$: Calculated: C, 50.95; H, 4.05; Cl, 7.92; N, 15.64 Found: C, 49.85; H, 4.05; N, 15.54

AR-51a: 1-(4-(furan-2-yl)-2-morpholinothiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^1): 2979 (-CH_3 stretching), 1660 (C=O stretching), 1469-1446 (C=C stretching, aromatic), 1329 (NO_2- stretching), 1241 (N-C of aromatic), 1115 (C-O-C stretching of morpholine), 1018 (C-O-C stretching of furan) ^{1}H NMR:(400 MHz, DMSO-d6)δ (ppm): 2.29 (t, 4H, morpholine N-CH_2), 3.52-3.381 (t, 4H, morpholine O-CH_2), 3.32 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.4 (s, 2H, –CH_2-C=O), 7.32-7.39 (m, 3H, aromatic proton of Furoyl at 4th position), 7.98 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 403.1, 404 (M+1)., Anal for $C_{17}H_{17}N_5O_5S$: Calculated: C, 50.61; H, 4.25; N, 17.36 Found: C, 50.51; H, 4.15; N, 16.38

AR-12a: 1-(2-(4-(4-methoxyphenyl) piperazin-1-yl)-4-phenylthiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^1): 3100 (aromatic stretching), 2800 (-CH_3 stretching), 1630 (C=O stretching), 1546 (C=C stretching, aromatic), 15303 (NO_2-stretching), 1246-1226 (-OCH_3- stretching), 1332 (N-C of aromatic), 833 (-C=C out of plane for mono substituted benzene), 1153 (C-N-C stretching of phenyl piperazine) ^{1}H NMR:(400 MHz, DMSO-d6)δ (ppm): 2.16 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.01-3.31 (m, 8H, piperazine), 3.70 (s, 3H, O-CH_3), 5.47 (s, 2H, –CH_2-C=O), 6.8-6.95 (m, 4H, aromatic proton of 4-methoxyphenyl) 7.40-7.65 (m, 5H,

aromatic proton at 4th position), 8.0 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 518, 519 (M+1) , Anal for $C_{26}H_{26}N_6O_4S$: Calculated: C, 60.22; H, 5.05; N, 16.21; Found: C, 59.95; H, 5.05; N, 16.12;

AR-22a: 1-(4-(4-chlorophenyl)-2-(4-(4-methoxyphenyl) piperazin-1-yl) thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr,Cm[1]).,3100 (aromatic stretching), 2800 (-CH3stretching), 1750 (C=O stretching), 1592 (C=C stretching, aromatic), 1546-1502 (NO_2-stretching), 1270-1253 (-OCH_3- stretching), 1310 (N-C of aromatic), 909-831 (-C=C out of plane for mono substituted benzene), 1114-1013 (C-N-C stretching of phenyl piperazine), 750 (-C-Cl Bending) ., ^{1}H NMR:(400 MHz, DMSO-d6)δ (ppm): 2.42 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.33-3.65 (m, 8H, piperazine), 4.21 (s, 3H, O-CH_3), 4.91 (s, 2H, –CH_2-C=O), 7.40-7.52 (m, 4H, aromatic proton of 4-methoxyphenyl) 7.77-7.811 (m, 4H, aromatic proton at 4th position), 7.15 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 552.13, 553 (M+1), Anal for $C_{26}H_{25}ClN_6O_4S$: Calculated: C, 56.47; H, 4.56; Cl, 6.41; N, 15.20; Found: C, 55.47; H, 4.16; Cl, 6.41; N, 15.30;

