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MICROWAVE-ASSISTED SYNTHESIS OF IMIDAZO[1,2-a]PYRIDINE DERIVATIVES AND THEIR ANTI-INFLAMMATORY ACTIVITY

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Keywords:

Imidazo[1,2-a]pyridine,biological activity, Microwave irradiation, Anti-inflammatory activity

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ABSTRACT: A series of novel Imidazo[1,2-a]pyridine derivatives were synthesized in satisfactory yield by microwave assisted synthetic method. The structures of the newly synthesized compounds are characterized by ^{1}H-nuclear magnetic resonance (NMR), Fourier transformed infrared (FTIR), mass spectral analysis (LC-MS) and screened for their *in-vitro* anti-inflammatory activity. Among the synthesized compounds N-(3,5-bis(trifluoromethyl)benzyl)-4-((2-(6-methyl-2-(p-tolyl)imidazo [1,2-a] pyridine-3-yl) acetamido) methyl) benzamide and N- (4-methoxybenzyl)-4- ((2-(6-methyl-2-(p-tolyl) imidazo [1,2-a]pyridin-3-yl) acetamido) methyl) benzamide are possessing high anti-inflammatory activity against standard drug Aspirin. A majority of the tested compounds had shown good consequence to moderate anti-inflammatory activity.

INTRODUCTION: Advent of microwaves, the magnetron, a remarkable device for generating fixed frequency microwaves, was designed by Randall and Booth in the University of Birmingham [1]. A magnetron is a vacuum device which converts DC electric energy into microwaves. In early days, it was recognized that microwaves could heat water in a dramatic fashion. Domestic and commercial appliances for heating and cooking food began to appear in the 1950s. The first microwave oven was introduced by Tappan in 1955, but the widespread use of domestic microwave ovens occurred during the 1970s and 1980s.

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The first application of microwave irradiation in chemical synthesis was published in 1986 [2]. A microwave (MW) is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum (300-300000 MHz). Microwave heating (dielectric heating) is a very efficient process due to the microwave couples directly with the molecules that are existed in the mixture of reaction, leading to a fast inclination in temperature and faster reactions.

The two fundamental mechanisms for transferring energy from microwaves to the substance are dipole rotation and ionic conduction. Dipole rotation is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave. Ionic conduction mechanism consists of the instantaneous superheating of the ionic substance due to the ionic motion generated by the electric field [3]. When the temperature increases, the transfer of energy becomes more efficient.

Since, their ionic character, ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction. Nowadays, microwave-assisted organic synthesis is extensively used in drug discovery laboratories.

Inflammation is the immediate defensive response to tissue injury in the form of stress held due to physical or chemical agents and microbes [4]. It is generally characterized by the redness, pain, heat, edema, and loss of function. The non-steroidal anti-inflammatory drugs (NSAIDs) are being preferred as the treatment of choice. However, its systemic toxicity limits their usage and urges the need for the modern anti-inflammatory drug. Our study intends to identify anti-inflammatory agents that could significantly treat inflammatory disorders [5].

Recently, growing interest has been made to synthesize the Imidazo[1,2-a]pyridine compounds [6]. Many compounds possess very promising biological activity as anticancer agents [7], antimicrobial [8], anti-tubercular [9], antisepsis [10], antiviral [11], antimalarial [12], anti-inflammatory [13], anticonvulsant [14, 15], anticandidal [16] activity. These compounds also can alleviate obesity-induced heart injury [17] *via* its anti-inflammatory actions.

