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Synthesis and Biological Evaluation of Some New 5-Acylamino-2-(3,4,5-Trimethoxyphenyl)Benzoxazoles as Potential Antibacterial and Anti-inflammatory Agents

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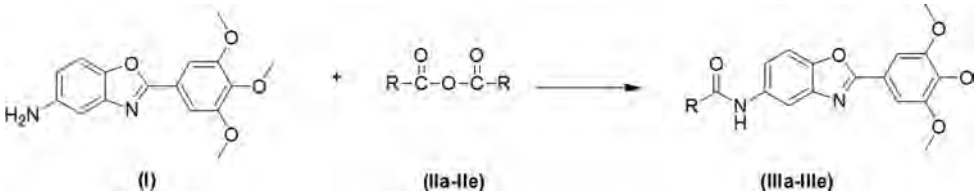
ABSTRACT Five 3,4,5-trimethoxyphenyl benzoxazole derivatives (**IIIa-IIIe**) were synthesized and evaluated for their antibacterial and anti-inflammatory activity. The structure of the compounds was confirmed by elemental and spectral analysis. The *in vitro* antimicrobial activity of the compounds was determined against some Gram-positive, Gram-negative bacteria, fungi *Candida albicans*, and *Aspergillus niger*. The results showed that the synthesized compounds possessed a broad spectrum of activity with minimum inhibitory concentrations values 500-31.25 µg/ml whereas, compound **IIIc** showed the most promising antimicrobial activity as compared to the standard ciprofloxacin and miconazole. Furthermore, compound **IIIb** showed the highest anti-inflammatory activity (68.1%), as compared to standard ibuprofen. In future, these compounds can be explored more for further development of novel antimicrobial and anti-inflammatory agents.



KEYWORDS 3,4,5-trimethoxyphenyl, Anti-inflammatory, Antimicrobial, Benzo[d]oxazole, Spectral analysis

INTRODUCTION

The prevalence of bacterial infection has increased rapidly during the past two decades.[1] Furthermore, many drug-resistant pathogens have emerged in recent years because of the increasing use or abuse of antibacterial agents for all kinds of human infectious diseases.[2-4] In addition to bacterial infection, many factors can lead to inflammation, such as biological agents, physical agents, chemical injuries, and allergic reactions. Such conditions may lead to bacteremia, toxemia, septicemia, and pyemia. As a result, the development of novel antibacterial and anti-inflammatory agents are crucial for ongoing effective therapeutic intervention.[5-8] Benzoxazole occupies a distinct niche in heterocyclic chemistry and represents a key motif in medicinal chemistry because of their capability to exhibit an array of bioactivities such as antimicrobial,[9-12] anticancer,[13,14] anti-inflammatory,[15-19] antitubercular,[20] and Alzheimer's disease.[21] In this work, as part of our ongoing studies toward the development of novel antibacterial agents and anti-inflammatory agent, we prepared new series of 5-acylamino-2-(3,4,5-trimethoxyphenyl)benzoxazole derivatives in which the phenyl ring was replaced with different substituents, to investigate their effects on activity.

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RESULTS AND DISCUSSION

Chemistry

The compounds were prepared according to the synthetic **Scheme 1**. 2-(3,4,5-trimethoxyphenyl)-benzoxazole-5-amine **(I)** was prepared by heating an equimolar mixture of 2,4-diaminophenol dihydrochloride with 3,4,5-trimethoxybenzoic acid in the presence of polyphosphoric acid (PPA) at 80° C for 3-4 h. The synthesis of intermediate was achieved by reaction of different acids with dicyclohexylcarbodiimide to form substituted anhydrides **(IIa-IIe)**. These substituted anhydrides **(IIa-IIe)** were reacted with benzoxazolamine (**I**) to give final compounds in variable yield (40-70%) **(IIIa-IIIe)**. The structures of synthesized compounds were confirmed by elemental analysis, Fourier-transform infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and Mass spectrometry.

The IR spectroscopic data of benzoxazole derivatives showed absorption bands at 1640-1660/cm (–NH-CO-) and 3300-3355/cm (-NH) indicating a synthesis of these compounds. ^{1}H NMR spectra of the desired compounds revealed the signals of methyl/ethyl, methoxy/dimethoxy, hydroxy and aromatic protons of benzoxazole ring. The singlet around 3.36-3.92 ppm showed the presence of three -OCH_3 group. The aromatic protons close to benzoxazole appeared as a singlet between 6.44 and 7.12 ppm, and other aromatic proton appeared as a multiplet peaks within the range 7.0-7.9 ppm. The NH protons were observed as D_2O exchangeable protons, while the peaks in ^{13}C NMR spectra also confirmed the synthesis of the target compound **(IIIa-IIIe)**. Mass spectra of compounds showed molecular ion peaks [M+1] at an *m/z* corresponding to their molecular formula.