AR-32a: 1-(4-(2-chlorophenyl)-2-(4-(4-methoxyphenyl) piperazin-1-yl) thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm[1]): 3140 (aromatic stretching), 2900-2830 (-CH_3 stretching), 1690-1700 (C=O stretching), 1529 (C=C stretching, aromatic), 1502-1449 (NO_2- stretching), 1269-1248 (-OCH_3- stretching), 1310 (N-C of aromatic), 860-820 (-C=C out of plane for mono substituted benzene), 1166-1030 (C-N-C stretching of phenyl piperazine), 748 (-C-Cl Bending)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.37 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.08-3.87 (m, 8H, piperazine), 4.28 (s, 3H, O-CH_3), 4.90 (s, 2H, –CH_2-C=O), 6.79-6.94 (m, 4H, aromatic proton of 4-methoxyphenyl) 7.3-7.54 (m, 4H, aromatic proton at 4th position), 8.21 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 553, 554 (M+1)., Anal for $C_{26}H_{25}ClN_6O_4S$: Calculated: C, 56.47; H, 4.56; Cl, 6.41; N, 15.20 Found: C, 55.47; H, 4.46; N, 15.20;

AR-42a: 1-(4-(3-chlorophenyl)-2-(4-(4-methoxyphenyl) piperazin-1-yl) thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm[1]): 3120 (aromatic stretching), 2830 (-CH_3 stretching), 1700 (C=O stretching), 1529 (C=C stretching, aromatic), 1502 (NO_2-stretching), 1269 (-OCH_3- stretching), 1310 (N-C of aromatic), 860-820 (-C=C out of plane for mono substituted benzene), 1182 (C-N-C stretching of phenyl piperazine), 682 (-C-Cl Bending)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.42 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.10-3.38 (m, 8H, piperazine), 3.70 (s, 3H, O-CH_3), 5.48 (s, 2H, –CH_2-C=O), 6.7-6.95 (m, 4H, aromatic proton of 4-methoxyphenyl) 7.48-7.65 (m, 4H, aromatic proton at 4th position), 7.21 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 553, 554 (M+1)., Anal for $C_{26}H_{25}ClN_6O_4S$: Calculated: C, 56.47; H, 4.56; Cl, 6.41; N, 15.20 found: C, 55.97; H, 4.46; N, 15.20;

AR-52a: 1-(4-(furan-2-yl)-2-(4-(4-methoxy-phenyl) piperazin-1-yl) thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm[1]): 3100 (aromatic stretching), 2829 (-CH_3 stretching), 1630 (C=O stretching), 1566-1536 (C=C stretching, aromatic), 1493-1462 (NO_2-stretching), 1331 (N-C of aromatic), 1152 (C-O-C stretching of morpholine), 1178 (C-O-C stretching of furan), 925-882 (-C=C out of plane for mono substituted benzene)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.42 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.47-3.76 (m, 8H, piperazine), 3.34 (s, 3H, O-CH_3), 5.46 (s, 2H, –CH_2-C=O), 6.66-6.76 (m, 4H, aromatic proton of 4-methoxyphenyl) 7.3-7.42 (m, 3H, aromatic proton of Furoyl at 4th position), 7.88 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 508, 509 (M+1) ., Anal for $C_{24}H_{24}N_6O_5S$: Calculated: C, 56.68; H, 4.76; N, 16.53 Found: C, 55.68; H, 4.46; N, 16.13;

AR-13a: 2-(2-methyl-4-nitro-1H-imidazol-1-yl)-1-(2-(4-methylpiperazin-1-yl)-4 phenylthiazol-5-

yl) ethanone

IR (KBr, Cm^{1}): 3151 (aromatic stretching), 2983-2948 (-C-H stretching) 2890-28081 (-CH_3 stretching), 1655 (C=O stretching), 1546 (C=C stretching, aromatic), 1489-1455 (NO_2- stretching), 1343 (N-C of aromatic), 832 (-C=C out of plane for mono substituted benzene), 1145-1139 (C-N-C stretching of methyl piperazine)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.27 (s, 1H –CH_3 Alkane piperazine) 2.44-2.45 (m, 8H, piperazine), 3.33 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 3.49 (s, 3H, O-CH_3), 5.46 (s, 2H, –CH_2-C=O), 7.47-8.18 (m, 5H, aromatic proton at 4th position), 7.13 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 426, 427 (M+1) ., Anal for $C_{20}H_{22}N_6O_3S$: Calculated: C, 56.32; H, 5.20; N, 19.70; Found: C, 55.22; H, 5.30; N, 18.90;

