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Synthesis of novel 2, 3, 5-tri-substituted thiazoles with anti-inflammatory and antibacterial effect causing clinical pathogens

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ABSTRACT

Background: The present work is an extension of ongoing efforts toward the development and identification of new molecules as monotherapy displaying anti-inflammatory and anti-infective activities and a wide-range of gastrointestinal selectivity. A series of novel set of trisubstituted thiazole compounds (***AR-17a*** to ***AR-27a***) have synthesized and evaluated for their *in-vitro* and *in-vivo* anti-inflammatory activities. Synthesized trisubstituted thiazole compounds were also evaluated for their potential antibacterial activity against clinical pathogens causing infectious disease.

Material and Method: The structures of synthesized compounds were characterized by FTIR, ^{1}H NMR, Mass spectroscopic techniques and evaluated for their *in-vitro* and *in-vivo* anti-inflammatory effects using the human red blood cell (HRBC) membrane stabilization method and a carrageenan-induced rat paw oedema model, respectively, Diclofenac sodium and Ibuprofen were used as standard drugs. The synthesized compounds ***AR-17a*** *to* ***AR-27a*** screened for their *in-vitro* antibacterial activity against the gram-positive bacteria *Staphylococcus aureus (ATCC25923)* and Enterococcus *faecalis (ATCC29212)* and the gram-negative bacteria *Escherichia coli (ATCC8739)* and *Pseudomonas aeruginosa (ATCC9027)* using ciprofloxacin and cefdinir as standard drugs.

Result: Compounds ***AR-17a*** and ***AR-27a*** elicited maximum anti-inflammatory activity, providing 59% and 61% protection at 20 mg/kg, respectively, in the inflamed paw model. Among the tested compounds, ***AR-17a (6.25), (54)*** and ***AR-27a (1.56), (52)*** had the least minimum inhibitory concentration values and the highest zone of inhibition, indicating their marked antibacterial activities. The lowest conc. were observed at 1.56, 6.25 μg/mL for inhibition of bacteria by most of the compounds.

Conclusion: Novel set of trisubstituted thiazole compounds (***AR-17a*** to ***AR-27a***) have synthesized and characterized successfully. The preliminary screening revealed that these compounds possess promising anti-inflammatory and antibacterial activities. In addition, the objective of the study was achieved with few of the promising structures like ***AR-17a*** to ***AR-27a,*** which are prove to be potential monotherapy candidates for the treatment of chronic inflammatory diseases and bacterial infections.

Introduction

The discovery of nalidixic acid in 1962 and its entry to the market marked the beginning of several decades of quinolone development and use. Nalidixic acid is a comparatively poor antibacterial agent that was previously limited to the treatment of urinary tract infections caused by gram-negative organisms. Over the last few decades, quinolones have been transformed into a relevant class of antibacterial agents. At present, they are prescribe for many clinical conditions, including upper and lower respiratory tract infections, gastrointestinal infections, gynecological infections, sexually transmitted diseases, urinary tract infections, prostatitis, bacterial meningitis and osteomyelitis. They control the structure and function of nucleic acids, these observations helped

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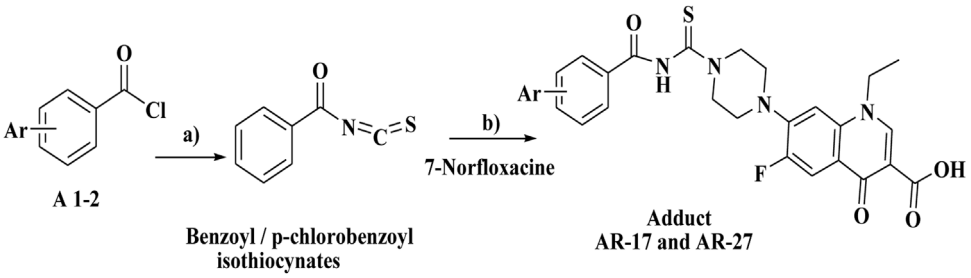

Scheme 1. Synthesis of novel fluoroquinolone adducts as intermediates.

to explain the mechanism of action of the quinolones against bacteria. Subsequently, Gellert et al. identified this enzyme that nicks double-stranded chromosomal DNA, introduces negative supercoils, and then seals the nicked DNA, and they called it "DNA gyrase" (or "topoisomerase II") [1,2].

The late 1970s and early 1980s saw the emergence of second-generation of quinolones, particularly fluoroquinolones such as norfloxacin, ciprofloxacin, ofloxacine, enoxacine, fleroxacine, and lomefloxacine, which exhibited stronger activity against gram-negative bacteria and moderate activity against gram-positive bacteria than earlier quinolones. In addition, the improved pharmacokinetic properties of the second-generation agents can be attributed to the C-7 piperazinyl substituent, but these analogs were soon replaced by the third-generation of quinolones [3,4].

Several norfloxacine (1-ethyl-6-fluoro-7-piprazinyl-4-oxo-3-carboethoxy-quinoline) derivatives were reported by Sharma et al. these hybrid molecules were derived by combining different pharmacophores of thiazolidinone at position 3, which could lead to development of compounds with interesting therapeutic profiles. Thiazolidindiones are strong and selective agonists to the nuclear peroxisome proliferator-activated receptor gamma (PPAR) present in liver, skeletal muscle and adipose tissue. In addition, thiazolidindiones have been reported to boost cell functions by reducing free fatty acid levels that ultimately lead to cell death [5]. Multi-drug treatment of inflammatory conditions associated with microbial infections pose a unique problem, especially in patients with impaired liver or kidney functions. Therefore, from the view points of pharmacoeconomic and patient compliance [6], monotherapy with a drug that has both anti-inflammatory and antimicrobial activities are desirable to great extent.

Therefore, in the present study, we aimed to synthesize a novel set of compounds using 1-(4-substituted) 2-methyl-4-nitro-1H-imidazole-1-yl) acetyl thiazoles using 7-(4 (4-chlorobenzamido) sulfanylenemethyl) piperazin-1-yl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid and different α-halo compounds Scheme 1.