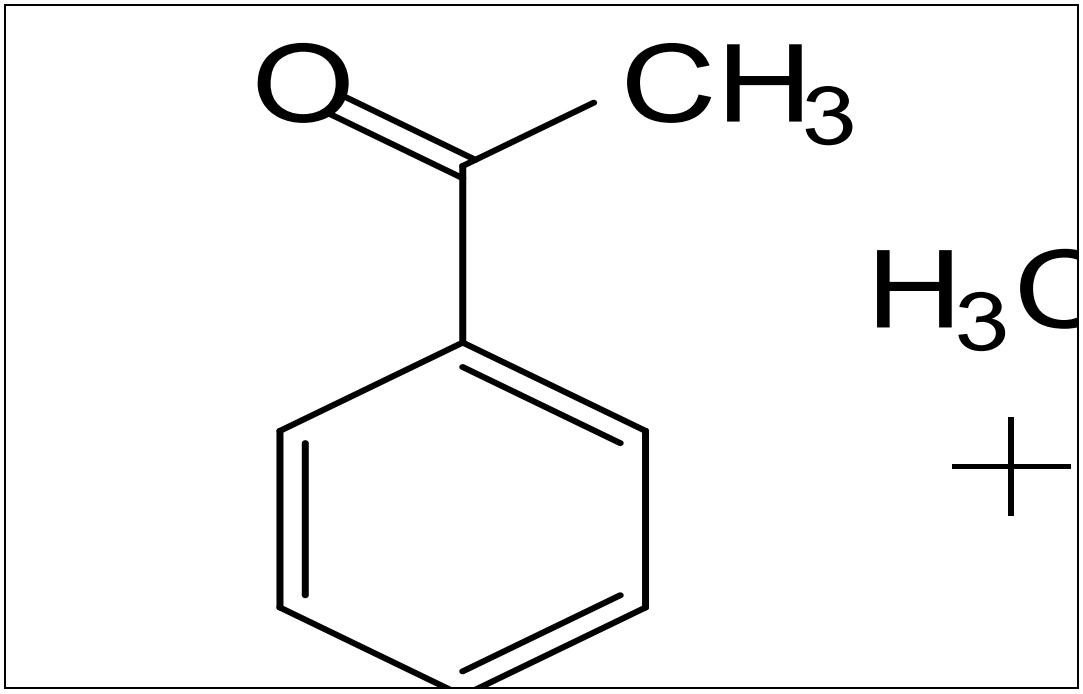
Synthesis of Imidazo[1,2-a]pyridine derivatives:

Scheme 1:

These derivatives have therapeutic potential in the treatment of obesity-induced artery injuries [18]. They also used to prevent the retinal ischemia [19]. The microwave technique has several advantages over traditional methods of synthesis [20]. Reduced reaction times with less effect on the environment and better reaction yields are some of the common advantages of using microwaves. In the present work, we have synthesized Imidazo[1,2-a]pyridine derivatives using microwave irradiation method and compared with the conventional method with anti-inflammatory activity.

EXPERIMENTAL SECTION:

MATERIALS AND METHODS: All chemicals used for the synthesis of the desired compounds were obtained from Merck, Loba chime and spectrochem India. The FT-IR spectrum studies of the synthesized compounds were recorded in FTIR 8300, KBr press, Shimadzu. Mass studies of the synthesized compounds were performed by using the instrument SHIMADZU QP 500. ^{1}H-NMR spectra were acquired on a Bruker 300MHz spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard. Chemical shifts are given in δ ppm. The microwave reactions were carried out in a biotage microwave synthesizer.



SCHEME 1: SYNTHETIC ROUTE FOR COMPOUND 7 a-l

6-Methyl-2-p-tolyl-imidazo [1,2-a] pyridine (1): To the cooled solution of 4-methyl acetophenone (1.5 g, 0.0111 mol) in methanol, aluminium chloride (0.075 g, 0.00056 mol) was added under stirring at 0-5 ºC. To this solution bromine (1.916 g, 0.0112 mol) was added slowly and stirred for 30 min. To this reaction mixture, aqueous sodium carbonate and 2-amino 5-methyl pyridine solution (1.27 g, 0.0118 mol) were added at 25-35 ºC, and the completion of the reaction was monitored by TLC. The reaction mass was poured into cold water, and the resulting solid was crystallized with ethanol and dried under vacuum to yield the cream color solid of compound 1 (2.3 g, yield: 95.0%, MS: m/z 223.1 (M+1).

