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Green Synthesis of Novel Pyridines via One-Pot Multicomponent Reaction and Their Anti-Inflammatory Evaluation

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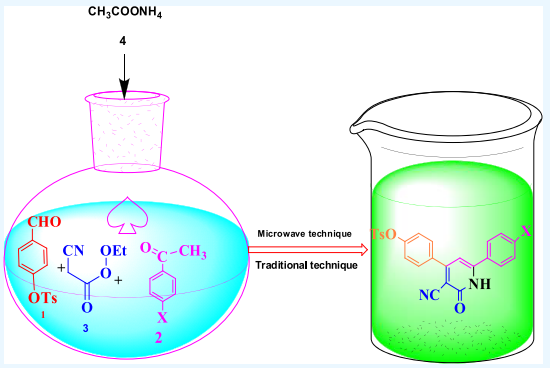
ABSTRACT: A functional and environmentally green procedure for the design of novel pyridine **5a−h** and **7a−d** derivatives through two pathways is presented. The first pathway is via a one-pot, four-component reaction of *p*-formylphenyl-4-toluenesulfonate (**1**), ethyl cyanoacetate (**2**), acetophenone derivatives **3a−h** or acetyl derivatives **6a−d**, and ammonium acetate (**4**) under microwave irradiation in ethanol. The advantages of this method are an excellent yield (82%−94%), pure products, a short reaction time (2−7 min), and low-cost processing. The second pathway was obtained by the traditional method with treatment of the same mixture under refluxing in ethanol, which afforded the same products, **5a−h** and **7a−d**, in less yield (71%−88%) and over a longer reaction time (6−9 h). The constructions of the novel compounds were articulated via spectral and elemental analysis. Overall, the compounds have been designed, synthesized, and studied for their in vitro anti-inflammatory activity using diclofenac as a reference drug (5 mg/kg). The most potent four compounds, **5a**, **5f**, **5g**, and **5h**, showed promising anti-inflammatory activity.



INTRODUCTION

It is known that pathogens, radiation, damaged cells, and other danger signals can all trigger inflammation as a host defensive mechanism.[1] Acute inflammation is characterized by swelling, redness, warmth, and discomfort, which can result from various infections or tissue damage. However, there are no traditional symptoms of acute inflammation in the context of chronic and low-grade inflammation, which is a major factor in the onset and development of aging and many chronic diseases, including cancer, respiratory disease, autoimmune disease, metabolic disease, neurodegenerative disease, and cardiovascular disease.[2] Even if a number of anti-inflammatory drugs are easily accessible in clinics, there is still a need for a safer and more effective strategy to treat inflammatory illnesses. Because of this, it is crucial to find new and improved anti-inflammatory medications, and numerous researchers have worked to develop new molecules that exhibit a range of properties, including anti-inflammatory ones.[3−5] Pyridine derivatives are a significant moiety of organic chemistry because of their widespread chemical, as well as medical, applications.[4,5] For example, cyanopyridine has been employed as an IKKb inhibitor, as an A_2 adenosine receptor antagonist, and as an anti-inflammatory and anticancer agent.[6−8] To date, numerous plans have been described for producing pyridine derivatives. Given these circumstances, the effective design of a recyclable and green catalyst that works in mild conditions is still a significant challenge for producing pyridines. Moreover, pyridine derivatives have appeared as a substantial scaffold in view of their prevalence in a considerable number of natural products[8] and their application to biological and pharmaceutical chemistry.[9−16] In recent years, chemists have been interested in developing pyridine derivatives because of their great importance, whether in organic chemistry or in medical applications.[17−31] Moreover, they are interested to use modern techniques in organic synthesis. One-pot multicomponent reactions are the most increasing academic and ecological method because of the possibility of achieving high synthetic efficiency and reaction design.[3,32−38] In addition, it is known that multicomponent reactions (MCRs) possess many advantages, such as eco-friendly efficiency, atom economy, and reduced reaction times with increased yields, and these advantages are very important in synthetic organic chemistry, especially when the target compounds are studied in their biological evaluation.[39−54]