Material and methods

All chemical reagents and solvents were used in accordance with the instructions of the supplier, and if necessary, were recrystallized/redistilled. Norfloxacine (purity >96%), Ciprofloxacin (purity >98%), and Cefdinir (purity >97%) were purchased from Relax Pharma Ltd. Mumbai, India. Diclofenac sodium (purity >98%) and ibuprofen (purity >99%) were obtained as gifts from Glenmark pvt. Ltd., Mumbai India. Carrageenan (λ) (C38895 G purity >97%) was purchased from Sigma Aldrich, USA. Acid chlorides with higher purity were obtained as gifts from Cambay Organics pvt. Ltd., Gujarat India. Alsevior reagent, ammonium thiocyanate, Mueller Hinton Agar media (Himedia-M173) and other chemicals of high-purity grade were purchased from Sahyadri scientific suppliers (Mumbai, India). Thin layer chromatography (TLC) was performed on microscopic slides coated with silica gel G and toluene; acetonitrile was used as the mobile phase. Spots were visualized by normal thin layer chromatography (TLC) and exposure to iodine vapor. An open capillary melting point apparatus was used to record melting points that were uncorrected. Infrared (IR) spectra were recorded with KBr on SHIMADZU Fourier Transform Infrared 8400S spectrometer (Kyoto, Japan). Mass spectra were recorded on a Jeol JMS-D-300 spectrometer Electron impact (EI) 70 eV. Nuclear Magnetic Resonance spectra (^{1}H NMR) were recorded in deuterated dimethyl sulfoxide (DMSO-d6) on Bruker advance at 400 *MHz* using Tetramethyl silane (TMS) as the internal standard. Chemical shifts (δ) were reported in parts per million (ppm). Elemental analysis was conducted using a Carlo-Erba 1108 instrument or Elementar's vario EL III and the vario EL cube microanalyzer. Fig. 1

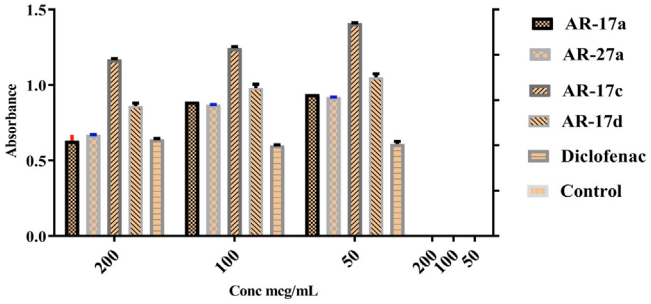

Fig. 1. *In-vitro* anti-inflammatory activity of the synthesized compounds (**AR-17**a - **AR-27**a).

Chemistry

Procedure for synthesis of novel fluoroquinolone adducts as intermediates

AR-17 Adduct: 7- (4(benzamido) sulfanylenemethyl) piperazin-1-yl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid.

To a stirred solution of 4.947 g (0.066 mol) ammonium thiocyanate in 60 mL acetone, 9.30 g (0.066 mol) benzoyl chloride was added at room temperature for 15–20 min. The reaction mixture was refluxed for 15 min and 15.95 (0.05 mol) of norfloxacine dissolved in 60 mL, acetone was then added into the reaction mixture after 10 min. The mixture was boiled gently and refluxed for 40 min. The reaction mixture was poured into 350 g of crushed ice and then stirred. The separated solid was filtered, washed with acetone and methanol, and dried to obtain the **AR-17** Adduct [7–9]. Mol. Formula: $C_{24}H_{23}FN_4O_4S$ Mass: *m/z*., 483 (M + 1). Yield: 76%, m. p. 220–222 °C., IR (KBr-cm^1), 3183, 3047, 2999, 2978, 2844, 2359, 2342, 2054, 1705, 1684, 1630, 1507, 1472, 1457, 1267, 1243, 1171, 1011, 806, 655. Fig. 2

AR-27 Adduct: 7-(4(4-chlorobenzamido) sulfanylenemethyl) piperazin-1-yl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid.

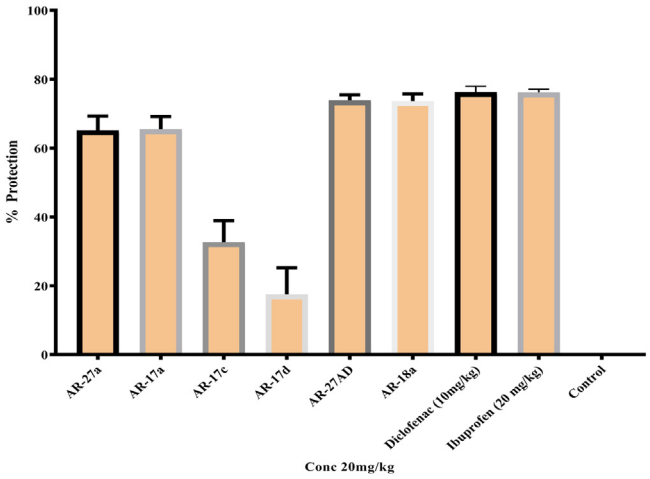

Fig. 2. *In vivo* anti-inflammatory activities of the synthesized compounds ***AR-17a–AR-27a***.

To a stirred solution of 4.947 g (0.066) mole ammonium thiocyanate and 60 mL acetone, 10.50 g (0.060 mol) 4-chlorobenzoyl chloride was added at room temperature for 15–20 min. The reaction mixture was refluxed for 15 min and 15.95 g (0.050 mol) norfloxacin dissolved in 60 mL acetone was then added into the reaction mixture after 10 min. Gentle boiling and refluxing was continued for 40 min. The reaction mixture was poured into 350 g of crushed ice and stirred. The separated solid were filtered, washed with acetone and methanol and dried to yield the ***AR-27*** Adduct. Mol. Formula: $C_{24}H_{22}ClFN_4O_4S$ m.p. 190−192 °C MASS: *m/z*., 517 (M + 1). Yield: 72 %., IR (KBr-cm^1): 3173 - 3110, 3052, 2961-2928, 2871- 2809, 2359 - 2342, 1735, 1717, 1668, 1616, 1516, 1436, 1447, 1269, 1239, 1171, 1089, 974, 810, 665.

General method for Synthesis of target compounds (AR-17a to AR-27a)

As shown in Fig. 3, Scheme 1, isothiocyanates were obtained by stirring 10 g (0.1379 mol) ammonium thiocyanate in 100 mL acetone at room temperature with 10 g (0.1263 mol) benzoyl chloride/*p*-chlorobenzoyl chloride for 15-20 min. The reaction mixture was then refluxed for 25 min. The adduct ***AR-17*** and ***AR-27*** were synthesized by the nucleophilic addition of benzoyl isothiocyanate and *p*-chlorobenzoyl isothiocyanate and in equimolar quantity at the reflux temperature, as discussed above. The target compounds (***AR-17a*** to ***AR-27a***) were synthesized as per the procedure reported by Giri et al. [10] and Franklin et al. [10,11]. Briefly, 1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on *(a)* was added in equimolar quantity to a solution of the adduct **AR-17** and adduct **AR-27** in acetonitrile (10 mL). The reaction mixture was heated in a water bath at 90−100 °C for 8 h, cooled, and filtered. To the filtrate, 50 mg of sodium bicarbonate was added to neutralize the liberated hydrochloride. The yellow precipitates were filtered, washed with ethanol dried, purified by recrystallization corresponding to the (***AR-17a*** to ***AR-27a***), and characterized by spectral and elemental analysis. The melting point was determined with an open glass capillary tube and yielded the uncorrected values. The reaction was monitored using thin layer chromatography (TLC) on a glass plate coated with silica gel G. TLC Plates were developed in iodine and toluene:acetonitrile (7:3) was used as the mobile phase as presented in Table 1.