BIOLOGICAL EVALUATION

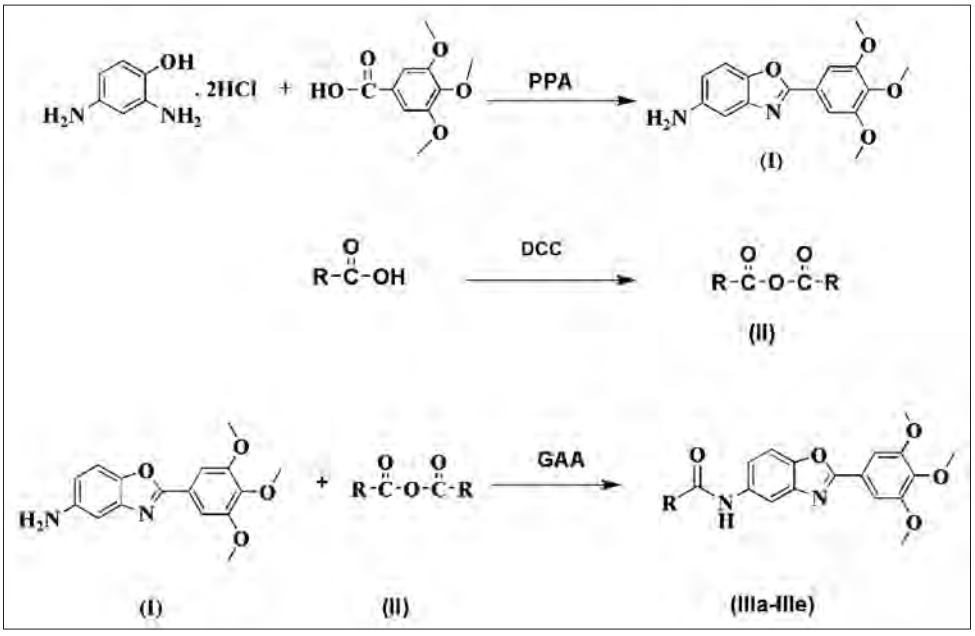
Anti-inflammatory activity

All the synthesized compounds were evaluated for anti-inflammatory activity by the carrageenan-induced rat paw edema method. The pharmacological data clearly implies that the synthesized compounds exhibited moderate to good anti-inflammatory properties ranging from 40% to 68% as shown in **Table 1**. Compounds with 2-chloro-4-nitrophenyl ring **(IIIb)** exhibited more reduction in rat paw edema in comparison to standard drug ibuprofen. Compounds with 2-bromophenyl ring **(IIIe)**, 3,4,5-trimethoxyphenyl ring **(IIId)**, and 3,5-dinitrophenyl ring **(IIIa)** showed a slight decrease in inhibitory activity. Whereas, compounds with 3,4-dimethoxyphenyl ring derivative **(IIIc)** produced weak anti-inflammatory activity as compared to ibuprofen.

In vitro antimicrobial activity

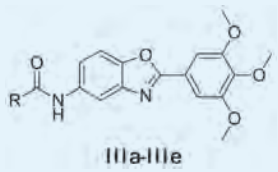
All analogs were screened for their antimicrobial activity against Gram-positive microorganism (*Staphylococcus aureus* [SA] and *Bacillus subtilis* [BS]), Gram-negative bacteria (*Escherichia coli* [EC] and *Pseudomonas aeruginosa* [PA]), and fungal microorganism (*Candida albicans* [CA] and *Aspergillus niger* [AN]). *In vitro* antibacterial and antifungal screening of the compounds **(IIIa-IIIe)** indicates that all of the synthesized compounds produce significant antimicrobial activity as shown in **Table 2**. The minimum inhibitory concentrations (MIC) of these compounds ranged from 500 to 15.6 µg/ml against bacterial and fungal species.

