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ORIGINAL PAPER

$[C_6(MIm)_2]_2W_{10}O_{32}$ catalyzed efficient one-pot pseudo-four component synthesis of AT-130 analogues under microwave irradiations

Mahboubeh Rostami · Ahmad R. Khosropour · Valiollah Mirkhani · Iraj Mohammadpoor-Baltork · Majid Moghadam · Shahram Tangestaninejad

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Abstract Di[1,6-bis(3-methylimidazolium-1-yl)hexane] decatangstate ($[C_6(MIm)_2]_2W_{10}O_{32}$) was found to be a novel, powerful and effective catalyst for the preparation of *N*-benzoylglycine carbamides as derivatives of AT-130 via one-pot multicomponent reaction performed under microwave irradiations. The products were obtained in high to excellent yields, thus providing a unique strategy to the large-scale synthesis of these compounds.

Keywords AT-130 · Aldehydes · *N*-benzoylglycine · Amines · Solvent-free · Microwave irradiation · Organic–inorganic hybrid polyoxometalates · One-pot reactions

Introduction

Recently, investigation for designing of new and effective anti hepatitis B virus (HBV) compounds is a challenge for biologists, pharmaceuticals and organic chemists [1]. Although several nucleosides such as adefovir [2], dipivoxil [3], telbivudine [4] and lamivudine [5] have been utilized for treating of HBV infections, still the viral resistance and the side effects of them make the current treatment not satisfactory [6, 7]. To address the resistance and toxicity problems of these nucleoside inhibitors, a major target in the field of pharmacology is to synthesis and develops non-nucleoside ones [8]. Since the discovery of the naturally occurring, clinically used of **1** as an anti-HBV agent AT-130, *N*-benzoylglycine carbamide pharmacophore has attracted considerable attention owing to the biological activity associated with such compounds (Fig. 1) [8].

For example, compound **2** extracted from Dichondra repens forens exhibiting high anti-HBV activity [9]. Consequently, the development of novel synthetic strategies leading to new unsaturated *N*-benzoylglycine carbamide derivatives is of paramount importance.

The development of hybrid organic–inorganic frameworks due to replacing toxic metal catalysts with degradable organic compounds has emerged as one of the most potentially significant fields of investigation in modern chemistry [10–12]. Recently, hybrids of ionic liquids with polyoxometalates (POMs) has grown tremendously; however, a limited number of these compounds has been investigated catalytically [13–16]. Considering the number of structures discovered, it must be realized that heterogeneous catalysis using organic cations bonded with POMs as Keggin anions, especially in microwave-assisted organic synthesis, is still in an immature state and being one of the underdeveloped area's research.

From the organic synthetic outlook, the design and development of succession allowing highly selective access to elaborate molecular scaffolds while combining structural diversity with eco-compatibility, are great challenges. In this context, combination of one-pot multicomponent reactions (MCRs) with microwave-assisted provide

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M. Rostami · A. R. Khosropour (✉) · V. Mirkhani · I. Mohammadpoor-Baltork · M. Moghadam · S. Tangestaninejad
Department of Chemistry, University of Isfahan, Esfahān 81746-73441, Iran
e-mail: khosropour@chem.ui.ac.ir

M. Rostami
Department of Medicinal Chemistry, School of Pharmacy, Isfahan University of Medical Sciences, Esfahān 81745-359, Iran

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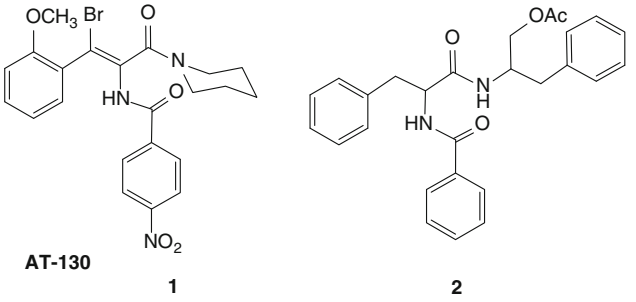


Fig. 1 Structures of *N*-benzoylglycine carbamides having anti-HBV properties

a strength tool to generate complex molecular scaffolds from simple and readily accessible precursors [17]. This interest fortunately led us to the novel synthesis of AT-130 type derivatives using simple and commercially available starting materials via a one-pot protocol. So, in continuation of our endeavors in developing novel and practical reactions to synthesize fine compounds [18–21], herein, we describe a new approach to synthesizing N-benzoylglycine carbamides in conjunction with microwave (μwave) irradiation to rapidly access differentially substituted motifs in a one-pot protocol utilizing a catalytic amount of $[C_6(MIm)_2]_2W_{10}O_{32}$ [19] (Scheme 1).