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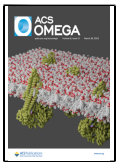
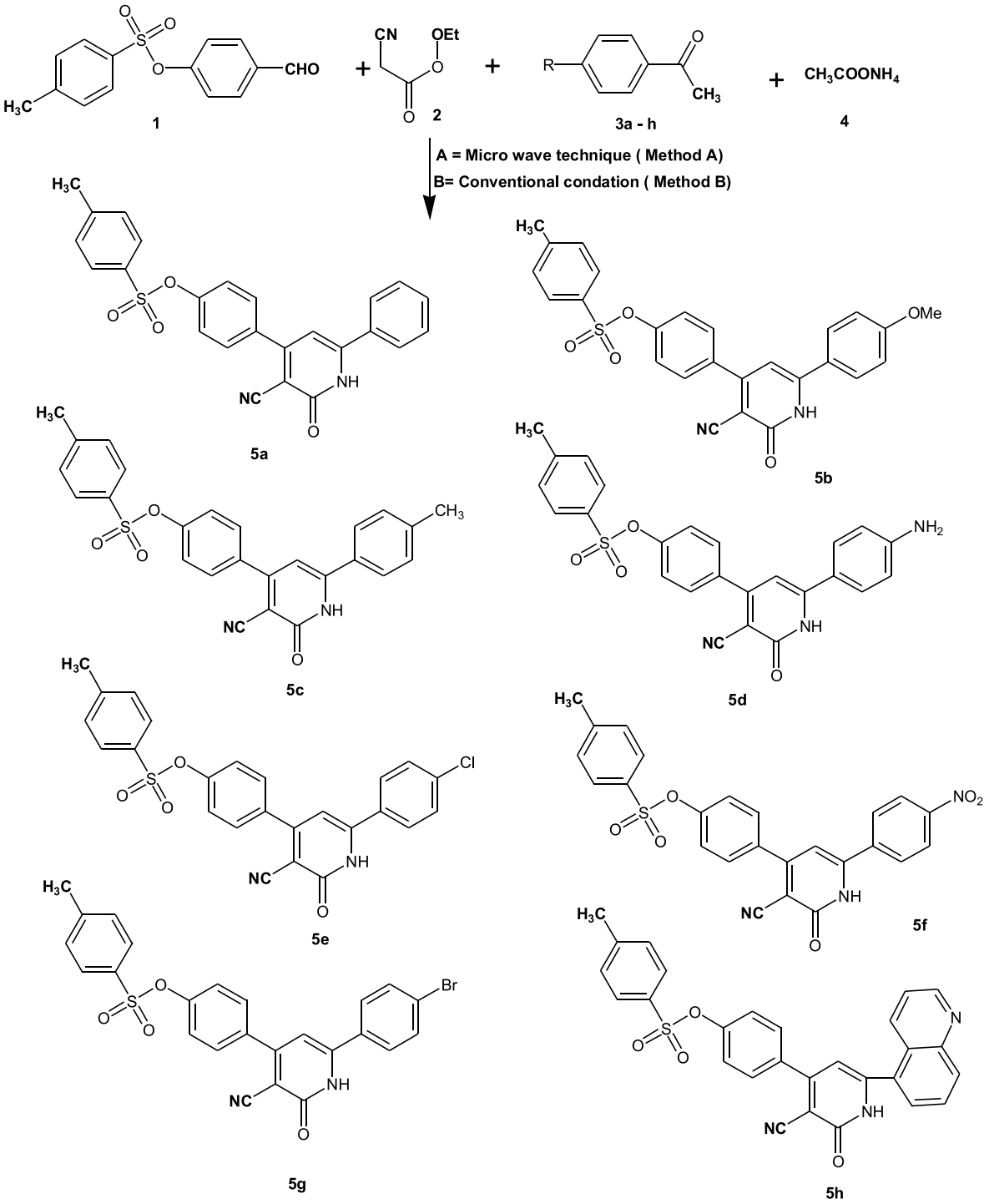


Scheme 1. Synthesis of 3-Cyanopyridines 5a−h



RESULTS AND DISCUSSION

Chemistry. Because microwave-assisted synthesis has been recognized as a green chemistry tool and has provided advantages in various organic synthesis,[51−54] in this article, an efficient and simple methodology has been designed to synthesize 3-pyridine derivatives **5a−h** via two procedures: by treatment of the reaction mixture under microwave irradiation (Method A) and by conventional heating (Method B). First, a one-pot, four-component reaction of *p*-formylphenyl-4-toluenesulfonate (**1**); ethyl cyanoacetate (**2**); acetophenone derivatives **3a−h**, namely, acetophenone (**3a**), 4-methoxyacetophenone (**3b**), 4-methylacetophenone (**3c**), 4-aminoacetophenone (**3d**), 4-chloro- acetophenone (**3e**), 4-nitroacetophenone (**3f**), 4-bromoacetophenone (**3g**), and 5-acetylquinoline (**3h**); and ammonium acetate (**4**) in molar ratio 1:1:1:2 in 5 mL of ethanol under microwave irradiation (**Method A**) (Scheme 1) provided excellent yields, a very short reaction time, and reduced the problems associated with hazardous solvents employed (safety, cost, and pollution). Conversely, the second method (**Method B**) was performed with treatment of the same mixture of the one-pot, four-component reaction using conventional heating methods under reflux in an

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alcoholic solvent, which afforded the same products in good yields (TLC, 71−84%) but longer reaction time (6−9 h) than **Method A** (Scheme 1). The optimized outcomes are recorded in Table 1.

