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Antimicrobial and Anti-Inflammatory Activity Studies of Novel Thiazolopyrimidines

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ABSTRACT

Novel thiazolopyrimidine derivatives (4a-l) were efficiently synthesized via the cyclo-condensation reactions of 2-(3-dimethylamino) acryloyl) phenyl 4-methylbenzene sulfonates with 2,3-dihydro-4-phenylthiazol-2-amines under microwave irradiation in ethanol catalyzed by iodine and the synthesized compounds were evaluated for their in vitro antimicrobial and anti-inflammatory activities. Among the newly synthesized compounds, 4d, 4h and 4l have exhibited potent antibacterial activity where as other derivatives 4b and 4j have showed moderate activity in comparison to standard drug amphcillin. The derivatives, 4d and 4l have displayed potent antifungal activity when their activity data was compared with standard drug norcadine. Some of the selected compounds were also screened for their anti-inflammatory activity and the results are compared with standard drug indomethacin. Among the derivatives, 4j possessed potent anti-inflammatory activity while 4b, 4f and 4k have exhibited moderate activity.

Keywords: Novel thiazolopyrimidine, Amphcillin

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most widely used therapeutics for the treatment of pain, fever and inflammatory conditions such as rheumatoid arthritis and osteoarthritis [1]. Recent findings have described the close relation between inflammation and cancer in which inflammation was reported to be a critical component of tumour progression. It was found that many cancers arise from sites of infection, chronic irritation and inflammation [2]. Since the discovery of aspirin as nonsteroidal anti-inflammatory drug and knowing the mechanism of action, the constant progress has been made towards developing novel anti-inflammatory drugs. To date, no drug is found to be safer for the long term treatment of anti-inflammatory conditions. Therefore, the development of safe, effective and inexpensive therapy for treating inflammatory conditions is biggest challenge for the medicinal researchers.

Thiazolopyrimidines are fused heterocycles, reported to play a key role in immune and inflammatory responses in various diseases and disorders. Thiazolopyrimidines have gained considerable attention because of their wide range of biological properties including growth factor receptor tyrosine kinase inhibitors [3] Tie-2 kinase inhibitors [4] CDC25B phosphatase inhibitors [5] dipeptidyl peptidase IV Inhibitors [6] acetylcholinesterase inhibitors [7] antimalarial and anti-HIV [8] CXCR2 receptor antagonists [9] antioxidant and antimicrobial [10] anticancer [11] and anti-inflammatory [12].

Furthermore, thiazole derivatives have possessed diverse pharmacological properties [13]. Pyrimidines have an important applications in pharmaceuticals and found to possess a wide range of biological properties such as antimalarial [14] HIV-1 inhibitor [15] anti-inflammatory [16] anticancer [17] and antiallergic [18] activities. The nucleic acid bases like thymine, cytosine, and uracil have been identified to contain pyrimidine moiety. They are used as substrates for the synthesis of several important pharmaceutical agents. On the other hand, it has been observed that several organic compounds containing aromatic sulfonate moiety were found to exhibit papillomavirus microbicidal [19] anti-human immunodeficiency virus-1 [20] antineoplastic [21] and anticancer [22] activities. The various literature methods for the synthesis of thiazolopyrimidines are associated with many drawbacks including longer reaction time with drastic conditions, low yields, difficulty in isolation of products, use of hazardous and expensive chemicals, and involvement of multistep synthetic routes.

In view of the above and in continuation of our previous work in heterocyclic chemistry [23] herein we submit a report of our findings on the synthesis and pharmacological evaluation of new thiazolopyrimidines.

MATERIALS AND METHOD

All the chemicals and reagents were of analytical grade. They were purchased from Loba, S. d. Fine and Spectrochem companies. The solvents were purchased from Loba Company and were used without further purifications. Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel-G coated TLC plates. IR spectra were recorded in KBr disc on a Schimadzu 650, FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H-NMR 200 MHz and ^{13}C-NMR 50 MHz). The chemical shifts are reported in parts per million (δ ppm) using tetramethylsilane as an internal standard. The splitting pattern abbreviations are as follows: s (singlet), d (doublet), t (triplet), and m (multiplet). Elemental analyses were performed on a Carlo Erba–1108 analyzer. Microwave-assisted reactions were carried out by using Cata Scientific Microwave System (2450 MHz, India).The crystallization of all intermediates and final products were carried out from ethanol.

SYNTHESIS

General procedure for the synthesis of 2,3-dihydro-4-phenylthiazol-2-amines (2a-d)

A mixture of 2-(2-aminothiazol-4-yl) phenol **1a** (0.01mol) and $LiAlH_4$ (0.01 mol) in freshly distilled tetrahydrofuran (10mL) was stirred at 0-5^{o}C temperature for 1h and then at room temperature for 3-4h. The progress of reaction was monitored by TLC using solvent mixture n-hexane and ethyl acetate (8:2). After the completion of reaction, the reaction mixture was filtered and poured into 100gm crushed ice. The solid separated out after stirring was filtered off, washed with cold water and dried. The crude product was purified by the crystallization method using ethyl alcohol.

2-(2-Amino-2,3-dihydrothiazol-4-yl) phenol (2a)

Yield 70%; mp 160-162^{o}C; IR (KBr, cm^{-1}): ν_{max} 3044 (Ar C-H stretch), 1670-1472 (Ar C=C stretch), 3320 (-NH stretch), 3450 (-OH stretch). ^{1}H NMR (200MHz, $CDCl_3$): 7.35-7.70 (5H, *J* = 8.0, m, Ar-H), 5.58 (1H, s, thiazole ring), 5.23 (1H, s, OH), 4.84 (1H, s, thiazole ring), 3.15 (2H, s, NH_2), 2.52 (1H, s, NH). ^{13}C NMR (50MHz, $CDCl_3$): δ 65.2, 100.3, 106.2, 114.4, 120.8, 127.5, 128.7, 139.0, 157.5; Elemental analysis: $C_9H_{10}N_2OS$, Calcd: C, 55.65; H, 5.19; N, 14.42; Found: C, 55.60; H, 5.15; N, 14.40.