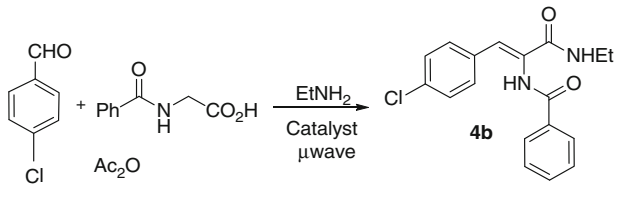
Results and discussion

In continuation of our endeavors in developing novel and practical reactions to synthesis fine compounds [18–21], herein, we describe a new approach to synthesis of *N*-benzoylglycine carbamides in conjunction with microwave (μwave) irradiation to rapidly access differentially substituted motifs in a one-pot protocol utilizing a catalytic amount of $[C_6(MIm)_2]_2W_{10}O_{32}$[12b] (Scheme 1).

To set the best experimental conditions, we initially studied the one-pot reaction of 4-chlorobenzaldehyde with *N*-benzoylglycine, acetic anhydride and ethylamine under a variety of reaction conditions under MW energy (Table 1).

All experiments were conducted in 10 ml Teflon-septum-sealed reaction vessels with a multimode MW reactor (Micro-Synth) to ensure an optimal reproducibility of the processes. During irradiation, the temperature at the bottom of the vials was monitored by an IR sensor which prevented overheating by controlling MW power levels.

Table 1 Optimization of the reaction of 4-chlorobenzaldehyde, *N*-benzoglycine and ethyl amine



Entry	Catalyst	mol%	Temp.(°C)	Time (min)	Yield (%)[a]
1	$K_5CoW_{12}O_{40}$	10	90	9	5
2	$DBMIHCl_2$[b]	10	90	9	42
3	$[BMIm]_4W_{10}O_{32}$[c]	10	90	9	72
4	$[C_6(MIm)_2]_2W_{10}O_{32}$	10	90	9	89
5	$[C_6(MIm)_2]_2W_{10}O_{32}$	7	90	9	75
6	$[C_6(MIm)_2]_2W_{10}O_{32}$	5	90	9	63
7	–	–	90	9	0
8	$[C_6(MIm)_2]_2W_{10}O_{32}$	10	85	9	83
9	$[C_6(MIm)_2]_2W_{10}O_{32}$	10	75	9	74
10	$[C_6(MIm)_2]_2W_{10}O_{32}$	10	100	9	90
11[d]	$[C_6(MIm)_2]_2W_{10}O_{32}$	10	90	240	45

[a] Isolated yield

[b] 1,6-bis(3-methylimidazolium-1-yl)hexane dichloride

[c] Tetrakis(1-butyl-3-methylimidazolium) dodecatangestat

[d] Under conventional heating

In the preliminary examination, we found that kind of catalyst and temperature of the reaction can be greatly affected on this transformation. Among those parameters, catalyst was found to be critical for this reaction. In the absence of catalyst, no reaction was observed.

In comparison with $K_5CoW_{12}O_{40}$, $DBMIHCl_2$ and $[BMIm]_4W_{10}O_{32}$, $[C_6(MIm)_2]_2W_{10}O_{32}$ generally gave better yields (Table 1, entries 1–4). $[C_6(MIm)_2]_2W_{10}O_{32}$ loadings as low as 10 mol% are well tolerated (Table 1, entry 4); however, further reductions in catalyst loading resulted in slow reactions and side product was formed (Table 1, entries 5 and 6). The temperature was another