Table 1. Comparison Efficiency between Microwave (MW) and Conventional Methods in the Preparation of Pyridine Derivatives 5−7

	MW irradiation **Method A**		conventional condition **Method B**	
compound	yield (%)	time (min)	yield (%)	time (h)
5a	93	7	84	6
5b	94	7	83	8
5c	90	5	73	9
5d	91	6	78	7
5e	93	4	72	8
5f	86	7	79	6
5g	90	6	84	7
5h	82	4	71	6
7a	88	2	75	8
7b	90	5	87	9
7c	82	5	75	7
7d	89	3	88	7

The new component structures were confirmed according to FTIR, NMR, and elemental analyses. The IR spectra of products **5a−h** revealed the disappearance of aldehydic C═O groups and the appearance of an NH group at 3189−3132 cm^{-1}; CN groups at 2236−2217 cm^{-1}; and a NH−C═O group between 1646 and 1639 cm^{-1}. The ^1H NMR spectra of products **5a−h** demonstrated, aside from the rising protons of aromatic signals and a new absorbance singlet, indications equivalent to NH groups at 12.92−12.20 ppm (which disappeared via deuteration); an aromatic proton consisting of a CH pyridyl in the region 8.57−6.12 ppm; and moreover, the CH_3 and OCH_3 groups in compounds **5b, 5c** that appeared at 2.44 ppm and at 3.85 ppm, respectively. Conversely, the NH_2 group in compound **5d** showed as a new signal at 5.83 ppm, and the CH_3 group of the tosyl moiety appeared around 2.44 ppm. The ^{13}C NMR spectra of **5a−h** showed new signals at 165.22−150.73 ppm because of the C═O (amidic group), aromatic signals at 158.1−122.83 ppm, the CN group at 122.00−114.86 ppm, and CH3 in the region of 21.67−21.39 ppm. For example, the ^{13}C NMR spectrum of compound **5c** demonstrated a novel signal at 162.83 ppm because of the C═O (amidic group), 116.83 ppm because of CN group, and at 21.66 and 21.39 ppm for the two CH_3 groups. However, the ^{13}C NMR spectrum of **5b** displayed a novel signal at 165.22 ppm because of the C═O (amidic group), 114.86 ppm for the CN group, and at 56.00 ppm for the OCH_3 group.

The reaction mechanism of compound **5a** is illustrated as an example of the formation of pyridines in Scheme 2.

Under the same reaction condition,[52−55] for designing of substitutedpyridines **7a−d** by two methods. via one-pot four components reaction of compound **1**, ethyl cyanoacetate (**2**), acetyl derivatives **6a−d** namely; 2-acetylpyridine(**6a**), 3-acetylpyridine (**6b**), 4-acetylpyridine (**6c**), 2-acetylthiophene (**6d**), and ammonium acetate (**4**) in molar ratio 1:1:1:2 in under microwave irradiation (**Method A**) and conventional method (**Method B**) gave 3-cyanopyridine derivatives **7a−d** which produce excellent yield within short reaction times in case of microwave irradiation but in case of traditional method give the same products 3-pyridins **7a−d** within longer reaction time and in good yields, (Scheme 3) (Table 1).

The IR spectra of components **7a−d** displayed the disappearance of the aldehydic C═O group and the appearance of NH groups in the region 3243−3089 cm^{-1}; carbonitryl groups at 2228−2219 cm^{-1}; and a C═O (amidic group) in between 1647 and 1641 cm^{-1}. The ^1H NMR spectrum of product **7d** showed, in addition to the aromatic protons signal, novel absorbance singlet signals because of the NH group at 12.67 ppm due to the NH group that disappeared via deuteration; the CH pyridyl group and CH aromatic groups in the region 8.03−7.03 ppm; and the CH_3 group of the tosyl moiety that appeared around 2.45 ppm. Moreover, its ^{13}C NMR spectrum exhibited a novel signal at 150.62 ppm for the C═O (amidic group), 116.55 ppm for the C═O group, and 21.67 ppm for the CH_3 group.

From the results recorded in Table 1, we note that microwave irradiation is, indeed, better than the traditional method in preparing pyridine either for an increased yield or reduced time.

Anti-Inflammatory Activity. The in vitro anti-inflammatory action of all tested compounds was estimated against carrageenan-induced paw edema in male Wister rats (180−200 g each) using diclofenac as a reference drug on the basis of a Winter et al. modified process.[55,56] Diclofenac was evaluated at 5 mg/kg[56] of body weight for the animal used. Prior to the test, all animals experienced at least a 1 week acclimatization period. All of the investigational procedure was done in accordance with the strategies of the Institutional Animals Ethics Committee (IEAC). Changes in paw volume (% of edema inhibition) were produced and compared by subplantar dose of 100.0 μL of 1.0% newly prepared carrageenan solution in bidistilled H_2O into the left hind paw of each rat.[3,56] The test agents were injected half an hour earlier to carrageenan addition, The comparison was done after 1, 3, and 6 h from induction of inflammation (Table 2) and showed a wide range of anti-inflammatory effects (7.59−46.9%; 1 h), (7.59−52.80%; 3 h) and (9.37−54.37%; 6 h) against to the reference drug diclofenac (28.26%, 1 h; 20.79%, 3 h; 20.79%, 6 h).