2-(2-Amino-2,3-dihydothiazol-4-yl)-5-methoxyphenol (2b)

Yield 80%; mp 120-121 ^{o}C; IR (KBr, cm^{-1}): ν_{max} 3036 (Ar C-H stretch), 1667-1465 (Ar C=C stretch), 3310 (-NH stretch). ^{1}H NMR (200MHz, $CDCl_3$): 7.00-7.12 (2H, *J* = 8.0, d, Ar-H), 7.25-

7.30 (2H, *J* = 8.0, d, Ar-H), 5.56 (1H, s, thiazole ring), 3.74 (1H, s, OCH_3), 4.82 (1H, s, thiazole ring), 3.15 (2H, s, NH_2), 2.46 (1H, s, NH). ^{13}C NMR (50MHz, $CDCl_3$): δ 56.21, 65.7, 100.0, 112.2, 126.5, 127.6, 128.5, 139.2, 157.1; Elemental analysis: $C_{10}H_{12}N_2OS$, Calcd: C, 57.67; H, 5.81; N, 13.45; Found: C, 57.65; H, 5.82; N, 13.44.

4-(2-Amino-2,3-dihydrothiazol-4-yl) benzene-1,3-diol (2c)

Yield 84%; mp 188-191 ^oC; IR (KBr, cm^{-1}): ν_{max} 3042 (Ar C-H stretch), 1674-1475 (Ar C=C stretch), 3312 (-NH stretch), 3455 (-OH stretch). ^1H NMR (200MHz, $CDCl_3$): 6.10 (1H, s, Ar-H), 6.34-6.42 (2H, *J* = 8.0, d, Ar-H), 7.05-7.17 (2H, *J* = 8.0, d, Ar-H), 5.41 (1H, s, thiazole ring), 5.50 (1H, s, OH), 5.52 (1H, s, OH), 4.84 (1H, s, thiazole ring), 3.14 (2H, s, NH_2), 2.45 (1H, s, NH). ^{13}C NMR (50MHz, $CDCl_3$): δ 65.8, 100.0, 102.4, 102.8, 107.2, 128.5, 139.2, 157.1, 157.2. Elemental analysis: $C_9H_{10}N_2O_2S$, Calcd: C, 51.41; H, 4.79; N, 13.32; Found: C, 51.45; H, 4.71; N, 13.20.

2-(2-Amino-2,3-dihydrothiazol-4-yl)-5-chlorophenol (2d)

Yield 80%; mp 137-141 ^oC; IR (KBr, cm^{-1}): ν_{max} 3037 (Ar C-H stretch), 1640-1480 (Ar C=C stretch), 3322 (-NH stretch), 3465 (-OH stretch). ^1H NMR (200MHz, $CDCl_3$): 6.65 (1H, s, Ar-H), 6.74-6.78 (2H, *J* = 8.0, d, Ar-H), 7.04-7.20 (2H, *J* = 8.0, d, Ar-H), 5.40 (1H, s, thiazole ring), 5.50 (1H, s, OH), 4.82 (1H, s, thiazole ring), 3.15 (2H, s, NH_2), 2.41 (1H, s, NH). ^{13}C NMR (50MHz, $CDCl_3$): δ 65.2, 102.4, 104.4, 119.2, 128.3, 132.4, 139.2, 157.1, 157.2; Elemental analysis: $C_9H_{9Cl}N_2OS$, Calcd: C, 47.27; H, 3.97; N, 12.25; Found: C, 47.22; H, 3.94; N, 12.25.

Synthesis of thiazolopyrimidines (4a-l)

The equimolar mixture of enaminone **3a** (0.01mol) and 2,3-dihydro-4-phenylthiazol-2-amine **2a** (0.01mol) was placed into 250 ml round bottom flask containing ethanol (10 mL) and 0.3-0.4 eq. of molecular iodine. The reaction mixture was subjected to microwave oven for 9-10 min at 100 ^oC temperature. The progress of reaction was monitored by using thin layer chromatography. After the completion of reaction, the mixture was concentrated, cooled and poured into ice cold water containing 10% sodium thiosulphate to neutralize excess of iodine. The reaction mixture was stirred for 10 min. and the separated solid was filtered, washed 5-6 times with cold water, dried and crystallized from alcohol to obtain the pure product. Following the same experimental procedure all other derivatives were synthesized.

2-(3-(2-Hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methyl benzene sulfonate (4a)

White solid; yield 88%; mp 148-151^oC; IR (KBr, cm^{-1}): ν_{max} 3051 (Ar C-H stretch), 2975 (C-H stretch), 3465 (OH stretch), 1640-1457 (Ar C=C stretch), 1340 (SO_3 stretch). ^1H NMR (200MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3), 3.67 (1H, s), 5.64 (1H, s), 4.51 (1H, d), 7.48 (1H, d), 5.16 (1H, s,

OH), 6.87-6.94 (4H, *J* = 8.75, m, Ar-H), 7.04-7.52 (4H, *J*= 8.56, m, Ar-H), 7.58-7.89 (4H, m, Ar-H). ^{13}C NMR (50MHz, $CDCl_3$): δ 21.6, 71.3, 84.3, 101.4, 106.8, 107.5, 112.9, 113.2, 119.8, 120.2, 124.5, 126.0, 127.5, 127.7, 129.6, 131.4, 132.3, 139.9, 143.9, 151.9, 155.4, 157.0, 162.3; Elemental analysis: $C_{25}H_{20}N_2O_4S_2$, Calcd: C, 63.01; H, 4.23; N, 5.88; Found: C, 63.04; H, 4.30; N, 5.75.