Scheme 1 Synthesis of AT-130 analogues

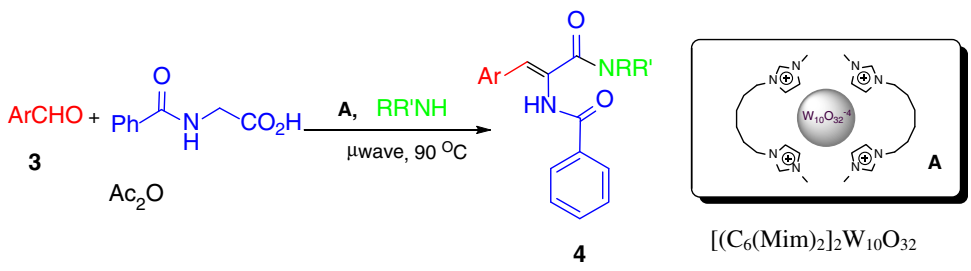
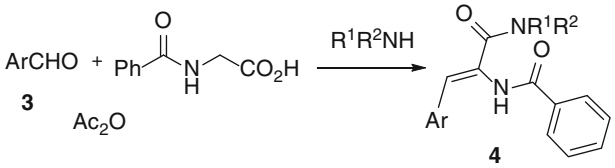
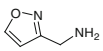
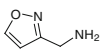
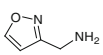


Table 2 Solvent-free synthesis of AT-130 analogues under microwave irradiation catalyzed by $[C_6(MIm)_2]_2W_{10}O_{32}$



Entry	Ar	Amine	Product	Time (min)	Yield (%)[a]
1	*p*-$CH_3OC_6H_5$	$C_2H_5NH_2$	**4a**	16	83
2	*p*-ClC_6H_5	$C_2H_5NH_2$	**4b**	17	90
3	*p*-$O_2NC_6H_5$	$C_2H_5NH_2$	**4c**	17	89
4	*p*-$CH_3OC_6H_5$		**4d**	16	92
5	*p*-ClC_6H_5		**4e**	18	90
6	*p*-$O_2NC_6H_5$		**4f**	18	94
7	*p*-$CH_3OC_6H_5$	$C_6H_5CH_2NH_2$	**4g**	18	87
8	*p*-ClC_6H_5	$C_6H_5CH_2NH_2$	**4h**	19	85
9	*p*-$O_2NC_6H_5$	$C_6H_5CH_2NH_2$	**4i**	19	90
10	*p*-$CH_3OC_6H_5$	*p*-$CH_3C_6H_4NH_2$	**4j**	16	84
11	*p*-ClC_6H_5	*p*-$CH_3C_6H_4NH_2$	**4k**	17	89
12	*p*-$O_2NC_6H_5$	*p*-$CH_3C_6H_4NH_2$	**4l**	18	91
13	*p*-$CH_3OC_6H_5$		**4m**	16	81
14	*p*-ClC_6H_5		**4n**	16	83
15	*p*-$O_2NC_6H_5$		**4o**	17	87

Reactions were performed in air atmosphere and the corresponding product was isolated with column chromatography in all cases

[a] Isolated yields

key factor that improved the yields. Then optimization of reaction conditions was also carried out at different temperatures. We investigated the reaction with a temperature-controlled program. At power 860 watt and 75 °C only 74 % of conversion was registered after 9 min (Table 1, entry 9). However, by increasing the temperature up to 90 °C, 89 % of carbamide adducts 4 was isolated (Table 1, entry 4b). Further increasing of the reaction temperature shows a little impact on the yield (Table 1, entry 10).

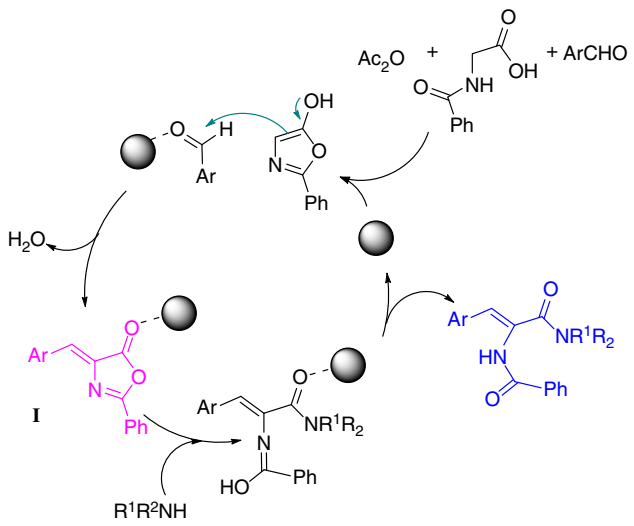
These investigations revealed that 4b could be obtained in 89 % yield at 90 °C in solventless condition under microwave irradiation for 9 min. To evaluate the beneficial of mediation of specific microwave effects, the reaction has also been examined by utilizing of preheated oil bath for the same duration and at the same final temperature as measured at the end of exposure during the microwave-assisted synthesis. It was found that reaction proceeded very slowly in 240 min and only 45 % yield of 4b was obtained under conventional heating at 90 °C (Table 1, entry 11).