AR-17a:1-ethyl-6-fluoro-1, 4-dihydro-7-(4-(5-(2-(2-methyl-4-nitro-1H-imidazol-1-yl) acetyl)-4-phenylthiazol-2-yl) piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid.

IR (KBr cm^1) : 3049 (Ar-H stretching), 2979 (-C-H stretching), 2842 - 2837 (CH_3 stretching), 1708 (C=O stretching of quinolone), 1665 (C=O stretching of aliphatic), 1510-1425 (C=C stretching, Ar-H), 2420 (m −COOH Stretching), 1400 - 1341 (NO_2 stretching), 1250 (N—C of Ar-H), 1172 - 1024 (C-*N*-C of piperazine), 904 - 804 (-C = C out of plane for benzene), 1194 (C–F stretching). ^{1}H NMR : (400 *MHz*, Dimethylsulfoxide-d 6) δ (ppm) : 1.23–1.44 (t, N−CH_2−CH_3), 2.09 (s C−CH_3 at 2nd position of nitroimidazole), 2.52 (q, N−CH_3−CH_3), 3.41–3.87 (m 2H-piperazine), 4.58 (s, 2H, −CH_2-C = O), 7.19–7.55 (s, 1H, aromatic proton at 3rd position of quinazoline), 7.51–7.89 (m, 5H, aromatic proton at 4th position), 8.2 (s 1H quinazoline at 3rd position), 9.0 (s 1H, −COOH). Mass: *m/z*., 645, 646 (M + 1) Elemental analysis for $C_{31}H_{28}FN_7O_6S$: Calculated : C, 57.67; H, 4.37; N, 15.19; Found: C, 58.27; H, 4.37; N, 15.09; UV visible peak λ-max: 282.40 *nm.*

AR-27a*: 7-(4-(4-(4-chlorophenyl)-5-(2-(2-methyl-4-nitro-1H-imidazol-1-yl) acetyl) thiazol-2-yl) piperazin-1-yl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid.*

IR (KBr cm^1): 3500 (−OH), 3137 (Ar-H stretching), 2835–2980 (-C-H), 1723 - 1715 (C=O stretching of quinolone), 1627 - 1618 (C=O stretching of aliphatic), 1539 - 1491 (C=C stretching, Ar-H), 3500 (−COOH stretching), 1385 (NO_2 stretching), 1296 - 1267 (−OCH3 stretching), 1358 - 1333 (N—C of Ar-H), 840 - 808 (-C = C out of plane for monosubstituted benzene), 1143-1088 (C-N-C of piperazine), 1198 (C–F stretching), 1349 (C-Cl stretching). ^{1}H NMR: (400 *MHz*, dimethylsulfoxide-d6) δ (ppm): 2.28 (t, N−CH_2-CH_3), 2.40 (q, N−CH2-CH3), 2.53 (s C−CH_3 at 2nd position of nitroimidazole) 3.21–3.88 (m 2H-piperazine) 5.24–5.50 (s, 2H, −CH_2-C = O), 7.03–7.50 (s, 1H, aromatic proton at 3rd position of quinazoline) 7.51–7.90 (m, 5H, aromatic proton at 4th position), 8.01–8.27 (s 1H, quinazoline at 3rd position) 9.0 (s 1H, −COOH). Mass: *m/z* 679, 680 (M + 1). Elemental analysis for $C_{31}H_{27}ClFN_7O_6S$: Calculated: C, 54.75; H, 4.00; N, 14.42; Found: C, 54.45; H, 4.00; N, 14.12.

AR-17c*:1-ethyl-6-fluoro-1, 4-dihydro-7-(4-(5-(2, 5-(dimethoxybenzoyl)-4-phenylthiazol-2-yl) piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid.*

IR (KBr cm^1): 3050 (Ar-H stretching), 2986 (−CH_3 stretching), 1720-1712 (C=O stretching of quinolone), 1693-1615 (C=O stretching of aliphatic) 1523-1463 (C=C stretching, Ar-H), 2317 (−COOH stretching), 1222 (−OCH_3 stretching), 1299-1260 (N—C of Ar-H) 1027,(C-N-C of piperazine), 905-889 (-C = C out of plane for benzene), 950 (C–F stretching). ^{1}H NMR : (400 *MHz*, dimethylsulfoxide-d6) δ (ppm): 1.51 (t, N−CH_2-CH_3), 2.55 (q, N−CH_2-CH_3), 3.33 (s O−CH_3), 3.51–3.63 (m piperazine) 6.46–6.69 (m, 2H, −CH_2-C = O), 7.03–7.24 (m, 5H, aromatic proton at 4th position) 8.21 (s, 1H, Ar-H proton at 3rd position of quinazoline) 9.0 (s 1H −COOH). Mass: *m/z* 642 and 643 (M + 1). Elemental analysis for $C_{34}H_{31}FN_4O_6S$: Calculated; C, 63.54; H, 4.86; N, 8.72; Found: C, 63.14; H, 4.21; N, 8.12.

AR-17d*: 1-ethyl-6-fluoro-1, 4-dihydro-7-(4-(5-(3-(nitrobenzoyl)-4-phenylthiazol-2-yl) piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid.*

IR (KBr cm^1) : 3076 (Ar-H stretching), 2861 (−CH_3 stretching), 1722-1705 (C=O stretching of quinolone), 1696 (C=O stretching of aliphatic) 1550-1471 (C=C stretching Ar-H), 2369-2342 (−COOH stretching), 1456 (NO_2 stretching), 1263 (−OCH_3 stretching), 1391–13939 (N—C of Ar-H), 1028 (C-N-C of piperazine), 934(-C = C out of plane for benzene), 1349 (C–F stretching) ^{1}H NMR: (400 *MHz*, dimethylsulfoxide - d6) δ (ppm): 1.40 (q, N−CH_2−CH_3), 2.21–2.54 (t, N−CH_2−CH_3), 4.60–4.95 (s O−CH_3), 3.59–3.90 (m piperazine) 7.02–7.14 (m, 2H, Ar-H proton at 2nd position of thiazole) 7.16–7.74 (m, 5H, Ar-H proton at 4th position), 7.81–8.06 (m, 5H, Ar-H proton at 5th position NO_2) 8.16 (s, 1H, Ar-H proton at 3rd position of quinazoline) 9.0 (s 1H −COOH). Mass: *m/z*., 628 (M + 1).