2-(3-(2-Hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl)-4,6-diiodophenyl 4-methyl benzene sulfonate (4b)

Brown solid; yield 87%; mp 110-112ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3084 (Ar C-H stretch), 2956 (C-H stretch), 3446 (-OH stretch), 1635-1460 (Ar C=C stretch), 1329 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.34 (3H, s, CH_3), 3.74 (1H, s), 5.85 (1H, s), 4.55 (1H, d), 7.60 (1H, d), 5.28 (1H, s, OH), 7.08 (2H, s, Ar-H), 7.11-7.53 (4H, *J* = 8.75, m, Ar-H), 7.58-7.86 (4H, *J* = 8.60, m, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 70.5, 84.7, 91.5, 93.1, 102.2, 114.0, 114.4, 117.2, 118.8, 127.0, 127.3, 128.8, 130.5, 131.6, 140.4, 141.0, 144.8, 152.4, 155.1, 157.2, 163.4; Elemental analysis: $C_{25}H_{18}I_2N_2O_4S_2$, Calcd: C, 41.23; H, 2.49; N, 3.84; Found: C, 41.17; H, 2.44; N, 3.80.

2,4-Dibromo-6-(3-(2-hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methyl benzene sulfonate (4c)

White solid; yield 86%; mp 154-156ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3088 (Ar C-H stretch), 2954 (C-H stretch), 3455 (-OH stretch), 1648-1461 (Ar C=C stretch), 1342 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.35 (3H, s, CH_3), 3.77 (1H, s), 5.80 (1H, s), 4.51 (1H, d), 7.63 (1H, d), 5.30 (1H, s, OH), 6.82-7.02 (4H, *J* = 8.70, m, Ar-H), 7.48 (2H, s, Ar-H), 7.50-7.96 (4H, *J* = 8.58 m, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 70.3, 84.1, 99.8, 107.3, 112.5, 114.2, 114.8, 115.3, 115.7, 120.8, 126.2, 127.2, 127.7, 129.1, 130.6, 133.6, 139.0, 143.0, 145.6, 151.2, 155.4, 162.2; Elemental analysis: $C_{25}H_{18}Br_2N_2O_4S_2$, Calcd: C, 47.33; H, 2.86; N, 4.42; Found: C, 47.28; H, 2.88; N, 4.43.

4-Chloro-2-(3-(2-hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methyl benzene sulfonate (4d)

White solid; yield 89%; mp 107-109ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3081 (Ar C-H stretch), 2955 (C-H stretch), 3463 (-OH stretch), 1650-1480 (Ar C=C stretch), 1319 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 3.73 (1H, s), 5.77 (1H, s), 4.60 (1H, d), 7.61 (1H, d), 5.44 (1H, s, OH), 6.71-7.44 (4H, *J* = 8.75, m, Ar-H), 7.62-7.80 (3H, m, Ar-H), 7.86-8.06 (4H, *J* = 8.62, m, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 71.1, 84.0, 101.3, 111.0, 113.1, 115.1, 116.2, 122.3, 126.1, 127.1, 127.7, 128.1, 128.5, 130.6, 132.3, 140.0, 143.0, 144.5, 151.2, 155.0, 162.6; Elemental analysis: $C_{25}H_{19}ClN_2O_4S_2$ Calcd: C, 58.76; H, 3.75; N, 5.48; Found: C, 58.74; H, 3.75; N, 5.50.

2-(3-(4-Methoxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methylbenzene sulfonate (4e)

White solid; yield 80%; mp 180-182ºC; IR (KBr, cm^{-1}): ν_{max} 3053 (Ar C-H stretch), 2983 (C-H stretch), 1637-1445 (Ar C=C stretch), 1334 (SO_3 stretch). ^{1}H NMR (200MHz, $CDCl_3$): δ 2.36 (3H, s, CH_3), 3.71 (1H, s), 5.72 (1H, s), 4.56 (1H, d), 7.47 (1H, d), 3.76 (1H, s, OCH_3), 6.82-6.90 (4H, *J* = 8.10, m, Ar-H), 7.02-7.57 (4H, *J* = 7.85, m, Ar-H), 7.53-7.78 (4H, *J* = 8.57, m, Ar-H). ^{13}C NMR (50MHz, $CDCl_3$): δ 21.6, 53.7, 71.2, 83.3, 101.5, 107.4, 113.3, 118.5, 119.7, 121.0, 127.2, 127.5, 128.1, 128.7, 129.0, 130.3, 130.7, 140.3, 142.5, 144.9, 152.8, 157.0, 162.4; Elemental analysis: $C_{26}H_{22}N_2O_4S_2$, Calcd: C, 63.65; H, 4.53; N, 5.71; Found: C, 63.64; H, 4.43; N, 5.68.

2,4-Diiodo-6-(3-(4-methoxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methyl benzene sulfonate (4f)

Pale brown solid; yield 88%; mp 104-106ºC; IR (KBr, cm^{-1}): ν_{max} 3082 (Ar C-H stretch), 2947 (C-H stretch), 1637-1458 (Ar C=C stretch), 1331 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 3.73 (1H, s), 5.87 (1H, s), 4.52 (1H, d), 7.65 (1H, d), 3.75 (1H, s, OCH_3), 7.10 (2H, s, Ar-H), 7.12-7.57 (4H, *J* = 8.84, m, Ar-H), 7.55-7.83 (4H, *J* = 8.55, m, Ar-H).^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 54.2, 70.8, 84.4, 91.5, 93.0, 102.0, 113.7, 114.4, 116.2, 118.8, 127.2, 127.9, 128.3, 130.3, 131.7, 140.1, 141.9, 144.8, 152.7, 155.1, 163.1; Elemental analysis: $C_{26}H_{20}I_2N_2O_4S_2$, Calcd: C, 42.06; H, 2.72; N, 3.77; Found: C, 42.12; H, 2.74; N, 3.80.