The high catalytic performance of $[C_6(MIm)_2]_2W_{10}O_{32}$ was also confirmed for the large-scale reaction. Encouraged by the above results, we increased the scale of the template reaction to 10.0 mmol, keeping the reaction stoichiometry intact. The reaction was found to proceed successfully, and the corresponding product was obtained in 87 %. Next, we focused on recycling A in the above reaction and found that the catalyst could be recycled intact after light centrifugation and subsequent decantation of the organic layer in 85 % average yield up to five times without any pretreatment.

As exemplified the excellent yields (81–94 %) of the *N*-benzoylglycine carbamide 4 were obtained regardless of having an electron-withdrawing or electron-donating group in on aldehyde (Table 2, entries 1–15).

The effect of amine was also examined which by primary amines [ethyl amine (Table 2, entries 1-3, benzylamine (Table 2, entries 7–9] and [isoxazol-3-yl)methanamine] (Table 2, entries 13–15), secondary ones [piperidine (Table 2, entries 4–6)] and anilines [*p*-toluidine (Table 2, entries 10–13)] the desired products were obtained more than 80 %. The structures of all products were established completely based on spectroscopic evidence.

A proposed reaction mechanism is depicted in Scheme 2. The first step involves facile producing of 2-phenyloxazol-5-one (I) that attacks to the activated



Scheme 2 Proposed mechanism

aldehyde via Knoevenagel type condensation and produced the intermediate (II). Ultimately, amine as nucleophile attacks to II which activated by the catalyst and subsequent nucleophilic addition furnished the ring-opened cycloadduct.

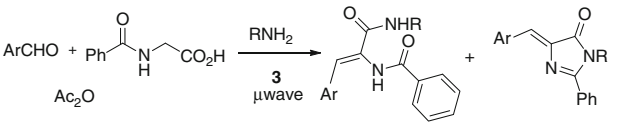
We must lay emphasis on this fact that the time of irradiation due to the possibility of intramolecular reaction for prolonged periods was a key factor. Then strict control of the reaction time must be maintained during the reaction in order to avoid the formation of these unwanted side products. In fact, in some of the experiments aimed at the synthesis of *N*-benzoylglycine carbamides, the corresponding of the 1H-imidazol-5(4H)-one (5) were detected.

In order to investigate the general tendency of the *N*-benzoylglycine carbamides to produce 1H-imidazol-5(4H)-ones via the optimized conditions, we continued irradiation on the several *N*-benzoylglycine carbamides without isolation from the mixture of reaction. The results are shown in Table 3.

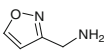
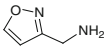
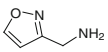
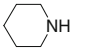
As illustrated, these processes required longer reaction times (55–120 min) to obtain these heterocycles. Encouraged by these results, this procedure draws a distinction between secondary and primary amines, as the ring closure adducts were obtained only in the case of primary ones exclusively (Table 3, entry 13).

An alternative examination was finally developed in an attempt to further investigate the generality of this result with carrying out the reaction on p-phthaldialdehyde (3p) as a more complicated substrate.

Table 3 Time dependence of the reaction to produce the 1H-imidazole-5(4*H*)-one in the presence of $[C_6(MIm)_2]_2W_{10}O_{32}$