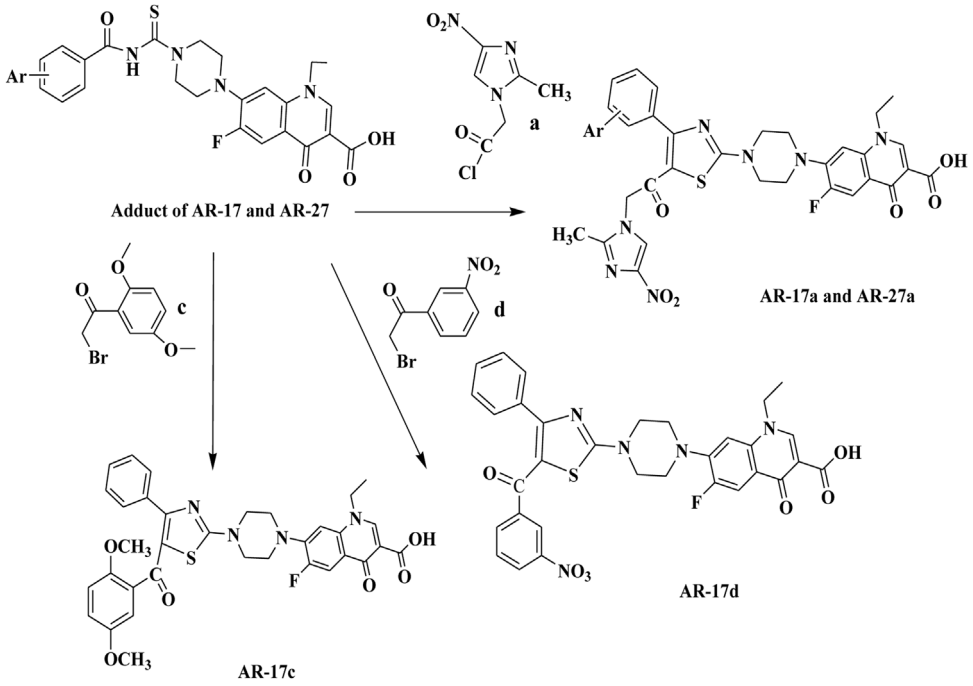

Fig. 3. Synthesis of 7-(4-(benzamido) sulfanylenemethyl) piperazin-1-yl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic (Adduct of ***AR-17*** and ***AR-27***). Synthesis of target compounds, 2, 3, 5-trisubstituted thiazole (***AR-17****a*, ***AR-17****c*, ***AR-17****d* and ***AR-27****a*) with different α-halo compounds (a, d and c).
Reagents and conditions: **a)** NH_4SCN, acetone, reflux 15–25 min; **b)** reflux for 20 min, pour reaction mixture onto crushed ice; **c)** acetonitrile, stir at 100 °C for 8 h.

Table 1
Physicochemical properties of synthesized compounds (***AR-17***a to ***AR-27***AD).

Compounds	Ar	X = (N-Nor)	Melting Point[a] ^{0}C	Rf Value[b]	% Yield
AR-17*a*	H-	—N N—Norfloxacine	221-223	0.54	48%
AR-27*a*	*p*-Cl-	—N N—Norfloxacine	248-249	0.76	45%
AR-17*c*	H-	—N N—Norfloxacine	260-262	0.61	54%
AR-17*d*	H-	—N N—Norfloxacine	220-224	0.57	82%
AR-18*a*		Diethylamine	140-141	0.59	72%
AR-27*AD*	*p*-Cl-	—N N—Norfloxacine	190-192	0.68	72%

[a] Melting point was determined with a melting point apparatus using an open glass capillary tube and presented as uncorrected values.
[b] All reactions were monitored by thin layer chromatography (TLC) using glass plate coated with silica gel G. TLC Plates were developed in iodine and a) toluene : methanol (8.5 : 1.5).

Elemental analysis for $C_{32}H_{26}FN_5O_6S$: Calculated; C, 61.24; H, 4.18; N, 11.16; Found: C, 61.64; H, 4.41; N, 11.22.

AR-18a*:1-(2-(diethylamino)-4-phenylthiazol-5-yl)-2-(2-methyl-4-nitro-1H-imidazol-1-yl) ethanone*.

IR (KBr cm^1):3134 (aromatic stretching), 2980-2938 (-C-H stretching alkane) 2875 ($-CH_3$ stretching), 1623 (C=O stretching), 1471-1439 (C=C stretching, aromatic), 1531-1501 (NO_2 stretching), 1395-1364 (N—C of aromatic), 998-842 (-C = C out of plane for benzene), 1344-1249 (C-N-C stretching of amine). ^{1}H NMR: (400 MHz, DMSO-d_6)δ (ppm) : 1.20–1.23 (q, N—CH_2-CH_3), 2.09–2.13 (t, N—CH_2-CH_3), 4.80 (s, 2H, —CH_2-C = O), 3.30 (s, 3H proton at 2nd position of nitroimidazole —CH_3) 7.50–7.69 (m, 5H, aromatic proton at 4th position), 8.13 (s, 1H, aromatic proton at 5th position of nitroimidazole). Mass: *m/z*., 399, 400 (M + 1), Elemental analysis for $C_{19}H_{21}N_5O_3S$: Calculated: C, 57.13; H, 5.30; N, 17.53; Found: C, 57.43; H, 5.10; N, 17.31.

Pharmacological evaluation

In-vitro *anti-inflammatory activity of the synthesized compounds by human red blood cells membrane stabilization method*

HRBC membrane is similar to a lysosomal membrane apparatus. Importantly, the prevention of hypotonicity induced HRBC

membrane lysis was used as a measure of anti-inflammatory activity of drugs, [12–14]. As such, HRBC membrane stabilization has been employed as a method to study anti-inflammatory activity. Blood was collected from a healthy volunteer and mixed with an equal volume of sterilized alsevior solution (2% dextrose, 0.8% sodium citrate, 0.5% citric acid, and 0.42% sodium chloride in water). The blood sample was centrifuged at 3000 rpm at room temperature for 30 min and the packed cells were washed with isosaline (0.85%, pH 7.2). A 10% (v/v) suspension was then treated with isosaline. The assay mixture contained diclofenac sodium as the reference drug (50, 100, and 200 μg/mL), 1 mL of phosphate buffer (0.15 M, pH 7.4), 2 mL of hyposaline (0.36%) and HRBC suspension (0.5 mL). However, instead of 2 mL hyposaline, distilled water was used as the control. All assay mixtures were incubated at 37 °C for 30 min. and centrifuged at 3000 rpm at room temperature for 30 min. The hemoglobin content in the supernatant solution was estimated using optical density (OD) derived with an Ultraviolet-visible spectrophotometer at 560 *nm*. Percentage hemolysis was then calculated by considering the 100% hemolysis produced in the presence of distilled water [15–18]. Percentage of HRBC membrane stabilization or protection was calculated using OD of the test and control with the following formula;

$$\%\text{Protection} = 100\text{-}(\text{ODtest}/\text{ODcontrol})\text{x}100$$

In-vivo *methods for the anti-inflammatory activity by carrageenan-induced rat hind paw edema*

All experimental procedures were approved by the Institutional Animal Ethics Committee RCPIPER/IAEC/2013-14/09 (Reg. No. 651/C/02/CPCSEA) constituted under 'Prevention of Cruelty to the Animals Act 1960; Government of India. The adopted method [19,20] resembles that described by Winter et al. animals were tested for toxicity of dimethylsulfoxide up to 10% v/v in saline and 5% dimethylsulfoxide was selected as a vehicle to suspend the standard drugs and test compounds. Albino rats of either sex (weight, 150–250 g) were starved for 18 h prior to the experiment. Animals were weighed, marked at the tibiotarsal articulation for identification and divided into groups of six. The standard drugs, ibuprofen (20 mg/kg body weight) and diclofenac sodium (10 mg/kg body weight), and the test compounds were administered orally (20 mg/kg body weight) as a suspension using 5% dimethylsulfoxideas a vehicle. One h later, foot paw edema 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 using a mercury plethysmometer. Edema was measured three hours after carrageenin administration. The swelling in test group animals was used to calculate the percent inhibition standard error of the mean (SEM) of edema achieved by the compound at the test dose compared to the vehicle control group. The % protection of edema was calculated according to the formula;

$$\%\ \text{anti-inflammatory activity} = 100 \times (1\text{-Vt}/\text{Vc})$$

Where Vt and Vc represent volume of edema in test compounds and control groups, respectively.