AR-23a: 1-(4-(4-chlorophenyl)-2-(4-methylpiperazin-1-yl) thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^{1}): 3141 (aromatic stretching), 2975-2943 (-C-H stretching) 2886-2808 (-CH_3 stretching), 1750-1667 (C=O stretching), 1546 (C=C stretching, aromatic), 1486-1446 (NO_2-stretching), 1339 (N-C of aromatic), 890-823 (-C=C out of plane for mono substituted benzene), 1142-1138 (C-N-C stretching of methyl piperazine), 652 (-C-Cl Bending)., ^{1}H NMR:(400 MHz, DMSO-d6-d6) δ (ppm): 2.27 (s, 1H –CH_3 Alkane piperazine) 2.06-2.59 (m, 8H, piperazine), 3.49 (s, s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.43 (s, 2H, –CH_2-C=O), 7.38-8.29 (m, 4H, aromatic proton at 4th position), 7.21 (s, 1H, aromatic proton at 5th position of nitroimidazole)., MS: m/z., 460, 461 (M+1)., Anal for $C_{20}H_{21}ClN_6O_3S$: C, 52.11; H, 4.59; N, 18.23; Found: C, 52.02; H, 4.29; N, 17.23;

AR-33a: 1-(4-(2-chlorophenyl)-2-(4-methy-lpiperazin-1-yl)thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^{1}): 3121 (aromatic stretching), 2975 (-C-H stretching) 2886 (-CH_3 stretching), 1667 (C=O stretching), 1549 (C=C stretching, aromatic), 1486 (NO_2- stretching), 1270 (N-C of aromatic), 890-823 (-C=C out of plane for mono substituted benzene), 1142-1138 (C-N-C stretching of methyl piperazine), 650 (-C-Cl Bending)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.15 (s, 1H –CH_3 Alkane piperazine) 2.54 (m, 8H, piperazine N-CH_2), 3.33 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.27 (s, 2H, –CH_2-C=O), 7.50-8.01 (m, 4H, aromatic proton at 4th position), 7.13 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 460, 461 (M+1)., Anal for $C_{20}H_{21}ClN_6O_3S$: Calculated: C, 52.17; H, 4.59; N, 18.23; found: C, 51.11; H, 4.79; N, 18.11

AR-43a: 1-(4-(3-chlorophenyl)-2-(4-methyl-piperazin-1-yl)thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone

IR (KBr, Cm^{1}): 3141-3118 (aromatic stretching), 2952 (-C-H stretching) 2836 (-CH_3 stretching), 1687-1666 (C=O stretching), 1546 (C=C stretching, aromatic), 1505-1494 (NO_2-stretching), 1300-1350 (N-C of aromatic), 807 (-C=C out of plane for mono substituted benzene), 1142-1138 (C-N-C stretching of methyl piperazine), 622 (-C-Cl Bending)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.10 (s, 1H –CH_3 Alkane piperazine) 2.42-2.52 (m, 8H, piperazine), 3.35 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.30 (s, 2H, –CH_2-C=O), 7.51-8.30 (m, 4H, aromatic proton at 4th position), 7.23 (s, 1H, aromatic proton at 5th position of nitroimidazole), MS: m/z., 460, 461 (M+1)., Anal for $C_{20}H_{21}ClN_6O_3S$: Calculated: C, 52.11; H, 4.59; N, 18.23; found: C, 52.14; H, 4.49; N, 18.13;

AR-53 a: 1-(4-(furan-2-yl)-2-(4-methyl-piperazin-1-yl)thiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl)ethanone

IR (KBr,Cm^{1}): 3110 (aromatic stretching), 2978 (-C-H stretching) 2818 (-CH_3 stretching), 1685 (C=O stretching), 1546 (C=C stretching, aromatic), 1489-1455 (NO_2- stretching), 1343 (N-C of aromatic), 1168 (C-O-C stretching of furan), 832 (-C=C out of plane for mono substituted benzene), 1145-1139 (C-N-C stretching of methyl piperazine)., ^{1}H NMR:(400 MHz, DMSO-d6) δ (ppm): 2.22 (s, 1H –CH_3