2,4-Dibromo-6-(3-(4-methoxyphenyl)-8a*H*-thiazolo[3,2-*a*] pyrimidin-5-yl) phenyl 4-methyl benzene sulfonate (4g)

White solid; yield 85%; mp 127-128ºC; IR (KBr, cm^{-1}): ν_{max} 3083 (Ar C-H stretch), 2956 (C-H stretch), 1640-1465 (Ar C=C stretch), 1332 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.37 (3H, s, CH_3), 3.80 (1H, s), 5.83 (1H, s), 4.56 (1H, d), 7.69 (1H, d), 3.74 (1H, s, OCH_3), 6.81-7.08 (4H, *J* = 8.82, m, Ar-H), 7.52 (2H, s, Ar-H), 7.53-7.99 (4H, *J* = 8.45, m, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.7, 53.4, 71.6, 84.3, 91.6, 93.3, 101.5, 113.0, 114.3, 117.1, 119.5, 124.2, 127.2, 127.6 , 128.2, 129.5, 130.0, 140.1, 144.0, 145.1, 152.0, 157.1, 162.4; Elemental analysis: $C_{26}H_{20}Br_2N_2O_4S_2$, Calcd: C, 48.16; H, 3.31; N, 4.32; Found: C, 48.20; H, 3.18; N, 4.40.

4-Chloro-2-(3-(4-methoxyphenyl)-8a*H*-thiazolo[3,2-*a*]pyrimidin-5-yl)phenyl 4-methyl benzene sulfonate (4h)

White solid; yield 84%; mp 92-94ºC; IR (KBr, cm^{-1}): ν_{max} 3078 (Ar C-H stretch), 2965 (C-H stretch), 1635-1450 (Ar C=C stretch), 1327 (SO_3 stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 3.71 (1H, s), 5.73 (1H, s), 4.62 (1H, d), 7.63 (1H, d), 3.77 (1H, s, OCH_3), 6.70-7.45 (4H, *J* = 8.21, m, Ar-H), 7.61-7.76 (3H, *J* = 7.85, m, Ar-H), 7.81-8.05 (4H, *J* = 8.60, m, Ar-H). ^{13}C-

NMR (50MHz, $CDCl_3$): δ 21.6, 54.7, 69.7, 84.5, 101.5, 109.2, 112.7, 115.2, 115.4, 118.3, 127.7, 128.3, 128.6, 128.7, 129.1, 130.3, 140.1, 142.0, 143.4, 152.2, 154.0, 163.1; Elemental analysis: $C_{26}H_{21}ClN_2O_4S_2$ Calcd: C, 59.48; H, 4.03; N, 5.34; Found: C, 59.54; H, 4.10; N, 5.44.

2-(3-(2,4-Dihydroxyphenyl)-8a*H*-thiazolo[3,2-*a*]pyrimidin-5-yl)phenyl 4-methylbenzene sulfonate (4i).

White solid; yield 85%; mp 151-153 ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3082 (Ar C-H stretch), 2960 (C-H stretch), 1645-1454 (Ar C=C stretch), 1337 (SO_3 stretch), 3470 (-OH stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 3.75 (1H, s, Methine), 5.29 (1H, s, OH), 5.30 (1H, s, OH), 5.34 (1H, d, Pyrimidine), 5.67 (1H, s, thiazole), 6.43 (1H, s), 6.50 (1H, d,), 6.70-7.25 (5H, *J* = 8.21, m, Ar-H), 7.31 (2H, *J* = 7.85, d, Ar-H), 7.57 (1H, d, pyrimidine), 7.74 (2H, *J* = 7.85, d, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 68.2, 85.1, 97.5, 98.0, 101.3, 105.1, 105.5, 112.7, 113.2, 118.3, 125.7, 126.0, 126.4, 127.1, 127.5, 128.8, 129.1, 140.1, 142.0, 144.4, 147.2, 155.8, 156.1, 161.3; Elemental analysis: $C_{25}H_{20}N_2O_5S_2$ Calcd: C, 60.96; H, 4.09; N, 5.69; Found: C, 60.86; H, 4.05; N, 5.72.

2-(3-(2,4-Dihydroxyphenyl)-8a*H*-thiazolo[3,2-*a*]pyrimidin-5-yl)-4,6-diiodophenyl 4-methylbenzene sulfonate (4j).

Brown solid; yield 85%; mp 101-103 ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3080 (Ar C-H stretch), 2966 (C-H stretch), 1630-1442 (Ar C=C stretch), 1324 (SO_3 stretch), 3473 (-OH stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 3.71 (1H, s, Methine), 5.28 (1H, s, OH), 5.30 (1H, s, OH), 5.35 (1H, d, Pyrimidine), 5.64 (1H, s, thiazole), 6.50 (1H, d,), 6.72 (1H, d), 7.31 (2H, *J* = 7.85, d, Ar-H), 7.50 (1H, s, Ar-H), 7.57 (1H, d, pyrimidine), 7.78 (2H, *J* = 7.85, d, Ar-H), 7.80 (2H, *J* = 7.85, d, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 70.4, 84.7, 91.4, 93.3, 98.8, 101.1, 102.0, 107.0, 110.4, 114.2, 118.8, 127.0, 127.3, 128.4, 128.8, 129.5, 132.4, 140.3, 141.1, 144.8, 156.4, 157.1, 160.2, 163.4; Elemental analysis: $C_{25}H_{18}I_2N_2O_5S_2$, Calcd: C, 40.34; H, 2.44; N, 3.76; Found: C, 40.27; H, 2.34; N, 3.80.

2-(3-(4-Chloro-2-hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*]pyrimidin-5-yl)-4,6-diiodophenyl 4-methylbenzene sulfonate (4k).

Light brown solid; yield 80%; mp 77-80 ºC; IR (KBr, cm^{-1}): ν $_{max}$ 3086 (Ar C-H stretch), 2975 (C-H stretch), 1650-1452 (Ar C=C stretch), 1334 (SO_3 stretch), 3460 (-OH stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 3.73 (1H, s, Methine), 5.30 (1H, s, OH), 5.36 (1H, d, Pyrimidine), 5.60 (1H, s, thiazole), 6.51 (1H, d,), 6.74 (1H, d), 7.33 (2H, *J* = 7.85, d, Ar-H), 7.55 (1H, s, Ar-H), 7.60 (1H, d, pyrimidine), 7.75 (2H, *J* = 7.85, d, Ar-H), 7.83 (2H, *J* = 7.85, d, Ar-

H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 70.4, 84.5, 91.4, 93.0, 98.5, 101.4, 102.1, 106.0, 111.4, 113.2, 119.8, 126.0, 127.3, 128.0, 128.5, 129.4, 132.0, 133.5, 140.0, 141.7, 143.7, 156.0, 157.4, 163.2; Elemental analysis: $C_{25}H_{17}ClI_2N_2O_4S_2$, Calcd: C, 39.36; H, 2.25; N, 3.67; Found: C, 39.27; H, 2.34; N, 3.70.