Antibacterial screening

The *in-vitro* antibacterial screening was carried out by the agar well diffusion technique with Mueller Hinton Agar no.2 as the nutrient medium. The agar well diffusion method was favored for use in this study as it was found to be improved compared to the disc diffusion method [21,22]. The test bacteria (0.2 mL; 108 cells/per McFarland standard) were inoculated into the molten Mueller Hinton agar media. Following suitable homogenization, it was poured into sterile 100 mm petri plates and allowed to solidify. After solidification of the media, a 0.85-cm well was made in the plates using a sterile cork-borer. Preliminary screening was conducted for all compounds at 100 μg /mL concentration against the selected clinical pathogens. Each well was filled with 0.1 mL of the test solution (100 μg/mL). The plates were incubated for 24 h in an incubator at 37 °C. For antibacterial activity, ciprofloxacin and cefdinir were used as standards. The mean value obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain, where pure solvent dimethylsulfoxide was inoculated into the well. The inhibition zone formed by these compounds against the particular test bacterial strain was used to determine the antibacterial activities of the target synthesized compounds. Zone of inhibition produced by the test compounds was measured in mm in various axes and the average reading was considered. The activity index was calculated against the standard. The results are shown in Table 4.

Minimum Inhibitory Concentration Assay against gram-negative and gram-positive bacteria (100 to 0.39 μg / mL)

Minimum inhibitory concentration evaluation is a method used to determine the lowest concentration of a particular test compound or antibiotic needed to kill bacteria. This assay was classically carried out on free-floating planktonic microbe cells [23,24]. The synthesized test compounds were dissolved in dimethylsulfoxide (DMSO) at a concentration of 100 mg/mL. Serial dilutions of the test compounds and antibiotics (representing different concentrations (100, 50, 25, 12.50, 6.25. . .0.39 μg / mL) of the synthesized test compounds) were added to a growth medium in separate test tubes.Stock solutions of the cefdinir and ciprofloxacine were also prepared in dimethylsulfoxide at a concentration of 100 μg/mL followed by a two-fold dilution at concentrations of 100, 50, 25, 12.5, 6.25. . .0.39 μg/mL). Each tube had growth media inoculated with a standard concentration of bacteria and the respective antibiotic concentration.

Results and discussion

A novel series of trisubstituted thiazole analogues (***AR-17****a* - ***AR-27****a*) were designed and synthesized. The synthesized compounds (***AR-17****a*-***AR-27****a*) were evaluated for their *in-vitro* and *in-vivo* anti-inflammatory activities. The *in-vitro* anti-inflammatory activity was carried out by membrane stabilization of HRBC, which caused heat-induced hemolysis of red blood cells as one of the modes of inflammation. Furthermore, *in-vivo* anti-inflammatory activity was evaluated in a carrageenan-induced rat paw edema model at doses of 20 mg/kg body weight using diclofenac sodium as the reference standard. The compounds (***AR-17****a*-***AR-27****a*) were designed and synthesized by keeping (1-chloro-3-(2-methyl-4-nitro1H-imidazole-1-yl) propane-2-on at the fifth position and 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid at the second position of the thiazole ring. The fourth position of thiazole was substituted by introducing the electron-withdrawing group (–Cl) at different positions in the phenyl moiety. The compounds *(**AR-17**a to **AR-27**a)* were synthesized with 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid secondary amine at the second position of the thiazole. The present work is an extension of ongoing efforts toward the development and identification of new molecules as monotherapy displaying anti-inflammatory and anti-infective activities and awide-range of gastrointestinal selectivity. On this basis, some1-(4-substituted) 2-methyl-4-nitro-1h-imidazole-1-yl) acetyl thiazole-2-(piperazin-

1-yl) 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-quinoline-3-carboxylic acids [25] were synthesized. The C-7 piperazinyl group, in addition to the C-6 fluorine substituent, displays anti-bacterial potency that is far superior to that of earlier classical quinolone for both gram-positive and gram-negative bacteria [26]. The second position of thiazole was substituted by norfloxacin moity and the synthesized compounds were tested for their anti-inflammatory and antibacterial activities.

Compounds were tested for their antibacterial activity against four bacteria, Gram positive bacteria *Staphylococcus aureus (ATCC25923), Entrerococcus faecalis (ATCC29212)* and Gram negative bacteria, *Escherichia coli (ATCC8739)* and *Pseudomonas aeruginosa (ATCC9027)* at 100 μg/mL concentrations against. The controls were maintained for each bacterial strain, where pure solvent dimethylsulfoxide DMSO was inoculated into the well. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. Zone of inhibition produced by test compounds were measured in mm in various axis, average readings were considered, and the activity index was calculated against the standard. The results are shown in Table 4.

Compounds ***AR-17a*** and ***AR-27a*** showed an excellent effect at the tested concentrations against, gram-positive bacteria *S. ureus, E. faecalis* and gram-negative bacilli, *E. coli* and *P. aeruginosa.* All the tested synthesised compounds have shown very good minimum inhibitory concentration from the serial dilution 100 to 0.39 μg/mL. The lowest conc. were observed at 3.12, 6.25 μg/mL for inhibition of bacteria by most of the compounds. To summarize these findings, methyl substituent on piperazino moiety and *p*-chlorophenyl at second and forth position of thiazole respectively enhances antibacterial activity against all tested gram-positive and gram-negative bacteria.

Based on the study findings, the selectivity of the compound for antibacterial activity is predominantly dependent on the grouping of substitutions at the 2nd position of the thiazole, which causes stronger activity against gram-negative bacteria, while having a moderate activity against gram-positive. Second generation quinolones also have better pharmacokinetic properties due to their C-7 piperazinyl substituent. The phenyl ring with electron-withdrawing groups, such as –Cl at position 4, significantly contributes to the anti-inflammatory activity, whereas the substitution at position 5th by 2-methyl-4-nitro-1h-imidazole-1-yl for well documented molecules of thiazole establishes a framework for use as a monotherapy that display anti-inflammatory and anti-infective activities with a wide range of gastrointestinal selectivity.