N, N- dimethyl-1-(6-methyl-2-(p-tolyl)imidazo[1, 2-a]pyridin-3-yl)methenamine (2): In a 20 mL microwave vial, the compound 1 (2.0 g, 0.009 mol) was dissolved in acetic acid. To this solution, aqueous dimethylamine solution (0.486 g, 0.0108 mol) and formalin solution (0.324 g, 0.0108 mol) were added, and the reaction mixture was subjected to irradiation in the microwave for 5 min at 80 W. The completion of the reaction was monitored by TLC. The reaction mass was poured into crushed ice and basified using aqueous sodium hydroxide solution (20 ml). The resulting precipitate was filtered, washed with water, dried and crystallized from ethanol to give pale yellow solid of 2 (1.6 g, yield: 92.0%). MS: m/z 280.2 (M+1).

2- (6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin- 3-yl)acetonitrile (3): In a 20 ml microwave vial, the compound 2 (2.0 g, 0.0072 mol) was dissolved in 10ml of acetone. To this solution precooled methyl iodide (1.01 g, 0.0072 mol) was added, and the reaction mixture was stirred at RT for 3 h. The resulting solid was added into sodium cyanide (0.353 g, 0.0072 mol) solution and irradiated in the microwave for 10 min at 100W. The reaction mixture was poured into cold water and acidified with glacial acetic acid. The solid mass was filtered, dried and recrystallized using methanol to yield white solid of 3 (1.56 g, yield: 89%) MS: m/z 262.1 (M+1).

(6-Methyl-2-p-tolyl-imidazo[1, 2-a]pyridin-3-yl)-acetic acid (4): In a 50 ml microwave vial, compound **3** (3.0g, 0.0076 mol) was dissolved in methanol (20 ml). To that solution potassium hydroxide (1.7 g, 0.0304 mol) was added as an aqueous solution (10 ml). The reaction mixture was stirred for subjected to microwave irradiation for 5 min at 80W. The solvents were evaporated under reduced pressure. The crude product was dissolved in ice-cold water and neutralized with con. HCl. The resulting solid was filtered and dried in vacuum. (1.9 g, Yield: 78%) MS: *m/z* 281.1 (M+1).

Ethyl 4- ((2- (6- methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl) acetamido) methyl) benzoate (5): In a 50 ml microwave vial, the compound 4 (1.0 g, 0.0036 mol) was dissolved in dichloromethane (25 ml). To that solution, TBTU (2.44g, 0.0072 mol) and Triethylamine (1.09 ml, 0.0108 mol) were added. Then ethyl 4-(aminomethyl) benzoate (0.773g, 0.0043 mol) was added and irradiated in the microwave for 10 min at 80W. The completion of the reaction was monitored by TLC and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution, water, brine solution, which was separated and dried over anhydrous sodium sulphate. The evaporation of the solvent yielded target compound. (1.24 g, yield: 92%) MS: m/z 441.1 (M+1).

4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)a cetamido) methyl) benzoic acid (6): The compound 5 (1.0g, 0.0023 mol) was dissolved in methanol (30 ml). To that solution, 10 ml of sodium hydroxide solution was added. The reaction mixture was stirred for 1hr at room temperature. After completion of the reaction, the solvents were evaporated under reduced pressure. The crude product was dissolved in water and washed with ethyl acetate solution, the organic layer was discarded. The water layer contains the sodium salt of product which was neutralized with con. HCl. The obtained precipitate is filtered and dried in vacuum. (0.86 g Yield: 89%). MS: m/z 414.2 (M+1).

A general method for Synthesis of compounds (7a-l): In a 20 ml microwave vial, the compound 6 (0.2 g, 0.00048 mol) was dissolved in dichloromethane (10 ml). To that solution, TBTU (0.32 g, 0.00096 mol) and diisopropylamine (0.145 ml, 0.0014 mol) was added and stirred for 5 min under nitrogen atmosphere. The amine (0.632 mmol) was added and irradiated in the microwave

for 5 min at 80 W. The completion of the reaction was monitored by TLC, and the reaction mixture was extracted with ethyl acetate.