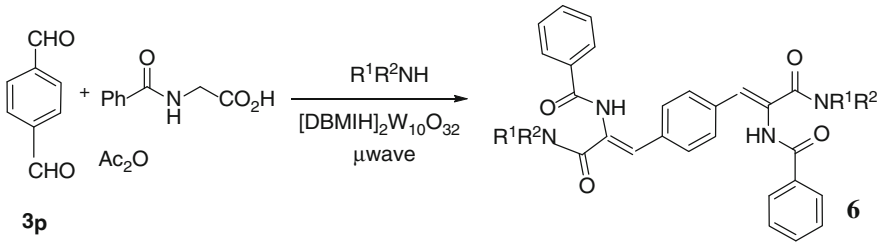
4 5

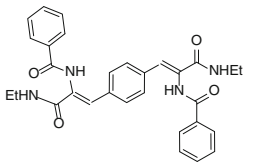
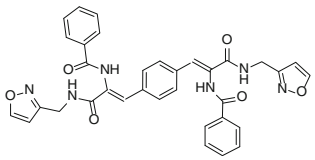
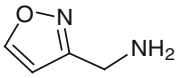
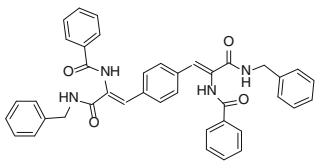
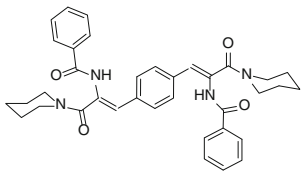
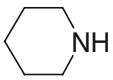
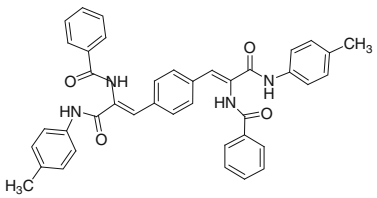
Entry	Ar	RNH_2	Time (min)	Yield (%)	
				4	**5**
1	*p*-$CH_3OC_6H_5$	$C_2H_5NH_2$	80	74	15
2	*p*-ClC_6H_5	$C_2H_5NH_2$	60	60	30
3	*p*-$O_2NC_6H_5$	$C_2H_5NH_2$	55	45	48
4	*p*-$CH_3OC_6H_5$	$C_6H_5CH_2NH_2$	85	74	20
5	*p*-ClC_6H_5	$C_6H_5CH_2NH_2$	70	61	34
6	*p*-$O_2NC_6H_5$	$C_6H_5CH_2NH_2$	65	55	40
7	*p*-$CH_3OC_6H_5$	*p*-$CH_3C_6H_4NH_2$	110	60	31
8	*p*-ClC_6H_5	*p*-$CH_3C_6H_4NH_2$	85	55	40
9	*p*-$O_2NC_6H_5$	*p*-$CH_3C_6H_4NH_2$	75	50	43
10	*p*-$CH_3OC_6H_5$		100	79	10
11	*p*-ClC_6H_5		85	80	10
12	*p*-$O_2NC_6H_5$		80	68	20
13	*p*-$O_2NC_6H_5$		120	94	0

Reactions were performed in air atmosphere and the corresponding product was isolated with column chromatography in all cases

[a] Isolated yields

Table 4 Solvent-free synthesis of bis-*N*-benzoylglycine carbamides under microwave irradiation catalyzed by $[C_6(MIm)_2]_2W_{10}O_{32}$



Entry	Product	Amine	Product	Time (min)	Yield (%)[a]
1		$C_2H_5NH_2$	**6a**	25	92
2			**6b**	32	90
3		$C_6H_5CH_2NH_2$	**6c**	28	94
4			**6d**	25	95
5		*p*-$CH_3C_6H_4NH_2$	**6e**	30	91

[a] Isolated yields

One-pot reaction of 3p versus different amines, were registered acceptable results by collecting bis-*N*-benzoylglycine carbamides **(6 a-e)** in high to excellent yields, although these require higher catalyst loadings (Table 4).

This reaction carried out well with different amines, including primary (Table 4, entries 1–3) or secondary amines (Table 4, entry 4) and even anilines with electron-donating groups (Table 4, entry 5). To the best of our knowledge, this type of *N*-benzoylglycine carbamides is not unprecedented and has been previously observed.

In conclusion, we have demonstrated a novel and highly effective procedure for the synthesis of *N*-benzoylglycine carbamides as derivatives of AT-130 via one-pot pseudo-four component reaction under microwave irradiations in the presence of $[C_6(MIm)_2]_2W_{10}O_{32}$. Moreover, other noteworthy features of this approach as: (1) The product can be separated by easy work-up and (2) $[C_6(MIm)_2]_2W_{10}O_{32}$ could be reused for five times after simple treatment. The clean reaction profiles, operational and experimental simplicity, enhanced reaction rates, and with options of further transformations of the *N*-benzoylglycine carbamides into synthetically interesting biologically active compounds, this synthetic methodology is ideally is suited for automated applications in organic synthesis.