From the recorded results in Table 2, it appears that of all 15 compounds evaluated for anti-inflammatory activity, the titled compounds could be promising anti-inflammatory candidates when using diclofenac as a reference drug (28.26%; 1 h). It was found that the most potent four compounds were **5a**, **5f**, **5g**, and **5h** with a % edema inhibition of (46.9%; 1 h), (34.27%; 1 h), (43.46%; 1 h), and (30.74%; 1 h), respectively.

EXPERIMENTAL SECTION

Chemistry. The uncorrected melting point was reported using a Kofler melting point apparatus. With an FT-IR-ALPHBROKER-Platinum-ATR, infrared (IR) spectra were recorded. On a Bruker Bio Spin AG spectrometer, the ^1H NMR and ^{13}C NMR spectra were obtained in DMSO-d_6 at 400.0 and 100.0 MHz, respectively. A PerkinElmer CHN-analyzer model provided the elemental analyses. For microwave irradiations, a Kenstar OM9925E microwave (MW) oven (2450 MHz, 800 W) was used.

General Procedure for the Synthesis of Compounds 5−7. Method A: Microwave Irradiation. A solution of 4-formylphenyl-4-methylbenzenesulfonate (**1**); ethyl cyanoacetate (2 mmol, 0.22 mL); acetophenone derivatives, namely, acetophenone, 4-methylacetophenone, 4-methoxyacetophe-

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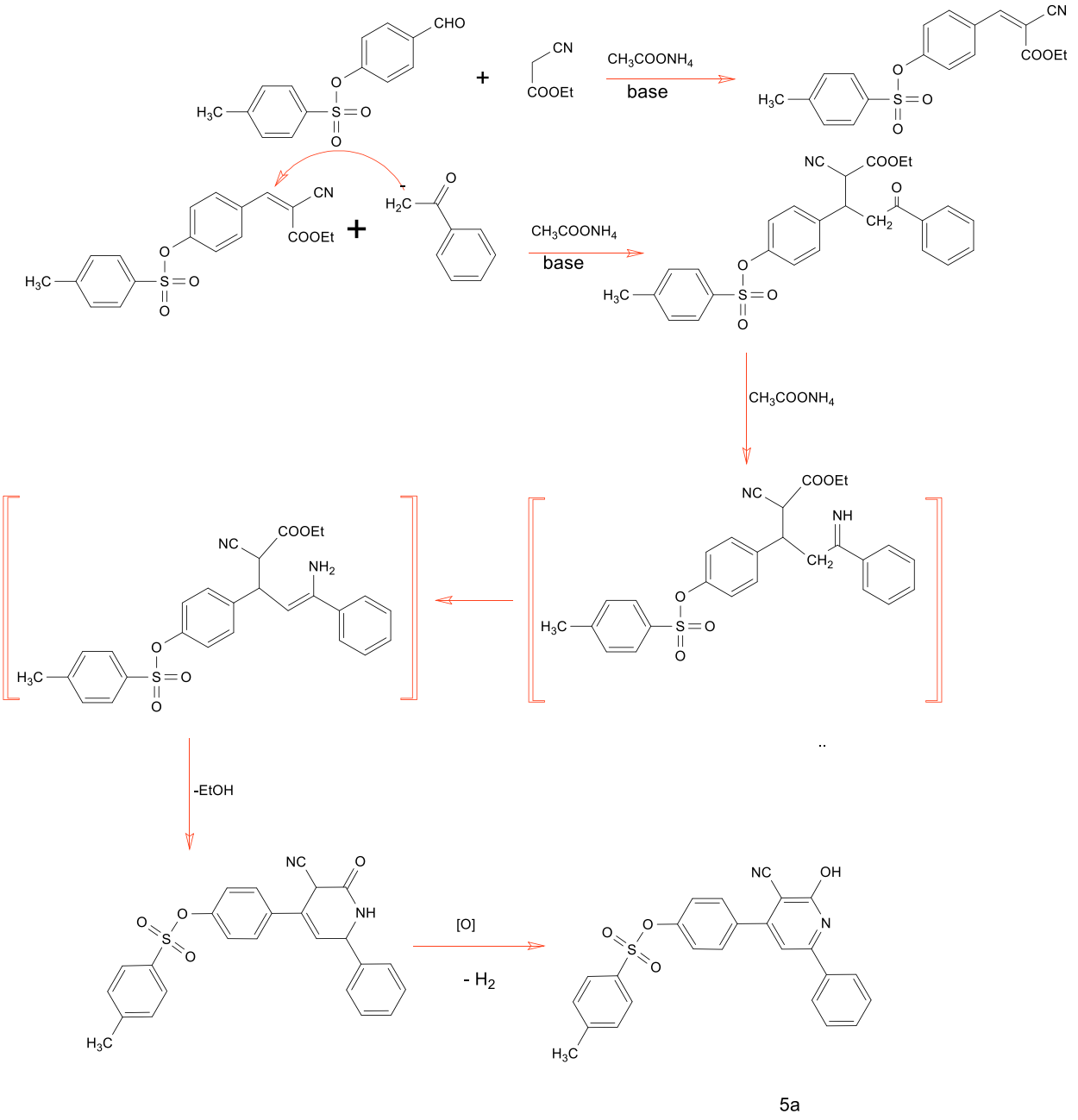
Scheme 2. Reaction Mechanism of Formation of 3-Cyanopyridines