The organic layer was washed with sodium bicarbonate solution, water, brine solution, which was separated and dried over anhydrous sodium sulphate. The evaporation of the solvent yielded the target compounds.

N-benzyl-4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl) acetamido) methyl) benzamide (7a): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.30 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 4.04 (d, 2H, CH_2); 4.40 - 4.41 (d, 2H, CH_2); 4.49 - 4.50 (d, 2H, CH_2); 7.12 - 7.14 (m, 1H, Ar-H); 7.24 - 7.26 (m, 3H, Ar-H); 7.32 (m, 4H, Ar-H); 7.36 - 7.38 (m, 2H, Ar-H); 7.48 - 7.51 (d, 1H, Ar-H); 7.68 - 7.70 (d, 2H, Ar-H); 7.87 - 7.89 (d, 2H, Ar-H); 8.18 (s, 1H, Ar-H); 8.89 (s, 1H, NH); 9.03 (s, 1H, NH). FT-IR: 3450 (N-H); 3080 (Ar-H), 2929 (C-H), 1634 (C=O), 1553 (C=N), 1439 (C=C), 1392 (C-N). MS: m/z 503.1 (M+1), 0.136g, Yield: 56.2%.

N- (2-chlorobenzyl)- 4- ((2-(6-methyl-2-(p-tolyl) imidazo[1,2-a]pyridin-3-yl) acetamido) methyl) benzamide (7b): ^{1}H-NMR (400 MHz, $CDCl_3$) ppm: 2.31 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 4.04 (d, 2H, CH_2); 4.43 (d, 2H, CH_2); 4.70 - 4.71 (d, 2H, CH_2); 7.17 - 7.19 (m, 1H, Ar-H); 7.22 (m, 1H, Ar-H); 7.23 - 7.24 (m, 2H, Ar-H); 7.37 (m, 4H, Ar-H); 7.36 - 7.38 (m, 2H, Ar-H); 7.43 - 7.45 (d, 1H, Ar-H); 7.55 - 7.57 (d, 2H, Ar-H); 7.61 – 7.66 (d, 2H, Ar-H); 7.97 (s, 1H, Ar-H); 8.19 (s, 1H, NH); 8.63 (s, 1H, NH). FT-IR: 3437 (N-H); 3014 (Ar-H), 2920 (C-H), 1670 (C=O), 1543 (C=N), 1441 (C=C), 1334 (C-N). MS: m/z 538.1 (M+1), 0.124g, Yield: 48.06%.

N- (4-fluorobenzyl)- 4- ((2- (6-methyl- 2-(p-tolyl) imidazo[1,2-a]pyridin-3-yl)acetamido)methyl) benzamide (7c): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.31 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 4.04 (d, 2H, CH_2); 4.38 - 4.39 (d, 2H, CH_2); 4.44 - 4.46 (d, 2H, CH_2); 7.12 - 7.19 (m, 3H, Ar-H); 7.24 - 7.26 (d, 2H, Ar-H); 7.32 – 7.36 (m, 4H, Ar-H); 7.50 - 7.53 (d, 1H, Ar-H); 7.65 - 7.67 (d, 2H, Ar-H); 7.83 - 7.85 (d, 2H, Ar-H); 8.21 (s, 1H, Ar-H); 8.85 – 8.88 (t, 1H, NH); 9.00 - 9.03 (t, 1H, NH). FT-IR: 3427 (N-H); 3019 (Ar-H), 2922 (C-H), 1667 (C=O), 1545 (C=N), 1423 (C=C), 1330 (C-N) MS: m/z 521.2 (M+1), 0.135g, Yield: 54.1%.