Experimental section

All products were identified by comparison of their physical and spectral data with those of authentic samples. $[C_6(MIm)_2]_2W_{10}O_{32}$ was synthesized according to the our previous papers [19, 22]. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT–IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. NMR spectra were measured on a Bruker DPX 400 MHz spectrometer with chemical shift (δ) given in ppm. All experiments were conducted in 10 ml Teflon-septum-sealed reaction vessels with a multimode MW reactor (Micro-Synth) to ensure an optimal reproducibility of the processes. During irradiation, the temperature at the bottom of the vials was monitored by an IR sensor which prevented overheating by controlling MW power levels. TLC was performed on silica gel on precoated silica gel plates (Merck 60 F254, 0.25 mm).

General method for the synthesis of 4

To a mixture of 1 mmol of aldehyde, 1 mmol (0.179 g) hippuric acid and 0.1 mmol (0.285 g) of **A** that well grinded in a mortar, was added 1 ml of fresh distilled acetic anhydride and then the mixture was submitted to microwave irradiation at 90 °C (850 W) using a micro-SYNTH lab station reactor for 9 min, In a high pressure Teflon reactor equipped with a magnetic stir bar and an IR sensor (for controlling the reaction temperature) (average temperature of the reaction 90 °C) for preferred time, the progress of the reaction was monitored by TLC of the reaction mixture, then after the completion of azlactone synthesis, 1 mmol of amine was added to the reaction vessel and irradiation continued until the reaction completion determined according to the TLC monitoring during the irradiation time. For working up the reaction, the mixture was cooled down to the room temperature, after the addition of aqueous solution of sodium hydrogen carbonate, the mixture of catalyst and related carbamoylbenzamides was filtered off and with the re-crystallization in hot ethanol, the catalyst was recovered and the crystalline product isolated. The recovered catalyst can be used in the further reaction cycle with a simple treating in a vacuumed oven with temperature of 80 °C.

*N-((Z)-1-(ethylcarbamoyl)-2-(4-chlorophenyl)vinyl)benzamide:**4b***

White crystalline solid, Mp: 216–218 °C. FTIR (KBr thin film) υ (cm^{-1}); 3,243 (br), 2,926, 2,854, 1,644, 1,482, 1,446, 1,311, 1,093, 713, 526; ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm): 9.86 (s, 1H, NH benzamide), 8.17 (t, 1H, $J = 5.50$ Hz, NH carbamoyl), 7.97 (d, 2H, $J = 7.50$ Hz, Ar), 7.46-7.59 (m, 7H, Ar), 7.13 (s, 1H, C=CH); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.61, 164.52, 133.74, 133.60, 131.60, 131.33, 131.15, 131.01, 128.22, 127.85, 127.06, 121.45, 33.98, 14.66; Mass (*m/z*): *m/z* calcd for $C_{18}H_{17}ClN_2O_2$ (M^+) 328.1, found 328.48, 310.41, 266.86, 105.06, 90.99, 76.99.

*N-((Z)-3-(4-methoxyphenyl)-1-oxo-1-(piperidin-1-yl)prop-2-en-2-yl)benzamide:**4d***

White crystalline, Mp: 154–156 °C. FTIR (KBr thin film) υ (cm^{-1}): 3,207, 2,939, 2,852, 1,656, 1,614, 1,581, 1,508, 1,478, 1,377, 1,344, 1,281, 1,244, 1,179, 1,133, 692, 530; ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H, benzamide), 7.93 (d, 2H, $J = 7.45$ Hz, Ar), 7.55 (t, 1H, $J = 7.20$ Hz, Ar), 7.47 (t, 2H, $J = 7.40$ Hz, Ar), 7.17 (d, 2H, $J = 8.40$ Hz, Ar), 6.87 (d, 2H, $J = 8.40$ Hz, Ar), 6.59 (s, 1H, C=CH), 3.72 (s, 3H, OCH_3), 3.19 (bs, 4H, aliphatic), 0.6–1.37 (bm, 6H, aliphatic); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 164.29, 164.16, 158.45, 133.30, 131.70, 130.11, 129.10, 128.29, 127.71, 126.86, 115.68, 113.74, 55.16, 46.92, 23.92–24.38 (t, 3C); Mass (*m/z*): *m/z* calcd for $C_{22}H_{24}N_2O_3$ (M^+) 364.18, Found 364.05, 345.01, 278.98, 148.01, 104.96,76.97, 51.00.

