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Research Article

MICROWAVE-ASSISTED SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL EVALUATION OF PHENYLACRYLAMIDE DERIVATIVES OF TRIAZOLES DERIVED FROM OXAZOLONES

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ABSTRACT

Objective: The aim of the present study is to synthesize novel phenylacrylamide derivatives as potent bioactive agents.

Methods: Novel *N*-(3-(4*H*-1,2,4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids (7a-c) have been synthesized by the reaction of 4-(arylidene)-2-phenyloxazol-5(4*H*)-ones (5a-c) with 4-amino-1, 2, 4-triazole (6) in the presence of anhydrous sodium acetate in glacial acetic acid. Titled compounds (7a-c) were obtained in good yields using microwave technology which resulted in dramatic reductions in reaction times leading to the formation of phenylacrylamide derivatives (7a-c) at a faster rate.

Results: The structures of the newly synthesized compounds were characterized by Fourier-transform infrared, ^{1}H NMR, ^{13}C NMR, and mass spectral studies. This method can be an efficient method for the synthesis of phenylacrylamide derivatives (7a-c).

Conclusion: All the final compounds were screened for their antimicrobial and antioxidant activities and found to be biologically active. Among all the compounds, 7b was found to be potent antimicrobial and antioxidant.

Keywords: Phenyl acrylamides, Triazoles, Oxazolones, Antimicrobial activity, Antioxidant activity.

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INTRODUCTION

Infectious diseases are one of the leading causes of death worldwide. Treatment of infectious disease is an important and challenging problem. Some of azole derivatives used as common antibiotics such as amphotericin B possess a toxic effect on humans as well as on microbes. Besides this, although there are antimicrobial agents having different structures frequently used in the treatment of microbial infections, there is increasing resistance to these drugs [1]. To overcome the development of resistance, it is crucial to synthesize a new class of antibiotics. Antioxidants and scavenging free radicals are critical for maintaining optimal cellular and systemic health. Hence, in this area also, research is required for the development of new drugs [2-6].

The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs [7,8]. Among these heterocyclic compounds, oxazolone, phenyl acrylamides [9,10], and triazoles are having a wide variety of biological importance. Oxazolone plays very vital role in the development of various biologically active agents such as analgesic, anti-inflammatory, antidepressant, anticancer, antimicrobial, and antidiabetic. Oxazol-5-ones contain numerous reactive sites allowing for a diverse set of possible modifications. This diverse activity makes them excellent substrates for their use in diversity-oriented synthesis. Triazole moiety may be considered as a bioisostere of imidazole, which is a part of the azole group of antifungal drug (i.e., fluconazole). The 1, 2, 4-triazole nucleus has been incorporated into a wide variety of therapeutically important agents such as ribavirin (antiviral), rizatriptan (antimigraine), alprazolam (anxiolytic), vorozole, letrozole, and anastrozole (antitumoral) [11-23].

In the past few years, the use of microwave irradiation in organic synthesis has become increasingly popular within the theme in the scientific community because it is a new enabling technology for drug discovery and development. Microwave-assisted organic synthesis has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional heating methods.

In the present study, our main objective was to use the microwave technology [13,24,25] and the final molecules were designed to combine both oxazolone and 1, 2, 4-triazole moieties that were expected to have synergistic antimicrobial and antioxidant activities. In view of the above facts and in continuation of our efforts, we here in report the synthesis and biological activity of *N*-(3-(4*H*-1,2,4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids (7a-c). The synthetic approach is outlined in Scheme-I.