N- (3, 5- bis(trifluoromethyl)benzyl)- 4- ((2-(6-methyl- 2- (p-tolyl)imidazo [1, 2-a]pyridin-3-yl) acetamido) methyl) benzamide (7d): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.28 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 4.03 (d, 2H, CH_2); 4.38 - 4.39 (d, 2H, CH_2); 4.64 - 4.65 (d, 2H, CH_2); 7.11 - 7.13 (m, 1H, Ar-H); 7.22 - 7.25 (m, 2H, Ar-H); 7.36 – 7.38 (d, 2H, Ar-H); 7.48 - 7.50 (d, 1H, Ar-H); 7.65 - 7.67 (d, 2H, Ar-H); 7.84 - 7.89 (m, 2H, Ar-H); 8.01 (s, 3H, Ar-H); 8.17 (s, 1H, Ar-H); 8.85 – 8.88 (t, 1H, NH); 9.16 - 9.19 (t, 1H, NH). FT-IR: 3441 (N-H); 3081 (Ar-H), 2923 (C-H), 1638 (C=O), 1544 (C=N), 1421 (C=C), 1381 (C-N). MS: m/z 639.2 (M+1), 0.182g, Yield: 59.4%.

4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl) acetamido) methyl)- N- (4-methyl benzyl) benzamide (7e): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.26 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 4.07 (d, 2H, CH_2); 4.38 - 4.39 (d, 2H, CH_2); 4.42 - 4.43 (d, 2H, CH_2); 7.11 - 7.20 (m, 4H, Ar-H); 7.28 - 7.30 (d, 2H, Ar-H); 7.34 – 7.36 (d, 3H, Ar-H); 7.60 - 7.65 (m, 3H, Ar-H); 7.84 - 7.86 (d, 2H, Ar-H); 8.35 (s, 1H, Ar-H); 8.88 - 8.91 (t, 1H, NH); 8.95 - 8.98 (t, 1H, NH). FT-IR: 3425 (N-H); 3012 (Ar-H), 2934 (C-H), 1667 (C=O), 1532 (C=N), 1426 (C=C), 1349 (C-N). MS: m/z 517.3 (M+1), 0.124g, Yield: 46.1%.

N- (3-methoxybenzyl)-4-((2-(6-methyl-2-(p-tolyl) imidazo[1,2-a]pyridin-3-yl)acetamido) methyl) benzamide (7f): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.30 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.37 (s, 3H, OCH_3); 4.03 (d, 2H, CH_2); 4.39 - 4.40 (d, 2H, CH_2); 4.42 - 4.43 (d, 2H, CH_2); 7.11 - 7.14 (d, 1H, Ar-H); 7.23 - 7.25 (d, 1H, Ar-H); 7.36 - 7.43 (m, 4H, Ar-H); 7.47 – 7.55 (m, 2H, Ar-H); 7.65 - 7.72 (m, 3H, Ar-H); 7.87 - 7.89 (d, 2H, Ar-H); 7.97 - 7.99 (d, 1H, Ar-H); 8.17 (s, 1H, Ar-H); 8.85 - 8.88 (t, 1H, NH); 8.96 - 8.97 (t, 1H, NH). FT-IR: 3427 (N-H); 3023 (Ar-H), 2922 (C-H), 1672 (C=O), 1552 (C=N), 1443 (C=C), 1339 (C-N). MS: m/z 533.1 (M+1), 0.146g, Yield: 52.5%.

N- (4-methoxybenzyl)-4-((2-(6-methyl-2-(p-tolyl) imidazo[1,2-a]pyridin-3-yl)acetamido) methyl) benzamide (7g): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.35 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 3.72 (s, 3H, OCH_3); 4.07 (d, 2H, CH_2); 4.37 - 4.38 (d, 2H, CH_2); 4.39 - 4.40 (d, 2H, CH_2); 6.87 - 6.89 (d, 2H, Ar-H); 7.22 - 7.24 (d, 2H, Ar-H); 7.29 - 7.35 (m, 4H, Ar-H); 7.60 - 7.64 (m, 3H, Ar-H); 7.83 - 7.85

(m, 2H, Ar-H); 8.36 (s, 1H, Ar-H); 8.87 - 8.90 (t, 1H, NH); 8.92 - 8.96 (t, 1H, NH). FT-IR: 3427 (N-H); 3023 (Ar-H), 2922 (C-H), 1672 (C=O), 1552 (C=N), 1443 (C=C), 1339 (C-N). MS: m/z 533.2 (M+1), 0.168g, Yield: 60.4%.