From the antibacterial screening, it was observed that the compound **IIIc** and **IIIa** found to be more active against BS. For SA compound **IIIa** and **IIIc** produces excellent activity, while **IIIb** and **IIId** produce moderate activity as compared to standard ciprofloxacin. Compound **IIIc** exhibited more

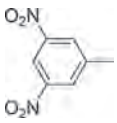
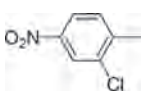
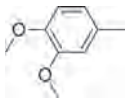
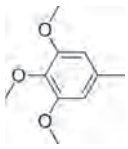


Scheme 1: Synthetic pathway of title compounds (IIIa-IIIe). R - IIIa=3,5-dinitrophenyl, IIIb=2-chloro-4-nitrophenyl, IIIc=3,5-dimethoxyphenyl, IIId=3,4,5-trimethoxyphenyl, and IIIe=2-bromophenyl. Solvents and reagent - PPA: Polyphosphoric acid, DCC: Dicyclohexylcarbodiimide, and GAA: Glacial acetic acid

Table 1: Anti-inflammatory activity of synthesized compounds using carrageenan-induced rat paw edema method



IIIa-IIIe

Compound	R	Paw edema volume (ml)		Increase in paw edema (ml) (Mean±SEM)	% Inhibition in paw volume[a]
		0 h	3 h		
IIIa		0.56	0.78	0.22±0.010	50.0
IIIb		0.67	0.81	0.14±0.023	68.1
IIIc		0.60	0.86	0.26±0.390	40.9
IIId		0.58	0.78	0.20±0.017	54.5
IIIe		0.66	0.84	0.18±0.012	59.1
Control	-	0.70	1.14	0.44±0.048	-
Ibuprofen	-	0.65	0.80	0.15±0.022	65.9

nt: Not tested, -: Not applicable, [a]$P<0.05$ (significant difference). *P* values were compared with control group (3 h after inducing edema) (Turkey's test). Number of animals (rats) in each group=5. SEM: Standard error of mean

inhibitory activity against PA than ciprofloxacin whereas; **IIIa** and **IIIb** produce activity similar to standard. On the other hand, compound **IIIc** possess good activity against Gram-negative bacteria EC.

Regarding antifungal screening, it was observed that compound **IIIc** found to produce activity similar to standard against AN. Compounds showed narrow range of activity against CA possessing MIC value between 62.5 and 125 µg/ml.

Among all the synthesized compounds it was observed that compound **IIIc** was found to be highly active, and showed good antimicrobial and antifungal activity, whereas **IIIe** was the least active among all the compounds.

EXPERIMENTAL

Chemistry

The chemicals used in the experiment were procured from Merck (India, Germany), Himedia (Mumbai, India), and Qualigens (India). The starting materials were purchased from Sigma-Aldrich Chemical Co., USA, and were used without further purification. The melting points were recorded using LAB India MR-VIS visual melting point apparatus and are uncorrected. IR spectra were recorded using Bruker Optics spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker, DPX-300 spectrometer (300 MHz) using tetramethylsilane as the internal reference and Chemical shift (δ) values are reported in parts per million (ppm) while, splitting patterns of peaks such as singlet, doublet, triplet, and multiplet in proton NMR spectra are marked as s, d, t, and m, respectively. Mass spectra were recorded on a LC-MS-LCQ (Agilent, Advantage-Max) instrument equipped with electrospray ion source and elemental analyses were performed on a Flash 2000 organic elemental analyzer. Progress of the reaction and purity of the compounds were monitored using thin layer chromatography on precoated plates (Merck, Germany) and compounds were purified using column chromatography.

Synthesis of 2-(3, 4, 5-trimethoxyphenyl)-benzoxazol-5-amine (I)

2-(3, 4, 5-trimethoxyphenyl)benzoxazol-5-amine **(I)** was synthesized by heating 0.01 mol of 2, 4-diaminophenol dihydrochloride with 0.01 mol of 3, 4, 5-trimethoxybezoic

Table 2: Antimicrobial activity results (MIC µg/ml) of synthesized compounds

Compound	BS	SA	EC	PA	CA	AN
IIIa	62.5	31.25	125	62.5	62.5	62.5
IIIb	125	62.5	125	62.5	62.5	62.5
IIIc	31.25	31.25	62.5	31.25	62.5	15.6
IIId	125	62.5	125	125	125	62.5
IIIe	250	250	250	500	125	125
Ciprofloxacin	7.8	3.9	7.8	62.5	-	-
Miconazole	-	-	-	-	3.9	15.6