METHODS

All the chemicals were of LR grade and were obtained from SD Fine Chemicals and Avra Chemicals. Melting points (MP) were determined in open capillaries on Sheetal precision MP apparatus. Each reaction was monitored by thin-layer chromatography (TLC) using appropriate solvent system, which was selected by trial and error method. Pre-coated TLC plates (0.25 mm silica gel) were obtained from E. Merck. Mass spectral analysis using electrospray ionization (ESI) using a quadrupole time-of-flight mass analyzer (QSTAR XL, Applied Biosystems/MDS Sciex, Foster City, CA, USA) equipped with an ESI source and mass spectra were reported in m/z value as molecular ion peak. The instruments used for obtaining the spectroscopic data were as follows: Infrared (IR) spectra were recorded on Fourier-transform IR spectrophotometer SHIMADZU-435instrument by KBr, dilated cardiomyopathy disc method. Ultraviolet (UV) spectra were recorded on OPTIZEN3220 UV-visible spectrophotometer instrument. All^{1}HNMR spectra were recorded on ^{1}H NMR ($CDCl_3$, avance300 MHz) instrument, and the samples were made in dimethyl sulfoxide (DMSO)-d_6 using tetramethylsilane as the internal standard.

Chemistry

In the present study, we have designed and synthesized few number of oxazolone and 1, 2, 4-triazole fused systems as outlined in Scheme-I that were expected to have antimicrobial and antioxidant activities. Benzoyl glycine (3) on reaction with ring substituted aromatic aldehydes (4a-c) in the presence of acetic anhydride and anhydrous sodium acetate yielded various ring substituted 4-arylidene-2-phenyl oxazol-5(4*H*)-ones (5a-c). This on further reaction with amino triazole in the presence of anhydrous sodium acetate and glacial acetic acid by microwave technology produced *N*-(3-(4*H*-1,2,4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acid derivatives (7a-c). Phenyl acryl amides containing triazole derivatives were synthesized.

Synthesis of benzoyl glycine (3)

A solution of 25 g (0.33 mol) of glycine in 250 ml of 10% NaOH was prepared and 45 ml (0.38 mol) benzoyl chloride was added to the above solution in five portions. The mixture was shaken vigorously after each addition until all the chlorides have been reacted. The mixture was cooled by adding few grams of crushed ice and was acidified by adding concentrated HCl slowly with constant stirring. The resulting crystalline precipitate of benzoyl glycine was filtered and washed with cold water and dried. The solid was treated with 100 ml of hot CCl_4 to remove benzoic acid. The dried product was recrystallized with boiling water [26].

Synthesis of 4-arylidene-2-phenyl-oxazol-5(4*H*)-ones (5a-c)

Place 8.6 g (0.476 mol) of benzoyl glycine, 5 ml (0.476 mol) aryl aldehydes, 14 ml (1.46 mol) acetic anhydride, and 3.9 g (0.476 mol) anhydrous sodium acetate in a 250 ml conical flask. Heat the flask on electric hot plate with constant shaking until the mixture liquefies completely, reflux the contents for 2 h on water bath. To the contents of flask, add 10 ml ethanol slowly and allowed the mixture to stand overnight. The crystalline precipitate was filtered with suction and washed with 2 portions of ice-cold alcohol (6 ml) and finally with 2 portions of boiling water. The product was dried and recrystallized using benzene. The procedure was repeated using different other aldehydes to get other derivatives.

Synthesis of *N*-(3-(4*H*-1, 2, 4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids (7a-c)

The equimolar mixture of oxazolones (5a-c) (0.01 moles), 4-amino-1, 2, 4-triazole (6)(0.01 moles) and sodium acetate (0.82 g, 0.01 moles) in glacial acetic acid (25 ml) was irradiated in microwave for 1–3 min at 800 watts. Reaction mixture was monitored by TLC. Contents of the flask were poured in ice water. The solid was separated, filtered, and washed with cold water and dried under vacuum pump (Fig. 1).

Biological activity

Titled compounds were tested for their *in vitro* antimicrobial activity against Gram-positive bacteria *Bacillus subtilis* MTCC 441 and Gram-negative bacteria *Escherichia coli* MTCC 443 strains using filter paper disc method for the zone of inhibition and minimum inhibitory concentration (MIC) was determined by broth micro dilution method. All the three novel compounds were screened for antioxidant activity by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) method.