none, 4-aminoacetophenone, 4-chloroacetophenone, 4-bromoacetophenone, 4-nitroacetophenone, 1-acetylnaphthalene, 2-acetylthiophene, 2-acetylpyridine, 3-acetylpyridine, and 4-acetylpyridine; and ammonium acetate in molar ratio 1:1:1:2 in 5 mL of ethanol was allowed to irradiate in an MW oven for 2−7 min, as shown in Table 1. After cooling to 25 °C, the solid products were filtered off, washed with water, dried, and crystallized from the ethanol.

Method B: General Method (Conventional Heating). To 30 mL of ethanol was added a solution of 4-formylphenyl-4-methylbenzenesulfonate (**1**); ethyl cyanoacetate (2 mmol, 0.22 mL); acetophenone derivatives, namely, acetophenone (**3a**), 4-methoxyacetophenone (**3b**), 4-methylacetophenone (**3c**), 4-aminoacetophenone (**3d**), 4-chloroacetophenone (**3e**), 4-nitroacetophenone (**3f**), 4-bromoacetophenone (**3g**), and 5-acetylquinoline (**3h**); and ammonium acetate in ratio 1:1:1:2. The reaction mixture was refluxed for an appropriate period of time, which is recorded in Table 1, to cause the desired compounds to precipitate. The resulting solid was then filtered off, washed with water, dried, and crystallized from the ethanol.

Characterization of New Compounds. *4-(3-Cyano-2-oxo-6-phenyl-1,2-dihydropyridin-4-yl)phenyl-4-toluenesulfonate (**5a**).* Melting point, 279−280 °C; IR (cm^{-1}), 3185 (NH), 2219 (CN), 1645 (C═O); ^1H NMR (DMSO-d_6), δ 12.73 (s, 1H, NH replaced by D_2O), 7.92−7.25 (m, 13H, H_{arom}; 1H, CH of pyridinium), 2.45 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 155.03, 153.55, 151.66, 150.72, 146.51, 143.52, 133.03, 129.92, 129.39, 128.67, 128.27, 122.00, 21.67; *Anal.* calcd for $C_{25}H_{18}N_2O_4S$ (442.48): C (67.86%), H (4.10%), N (6.33%). Found: C (67.64%), H (4.25%), N (6.16%).

*4-[3-Cyano-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5b**).* Melting point,

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Scheme 3. Synthesis of 3 -cyanopyridines 7a - 7d