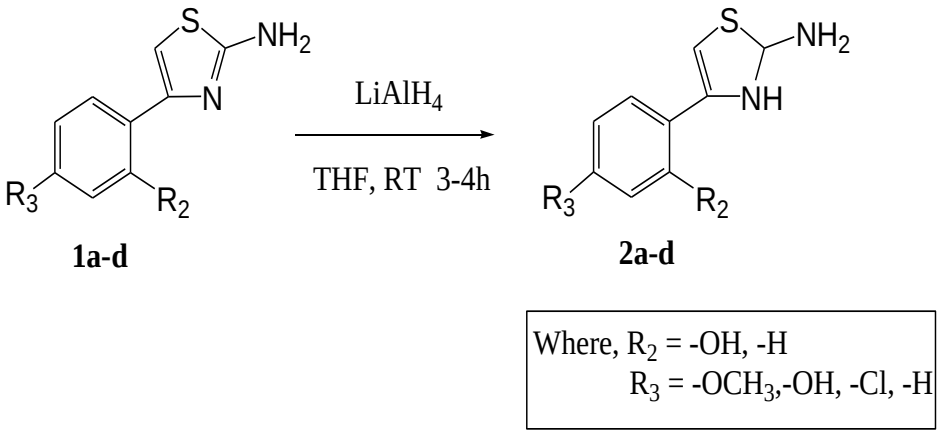
2,4-Dibromo-6-(3-(4-Chloro-2-hydroxyphenyl)-8a*H*-thiazolo[3,2-*a*]pyrimidin-5-yl)phenyl 4-methylbenzene sulfonate (4l)

White solid; yield 90%; mp 188-191 ^{o}C; IR (KBr, cm^{-1}): ν_{max} 3080 (Ar C-H stretch), 2970 (C-H stretch), 1663-1455 (Ar C=C stretch), 1344 (SO_3 stretch), 3473 (-OH stretch). ^{1}H-NMR (200MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 3.78 (1H, s, Methine), 5.35 (1H, s, OH), 5.34 (1H, d, Pyrimidine), 5.63 (1H, s, thiazole), 6.50 (1H, d,), 6.80 (1H, d), 7.40 (2H, *J* = 7.85, d, Ar-H), 7.62 (1H, s, Ar-H), 7.65 (1H, d, pyrimidine), 7.71 (2H, *J* = 7.85, d, Ar-H), 7.81 (2H, *J* = 7.85, d, Ar-H). ^{13}C-NMR (50MHz, $CDCl_3$): δ 21.6, 70.5, 84.7, 91.7, 93.2, 99.0, 101.0, 101.5, 106.8, 110.4, 114.3, 120.5, 127.0, 127.3, 128.5, 128.9, 129.5, 133.0, 133.5, 140.3, 142.6, 144.5, 155.8, 158.0, 163.8; Elemental analysis: $C_{25}H_{17}Br_2ClN_2O_4S_2$, Calcd: C, 44.90; H, 2.56; N, 4.19; Found: C, 44.87; H, 2.45; N, 4.20.

RESULTS AND DISCUSSION

Chemistry

The synthesis of thiazolopyrimidines **4a-l** was carried out by an efficient and versatile synthetic route as outlined in **Scheme 2**. In the first stage, the important substrates 2-(3-dimethylamino)acryloyl)phenyl 4-methylbenzene sulfonates **3a-d** were prepared following our previous protocol[24] and 2,3-dihydro-4-phenylthiazol-2-amines **2a-d** were prepared from commercially available 2-amino-4-phenyl thiazoles **1a-d**. 2-Amino-4-phenyl thiazole **1a** on treating with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran gives 2,3-dihydro-4-phenylthiazol-2-amine 2a in 90% yield at room temperature. The structure of this compound was confirmed by spectroscopic methods. The ^{1}H NMR spectrum of this compound has showed singlet at δ 5.23 ppm, δ 3.15 ppm and δ 2.52 ppm is due to the protons from -OH, $–NH_2$ and -NH functional groups. The singlet appeared at δ 5.58 and δ 4.84 is for the protons of thiazole ring. In the IR spectrum of same compound the weak band at 3320 cm^{-1} and strong band at 3450 cm^{-1} are due to N-H and O-H group stretching vibrations. Similarly, other derivative 2b was prepared and its structure was assigned by spectroscopic methods **Scheme 1**.



Scheme 1: Synthesis of 2,3-dihydro-4-phenylthiazol-2-amines.

Our previous results in organic synthesis using microwaves have motivated us to employ this strategy for some new transformations. Therefore, we firstly investigated the synthesis of thiazolopyrimidine *via* the condensation of 2-(3-dimethylamino) acryloyl)phenyl 4-methylbenzene sulfonate 3a with 2,3-dihydro-4-phenylthiazol-2-amine 2a in water using microwaves at the temperature range of 90-100 ^{o}C for 10-15 min. However, under these reaction conditions no product was obtained. Therefore, we thought to carry out the same reaction in ethanol maintaining the temperature in the range of 80-100 ^{o}C for 10 min. The progress of reaction monitored by thin layer chromatography showed the formation of product which was isolated in 40% yield. In order to improve the yield, the reaction was conducted in the presence of catalytic amount of iodine (0.3-0.5 eq.) in ethanol (10mL), maintaining the temperature in the range of 70-110 ^{o}C to give thiazolopyrimidine 4a in 90% yield in 10 min.