4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl) acetamido)methyl)-N-(pyridin-4-ylmethyl) benzamide (7h): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.30 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 4.03 (d, 2H, CH_2); 4.38 - 4.40 (d, 2H, CH_2); 4.48 - 4.50 (d, 2H, CH_2); 7.11 – 7.14 (m, 1H, Ar-H); 7.23 - 7.30 (m, 4H, Ar-H); 7.36 - 7.38 (d, 2H, Ar-H); 7.47 - 7.50 (d, 1H, Ar-H); 7.66 - 7.68 (d, 2H, Ar-H); 7.85 - 7.87 (d, 2H, Ar-H); 8.17 (s, 1H, Ar-H); 8.49 - 8.50 (m, 2H, Ar-H); 8.85 - 8.88 (t, 1H, NH); 9.07 - 9.10 (t, 1H, NH). FT-IR: 3459 (N-H); 3024 (Ar-H), 2934 (C-H), 1636 (C=O), 1559 (C=N), 1427 (C=C), 1346 (C-N). MS: m/z 504.2 (M+1), 0.129g, Yield: 49.2%.

N- (4-chlorobenzyl)- 4- ((2-(6-methyl-2-(p-tolyl) imidazo [1,2-a]pyridin-3-yl) acetamido) methyl) benzamide (7i): ^{1}H-NMR (400 MHz, $CDCl_3$) ppm: 2.33 (s, 3H, CH_3); 2.38 (s, 3H, CH_3); 4.05 (d, 2H, CH_2); 4.42 - 4.43 (d, 2H, CH_2); 4.58 - 4.60 (d, 2H, CH_2); 6.13 – 6.15 (t, 1H, NH); 6.37 – 6.40 (t, 1H, NH); 7.08 - 7.11 (m, 1H, Ar-H); 7.14 - 7.16 (d, 2H, Ar-H); 7.21 - 7.23 (d, 2H, Ar-H); 7.27 - 7.32 (m, 4H, Ar-H); 7.49 - 7.51 (d, 1H, Ar-H); 7.56 - 7.58 (d, 2H, Ar-H); 7.64 – 7.66 (d, 2H, Ar-H); 7.75 (s, 1H, Ar-H). FT-IR: 3456 (N-H); 3012 (Ar-H), 2914 (C-H), 1635 (C=O), 1558 (C=N), 1427 (C=C), 1323 (C-N). MS: m/z 537.2 (M+1), 0.184g, Yield: 65.4%.

4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamido)methyl)-N-(4-(trifluoro methyl) benzyl)benzamide (7j): ^{1}H-NMR (400 MHz, $CDCl_3$) ppm: 2.35 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 4.04 (d, 2H, CH_2); 4.41 - 4.43 (d, 2H, CH_2); 4.69 - 4.70 (d, 2H, CH_2); 6.15 - 6.18 (t, 1H, NH); 6.56 - 6.58 (t, 1H, NH); 7.14 - 7.21 (m, 5H, Ar-H); 7.45 - 7.47 (d, 2H, Ar-H); 7.51 - 7.53 (m, 2H, Ar-H); 7.59 - 7.61 (m, 3H, Ar-H); 7.67 - 7.69 (d, 2H, Ar-H); 7.83 (s, 1H, Ar-H). FT-IR: 3457 (N-H); 3028 (Ar-H), 2936 (C-H), 1639 (C=O), 1549 (C=N), 1435 (C=C), 1327 (C-N). MS: m/z 571.2 (M+1), 0.189g, Yield: 62.7%.