Table 2: Anti-inflammatory activity carrageenan- induced rat hind paw oedema % protection

Compound	Dose mg/kg	I hr	II hr	III hr
AR-11-a	10	20.19	19.41	5.20
AR-11-a	20	52.68	49.92	35.42
AR-11-a	40	67.51	62.28	48.67
AR-21-a	10	68.77	70.27	64.37
AR-21-a	20	39.43	51.33	52.60
AR-21-a	40	51.10	48.98	49.10
AR-31-a	10	42.27	54.30	61.29
AR-31-a	20	69.72	67.29	68.29
AR-31-a	40	43.22	33.49	38.18
AR-41-a	10	34.38	36.13	-0.106
AR-41-a	20	39.74	28.16	30.01
AR-41-a	40	-15.45	-5.79	-15.9
AR-51-a	10	51.47	56.02	53.86
AR-51-a	20	59.97	48.2	41.24
AR-51-a	40	61.23	55.55	56.62
AR-12-a	20	76.67	75.43	73.17
AR-22-a	20	60.91	35.68	18.34
AR-32-a	20	61.54	58.05	51.11
AR-42-a	20	88.65	87.94	73.38
AR-52-a	20	53.35	58.52	53.65
AR-13-a	20	43.26	64.78	70.62
AR-23-a	20	34.12	-22.92	33.18
AR-43-a	20	76.04	67.91	63.52
Std. Diclofenac	10	77.87	74.64	76.45
Std. Ibuprofen	20	76.24	75.21	74.23

Oral administration for all test compounds, $P < 0.05$, Student's t-test versus controls, the standard drugs (dose and % protection) were Diclofenac sodium (10 mg/kg, 75 %) and ibuprofen (20 mg/kg, 74%)

Alkane piperazine) 2.55 (m, 8H, piperazine), 3.32 (s, 3H proton at 2nd position of nitroimidazole –CH_3) 5.46 (s, 2H, –CH_2-C=O), 7.61-8.21 (m, 3H, aromatic proton of furoyl at 4th position), 7.13 (s, 1H, aromatic proton at 5th position of nitroimidazole)., MS: m/z., 416, 417,418 (M+1)., Anal for $C_{18}H_{20}N_6O_4S$: Calculated: C, 51.91; H, 4.84; N, 20.18; found: C, 51.21; H, 4.44; N, 19.80;

Pharmacological Screening

Animals: Albino rats (150–250 g) of either sex were provided with pellet diet (Lipton, India) and water *ad libitum* and kept under standard laboratory condition at 25 ± 2ºC.The experimental protocol was approved by the institutional ethics committee constituted *[RCPIPER/IAEC/2013-14/09]*by the Ministry of Social Justice and Empowerment, (Government of India).

Anti-Inflammatory Activity

We have used the method previously described by Winter et *al*[25]. The animals were studied for toxicity of DMSO up to 10% v/v in saline, and 5% DMSO was selected as a vehicle to suspend the standard drugs and the test compounds. Albino rats of either sex weighing between 150 - 250 g were starved for 18 hours prior to the experiment. The animals were weighed, marked for identification and divided into groups of six. The standard drug, diclofenac sodium (10 mg/kg body weight) and ibuprofen (20 mg/kg body weight) and the test compounds were given orally (10, 20 and 40 mg/kg body weight) as a suspension using 5% DMSO as a vehicle. One hour later foot paw oedema was induced by injecting 0.1 mL of 1% carrageenin subcutaneously into the planter portion of the right hind paw of each rat. Initial foot paw volume was measured immediately by mercury plethysmometer.