For the optimization of the reaction conditions, same condensation reaction was investigated by using different amounts of catalyst at 100 ^{o}C temperature for the time period of 9-10 min and results are entered in Table 1. The smooth transformation of reactants to product was observed when the amount of catalyst employed was 0.3 eq. at 100 ^{o}C temperature to give 90% yield (Entry 3, Table-1). However, the yield remains unchanged when the amount of catalyst was further increased from 0.3 to 0.4 and 0.5 eq.

For the optimization of the reaction temperature, the condensation of 2-(3-dimethylamino)acryloyl)phenyl 4-methylbenzene sulfonate 3a with 2,3-dihydro-4-phenylthiazol-2-amine 2a in alcohol was carried out using microwaves in the presence of catalytic amount of iodine (0.3 eq.) at different temperatures ranging from 70 to 110 ^{o}C, with an increment of 10 ^{o}C temperature each time, the satisfactory yield (90%) of 4a was obtained at 100 ^{o}C temperature

(Entry 4, Table-2), whereas the yield remains unchanged when the temperature was further increased to 110 ^{o}C (Entry 5, Table-2).

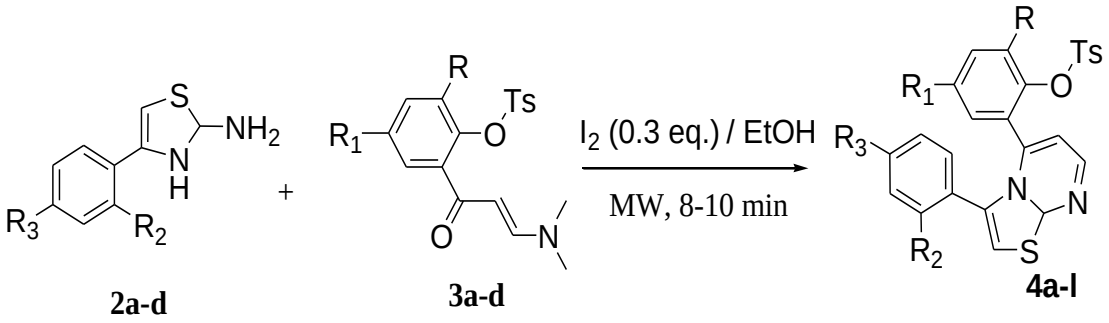
Table 1: Catalyst optimization for the synthesis of 4a

Entry	Catalyst (I_2)	Time (min)	T(^{o}C)	Yield (%)[a]
1	0.1 eq.	10	100	60.0
2	0.2 eq.	10	100	80.0
3	0.3 eq.	10	100	90.0
4	0.4 eq.	10	100	90.0
5	0.5 eq.	10	100	90.0

Table 2: Temperature optimization for the synthesis of 4a

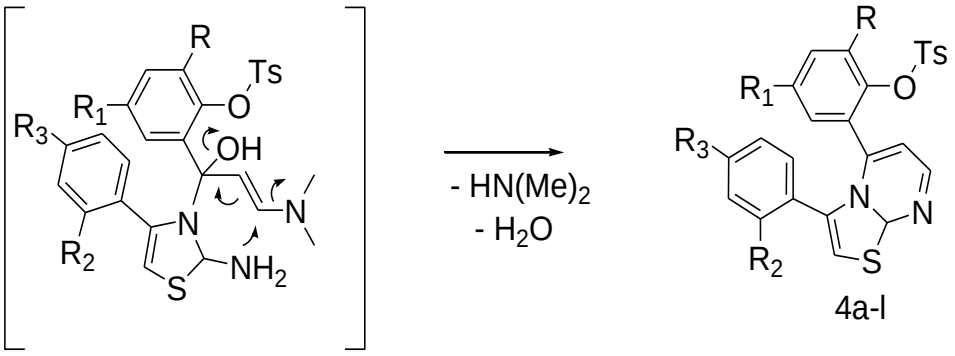
Entry	Catalyst (I_2)	Time (min)	T(^{o}C)	Yield (%)[a]
1	0.3 eq.	09	70	40.0
2	0.3 eq.	10	80	60.0
3	0.3 eq.	08	90	80.0
4	0.3 eq.	10	100	90.0
5	0.3 eq.	09	110	90.0

The progress of reaction was monitored at different temperatures. The good yield of 4a was obtained at temperature 100^{o}C, whereas the yield remains unchanged when the temperature was further increased to 110 ^{o}C. The optimum condition based on the yield and reaction time was 100 ^{o}C with 90% yield in 8-10 min. The IR spectrum for compound 4a showed bands at 3051 cm^{-1} for Ar C-H, 3465 cm^{-1} for O-H, 1640-1457 cm^{-1} for Ar C=C and 1340 cm^{-1} for SO_3 stretching vibrations. The ^{1}H NMR spectrum of this compound showed singlet at δ 2.31 for CH_3 group protons from tosyl group, singlet for methine proton at δ 3.67, singlet for thiazole ring proton at δ 5.64, doublets for two protons from pyrimidine ring at δ 4.51 and δ 7.48 respectively and singlet for OH group proton at δ 5.16. The ^{13}C NMR spectrum of this compound also supports the structure showing the absorption peaks at δ 21.6, 71.3, 84.3, 101.4, 143.9, and 157.0 correspond to the carbon atoms for CH_3, methine, carbon atoms from thiazole ring and carbon atoms from pyrimidine ring respectively. Therefore, the preparation of all thiazolopyrimidines 4a-l under microwave irradiations was carried out at 100 ^{o}C, which was afforded the desired products in excellent yield (80-90%) and reasonable reaction times 8-10 min.



Scheme 2: Synthesis of thiazolopyrimidines 4a-l

The applicability of present method was also studied on large scale reaction by employing the equimolar amounts (5mmol) of compound 3a and 2a at low to high power setting (100W, 100 ^{o}C temperature) in ethanol/iodine as reaction media to give excellent yield of the desired thiazolopyrimidines. The structure of all the newly synthesized compounds was confirmed from IR, ^{1}H NMR and ^{13}C NMR spectroscopic methods and elemental analysis. Scheme 3 represents the possible mechanism for the formation of thiazolopyrimidines.