BS: *Bacillus subtilis*, SA: *Staphylococcus aureus*, EC: *Escherichia coli*, PA: *Pseudomonas aeruginosa*, CA: *Candida albicans*, AN: *Aspergillus niger*

acid in 24 g of PPA with stirring for 3-4 h at 80°C. At the end of the reaction, the residue was poured into ice-water mixture, and neutralized with 10N NaOH and extracted with toluene. The toluene solution was dried over anhydrous sodium sulfate and evaporated under diminished pressure. The residue was boiled with 100 mg charcoal in ethanol and filtered. After the evaporation of the solvent, the crude product obtained and recrystallized with ethanol.[22] Yield: 84%, m.p.: 202-204°C. ATR-FTIR (cm^{-1}): 3340.6 (-NH_2), 2925.5 (-CH stretching), 1619.8, 1526.2 (C=C), 1472.8 (-CH bend), 1120.6 (C-O), 784.8 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 3.66 (s, 2H, -NH_2), 3.91 (s, 9H, 3x-OCH_3), 6.62 (d, 1H, H6 of benzoxazole), 6.96 (s, 1H, H4 of benzoxazole), 7.29 (d, 1H, H7 of benzoxazole), 7.38 (s, 2H, Hb, Hf).

General procedure for synthesis of anhydride (IIa-IIm)

Substituted acid derivative (0.02 mol) was dissolved in 50 ml of methylene chloride; dicyclohexylcarbodiimide (0.01 mol) was added, and the reaction mixture was stirred at room temperature for 3-4 h. The precipitated dicyclohexylurea which was formed during the reaction was removed by filtration. The solvent evaporated under vacuum, the oily product obtained was collected and used without purification.[23]

3,5-Dinitrobenzoic anhydride (IIa)

Yield: 78%, m.p.:180-182°C. ATR-FTIR (cm^{-1}): 2910.8 (-CH stretching), 1810.8, 1765.2 (-COOCO-) 1620.2, 1515.8 (C=C), 1528.2 (Ar-NO_2), 1479.1 (-CH bend), 1121.2 (C-O), 779.6 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 9.20 (s, 2H, Hb, Hf), 9.42 (s, 2H, Hb', Hf'), 9.80 (s, 2H, Hb, Hd').

2-Chloro-5-nitrobenzoic anhydride (IIb)

Yield: 69%, m.p.:122-125°C. ATR-FTIR (cm^{-1}): 2892.4 (-CH stretching), 1804.4, 1760.8 (-COOCO-) 1618.8, 1520.2 (C=C), 1526.8 (Ar-NO_2), 1470.7 (-CH bend), 1168.9 (Ar-Cl), 1180.8 (C-O), 786.9 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 9.20 (s, 2H, Hb), 9.42 (s, 2H, Hb), 9.80 (s, 2H, Hb).

3,4-Dimethoxybenzoic anhydride (IIc)

Yield: 52%, m.p.:110-114°C. ATR-FTIR (cm^{-1}): 2907.2 (-CH stretching), 1810.4, 1750.5 (-COOCO-) 1610.2, 1532.6 (C=C), 1468.9 (-CH bend), 1116.6 (C-O), 781.2 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 3.72 (s, 9H, 3x-OCH_3), 3.80 (s, 3H, -OCH_3), 6.87 (d, 2H, He), 7.53 (s, 2H, Hb), 7.58 (d, 2H, Hf).

3,4,5-Trimethoxybenzoic anhydride (IId)

Yield: 58%, m.p.:118-120°C. ATR-FTIR (cm^{-1}): 2958.2 (-CH stretching), 1810.4, 1750.5 (-COOCO-) 1610.2, 1468.5 (C=C), 1465.9 (-CH bend), 1108.4 (C-O), 781.2 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 3.73 (s, 12H, 4x-OCH_3), 3.80 (s, 12H, 4x -OCH_3), 7.12 (s, 2H, Hb, Hf).

2-Bromobenzoic anhydride (IIe)

Yield: 75%, m.p.:92-96°C. ATR-FTIR (cm^{-1}): 2972.52 (-CH stretching), 1815.50, 1746.48 (-COOCO-) 1618.91, 1456.52 (C=C), 1468.45 (-CH bend), 1112.46 (C-O), 782.80 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): 7.41 (t, 4H, 3x-OCH_3), 3.80 (s, 3H, -OCH_3), 6.87 (d, 2H, He, He'), 7.53 (s, 2H, Hb), 7.58 (d, 2H, Hf).