*N-((Z)-1-(benzylcarbamoyl)-2-(4-chlorophenyl)vinyl)benzamide:**4h***

White crystalline, Mp: 194–195. FTIR (KBr thin film) υ (cm^{-1}) 3,261, 3,066, 2,923, 1,641, 1,559, 1,516, 1,480, 1,424, 1,370, 1,269, 1,089, 1,012, 694, 523; ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm): 9.96 (s, 1H, NH benzamide), 8.72 (t, 1H, $J = 5.90$ Hz, NH carbamoyl), 7.99 (d, 2H, $J = 5.00$ Hz, Ar), 7.57 (d, 3H, $J = 10.00$ Hz, Ar), 7.50 (t, 2H, $J = 15.00$ Hz, Ar), 7.41 (d, 2H, $J = 5.00$ Hz, Ar), 7.30 (d, 4H, $J = 5.00$ Hz, Ar), 7.18–7.26 (m, 2H, Ar), 4.38 (d, 2H, $J = 6.00$ Hz, CH_2); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.84, 164.84, 139.61, 133.59, 131.63, 131.37, 131.10, 130.91, 128.22, 128.04, 127.89, 127.81, 127.05, 126.49, 121.63, 42.55; Mass (*m/z*): m/z calcd for $C_{23}H_{19}ClN_2O_2$ (M^+) 390.86, found 390.44, 372.19, 303.11, 105.06, 76.99, 51.00.

*N-((Z)-1-(p-tolylcarbamoyl)-2-(4-chlorophenyl)vinyl)benzamide:**4k***

White crystalline solid, Mp: 241–243 °C. FTIR (KBr thin film) υ (cm^{-1}): 3,205, 3,046, 1,639, 1,607, 1,560, 1,513, 1,485, 1,371, 1,294, 1,261, 1,013, 906, 815, 696, 531, 513; ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm): 10.11 (s, 1H, NH benzamide), 10.08 (s, 1H, NH carbamoyl), 7.99 (d, 2H, $J = 7.50$ Hz, Ar), 7.58–7.63 (m, 5H, Ar), 7.52 (t, 2H, $J = 7.70$ Hz, Ar), 7.44 (d, 2H, $J = 8.55$ Hz, Ar), 7.12 (d,

2H, $J = 8.35$ Hz, Ar), 7.09 (s, 1H, C=CH), 2.28 (s, 3H, CH_3); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.85, 163.92, 136.66, 133.30, 132.83, 132.27, 131.73, 130.97, 128.82, 128.47, 128.30, 127.85, 126.47, 120.03, 20.41; Mass (*m/z*): *m/z* calcd for $C_{23}H_{19}ClN_2O_2$ (M^+) 390.86, found 372.09 (M^+-18), 194.18, 105.10, 77.13; Anal Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 71.00; H, 5.48; N, 6.98.

*N-((Z)-1-(5-methylisoxazol-3-ylcarbamoyl)-2-(4-nitrophenyl)vinyl)benzamide:**4o***

White crystalline, Mp: 238–240. FTIR (KBr thin film) υ (cm^{-1}) 3,257, 3,073, 2,931, 1,655, 1,627, 1,526, 1,471, 1,426, 1,341, 1,280, 699, 525; ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H, NH benzamide), 10.31 (s, 1H, carbamoyl), 8.23 (d, 2H, $J = 8.70$ Hz, Ar), 7.98 (d, 2H, $J = 7.55$ Hz, Ar), 7.84 (d, 2H, $J = 8.75$ Hz, Ar), 7.61 (t, 1H, $J = 7.20$ Hz, Ar), 7.52 (t, 2H, $J = 7.60$ Hz, Ar), 7.22 (s, 1H, C=CH), 6.68 (s, 1H, CH isoxazole), 2.39 (s, 3H, CH_3); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 169.32, 165.99, 163.89, 158.44, 146.64, 141.09, 133.15, 132.96, 131.94, 130.38, 128.33, 128.01, 126.32, 123.57, 96.66, 12.07; Mass (*m/z*): *m/z* calcd for $C_{20}H_{16}N_4O_5$ (M^+) 392.11, found 294.06 (M^+-98), 130.93, 104.97, 76.96, 50.99.