Scheme 3: Mechanistic route for the formation of thiazolopyrimidines

Structure Activity Relationship Study (SARs)

All synthesized compounds in a series 4a-l were screened for their antimicrobial activities using ampicillin and norcadine as standard drugs by the agar cup plate method as reported in Indian and British Pharmacopoeia. The results of survey, Table 3, indicate that all the tested compounds are active against bacterial and fungal strains. However, the compounds 4d and 4l are potent against both Gram-positive and Gram-negative bacteria. This increased potency may be due to the presence of thiazolopyrimidine ring, aryl sulfonate moiety and the introduction of hydroxy and chloro groups in the benzene ring in the positions 2 and 4 respectively. The compounds, 4b and 4j

are equipotent and some what less active than 4d and 4l against bacteria. Unfortunately, compounds 4a and 4e are moderately active against both bacterial and fungal strains even though the molecule contains thiazolopyrimidine ring. The compounds, 4d and 4l exhibit increased potency against fungal strains this may be because of the presence of chloro and hydroxy groups with thiazolopyrimidine ring and aryl sulfonate moiety. The compounds 4e and 4f were found to be ineffective against *fungi Aspergillus niger* with zero zone of inhibition. The zone of inhibition was also zero for the compound 4a against fungi *Fusarium oxysporium and aspergillus flavus*.

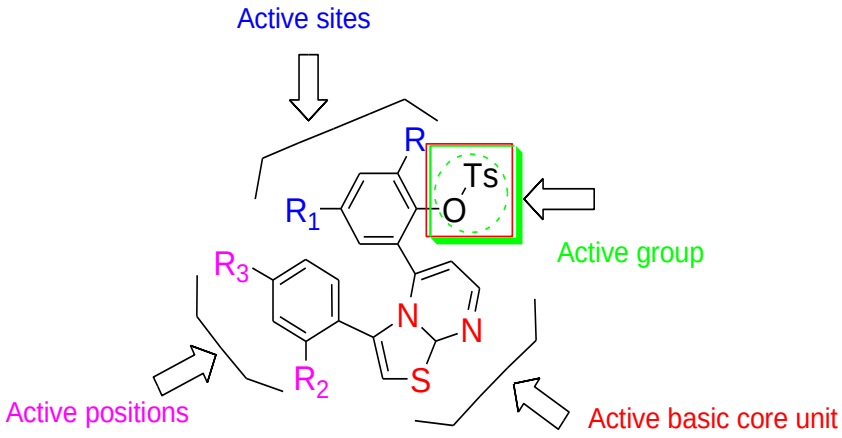


Figure 1: Structure activity relationship of thiazolopyrimidines.

Some selected thiazolopyrimidines from the series 4a-l were evaluated for their anti-inflammatory activity and the results were compared. The activity data reveals potent activity for the derivatives, 4f and 4j with % reduction in edema values 11.62 and 13.95 respectively after 6h. This increased activity may be attributed to the presence of diiodo, methoxy, dihydroxyl and aryl sulfonate groups in the thiazolopyrimidine structure at the appropriate positions. The compound, 4f is less potent than 4j this may be because of the absence of hydroxyl groups in the structure. The compounds, 4b, 4k and 4l are equipotent and have showed moderate activity at the concentration 50 mg/kg and the results are compared with standard drug indomethacin. They contain important groups in their chemical structure such as hydroxyl and iodo, hydroxyl and chloro, and hydroxyl and bromo respectively. Thiazolopyrimidine 4a with % REV 7.18 and its analogues 4c and 4d with % REV 9.09 and 9.72 have showed some low anti-inflammatory activity at the same concentration. The low activity of these compounds indicates that the minor changes in the aromatic ring by the substitutions of functional groups profoundly influence the activity figure 1. Anti-inflammatory activity data (Table 4) reveals that, most of the tested compounds are found to exhibit good anti-inflammatory effects on the edema paw volumes of treated animals.

Study of antimicrobial and anti-inflammatory activity

Antimicrobial activity

The antibacterial activity of the test samples was determined by agar cup plate method [25] using ampicillin (100 µg / ml) as standard drug and four pathogens such as *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. A sterile borer was used to prepare cups of 10 mm diameter in the agar media spread with the microorganisms. 0.1 ml of inoculums was spread on the agar plate by spread plate technique. Accurately measured (0.1 ml) solution of each synthesized compound and standard samples were added to the cups with a micropipette. All the plates were kept in a refrigerator at 2 to 8 ^{o}C for a period of two hours for effective diffusion of test compounds and standards. Later, they were incubated at 37 ^{o}C for 24h. The presence of definite zones of inhibition around the cup indicated antibacterial activity. The solvent control was run simultaneously to assess the activity of dimethyl sulphoxide (DMSO), which was used as a solvent for extracts. The diameter of the zone of inhibition was measured and recorded. The antifungal activity of synthesized compounds was determined by using *Aspergillus niger, Aspergillus flavus,* and *Fusarium oxysporium* pathogens. Dimethyl sulphoxide was used as control and dextrose agar as culture medium for antifungal activity. Norcadine (100 µg / ml) was used as standard drug for the comparison and determination of their antifungal activities. This method is based on diffusion of antifungal component from reservoir hole to the surrounding inoculated Sabouraud dextrose agar medium, so that the growth of fungus is inhibited as zone around the hole. Using flamed sterile borer the medium was bored and the prepared extracts of three concentrations were taken and 0.1ml each extract was added in each bore. This procedure was carried out for the both fungi. The surface of Sabouraud's agar plate was dried out at 35 ^{o}C. The above operation was carried out in aseptic condition and 0.1 ml test solution was added to the respective bore and 0.1 ml norcadine was taken as standard reference. A control having only dimethyl sulphoxide was maintained in each plate. The plates were incubated at 35 ^{o}C for 48 h. In the end values of zones of inhibition were recorded in mm.

Table 3: Antimicrobial Activity of Thiazolopyrimidines.