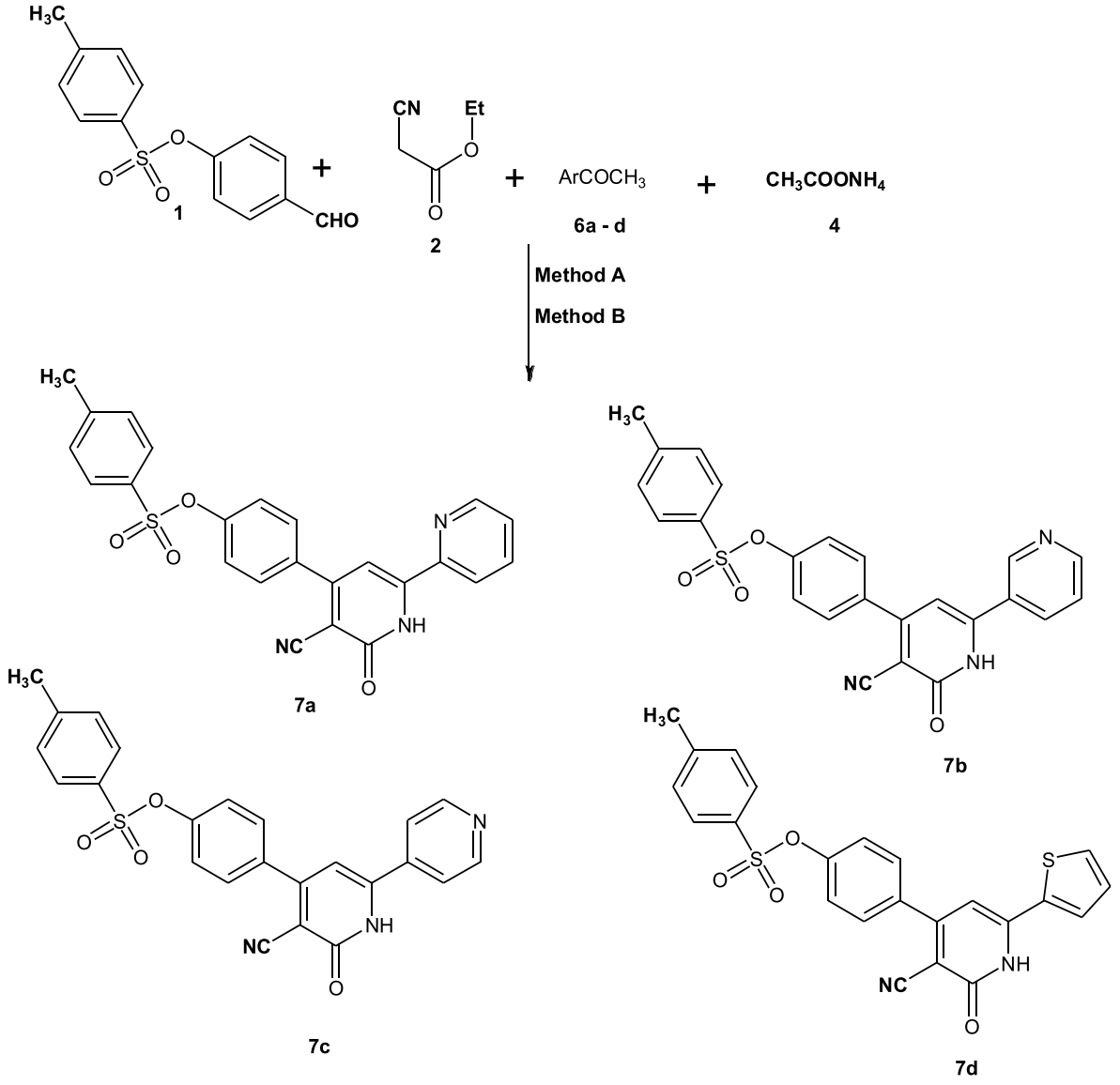

Table 2. Anti-Inflammatory Effect of Test Compounds 5−7 and Reference Drug Diclofenac

paw volume (mL)			% edema inhibition			
treatment	1 h	3 h	6 h	1 h	3 h	6 h
5a	1.50 ± 0.05	1.43 ± 0.23	1.46 ± 0.88	46.90	52.80	54.37
5b	2.53 ± 0.08	2.50 ± 0.05	2.60 ± 0.05	10.60	17.49	18.75
5c	2.46 ± 0.06	2.36 ± 0.03	2.90 ± 0.10	13.07	22.11	09.37
5d	2.56 ± 0.08	2.53 ± 0.03	2.66 ± 0.03	09.54	16.50	16.87
5e	2.56 ± 0.08	2.46 ± 0.03	2.70 ± 0.05	09.50	18.81	19.87
5f	1.86 ± 0.03	1.76 ± 0.03	1.66 ± 0.12	34.27	41.91	48.12
5g	1.60 ± 0.05	1.46 ± 0.03	1.70 ± 0.05	43.46	51.81	46.87
5h	1.96 ± 0.03	1.90 ± 0.05	2.33 ± 0.14	30.74	37.29	27.18
7a	2.66 ± 0.07	2.53 ± 0.08	2.70 ± 0.05	08.36	16.50	15.62
7b	2.63 ± 0.08	2.63 ± 0.08	2.80 ± 0.11	07.59	14.19	12.50
7c	2.75 ± 0.08	2.70 ± 0.05	2.83 ± 0.08	09.24	10.89	11.56
7d	2.40 ± 0.20	2.43 ± 0.03	2.86 ± 0.08	15.19	19.80	14.62
vehicle	2.83 ± 0.08	3.03 ± 0.08	3.20 ± 0.11	0	0	0
diclofenac	2.03 ± 0.08	2.40 ± 0.11	2.60 ± 0.04	28.26	20.79	20.79

289−290 °C; IR (cm^{-1}), 3137 (NH), 3041 (CH_{arom}), 2961 (CH_{aliph}), 2227 (CN), 1643 (C═O); ^1H NMR (DMSO-d_6), δ 12.57 (s, 1H, NH replaced by D_2O), 7.91−6.77 (m, 12H, CH arom + 1H, CH of pyridinium), 3.85 (s, 3H, OCH_3), 2.44 (s,

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3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 165.22, 162.28, 158.42, 150.66, 146.52, 136.46, 135.66, 131.88, 130.94, 130.71, 129.99, 128.66, 124.14, 122.82, 116.24, 114.86, 56.00, 21.66. *Anal.* calcd for $C_{26}H_{20}N_2O_5S$ (472.51): C (66.09%), H (4.27%), N (5.93%). Found: C (66.13%), H (4.32%), N (5.87%).