General procedure for synthesis of N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5-yl) substituted benzamides (IIIa-IIIe)

To the mixture of benzoxazolamine **(I)** (0.012 mol), respective anhydride **(IIa-IIe)** (0.01 mol), zinc dust (0.010 g), glacial acetic acid (0.01 mol), and DCM (15 ml) were placed in 100ml flask. Contents were refluxed for 4 h with constant stirring at room temperature. Then, it was poured into ice cold water (50 ml), and the precipitated product was collected and recrystallized in ethyl acetate/ methanol.

N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5-yl)-3,5-dinitrobenzamide(IIIa)

Yield: 64%, m.p.:154-156°C. ATR-FTIR (cm^{-1}): 3302.4 (NH), 2912.8 (-CH stretching), 1660.4 (-CONH-), 1628.2, 1521.4 (C=C), 1532.2 (Ar-NO_2), 1472.6 (-CH bend), 1161.10 (Ar-Cl), 1111.2 (C-O), 750.2 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 9H, 3x-OCH_3), 6.44 (s, 2H, Ar-H close to –OCH_3), 7.65(s, 2H, H4, H6 of benzoxazole), 8.02 (s, 1H, -NH), 8.84 (s, 2H, Ha, He) 8.88 (s, 1H, Hd). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.20, 56.82, 104.64, 105.18, 106.20, 110.92, 112.42, 120.56, 122.18, 128.58, 129.92, 135.18, 136.40, 139.15, 141.72, 145.66, 149.48, 149.52, 162.70, 164.82. MS (m/z): 495 $[M+1]^+$.

2-Chloro-N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5-yl)-5-nitrobenzamide(IIIb)

Yield: 52%, m.p.:144-146°C. ATR-FTIR (cm^{-1}): 3325.2 (NH), 2920.4 (-CH stretching), 1662.6 (-CONH-), 1614.1, 1510.2 (C=C), 1541.2 (Ar-NO_2), 1470.8 (-CH bend), 1160.20 (Ar-Cl), 1100.42 (C-O), 755.2 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 9H, 3x-OCH_3), 7.12 (s, 2H, Ar-H close to –OCH_3), 7.41-7.46 (d, 3H, H7, H4 and H6 of benzoxazole), 8.11 (s, 1H, -NH), 8.38-8.44 (br, 3H, Hf, He, Hc). ^{13}CNMR (75 MHz, CDCl3): δ 56.20, 56.84, 58.42, 104.59, 106.28, 110.92, 112.44, 120.59, 127.48, 133.76, 135.18, 135.74, 136.52, 138.45, 141.71, 145.62, 149.81, 150.92, 151.28, 162.70, 164.82. MS (m/z): 484 $[M+1]^+$.

3,4-Dimethoxy-N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5-yl)-benzamide(IIIc)

Yield: 48%, m.p.:110-111°C. ATR-FTIR (cm^{-1}): 3352.40 (NH), 2925.27 (-CH stretching), 1660.62 (-CONH-), 1610.15, 1442.02 (C=C), 1440.88 (-CH bend), 1110.57 (C-O), 810.02 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36(s, 6H,2x-OCH_3), 3.92 (s, 9H,1x-OCH_3), 7.02 (s, 2H, Ar-H close to –OCH_3), 7.06 (s, 1H, He),7.44-7.50 (br, overlapped, 3H, Hb, Hf of Ar-H, H7 of benzoxazole), 7.62-7.64 (d, 2H, H4, H6 of benzoxazole), 8.00 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.24, 56.84, 60.21, 103.94, 104.62, 106.28, 110.98, 112.15, 115.49, 120.54, 120.82, 127.50, 135.19, 139.26, 141.78, 145.62, 149.91, 151.36, 153.28, 162.79, 164.88. MS (m/z): 465 $[M+1]^+$.

3,4,5-Trimethoxy-N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5-yl)-benzamide(IIId)

Yield: 40%, m.p.:118-120°C. ATR-FTIR (cm^{-1}): 3355.62 (NH), 2955.67 (-CH stretching), 1662.62 (-CONH-), 1610.25, 1452.52 (C=C), 1462.78 (-CH bend), 1100.75 (C-O), 790.4 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (s, 9H, 3x-OCH_3), 3.64 (s, 9H, 3x-OCH_3), 6.94 (s, 2H, Ar-H close to –OCH_3), 7.05 (s, 2H, Hb, Hf), 7.52-7.58 (d, 2H, H4, H6 of benzoxazole), 7.53-7.56 (d, 2H, H4, H6 of benzoxazole), 7.99 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.22, 56.85, 58.42, 60.12, 60.36, 104.68, 106.29, 110.92, 112.48, 120.52, 128.56, 135.10, 139.20, 141.74, 142.68, 145.69, 150.98, 151.39, 162.76, 164.80. MS (m/z): 495 $[M+1]^+$.