4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamido)methyl)-N-(pyridin-3-yl methyl) benzamide (7k): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.29 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 4.03 (d, 2H, CH_2); 4.38 - 4.39 (d, 2H, CH_2); 4.48 - 4.50 (d, 2H, CH_2); 7.12 – 7.14 (d, 1H, Ar-H); 7.22 - 7.24 (d, 2H, Ar-H); 7.33 - 7.37 (m, 3H, Ar-H); 7.48 - 7.50 (d, 1H, Ar-H); 7.65 - 7.71 (m, 3H, Ar-H); 7.83 - 7.85 (d, 2H, Ar-H); 8.17 (s, 1H, Ar-H); 8.44 - 8.46 (m, 1H, Ar-H); 8.54 - 8.55 (d, 1H, Ar-H); 8.85 - 8.88 (t, 1H, NH); 9.05 - 9.08 (t, 1H, NH). FT-IR: 3440 (N-H); 3012 (Ar-H), 2918 (C-H), 1667 (C=O), 1536 (C=N), 1451 (C=C), 1348 (C-N). MS: m/z 504.2 (M+1), 0.159g, Yield: 60.6%.

N-(3,4-dichlorobenzyl)-4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamido) methyl)benzamide (7l): ^{1}H-NMR (400 MHz, DMSO-*d6*) ppm: 2.30 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 4.03 (d, 2H, CH_2); 4.39 - 4.40 (d, 2H, CH_2); 4.56 - 4.58 (d, 2H, CH_2); 7.12 - 7.14 (m, 1H, Ar-H); 7.23 - 7.25 (d, 2H, Ar-H); 7.36 - 7.43 (d, 3H, Ar-H); 7.48 - 7.55 (m, 2H, Ar-H); 7.65 - 7.72 (d, 2H, Ar-H); 7.87 - 7.89 (d, 2H, Ar-H); 7.96 – 7.99 (d, 1H, Ar-H); 8.17 (s, 1H, Ar-H); 8.85 – 8.88 (t, 1H, NH); 8.96 – 8.99 (t, 1H, NH). FT-IR: 3455 (N-H); 3016 (Ar-H), 2916 (C-H), 1674 (C=O), 1558 (C=N), 1412 (C=C), 1235 (C-N). MS: m/z 571.2 (M+1), 0.176g, Yield: 58.4%.

Anti-Inflammatory Activity:

Anti-Denaturation Assay: The experiment was carried out with minor modification [21]. The standard drug and extract were dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). The final concentration of DMF in all solutions was less than 2.5%. Test Solution (4 ml) containing different concentrations of the drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 37 °C in an incubator for 15 min. Denaturation was induced by keeping the mixture of reaction at 70 °C in a water bath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition of denaturation was calculated by using the following formula.

$$\% \text{ of Inhibition} = 100 \times (At - Ac) / At$$

Where, At = O.D. of test solution

Ac = O.D. of control

RESULTS AND DISCUSSION:

Chemistry: Synthesis was carried out using modified reported procedures for conventional synthesis [22]. 4-methyl acetophenone was used as an inceptive material for synthesis of compounds (7a-l) and showed in Scheme-1. All the molecules were characterized by using ^{1}H-NMR, Mass and FTIR spectral analysis. Structure with the percentage yield of the compounds was depicted in **Table 1** and compared with the conventional method.

The compounds were also synthesized in the conventional method (7), and the yield of each compound was compared with the authentic samples. It has been observed that the yield of all the compounds was increased in microwave-assisted synthesis method. 6-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine was synthesized by the reaction of 4-methyl acetophenone with 2-amino-5-methyl pyridine in the presence of bromine and aluminum chloride. Compound 1 further reacts with formalin and dimethylamine in microwave irradiation at 80W for 5 min to lend the product of 2 with 92% yield.

The dimethyl aminomethyl derivative was undergone microwave irradiation with sodium cyanide and methyl iodide at 100W for 10 min to yield (89%) the compound 3. The cyano derivative was irradiated at 80W for 5mins for hydrolysis using potassium hydroxide in methanol to produce compound 4. The acid derivative was undergone the microwave irradiation at 80W for 10 min in the presence of TBTU, Ethyl 4-(aminomethyl)benzoate and triethylamine. The resulting compound 5 showed a molecular ion peak at m/z 442 and yielded 92%. The ester was further hydrolyzed with sodium hydroxide in methanol at room temperature to yield compound 6.