The chemical structures of these compounds, their physicochemical properties, and results of *in-vitro* / *in vivo* anti-inflammatory and antibacterial activities are shown in Tables 1–4 respectively. Figs. 1 and 2 represent the *in-vitro* / *in vivo* anti-inflammatory against standards groups and control groups. The computational properties of the novel series tested by mole inspiron and PASS Inet are represented in Tables 5 and 6, which strongly support the protocol. The infrared (IR) spectrum of novel 1-(4-substituted) 2-methyl-4-nitro-1H-imidazole-1-yl) acetyl thiazole -2-(piperazin-1-yl) 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-quinoline-3-carboxylic acids(***AR-17a, AR-27a AR-17c*** and ***AR-17d***) revealed absorption bands at 3049, 3137, 3050, and 3076 cm^1,respectively, whichi ndicates the aromatic (Ar-H) stretching. Similarly, the absorption bands at 1708, 1723-1715, 1720-1712, and 1727−1705 cm^1 indicate the presence of C=O stretching of the quinolone ring attached to the second position of the thiazole ring system. On the other hand, 1665, 1627-1618, 1693-1615, and 1696 cm^1 indicate the presence of C=O stretching of the aliphatic group attached to the fifth position of the thiazole nucleus. Other significant absorption bands were also observed at 1172-1024, 1143-1088, 1027, and 1028 cm^1,which can be attributed to C-N-C stretching of piperidine, and 1400-1341, 1385, and 1456 cm^1 of the -NO_2- group. In addition, 1222 and 1263 cm^1 revealed that the (−OCH_3 group in ***AR-17c*** and ***17d***) C–F was prominently observed in the IR spectra. The ^{1}H NMR spectra of compounds ***AR-17a, AR-27a*** and ***AR-17d*** recorded at 400 *MHz* showed singlets at δ 8.2, 8.01, 8.21, and 8.16 ppm, integrating for one proton, which is attributed to the presence of aromatic proton at the fifth position of nitroimidazole and quinazoline. The aromatic protons of the third position of quinazoline res-

Table 2
In-vitro anti-inflammatory activities of the synthesized compounds (***AR-17a*** to ***AR-27 AD)*** using the human red blood cell membrane stabilization method.

Compounds	Conc. μg /mL	Absorbance *(nm)* (Mean ± SEM)	% Protection
AR-17a	200	0.63 ± 0.0284	60.73
	100	0.89 ± 0.0006	44.25
	50	0.94 ± 0.0009	41.21
AR-27a	200	0.67 ± 0.0009	58.42
	100	0.87 ± 0.0003	45.33
	50	0.92 ± 0.0009	42.71
AR-17c	200	0.78 ± 0.0033	51.46
	100	0.83 ± 0.0058	48.13
	50	0.94 ± 0.0116	41.25
AR-17d	200	0.86 ± 0.0200	46.25
	100	0.98 ± 0.0252	38.54
	50	1.05 ± 0.0241	34.17
AR-27AD	200	0.60 ± 0.0030	62.81
	100	0.64 ± 0.0051	60.17
	50	0.50 ± 0.0052	68.67
Diclofenac sodium	200	0.64 ± 0.0051	60.17
	100	0.60 ± 0.0030	62.81
	50	0.49 ± 0.0032	59.50
Control	Unknown	1.60 ± 0.0000	0.00

Values expressed as Mean ± SEM (Standard error of mean) ***AR-18a*** = nd (not done).

Table 3
In-vivo anti-inflammatory activities of the synthesized compounds ***AR-17a*** to***AR-18a*** on rat hind paws edema by the carrageenan-induced edema.

Compounds	Dose mg/kg	I h	II h	III h
AR-17a	20	0.17 ± 0.06 (68.71)	0.36 ± 0.06 (66.32)	0.61 ± 0.09 (61.46)
AR-27a	20	0.20 ± 0.04 (62.91)	0.37 ± 0.03 (65.68)	0.64 ± 0.04 (59.04)
AR-17c	20	0.21 ± 0.03 (59.81)	0.44 ± 0.03 (58.16)	0.78 ± 0.05 (50.08)
AR-17d	20	0.47 ± 0.06 (10.81)	0.90 ± 0.06 (15.79)	1.33 ± 0.11 (15.91)
AR-27AD	20	0.13 ± 0.02 (75.73)	73.08 ± 0.04 (73.08)	0.43 ± 0.06 (72.85)
AR-18a	20	0.14 ± 0.02 (75.47)	0.29 ± 0.04 (75.70)	0.45 ± 0.06 (76.43)
Dicl. Sod	10	0.12 ± 0.01 (77.87)	0.27 ± 0.02 (74.64)	0.37 ± 0.05 (76.45)
Ibuprofen	20	0.13 ± 0.03 (76.34)	0.26 ± 0.05 (75.27)	0.41 ± 0.20 (74.23)
Control	–	0.53 ± 0.16 (0.00)	1.07 ± 0.24 (0.00)	1.57 ± 0.24 (0.00)

Oral administration of all test compounds.
The standard drugs (dose and % protection) were Ibuprofen (20 mg/kg, 75%) and Diclofenac sodium (10 mg/kg, 77%). n = 6, ANOVA followed by Dunnett's multiple comparison test.
***P < 0.001, **P < 0.01 and *P < 0.5 compared to control.
Values expressed as Mean ± SEM (Standard error of mean).

Table 4
In-vitro antibacterial activity data of synthesized compounds (***AR-17a*** to ***AR-27*** *AD).*

Compounds	Antibacterial activity[a] MIC_{50} in μg/mL (Zone of inhibition in mm[b])			
	E. faecalis ATCC 29212	*S. aureus ATCC 25923*	*P. aeruginosa ATCC 9027*	*E. coli ATCC8739*
AR-17a	6.25 (54)	3.12 (51)	1.56 (35)	3.125 (38)
AR-27a	6.25 (48)	1.56 (52)	6.25 (37)	3.125 (42)
AR-17c	12.5 (46)	12.5 (39)	12.5 (30)	12.5 (34)
AR-17d	12.5 (44)	6.25 (40)	12.5 (31)	6.25 (28)
AR-18a	12.5 (49)	6.25 (33)	6.25 (42)	12.5 (40)
AR-27AD	6.25 (49)	1.56 (53)	6.25 (47)	3.125 (42)
Ciprofloxacin	3.125 (46)	1.56 (50)	3.125 (40)	0.78 (34)
Cefdinir	3.25 (48)	3.25 (53)	6.25 (38)	1.56 (39)
+ve Control	–	–	10	–
-ve Control	–	–	–	–

[a] Minimum inhibitory concentration (MIC) evaluated in a concentration range (100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, and 0.39 μg / mL).
[b] Zone of inhibition in mm, ciprofloxacin (100 μg / mL) and cefdinir (100 μg / mL) were used as standard drugs.

Table 5
The Computational Molecular properties for synthesized compounds.