Oedema was measured three hours after carrageenin administration. The swelling in test group animals was used to calculate the percent inhibition ± SEM of oedema achieved by the compound at the test dose compared with the vehicle control group. The % protection of oedema was calculated according to the formula, % anti-inflammatory activity = 100 x (1-Vt/Vc) where, Vt and Vc were the volume of oedema in test compounds and control groups, respectively.[26]

RESULTS AND DISCUSSION

Novel trisubstituted thiazole analogues (***AR-11a-AR-53a***) were designed and synthesized. The synthesized compounds (***AR-11a-AR-53a***) were evaluated for their *in vivo* anti-inflammatory activity. The *in vivo* anti-inflammatory activity was performed in carrageenin-induced rat hind paw oedema model at three graded doses employed at 10, 20 and 40 mg/kg body weight using diclofenac sodium and Ibuprofen. The chemical structures of these compounds results of *in vivo* anti-inflammatory activity are shown in table **1** and **2** respectively. Taking into account the assorted biological activities of (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on derivatives as important member of antiprotozoal agent was used at fifth position of thiazole, However it is evident that anti-inflammatory activities of thiazole derivatives are extensively reported and clinically proved. The compounds (***AR-11a-AR-53a***) were designed and synthesized by keeping (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on at fifth position and morpholin/ methoxy-phenylpiperazinyl / methylpiperazinyl moiety at second position of thiazole ring. The forth position of thiazole was substituted by introducing electron withdrawing group (–Cl), at different position in phenyl moiety.

The compounds ***(AR-12a to AR-53a)*** were synthesized having methoxy and methyl group at para position of phenylpiperazinyl and piperazinyl respectively to explore the effect of presence of substituted aromatic ring and aliphatic chain on biological activity of profile of the candidate.

The compounds ***(AR-11a to AR-51a)*** were synthesized having morpholin ring at second position of thiazole. Among all the tested compounds ***AR-21a, AR-31a, AR-12a*** *and* ***AR-42a*** showed maximum anti-inflammatory activity of 70% protection at 20 mg/kg and 56%

protection at 40 mg/kg to inflamed paw, while other compounds showed Moderate to less protection at 10 mg/kg, 20 mg/kg&40 mg/kg to inflamed paw.

In the series the first compound from each set were screened at three graded doses employed at 10, 20 and 40 mg/kg body weight using diclofenac sodium. While rest of the compounds were screened at single grade dose of 20mg/kg

In the series, ***AR-21a*** showed comparable anti-inflammatory activity at all the three graded doses employed, i.e. 64.76% at 10 mg/kg, 52.59% at 20 mg/kg and 49.09% at 40 mg/kg, for ***AR-31a*** the % protection was found to be 61.29% at 10 mg/kg, 68.29% at 20 mg/kg and 38.16% at 40 mg/kg, Similarly for ***AR-12a*** *and* ***AR-42a*** the % protection was displayed 73.17% and 73.38% at 20 mg/kg respectively which are the highest % protection among the mentioned series.

Other Compounds showed moderate to less activity as compared to above four compounds. All the targeted trisubstituted thiazole ***(AR-11a to AR-53a)*** were found to have moderate anti-inflammatory activity as compared to the standard drug diclofenac sodium and Ibuprofen, which showed 75% protection at 10 mg/kg dose and 74% protection at 20 mg/kg dose.

To summarize these findings, methyl substituent on piperazine moiety and *p*-chlorophenyl at second and forth position of thiazole respectively enhances lipophilicity & potency of tested compounds.

The presence of methoxyphenylpiperazinyl / methylpiperazinyl moiety and chlorophenyl at second and forth position of thiazole respectively enhances the anti-inflammatory activity. However all targeted trisubstituted thiazole containing (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on were found to have good to moderate anti-inflammatory activity, it is therefore, suggested that this scheme to be studied further to explore its full structure-activity relationship potential particularly single candidate as monotherapy in the treatment of chronic inflammatory diseases having both anti-inflammatory and antimicrobial activities.

CONCLUSION

The synthesized targeted compounds ***(AR-11a to AR-53a)*** were evaluated for their *in vivo* anti-inflammatory activity. On the basis of structure-activity relationship studies of ***(AR-11a to AR-53a)*** it can be concluded that presence of (–Cl) chloro substituted electron withdrawing group at different position in phenyl moiety at the fourth position of the thiazole contributes significantly to anti-inflammatory activity profile of the candidates, similarly by keeping (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on at fifth position it is predictable to have good anti-infective property which highly desirable to be evaluated.