The corresponding acid was irradiated at 80W for 10 min with benzylamines derivatives in the presence of TBTU and triethylamine solution to give the final product of imidazo[1, 2-a]pyridine derivatives 7a-l in good yield. Compound 7a showed a molecular ion peak of m/z 503 in the mass spectrum. Similarly, in ^{1}H-NMR spectra, the signals at 2.30 and 2.35 ppm represented the methyl groups. Three doublet signals at 4.04, 4.41 and 4.49 ppm appeared for -CH_2 groups. The peaks showed in the region of 7.12 to 8.18 ppm represented for aromatic protons.

TABLE 1: SYNTHESIS OF IMIDAZO[1,2-A]PYRIDINE DERIVATIVES

Compound	R	Conventional method	Microwave method
		Yield (%)	
7(a)		31.5	56.2
7(b)		22.7	48.06
7(c)		24.6	54.1
7(d)		22.5	59.4
7(e)		38.5	46.1
7(f)		19.9	52.5
7(g)		24.6	60.4
7(h)		32.3	49.2
7(i)		39.3	65.4
7(j)		22.6	62.7
7(k)		35.8	60.6
7(l)		26.7	58.4

***In-vitro* Anti-Inflammatory Activity:** Denaturation of proteins is one of the major causes of inflammation. The inhibition of heat-induced denaturation of BSA is a well-documented method for estimation of the *in-vitro* anti-inflammatory activity. In general, the denaturation process involves electrostatic hydrogen, hydrophobic and disulphide bonding. The anti-denaturation property of BSA drives major interest due to their aromatic tyrosine-rich domain and the aliphatic threonine and lysine-rich regions. The heat-induced denaturation was found too much effective in inducing Type III delayed hypersensitivity like that of the native proteins [23].

In our study, all the imidazo[1,2-a]pyridine derivatives were screened for their anti-inflammatory property **Fig. 1**. The inhibitory potential of heat-induced BSA denaturation was determined as shown in the Figure. Among the synthesized derivatives, 7d and 7g have shown significantly maximum inhibition (69.45% and 69.60%) against BSA denaturation compared to that of standard aspirin (72.98%). This may be due to the presence of electron donating groups *viz.* methoxy and trifluoromethyl groups present in the structure of the compounds. The compounds 7b, 7e contain electron withdrawing groups of halogen moiety that have shown the moderate inhibitory activity of 58.38% and 47.89% respectively. The remaining compounds have shown mere inhibition against denaturation of bovine serum albumin. The results suggested that synthesized imidazo[1,2-a] pyridine derivatives showed anti-inflammatory potential which might be due to their interaction with aliphatic regions around the lysine residue of BSA [24]. These compounds may also activate tyrosine-rich motif receptor along with threonine which could cause a major impact in biological terrain linked with sickness, rheumatoid arthritis and even cancer development [25].

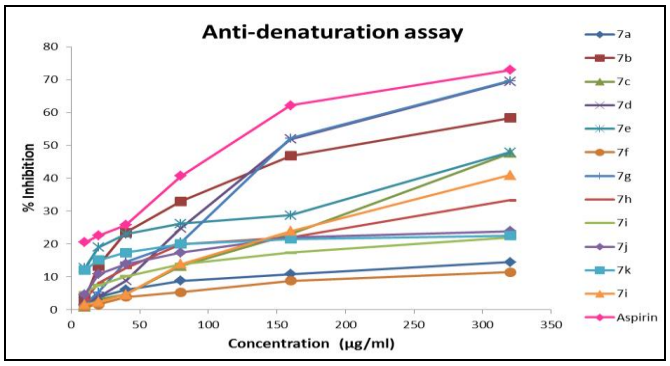


FIG. 1: *IN-VITRO* ANTI-INFLAMMATORY ACTIVITY OF IMIDAZO[1,2-A]PYRIDINE DERIVATIVES (7a-l)

CONCLUSION: The synthesized imidazo[1,2-a]pyridine derivatives exhibited significant inhibition against protein denaturation and thereby established its anti-inflammatory potential. The highly reactive compounds can be further developed as a potent anti-inflammatory agent after validating its potent anti-inflammatory property *in-vivo*.

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