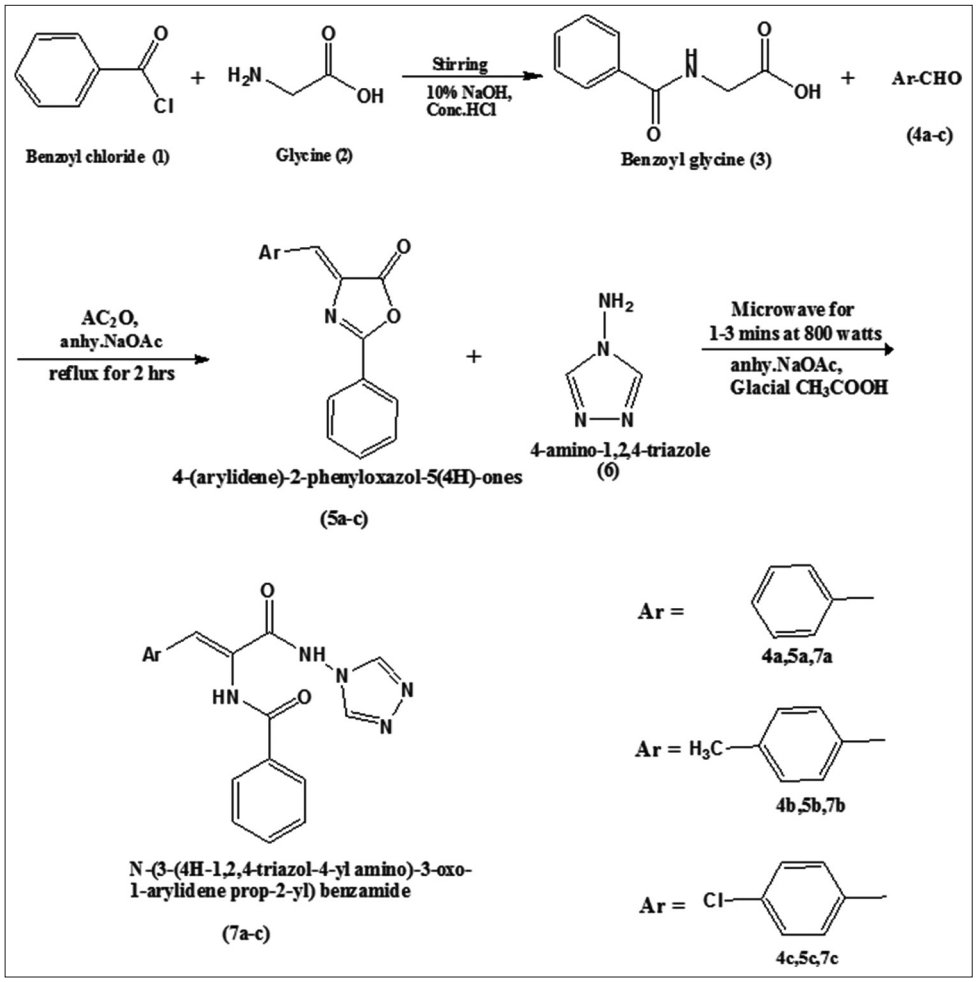

Fig. 1: Synthesis of final compounds (7a-c)

Antimicrobial activity

Paper disc method

The synthesized compounds were tested for their antimicrobial (antibacterial and antifungal) activities by disc-diffusion method [27] using Mueller-Hinton medium for bacteria. In the disc-diffusion method, sterile paper discs (Ø5 mm) impregnated with compound dissolved in DMSO at concentrations of 100 µg/ml were used. Discs containing DMSO were used as control. The microorganism cultures were spread over the following appropriate media: Mueller-Hinton agar for *B. subtilis* and *E. coli* in Petri dishes. Then, the paper discs impregnated with the solutions of the compound tested were placed on the surface of the media inoculated with the microorganism. The plates were incubated at 35°C for 24 h for the microorganism cultures. After incubation, the growth inhibition zones around the discs were observed, indicating that the examined compound inhibits the growth of microorganism [28,29]. Each assay in this experiment was repeated 3 times. Benzylpenicillin was used as a standard drug.