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REFERENCES

1. Franklin, P. X., Pillai, A. D., Rathod, P. D., Yerande, S., Nivsarkar, M., Padh, H., & Sudarsanam, V. (2008). 2-Amino-5-thiazolyl motif: A novel scaffold for designing anti-inflammatory agents of diverse structures. *European Journal of Medicinal Chemistry*, *43*(1), 129-134.

2. Pillai, A. D., Rathod, P. D., Xavier, F. P., Padh, H., Sudarsanam, V., & Vasu, K. K. (2005). Tetra substituted thiophenes as anti-inflammatory agents: Exploitation of analogue-based drug design. *Bioorganic & Medicinal Chemistry*, *13*(24), 6685-6692.

3. Molvi, K. I., Mansuri, M., Sudarsanam, V., Patel, M. M., Andrabi, S. M. A., & Haque, N. (2008). Synthesis, anti-inflammatory,

analgesic and antioxidant activities of some tetrasubstituted thiophenes. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *23*(6), 829-838.

4. Molvi, K. I., Sudarsanam, V., Patel, M. M., & Haque, N. (2008). Design, synthesis and pharmacological evaluation of novel tetrasubstituted thiophene analogues as anti-inflammatory agents. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *23*(6), 819-828.
5. Molvi, K. I., Vasu, K. K., Yerande, S. G., Sudarsanam, V., & Haque, N. (2007). Syntheses of new tetrasubstituted thiophenes as novel anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *42*(8), 1049-1058.
6. Mansuri, M., Ahmed, A., Shaikh, A., Haque, N., Sheth, A. K., & Molvi, K. I. (2012). Synthesis, antibacterial, anti-inflammatory and antiplatelet activities of some trisubstituted thiazoles. *Inventi Rapid: Med Chem*., 4, 1-6
7. Bekhit, A. A., Hymete, A., Asfaw, H., & Bekhit, A. E. D. A. (2012). Synthesis and Biological Evaluation of Some Pyrazole Derivatives as Anti-Malarial Agents. *Archiv der Pharmazie*, *345*(2), 147-154.
8. Mohareb, R. M., Habashi, A., Ibrahim, N. S., & Sherif, S. M. (1987). Reaction of benzoyl isothiocyanate with active methylene reagents: a convenient synthesis of pyrazolo [5, 4-cÆyrazole, 1, 3-oxazine, thiazole and pyrimidine derivatives. *Synthesis*, (3), 228-231.
9. Shetty, N. S., Khazi, I. A. M., & Ahn, C. (2010). Synthesis, anthelmintic and anti-inflammatory activities of some novel imidazothiazole sulfides and sulfones. *Bull Korean Chem Soc*, *31*(8), 2337-2340.
10. Aejaz, A., Molvi, K. I., Sayyed, N., Shaikh, A. (2014). A Review on Thiazole: Recent Developments and Biological Activities. *Inventi Rapid: Med Chem*, 3, 1-19.
11. Giri, R. S., Thaker, H. M., Giordano, T., Williams, J., Rogers, D., Sudersanam, V., & Vasu, K. K. (2009). Design, synthesis and characterization of novel 2-(2, 4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-κB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *44*(5), 2184-2189.
12. Rostom, S. A., El-Ashmawy, I. M., El Razik, H. A. A., Badr, M. H., & Ashour, H. M. (2009). Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents. *Bioorganic & Medicinal Chemistry*, *17*(2), 882-895.
13. Das, J., Furch, J. A., Liu, C., Moquin, R. V., Lin, J., Spergel, S. H., & Wityak, J. (2006). Discovery and SAR of 2-amino-5-(thioaryl) thiazoles as potent and selective Itk inhibitors. *Bioorganic & Medicinal Chemistry Letters*, *16*(14), 3706-3712.
14. Potewar, T. M., Ingale, S. A., & Srinivasan, K. V. (2007). Efficient synthesis of 2, 4-disubstituted thiazoles using ionic liquid under ambient conditions: a practical approach towards the synthesis of Fanetizole. *Tetrahedron*, *63*(45), 11066-11069.
15. Cho, M. K., & Kim, S. G. (1998). Differential Expression of Xenobiotic-Matabolizing Enzymes by Benzylisothiazole in Association with Hepatotoxicity: Effects on Rat Hepatic Epoxide Hydrolase, Glutathione S-Transferases and Cytochrome P450s. *Toxicological Research*, *14*(3), 293-300.
16. Chang, S., Zhang, Z., Zhuang, X., Luo, J., Cao, X., Li, H., & Ding, K. (2012). New thiazole carboxamides as potent inhibitors of Akt kinases. *Bioorganic & Medicinal Chemistry Letters*, *22*(2), 1208-1212.
17. Park, J. H., El-Gamal, M. I., Lee, Y. S., & Oh, C. H. (2011). New imidazo [2, 1-b] thiazole derivatives: synthesis, *in vitro*