Comp.	Log P	TPSA	nrotb	Mol. Volume	n-atoms	n-ON	n –Viol.	n-OHNH
AR-17a	1.6	159.39	10	554.09	47	13	2	1
AR-27a	2.33	159.39	10	567.62	48	13	2	1
AR-17c	4.29	97.14	8	531.49	47	9	1	1
AR-17d	5.35	139.87	10	562.53	47	11	10	1
AR-27D	1.81	94.88	6	423	35	8	2	1
AR-18a	3.33	93.61	9	370.66	29	7	0	0

Table 6
Prediction Pa value (Predicted biological activity = Pa ≥ 0.5, 0.7, 0.3).

Sr. No.	Biological Activities	AR-17a	AR-27a	AR-17c	AR-17d	AR-27D	AR-18a
1	Cell adhesion molecule inhibitor	0,921	0,916	NA	0,916	NA	0,980
2	Antimycobacterial	0,774	0,770	0,537	0,770	0,491	0,623
3	Antibacterial	0,602	0,573	0,445	0,573	0,577	0,302
4	Phosphatase inhibitor	0,568	0,584	0,609	0,584	0,145	0,131
5	p21-activated kinase inhibitor	0,201	0,201	0,224	0,201	0,562	NA
6	Antiprotozoal	0,347	0,356	NA	0,356	0,491	0,480
7	Antiprotozoal (Trichomonas)	0,345	0,329	NA	0,329	0,491	0,512
8	tyrosine kinase 2 inhibitor	0,137	0,122	0306	0,122	0,158	0,310
9	MAP/Mac kinase kinase inhibitor	0,126	0,123	0,196	0,123	NA	NA
10	Antituberculotic	0,361	0,337	0,234	0,337	0,301	0,317
11	Interleukin 5 antagonist	NA	NA	0306	NA	0,104	0,094
12	Dual specificity phosphatase inh	0,270	0,263	0,373	0,263	0,165	0,241
13	Anti-Helicobacter pylori	0,216	0,180	0,125	0,180	0,491	0,336
14	Antineoplastic (bone cancer)	0,251	0,243	0,125	0,243	0,247	NA
15	Kinase inhibitor	NA	NA	0,148	0,191	0,072	0,325

onate as multiplets at δ ppm 7.19–7.55, 7.03–7.50, 7.03–7.24, and 7.02–7.14, whilst 7.51–7.89, 7.51–7.90, and 7.16–7.74 ppm indicate the proton at the fourth position. As such, further confirmation was carried out based on the presence of multiplets of piperadine at 3.41–3.87, 3.21–3.88, 3.51–3.63, and 3.59–3.90 ppm. Additional confirmation for the structures of compounds ***AR-17a*** and ***AR-27a*** was performed by recording their Mass spectra where the Mass spectrum of compounds ***AR-17a*** - ***AR-27a*** and ***AR-17c*** and ***AR-17d*** showed a molecular ion peak at *m/z*, 646, 679, and 642 (M + 1), which aligns with their molecular formula. The characterization data are given in the spectral section along with their chemical name of 1-(4-substituted) 2-methyl-4-nitro-1H-imidazole-1-yl) acetyl thiazole-2-(piperazin-1-yl)1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-quinoline-3-carboxylic acid.

Anti-adhesion molecule therapy and inflammatory bowel disease

The recent explosion of information on molecules governing the emigration of leukocytes from blood vessels and their accumulation at the loci of inflammation has completely changed the understanding of inflammation, and may lead to new strategies in the treatment of acute and chronic inflammation. We sought to illustrate current ideas regarding the pathogenesis of inflammation [27–30]. The biochemistry and function of the adhesive molecules involved in inflammation, and present our findings regarding their role in rheumatic disease. We also indicate how presently used drugs for the treatment of these diseases affect adhesion molecules. Bacterial products initiate or augment gastrointestinal inflammation with the recruitment and activation of leukocytes during inflammation of the colon (*e.g.*, *Clostridium difficile*) and stomach (*e.g.*, *Helicobacter pylori*) Neutrophils are also accumulated in the lamina propria in response to an acute gastrointestinal infection with invasive bacteria. Intestinal epithelial cell play an important role in the recruitment of inflammatory cells to the site of infection through the secretion of adhesion molecule [31–33]. NF-κB transcription factors appear to be the most relevant in inflammatory bowel and hepatic diseases as they are important in the regulation of endothelial cell adhesion molecules. Many signals, including bacterial and viral pathogens and inflammatory cytokines, elicit NF-κB translocation. At present, anti-TNF treatment in IBD is carried out using monoclonal antibodies, including infliximab (Remicade; Johnson and Johnson, Janssen Biotech, Inc., Horsham, PA, USA), adalimumab (ADM, Humira; AbbVie Inc., North Chicago, IL, USA), certolizumab (CZP, Cimzia; UCB Pharma, Brussels, Belgium), and

golimumab (Simponi; Johnson and Johnson). Infliximab (IFX) is a chimeric monoclonal antibody (mAb) against TNF-α and it was the first anti-TNF used in IBD. Its efficacy has been confirmed through different randomized clinical trials for inducing and maintaining remission both in CD and in UC [27–29,34,35]. The PASS Inet strongly supports the protocol with a **Pa** value more than 0.5. That is, cell adhesion Inhibitor Pa = 0.900, antimycobacterial more than (Pa = 0.700), Antiprotozoal more than Pa = 0.600 and finally antibacterial Pa = 0.500 or less by all the compounds, serving as an indication potent anti-inflammatory agent when tested by PASS Inet software.

Conclusions

Here, we synthesized and characterized a novel set of trisubstituted thiazole compounds which were evaluated for their *in-vitro* and *in-vivo* anti-inflammatory activities. Compounds ***AR-17a*** and ***AR-27a*** observed maximum HBRC membrane stabilization. This set of trisubstituted thiazole compounds provided equal maximum protection against paw inflammation in rats. Synthesized trisubstituted thiazole compounds were also screened for their potential antibacterial activity against pathogenic bacteria, which included *S. aureus*, *E. faecalis*, *E. coli,* and *P. aeruginosa*. The preliminary screening results revealed that these compounds possess promising antibacterial activity. In addition, the objective of the study was achieved with few of the promising structures, which are potential monotherapy candidates for the treatment of chronic inflammatory diseases and bacterial infections.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2020.02.002.