Microdilution assays

The MIC values for all tested compounds were determined using the microdilution broth method. The inocula of microorganisms were prepared from 24 h broth cultures, and suspensions were adjusted to 0.5 McFarland standard turbidity. The test compounds dissolved in DMSO were first diluted to the highest concentration (1 mg/ml) to be tested [29]. Then, serial two-fold dilutions were made in concentration ranges from 31. 25 µg/ml to 1 mg/ml in 10 ml sterile tubes. A prepared suspension of the standard microorganisms was added to each dilution in a 1:1 ratio. Growth (or its lack) of microorganisms was determined visually after incubation for 24 h at 37°C. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC [30]. Benzylpenicillin was used as standard drug for comparison in the antimicrobial studies. Control experiments using DMSO were done. The presented results were obtained from three independent measurements [31].

Results were interpreted in terms of the diameter of the inhibition zone and MIC as µg/ml as shown in Table 1 and Figs. 2 and 3.

Antioxidant activity DPPH free radical scavenging activity

DPPH solution (0.004% w/v) was prepared in 95% methanol. The stock solution was prepared by dissolving test compounds (7a-c) in 95% methanol (10 mg/100 ml or 100 µg/ml). 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml of this solution were taken in five test tubes, and the final volume was made up to 10 ml whose concentration was then 20 µg/ml, 40 µg/ml, 60 µg/ml, 80 µg/ml, and 100 µg/ml respectively. Freshly prepared DPPH solution was added in each of these test tubes, and after 10 min, the absorbance was tested at 517 nm using a spectrophotometer. Ascorbic acid was used as a reference standard [32,33].

% scavenging of the DPPH free radical was measured using the following equation:

$$\%\ \text{DPPH radical scavenging} = \frac{(\text{Absorbance of control} - \text{Absorbance of testsample})}{(\text{Absorbance of control})} \times 100$$

Results of % DPPH scavenging activity of the titled compounds are given in Table 2 and Fig. 4.

RESULTS AND DISCUSSION

Chemistry

Spectroscopic analysis

N-(3-(4H-1,2,4-triazol-4-ylamino)-3-oxo-1-phenylprop-1-en-2-yl) benzimidic acid (7a)

IR (KBr, cm^{-1}): 3435.34 (-OH), 2920.31 (aromatic-CH str), 1661.95 (amide-C=O str); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 7–8 (m, 10H,

Table 1: Antimicrobial activity of synthesized compounds (7a-c)

Compound	Antimicrobial activity	
	Zone of Inhibition in mm (MIC in µg/ml)	
	B. subtilis	*E. coli*
7a	8 (500)	6 (500)
7b	17 (62.5)	12 (250)
7c	16 (62.5)	11 (250)
Benzylpenicillin	16 (2)	12 (2)

MIC: Minimum inhibitory concentration, *B. subtilis: Bacillus subtilis, E. coli: Escherichia coli*