2-Bromo-N-(2-(3,4,5-trimethoxyphenyl)-benzoxazol-5yl)-benzamide(IIIe)

Yield: 70%, m.p.:134-136°C. ATR-FTIR (cm^{-1}): 3320.22 (NH), 2975.52 (-CH stretching), 1642.72 (-CONH-), 1620.20, 1454.56 (C=C), 1460.62 (-CH bend), 1100.27 (C-O), 800.06 (oop). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 9H, 3x-OCH_3), 6.92 (s, 2H, Ar-H close to –OCH_3), 7.21 (s, 1H, H7 of benzoxazole), 7.05 (s, 1H, Hd of Ar-H), 7.38-7.44 (t, 2H, Hd, He), 7.61-7.64 (d, 2H, Hc, Hf), 7.70-7.76 (d, 2H, H4, H6 of benzoxazole), 80.2 (s, 1H, -NH).). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.84, 56.99, 60.10, 104.54, 104.89, 106.38, 110.98, 112.78, 120.02, 121.15, 127.98, 129.18, 131.88, 134.42, 135.71, 136.86, 139.19, 141.79, 142.68, 145.66, 151.30, 152.18, 162.65, 164.59. MS (m/z): 484 $[M+1]^+$.

BIOLOGICAL EVALUATION

Anti-inflammatory activity

Wistar albino rats of either sex were used for evaluation of anti-inflammatory activity by carrageenan-induced paw edema method. The protocol for the animal experiment was approved by IAEC (Institutional Animal Ethics committee) of Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India. The synthesized compounds were evaluated for their *in vivo* anti-inflammatory activity by adopting method of Winter.[22] The animals were fasted overnight before administering the drug, but the water was provided *ad libitum*. Each group was divided into five animals. Prepared compounds were administered orally at the dose of 20mg/kg, and the paw volume was determined using plethysmograph (Ugo-Base, Italy). Control group received an equivalent volume of normal saline. The reference group receives ibuprofen at the dose of 20 mg/kg. After half an hour, the carrageenan (0.1 ml of 1.0% w/v solution) in sterile saline was injected into the subplantar tissue of the rat's hind paw. The paw volume of rat was measured at 0, 1, 2, and 3 h. The percent inhibition of edema was calculated using the formula:

$$\% \text{ inhibition} = 100 \times (1 - V_s/V_c)$$

Where V_s=The volume of edema in sample treated group and V_c=The volume of edema in control group.

Microbiology

All the compounds synthesized were screened for their *in vitro* antibacterial activity against Gram-positive bacteria SA (MTCC 737), and BS (MTCC 3610), and Gram-negative bacteria EC (MTCC 1687), and PA (MTCC 424). Ciprofloxacin was taken as standard. Dimethyl sulfoxide (1% DMSO) was used a control. Antifungal activity was evaluated against CA and AN, using Miconazole as a standard. 1% DMSO was used a control.

In vitro antimicrobial activity

The MIC determination was carried out using serial dilution method. Two-fold serial dilutions of the tested compounds solutions were prepared using Mueller-Hinton broth and Sabouraud Dextrose broth as media. The stock solution was prepared by dissolving each synthesized compound (5 mg) in 1 ml of DMSO, and then 1ml of a compound stock solution was taken and added to nutrient broth (4 ml). Two-fold serial dilution of the stock solution was made in nutrient broths starting from ~1000 µg/ml to 1.9 µg/ml. The standardization of bacterial/fungal test suspension was carried according to the McFarland standard method. The microorganism suspensions (10^6 CFU/mL) were used to inoculate the test compounds in their suitable broth. Test tubes were incubated at 37°C for 24-48 h and checked for the turbidity. The lowest concentrations showing no growth was taken as the MIC.[24-26]

CONCLUSION

A series of benzoxazole were synthesized **(IIIa-IIIe)** and evaluated for their anti-inflammatory and antimicrobial activity. Among the synthesized compounds, **IIIc** was found to be most active against Gram-positive, Gram-negative, and fungal strains while, compound **IIIb** produces more protection against inflammation than standard ibuprofen. These compounds can be explored more for further development of novel antimicrobial and anti-inflammatory agents.

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