Entry	Zone of inhibition in mm Bacteria				Zone of inhibition in mm Fungi		
	E C	***B S***	***PA***	***SA***	***FO***	***AF***	***AN***
4a	08	10	12	09	00	00	10
4b	14	16	19	14	13	19	08
4c	12	18	15	13	10	17	14
4d	18	21	20	16	22	18	15
4e	10	08	10	10	12	00	00
4f	08	12	12	17	10	14	00
4g	10	14	16	16	12	10	06
4h	20	24	18	20	14	12	07

4i	14	17	20	10	13	16	08
4j	12	18	15	13	10	17	14
4k	13	15	10	12	08	00	13
4l	18	18	20	19	25	20	10
Ampicillin	21	24	22	24	NT	NT	NT
Norcadine	NT	NT	NT	NT	27	20	25

E C = E. coli, BS = B. Subtilis, PA = P. aeruginosa, SA = S. aureus, FO = F. oxysporium, AF = A. flavus and AN = A. niger; Concentration: 100 µg mL^{-1}; Control: Dimethyl sulfoxide (DMSO); NT: Not Tested.

Study of anti-inflammatory activity

The normal control, indomethacin and test compounds were administered to the rats 30 minutes before the injection of 0.1ml of 1% carrageenan suspension in normal saline. The test drugs 50 mg/kg and the standard drug 10 mg/kg were dosed to the animals. The animals were divided into seven groups containing six animals in each group. Each group of the adult Wistar albino rats is divided into three sub groups marked as H (weights 25gm each for male and female), B (weights 30gm each for male and female) and T (weights 50gm each for male and female) respectively and they were used for the study. The animals were kept overnight on fasting. The anti-inflammatory activity study was carried by using Winter *et al.* method [26]. The experimental procedures were carried out under the guidelines of Institutional Animal Ethics Committee (IAEC) at National Toxicology Centre, Pune. A no. 26 gauge needle was used to inject the carrageenan suspension into the sub planar region of the right hind paw. Immediately thereafter the edema volume of the injected paws was measured plethysmographically by water displacement method. For comparison purpose the volume of edema at various prefixed time intervals 1h, 2h, 4h and 6h was measured. The difference between paw volumes of the treated animals was measured and the mean edema volume was calculated. Percentage reduction in edema volume was calculated by using the formula, % reduction = 100 x V0-Vt/V0. Where, V0 = Volume of the paw of control at time't'. Vt = Volume of the paw of drug treated at time't'. From the obtained data, the mean edema volume and percentage reduction in edema was calculated. The SD and SEM were calculated by using ANOVA, Dunnet's 't' test.

Table 4: Anti-inflammatory activity of Thiazolopyrimidines

Group (n)	Drug	Dose mg/kg	Difference in paw edema volume after							
			1 h Mean ± SEM	% REV	2 h Mean ± SEM	% REV	4 h Mean ± SEM	% REV	6 h Mean ± SEM	% REV
1	Control	0.1 ml	4.94 0.219	-	4.63[a] 0.210	-	4.93 0.446	-	4.73 0.262	-

2	Indomethacin	10	4.56[a] 0.256	7.69	4.16 0.171	10.15	4.29 0.231	12.98	3.96[a] 0.182	16.27
3	4a	50	4.88 0.001	1.21	4.47 0.057	3.45	4.68[b] 0.210	5.07	4.39[a] 0.240	7.18
4	4b	50	4.72 0.112	4.45	4.35[b] 0.012	6.04	4.50 0.332	8.72	4.21 0.241	10.99
5	4c	50	4.80[b] 0.213	2.85	4.44[b] 0.104	4.10	4.63[c] 0.315	4.08	4.30[b] 0.123	9.09
6	4d	50	4.74[b] 0.317	4.04	4.46[b] 0.218	3.67	4.59[b] 0.415	6.89	4.27[a] 0.231	9.72
7	4f	50	4.70[b] 0.011	4.85	4.32[a] 0.312	6.69	4.49[c] 0.515	8.92	4.18[b] 0.220	11.62
8	4g	50	4.78[b] 0.214	3.23	4.36[b] 0.230	5.83	4.54[b] 0.213	7.91	4.26[a] 0.030	9.93
9	4j	50	4.65 0.158	5.87	4.29[b] 0.072	7.34	4.41 0.132	10.54	4.07 0.245	13.95
10	4k	50	4.70[b] 0.210	4.85	4.40[a] 0.212	4.96	4.46[c] 0.415	9.53	4.23[b] 0.236	10.57
11	4l	50	4.74[b] 0.210	4.04	4.34[b] 0.103	6.26	4.59[b] 0.405	8.92	4.24[a] 0.011	10.35

n: Six albino rats in each group; REV: Reduction in edema volume; ± SEM: The standard error of the mean; Standard: Indomethacin drug; Significance level: [a]$p<0.05$, [b]$p<0.01$, [c]$p< 0.001$ compared with respective control.

CONCLUSION

The objectives of titled research work were to design, synthesize and evaluate novel thiazolopyrimidines for their antimicrobial and anti-inflammatory activities with the hope that the synthesized compounds will serve as potent antimicrobial and anti-inflammatory agents. We have developed a mild, economical and ecofriendly method for the synthesis of thiazolopyrimidines using microwave irradiation technique. The excellent yield, easy work-up and simple reaction procedure is novelty of the present work. The synthesized derivatives showed good reduction in edema volume, which was proved from the anti-inflammatory activity studies. Among the tested compounds, 4d, 4h and 4l were found to be more potent antibacterial and 4d and 4l as highly active antifungal drugs when compared with standard drugs ampicillin and norcadine. The *in* vitro anti-inflammatory activity screening of some selected derivatives reveals that the compound 4j of them exhibited more potent anti-inflammatory activity when compared with standard drug indomethacin. The present study also highlights the importance of the structural features responsible for the activities. The potent antimicrobial and anti-inflammatory activities of some synthesized compounds explore their medicinal importance and promising scope in future for further development in this field.

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