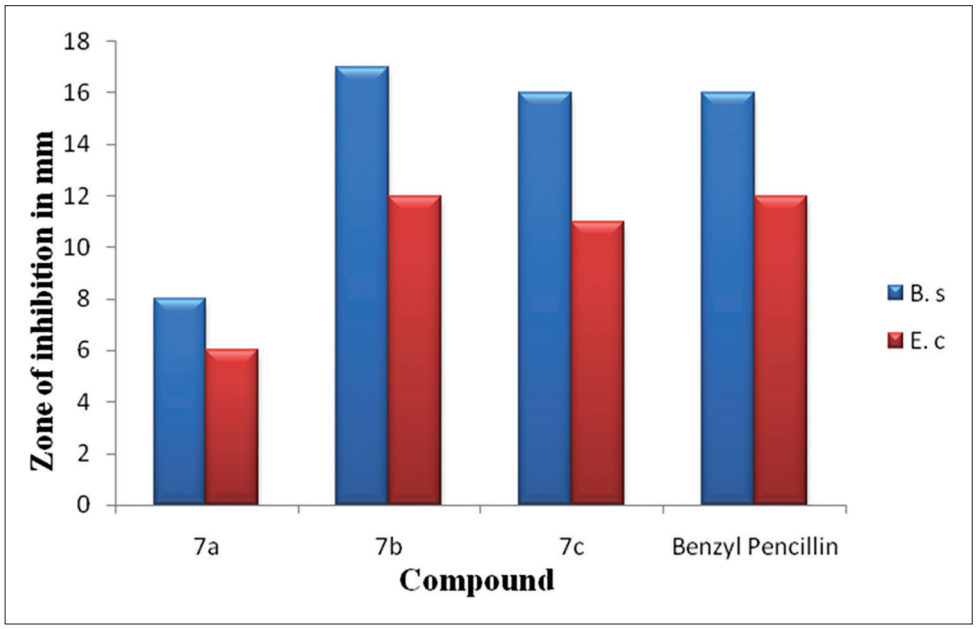

Fig. 2: Graphical representation of antimicrobial activity of 7a-c by paper disc method

Table 2: Antioxidant activity of the synthesized compounds (7a-c)

Compound	DPPH free radical scavenging activity (%)					
	20 μg/ml	40 μg/ml	60 μg/ml	80 μg/ml	100 μg/ml	IC_{50} (μg/ml)
7a	35.13±0.8	38.48±0.7	43.69±0.5	48.19±0.2	55.80±0.9	89.86
7b	38.60±0.1	47.30±0.8	53.92±0.5	69.41±0.5	78.50±0.5	28.23
7c	44.73±0.8	50.41±0.5	66.91±0.5	69.46±0.5	72.84±0.4	30.32
Ascorbic acid	55.12±0.2	65.08±0.2	75.26±0.2	85.82±0.4	93.74±0.2	8.96

DPPH: 2, 2-Diphenyl-1-picrylhydrazyl

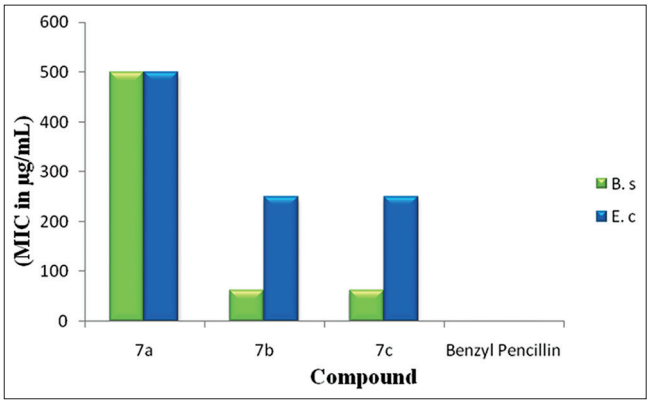

Fig. 3: Graphical representation of antimicrobial activity of 7a-c by microdilution method

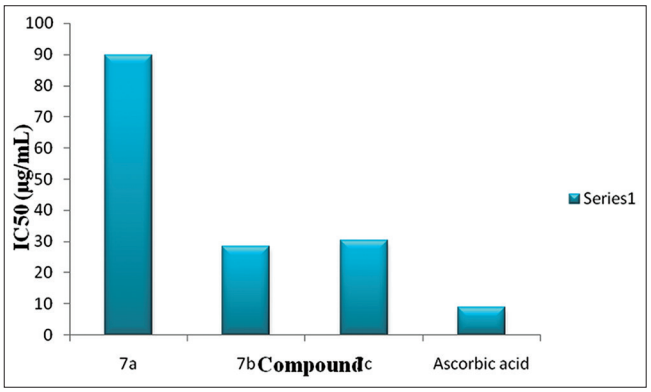

Fig. 4: Graphical representation of antioxidant activity of 7a-c by 2, 2-diphenyl-1-picrylhydrazyl free radical scavenging method

Ar-H), 7.6 (m, 1H, −CH=CH_2), 8.00 (m, 2H, triazole-H), 8.6 (s, 1H, N-Hlinkage), 9.7 (s, 1H, N-H of amide); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 110.34, 116.92, 120.76, 125.76, 127.62, 128.38, 129.48, 132.21, 135.21, 141.41, 164.43, 164.83, 169.49; ESI-MS (m/z): 333 [M^+].