References

[1] Johnson DS, Li JJ. The art of drug synthesis, pfizer global research and development. A John Wiley and sons, Inc., publication; 2007. p. 39–66.
[2] Andriole VT. The Quinolones: Past, Present, and Future. Clin Infec Dis 2005;41(Supplement 2):S113–9, http://dx.doi.org/10.1086/428051.
[3] Khan Ezzat, Khan Sher Ali, Zahoor M, Tahir MN, Noor Awal, Altaf Ataf Ali. Cu (II) Coordination polymers stabilized by pyridine-2,6- dicarboxylate anion and pyrazole derivatives through ligand hydrolysis. J Coord Chem 2018, http://dx.doi.org/10.1080/00958972.2018.1501562.
[4] Salehi Bahare, Ata Athar, Kumar Nanjangud VAnil, Sharopov Farukh, Alarcón KarinaRamírez, Ortega Ruiz, et al. Review antidiabetic potential of medicinal plants and their active components. Biomolecules 2019;9:551, http://dx.doi.org/10.3390/biom9100551.
[5] Kumar V, Kumar A, Sharma S, Singh N. Synthesis and antimicrobial activity of thiazolidinone norfloxacine hybrid. Indian J Adv Chem Sci 2011;50B:1496–503.
[6] Bekhit AA, Abdel AT. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory antimicrobial agents. Bioorg Med Chem 2004;12:1935–45.
[7] Molvi KI, Mansuri M, Sudarsanam V, Patel MM, Syed MA, Andrabi AA, et al. Synthesis, anti-inflammatory, analgesic and antioxidant activities of some tetrasubstituted thiophene. J Enz Inh Med Chem 2008;23(6):829–38.
[8] Franklin PX, Pillai AD, Rathod P, Yerande S, Nivsarkar M, Padh H, et al. 2-Amino-5-thiazolyl motif: a novel scaffold for designing anti-inflammatory agents of diverse structures. Eur J Med Chem 2008;43:129–34.
[9] Rathode P, Ph. D thesis submitted to North Gujarat University Five membered heterocycle as potential therapeutic agents; 2002. p. 265–6.
[10] Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudersanam V. 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. Eur J MedChem 2009;44(5):2184–9.
[11] Franklin PX, Pillai AD, Rathod PD, Yerande S. Nivsarkar M.2-Amino-5-thiazolyl motif: a novel scaffold for designing anti-inflammatory agents of diverse structures. Eur J Med Chem 2008;8(43):129–34.
[12] Franklin PX, Yerande S, Thakar HM, Inamdar GS, Giri RS, Padh H. Synthesis, anti-inflammatory and HIV-1 integrase inhibitory activities of 1, 2-bis [5-thiazolyl] ethane-1, 2-dione derivatives. Indones J Pharm Sci Technol 2009;71(3):259–63.
[13] Samad Nadira Binte, Debnath T, Michael Ye, Hasnat AD. Beong Ou Lim. In-vitro antioxidant and anti-inflammatory activities of Korean blueberry (Vaccinium corymbosum) extracts. Asian Pac J Trop Biomed 2014;4(10):807–15.
[14] Nitinkumar SS. Synthesis, anthelmintic and anti-inflammatory activities of some novel imidazothiazole sulfides and sulfones. Bull Korean Chem Soc 2010;31(8):2337.
[15] Priya M, Girija K, Ravichandran N. In-vitro study of anti-inflammatory and antioxidant activity of 4-(3h)-quinazolinone derivatives. Rasayan J Chem 2011;4(2):418–24.
[16] Govindappa M, Nagasravya S, Poojashri MN, Sadananda TS, Chandrappa. Antimicrobial, antioxidant and in-vitro anti-inflammatory activity of ethanol extract and active phytochemical screening of Wedeliatri lobata (L) Hitchc. J Pharm and phototherapy 2011;3(3):43–51.
[17] Augusto LS, Josean FT, Marcelo SD, Margareth D, Formiga F. Anti-inflammatory activity of alkaloids: an update from 2000 to 2010. Molecules 2011;16:8515–34, http://dx.doi.org/10.3390/molecules16108515.
[18] Ahmed MM, Khan MA, Rainford KD. Synthesis of thiophene and NO-curcuminoids for anti-inflammatory and anticancer activities. Molecule 2013;18:1483–501.
[19] Gadamsetty G, Maru S, Saradan C. Antioxidant and anti-inflammatory activities of the methanolic leaf extract of traditionally used medicinal plant Mimusops elengi L. J Pharm Sci and Res 2013;5(6):125–30.
[20] Mouldey, David R, Kurmukov AG, Raskin I. In-vitro and in-vivo anti-inflammatory activity of a seed preparation containing phenethyl isothiocyanate. J Pharm Exp Therap 2006;317:326–33.
[21] Winter CA, Risley EA, Nuss GW. Carrageenan induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs. Exp Bio Med 1962;111:544–7.
[22] Al-saadi MS, Faidallah HM, Rostom SAF. Synthesis and biological evaluation of some 2, 4, 5-trisubstituted thiazole derivatives as potential antimicrobial and anticancer agents. Arch Pharm Chem Life Sci 2008;341:424–34.
[23] Perez C, Paul M, Bazerque P. Antibiotic assay by agar well diffusion method. Acta Biol Med Exp 1990;15:113.
[24] Parekh J, Inamdhar P, Nair R, Baluja S, Chanda S. Synthesis and antibacterial activity of some schiff bases derived from 4-aminobenzoic acid. J Serb Chem Soc 2005;70:1155.
[25] Sumaira Naz, Zahoor M, Umar MN, Ali Barkat, Ullah Riaz, Abdelaaty, et al. Enzyme inhibitory, antioxidant and antibacterial potentials of synthetic symmetrical and unsymmetrical thioureas. Drug Des Devel Ther 2019;13:3485–95.
[26] Perumal M, Priya SE, Senthamil SP. Synthesis, characterization and antimicrobial evaluation of imidazolyl thiazolidinedione derivatives. Asian J Chem 2014, http://dx.doi.org/10.1016/j.arabjc.2014.08.010.
[27] Alagarsamy V, Solomon RV, Dhanaba K. Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3-H-quinazolin-4-one as analgesic, anti-inflammatory agents. Bioorg Med Chem 2007;15:235–41.
[28] Fluoroquinolones Soni K. Chemistry and action; a review. Ind Glob J Pharm Sci 2012;2(1):43–53.
[29] Wein M, Bochner BS. Adhesion molecule antagonist: future therapies for allergic diseases. Eur Resp J 1993;6:1239–42.
[30] Ala A, Dhillon AP, Hodgson HJ. Role of cell adhesion molecule in leukocyte recruitment in the liver and gut. Int J Exp Biol 2003;84:1–16.
[31] Lobaton T, Vermeire S, Van Assche G, Rutgeerts P. Anti-adhesion therapies for inflammatory bowel disease. Aliment Pharmacol Ther 2014;39(6):579–94.
[32] Panes J, Penalva M, Pique JM. New therapeutic targets inflammatory bowel disease (IBD): cell adhesion molecules. Immunologic 2003;22(2):203–14.
[33] Ghosh S, Remo P. Anti-adhesion molecule therapy for inflammatory bowel disease. Ther Adv Gastroenterol 2010;3(4):239–58.
[34] Park SC, Jeen YT. Anti-integrin therapy for inflammatory bowel disease. World J Gastroenterol 2018;24(17):1868–80, http://dx.doi.org/10.3748/wjg.v24.i17.1868.
[35] Bram Verstockt, Marc Ferrante, Vermeire S, Gert Van A. New treatment options for inflammatory bowel diseases. J Gastroenterol 2018;(53):585–90, http://dx.doi.org/10.1007/s00535-018-1449-z.