*4-[3-Cyano-6-(4-methylphenyl)-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5c**).* Melting point, 304−305 °C; IR (cm^{-1}), 3154 (NH), 3046 (CH_{arom}), 2936 (CH_{aliph}), 2219 (CN), 1639 (C═O); ^1H NMR (DMSO-d_6), δ 12.60 (s, 1H, NH exchanged by D_2O), 7.83−6.80 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 2.45 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 162.38, 158.81, 150.70, 146.50, 141.95, 135.57, 131.91, 130.73, 129.97, 128.66, 128.15, 122.83, 116.83, 21.66, 21.39. *Anal.* calcd for $C_{26}H_{20}N_2O_4S$ (456.51%): C (68.41%), H (4.42%), N (6.14%) Found: C (68.21%), H (4.19%), N (6.17%).

*4-[6-(4-Aminophenyl)-3-cyano-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5d**).* Melting point, 265−266 °C; IR (cm^{-1}), 3312, 3287, 3189 (NH_2 + NH), 2232 (CN), 1644 (C═O); ^1H NMR (DMSO-d_6), δ 12.20 (s, 1H, NH exchanged by D2O), 7.90−6.63 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 5.83 (s, 2H, NH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 162.26, 150.01, 139.99, 136.43, 132.84, 131.11, 130.54, 129.17, 129.01, 122.17, 122.00, 116.83, 21.64; *Anal.* calcd for $C_{26}H_{20}N_2O_4S$ (456.51): C (68.41%), H (4.42%), N (6.14%). Found: C (68.47%), H (4.36%), N (6.21%).

*4-[6-(4-Chlorophenyl)-3-cyano-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5e**).* Melting point, 267−269 °C; IR (cm^{-1}), 3158 (NH), 2217 (CN), 1639 (C═O); ^1H NMR (DMSO-d_6), δ 12.92 (s, 1H, NH exchanged by D_2O), 7.96−7.24 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 150.73, 146.51, 136.55, 135.43, 131.90, 130.83, 130.13, 129.39, 128.67, 122.86, 122.96, 116.65, 21.67. *Anal.* calcd for $C_{25}H_{17}ClN_2O_4S$ (476.93): C (62.96%), H (3.59%), N (5.87%). Found: C (78.76%), H (3.62%), N (6.03%).

*4-[6-(4-Nitroophenyl)-3-cyano-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5f**).* Melting point, 287−289 °C; IR (cm^{-1}), 3132 (NH), 2223 (CN), 1643 (C═O); ^1H NMR (DMSO-d_6), δ 12.87 (s, 1H, NH exchanged by D_2O), 7.81−6.34 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 2.45 (s, 3H, CH_3). *Anal.* calcd for $C_{25}H_{17}N_3O_6S$ (487.48): C (61.60%), H (3.51%), N (8.62%). Found: C (61.68%), H (3.52%), N (8.67%).

*4-[6-(4-Bromophenyl)-3-cyano-2-oxo-1,2-dihydropyridin-4-yl]phenyl-4-toluenesulfonate (**5g**).* Melting point, 301−303 °C; IR (cm^{-1}), 3179 (NH), 2230 (CN), 1646 (C═O); ^1H NMR (DMSO-d_6), δ 12.34 (s, 1H, NH replaced by D_2O), 7.98−7.36 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 2.45 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 151.22, 148.01, 139.43, 136.23, 131.99, 131.09, 130.48, 129.16, 128.87, 122.91, 122.06, 116.83, 21.68. *Anal.* calcd for $C_{25}H_{17}BrN_2O_4S$ (521.38): C (57.59%), H (3.29%), Br (15.33%), N (5.37%). Found: C (57.63%), H (3.36%), Br (15.31%), N (5.41%).

*4-[3-Cyano-6-(1-Naphtyl)-2-oxo-1,2-dihydropyridin-4-yl]-phenyl-4-toluenesulfonate (**5h**).* Melting point, 326−328 °C; IR (cm^{-1}), 3156 (NH), 3048 (CH_{arom}), 2973 (CH_{aliph}), 2228 (CN), 1645 (C═O); ^1H NMR (DMSO-d_6), δ 12.78 (s, 1H, NH replaced by D_2O), 8.57−7.02 (m, 15H, CH_{arom} + 1H, CH of pyridinium), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), 150.76, 145.49, 130.83, 130.76, 129.32, 128.48, 128.64, 128.11, 127.57, 124.79, 122.83, 116.72, 21.65. *Anal.* calcd for $C_{29}H_{20}N_2O_4S$ (492.54): C (70.72%), H (4.09%), N (5.69%). Found: C (70.61%), H (3.92%), N (5.52%).