N-(3-(4H-1,2,4-triazol-4-ylamino)-3-oxo-1-p-tolylprop-1-en-2-yl)benzimidic acid (7b)

IR (KBr, cm^{-1}): 3425.87 (-OH), 2945.01 (aromatic-CH str), 2921.76 (aliphatic-CH str), 1661.86 (amide-C=O str); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 2.4 (s, 3H, CH_3), 7.4-8 (m, 9H, Ar-H), 7.3 (m, 1H, −CH=CH_2), 8.1 (m, 2H, triazole-H), 8.7 (s, 1H, N-H linkage), 9.8 (s, 1H, N-H of amide); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 110.19, 114.78,116.64,120.97, 123.36, 125.15, 126.51,126.90,127.59, 128.32, 128.36,129.69,131.84,132.31, 138.97, 143.45,164.33,169.60; ESI-MS (m/z): 347 [M^+].

N-(3-(4H-1,2,4-triazol-4-ylamino)-1-(4-chlorophenyl)-3-oxoprop-1-en-2-yl)benzimidic acid (7c)

IR (KBr, cm^{-1}): 3399.50 (-OH), 2949.17 (aromatic-CH str), 1660.79 (amide-C=O str); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 7.2 (s, 1H, −CH=CH_2), 7.3-7.6 (m, 9H, Ar-H), 7.9 (m, 2H, triazole-H), 8.63 (s, 1H, N-H linkage), 9.6 (s, 1H, N-H of amide); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 110.19, 114.78, 116.64, 120.97, 123.36, 125.15, 126.51, 126.90, 127.59, 128.32, 128.36, 129.69, 134.84, 132.31, 138.97, 143.45, 153.18, 153.71, 164.45, 169. 97; ESI-MS (m/z): 367 [M^+].

The key precursors 4-(arylidene)-2-phenyloxazol-5(4*H*)-ones (5a-c) required for the synthesis of target compounds were obtained by the reaction of benzoyl glycine (3) with different aryl aldehydes (4a-c). The target compounds *N*-(3-(4*H*-1,2,4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids (7a-c) were obtained by the reaction of 4-(arylidene)-2-phenyloxazol-5(4*H*)-ones (5a-c) with 4-amino-1, 2, 4-triazole (6) in the presence of anhydrous sodium acetate in glacial acetic acid. IR spectrum of *N*-(3-(4*H*-1, 2, 4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids (7a-c) showed absorption bands at 3399.50–3435.34/cm, 2920.31–2949.17/cm, 2921.76/cm, and 1660.79–1661.95/cm due to –OH, aromatic C-H, aliphatic C-H, and amide C=O functional group stretching vibrations, respectively, indicating the evidence for the formation of the titled compounds (7a-c). ^{1}H NMR spectra of compounds (7a-c): 7b showed singlet at δ 2.4 due to -CH_3 protons; compounds 7c and 7a showed peaks at δ 7.2–7.6 integrates for vinyl protons; for all the compounds (7a-c), peaks appeared at δ 7.00–8.00 integrate for aromatic protons, multiplet at δ 7.9–8.1 due to triazole protons, singlet at δ 8.6–8.7 due to N-H linkage, singlet at δ 9.6–9.8 due to N-H of amide, clearly confirms the final products formation (7a-c). The mass spectra of 7a-c are in good agreement with the proposed structures. Reaction of 5a-c with 4-amino-1, 2, 4-triazole (6) in the presence of anhydrous sodium acetate in glacial acetic acid resulted in the formation of titled compounds, i.e., *N*-(3-(4*H*-1, 2, 4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acid derivatives (7a-c) in good yields (55–65%). Physical data of these compounds are reported in Table 3. Earlier phenylacrylamide derivatives have been prepared by conventional heating methods which take hours to days, and hence, yield was found to be very poor. In the present work, the efficiency of microwave flash heating has resulted in dramatic reductions in reaction times (reduced from days and hours to minutes and seconds) leading to the formation of phenylacrylamide derivatives at a faster rate in good yields. The time saved for this method using the Microwave heating approach was found to be ideal for the synthesis of phenylacrylamide derivatives.