anticancer evaluation, and in silico studies. *European Journal of Medicinal Chemistry*, *46*(12), 5769-5777.

18. Moldovan, C. M., Oniga, O., Pârvu, A., Tiperciuc, B., Verite, P., Pîrnău, A., & Pop, R. (2011). Synthesis and anti-inflammatory evaluation of some new acyl-hydrazones bearing 2-aryl-thiazole. *European Journal of Medicinal Chemistry*, *46*(2), 526-534.
19. Karegoudar, P., Karthikeyan, M. S., Prasad, D. J., Mahalinga, M., Holla, B. S., & Kumari, N. S. (2008). Synthesis of some novel 2, 4-disubstituted thiazoles as possible antimicrobial agents. *European Journal of Medicinal Chemistry*, *43*(2), 261-267.
20. Hoffer, M., & Grunberg, E. (1974). Synthesis and antiprotozoal activity of 1-(3-chloro-2-hydroxypropyl)-substituted nitroimidazoles. *Journal of Medicinal Chemistry*, *17*(9), 1019-1020.
21. Reji, T. F. A. F., Devi, S. K. C., Thomas, K. K., Sreejalekshmi, K. G., Manju, S. L., & Rajasekharan, K. N. (2008). Synthesis and cytotoxicity studies of thiazole analogs of the anticancer marine alkaloid dendrodoine. *Indian Journal of Chemistry (Section B)*, *47*, 1145-1150.
22. Mansuri, M. M., Seth, A. K., Molvi, K. I., Prajapati, B. R., & Desai, D. G. (2012). Synthesis and pharmacological evaluation of some 3-(4-(substituted) 2-morpholino-4-yl-4-phenyl-thiazole-5-carbonyl)-1-benzo-pyran-2-one. *Pharma Science Monitor*, *3*(2), 142-152.
23. Mansuri, M., Ahmed, A., Shaikh, A., Haque, N., Sheth, A. K., & Molvi, K. I. (2012). Synthesis, antibacterial, anti-inflammatory and antiplatelet activities of some trisubstituted thiazoles. *Inventi Rapid: Med Chem*..4, 1-6.
24. Darji, D. N., Pasha, T. Y., Bhandari, A., Molvi, K. I., Desai, S. A., & Makwana, M. V. (2011). Synthesis of Some Novel 2, 4, 5-Trisubstituted Thiazoles as Possible Antifungal Agents. *Journal of Pharmacy Research*, *4*(12). 4465-4466
25. Winter, C. A., Risley, E. A., Nuss, G. W. (1962). Carrageenan induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs. *Experimental Biology Med*, 111, 544-547.
26. Coruzzi, G., Adami, M., Guaita, E., de Esch, I. J., & Leurs, R. (2007). Antiinflammatory and antinociceptive effects of the selective histamine H 4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. *European Journal of Pharmacology*, *563*(1), 240-244.