*4-(5-Cyano-6-oxo-1,6-dihydro-2,2′-bipyridin-4-yl)phenyl-4-toluenesulfonate (**7a**).* Melting point, 256−258 °C; IR (cm^{-1}), 3243 (NH), 3049 (CH_{arom}), 2961 (CH_{aliph}), 2225 (CN), 1643 (C═O); ^1H NMR (DMSO-d_6), δ 12.83 (s, 1H, NH exchanged by D_2O), 8.75−6.83 (m, 12H, CH_{arom} + 1H, CH of pyridinium), 2.46 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 153.01, 149.08, 148.32, 146.99, 136.12, 134.54, 132.87, 135.65, 133.23, 131.26, 130.37, 127.34, 124.54 124.01, 116.32, 21.42. *Anal.* calcd for $C_{24}H_{17}N_3O_4S$ (443.47): C (65.00%), H (3.86%), N (9.48%). Found: C (65.07%), H (3.78%), N (9.68%).

*4-(5-Cyano-6-oxo-1,6-dihydro-2,3′-bipyridin-4-yl)phenyl-4-toluenesulfonate (**7b**).* Melting point, 268−270 °C; IR (cm^{-1}), 3196 (NH), 3042 (CH_{arom}), 2958 (CH_{aliph}), 2221 (CN), 1647 (C═O); ^1H NMR (DMSO-d_6), δ 8.75−6.83 (m, 14H, H_{arom} + NH), 2.45 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 162.83, 159.36, 156.58, 154.86, 154.24, 150.31, 149.66, 147.01, 146.41, 137.93, 132.70, 132.02, 130.81, 130.33, 118.43, 21.61. *Anal.* calcd for $C_{24}H_{17}N_3O_4S$ (443.47): C (65.00%), H (3.86%), N (9.48%). Found: C (59.98%), H (3.70%), N (9.53%).

*4-(5-Cyano-6-oxo-1,6-dihydro-2,4′-bipyridin-4-yl)phenyl-4-toluenesulfonate (**7c**).* Melting point, 286−288 °C; IR (cm^{-1}), 3207 (NH), 3089 (CH_{arom}), 2963 (CH_{aliph}), 2228 (CN), 1646 (C═O); ^1H NMR (DMSO-d_6), δ 8.89−6.89 (m, 14H, H_{arom} + NH), 2.46 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 160.08, 156.15, 156.01, 154.65, 154.00, 152.23, 150.54, 149.34, 146.65, 138.43, 136.68, 133.11, 130.90, 130.07, 117.89, 21.61. *Anal.* calcd for $C_{24}H_{17}N_3O_4S$ (443.47): C (65.00%), H (3.86%), N (9.48%). Found: C (59.81%), H (3.78%), N (9.50%).

*4-[3-Cyano-2-oxo-6-(2-thienyl)-1,2-dihydropyridin-4-yl]-phenyl-4-toluenesulfonate (**7d**).* Melting point, 302−304 °C; IR (cm^{-1}), 3089 (NH), 3032 (CH_{arom}), 2219 (CN), 1641 (C═O); ^1H NMR (DMSO-d_6), δ 12.67 (s, 1H, NH replaced by D_2O), 8.09−7.03 (m, 11H, CH_{arom} + 1H, CH of pyridinium), 2.45 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ 150.62, 149.17, 148.64, 146.50, 135.42, 132.02, 131.91, 130.84, 130.73, 129.44, 128.67, 122.88, 116.55, 21.67. *Anal.* calcd for $C_{23}H_{16}N_2O_4S_2$ (448.51): C (61.59%), H (3.60%), N (6.25%). Found: C (61.50%), H (3.37%), N (6.49%).

Anti-Inflammatory Activity. The in vitro anti-inflammatory action of all tested compounds were estimated against carrageenan-induced paw edema in male Wister rats (180−200 g each). Adult albino rats were divided into 11 groups of 8 animals, and diclofenac was used as a reference drug on the basis of a Winter et al.[55] modified process.[55,56] Diclofenac was evaluated at 5 mg/kg[56] of the body weight of each animal used. Prior to the test, all animals experienced a 1 week acclimatization period. All of the investigational procedure was done in accordance with the strategies of the Institutional Animals Ethics Committee (IEAC). Changes in paw volume (% of edema inhibition) were produced and compared by subplantar injection of 100 μL of 1% freshly prepared solution of carrageenan in distilled water into the left hind paw of each rat.[56] The test agents were injected 30 min prior to carrageenan injection. The comparison was done 1, 3, and 6 h after induction of inflammation, as shown in (Table 2).

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CONCLUSION

An environmentally green procedure for the preparation of novel pyridines via a one-pot, four-component reaction using two methods (MW irradiation and conventional methods) by treatment of a mixture of 4-formylphenyl-4-methylbenzenesulfonate, ethyl cyanoacetate, acetophenone derivatives, and CH_3COONH_4 in ratio 1:1:1:2. The advanced microwave irradiations result in a shorter reaction time and better yields than the conventional procedure. All compounds were synthesized and examined for their anti-inflammatory activity using diclofenac as a reference drug and showed promising anti-inflammatory activity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00066.

IR, ^{1}H NMR, and ^{13}C NMR spectral data for synthesized pyridines (PDF)

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Notes

The authors declare no competing financial interest.

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