Biological activity

Antimicrobial activity by disc diffusion method and microdilution method

The widespread of antimicrobial drugs and their resistance against microbial infections has led to serious health hazards. The resistance of widespectrum antimicrobial agents has prompted discovery and modification toward new antimicrobial agents. Applications of these findings motivated us to synthesize and screen the antimicrobial activity of imidazolones-linked chalcones.

A total of three novel compounds were synthesized and tested for their ability to inhibit microbial growth using two different microorganisms as test organisms, namely, bacterial species: *B. subtilis* and *E. coli.* Final compounds among the tested had highly potent antimicrobial activity, producing inhibition zones up to 17 mm in diameter. Every compound had at least some activity against one or more microbial strains.

A short review of results of antimicrobial screening of the compounds (7a-c) of this section is mentioned here:

Against B. subtilis

Maximum activity was found in compound 7b (p-CH_3) zone of inhibition - 17 mm with MIC-62.5 µg/ml, whereas minimum activity was found in compound **7**a(-H), zone of inhibition-8 mm with MIC - 500 µg/ml.

Against E. coli

Maximum activity was found in compound 7b (p-CH_3), zone of inhibition - 12 mm with MIC-250 µg/ml, whereas minimum activity was found in compound 7a (-H), zone of inhibition 6 mm - 500 µg/ml.

Antioxidant activity

DPPH free radical scavenging activity

DPPH free radical scavenging activity results displayed that title compounds (7a-c) are able to show marked antioxidant activity. Among which, compounds 7b (p-CH_3) and 7c (p-Cl) showed good activity. Remaining compound 7a showed moderate activity. The IC_{50} values of all compounds (7a-c) were found between 28.23 and 89.86 µg/ml with antioxidant activity. These compounds have showed less antioxidant potential with the standard ascorbic acid.

Ascorbic acid (reference antioxidant compounds) was used as a standard. The scavenging capacities were represented as percentage inhibition, and values were the means of three replicates (mean±SD, n=3).

CONCLUSION

In the present work, a new series of biologically active *N*-(3-(4*H*-1, 2, 4-triazol-4-ylamino)-3-oxo-1-arylidene prop-2-yl) benzimidic acids with an introduction of oxazolones and 1, 2, 4-triazole fused systems were synthesized by novel approach by the use of microwave technology, which offers several advantages such as high efficiency of heating, reduction in unwanted side reaction, uniform heating occurs throughout the material, process speed is increased, purity in final product, and very easy work up. The use of microwave is one of the major tools for rapid lead generation and lead optimization through which medicinal chemist will be able to deliver the new chemical entities. In future, the application of microwave technology looks bright because of its efficiency and its potential to produce the pure compounds. Microwave assists many organic reactions. It can be concluded that these compounds certainly hold great promise for discovering future drugs.

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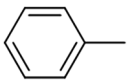
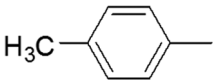
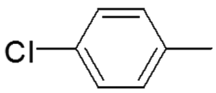
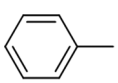
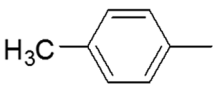
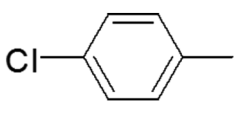
Table 3: Physicochemical data of synthesized compounds (5a-c and 7a-c)

Compound	Ar	MF	Reaction time (s)	MP (°C)	Yield (%)
5a		$C_{16}H_{11}NO_2$	_	174–175	78
5b		$C_{17}H_{13}NO_2$	_	177–178	70
5c		$C_{16}H_{10}ClNO_2$	_	173–174	79
7a		$C_{19}H_{16}N_4O_2$	60	165–168	55
7b		$C_{20}H_{18}N_4O_2$	70	188–190	65
7c		$C_{19}H_{15}ClN_4O_2$	180	186–188	65

MP: Melting points

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