General method for the synthesis of 6a-e

To a mixture of 1 mmol (0.134 g) of *p*-phthaldialdehyde, 2.1 mmol (0.376 g) hippuric acid and 0.2 mmol (0.570 g) of **A** that well grinded in a mortar, was added 1 ml of fresh distilled acetic anhydride and then the mixture was submitted to microwave irradiation at 90 °C (850 W) using a micro-SYNTH lab station reactor for 9 min, In a high pressure Teflon reactor equipped with a magnetic stir bar and an IR sensor (for controlling the reaction temperature) (average temperature of the reaction 90 °C) for preferred time. The progress of the reaction was monitored by TLC of the reaction mixture, then after the completion of azlactone synthesis, 2.1 mmol of amine was added to the reaction vessel and irradiation continued until the reaction completion determined according to the TLC monitoring during the irradiation time. For working up the reaction, the mixture was cooled down to the room temperature, after the addition of aqueous solution of sodium hydrogen carbonate, the mixture was filtered and re-crystallization in hot ethanol. The catalyst was recovered and the crystalline product isolated. The recovered catalyst can be used in the further reaction cycle with a simple treating in a vacuumed oven with temperature of 80 °C.

6a: Pale yellow powder, Mp: 232–234 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ (ppm): 10.00 (s, 2H, benzamide), 8.20 (bs, 2H, carbamoyl), 7.94 (d, 4H, $J = 7.30$ Hz, Ar), 7.44–7.58 (m, 10H, Ar), 7.15 (s, 2H, C=CH), 3.14 (q, 4H, $J = 6.50$ Hz, CH_2 Ethyl), 1.03 (t, 6H, $J = 7.20$ Hz, CH_3 Ethyl). ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.72, 164.69, 131.49, 129.22, 129.09, 128.29, 128.17, 128.09, 127.83, 127.72, 34.00, 14.71. FTIR (KBr thin film) υ (cm^{-1}): 3,000–3,700 (b), 2,873, 1,720, 1,611, 1,541, 1,449, 1,104, 671. Mass (*m/z*): *m/z* calcd for $C_{30}H_{30}N_4O_4$ (M^+), 510.23, Found 420.23 (M^+-90), 366.89, 353.83, 142.00, 104.95, 76.93, 63.01.

6b: Pale yellow powder, Mp: 275–278 °C. ^{1}HNMR(500 MHz, DMSO-d_6) δ (ppm); 11.35 (s, 2H, benzamide), 10.32 (s, 2H, carbamoyl), 7.94 (d, 4H, $J = 7.30$, Ar), 7.44–7.58 (m, 10H, Ar), 7.15 (s, 2H, C=CH), 6.68 (s, 2H, CH isoxsazole), 2.35 (s, 6H, CH_3). ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 168.12, 165.00, 162.89, 158.24, 132.15, 131.96, 130.94, 129.18, 127.33, 127.01, 125.12, 122.27, 95.99, 12.07. FTIR (KBr thin film) υ (cm^{-1}): 3,410, 3,197, 2,923, 1,697, 1,666, 1,616, 1,434, 1,325, 1,171, 1,108, 816, 704, 595, 452. Mass (*m/z*): *m/z* calcd for $C_{34}H_{28}N_6O_6$ (M^+) 616.21, Found 420.20, 281.03, 207.02, 194.15, 105.05, 76.91, 67.04, 54.08. Anal Calcd for $C_{34}H_{38}N_6O_6$: C, 65.23; H, 4.58; N, 13.63 found: C, 64.95; H, 4.65; N, 13.25.

6c: White powder, Mp: 228–230 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 2H, benzamide), 8.70–8.72 (t, 2H, $J = 5.65$ Hz, carbamoyl), 7.96 (d, 4H, $J = 7.45$ Hz, Ar), 7.44–7.58 (m, 10H, Ar), 7.20–7.31 (m, 9H, Ar), 7.17–7.20 (m, 3H, Ar), 4.36 (d, 4H, $J = 5.75$ Hz, CH_2 benzylic). ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.99, 164.89, 139.71, 134.47, 133.79, 131.58, 130.58, 129.35, 128.19, 128.06, 127.86, 127.73, 127.06, 126.49, and 42.57. FTIR (KBr thin film) υ (cm^{-1}) 3,315, 3,062, 2,924, 1,651.7, 1,521.6, 1,474, 1,276, 697. Mass (*m/z*): *m/z* calcd for $C_{40}H_{34}N_4O_4$ (M^+), 634.26, Found, 419.97, 326.98, 281.14, 207.12, 105.01, 77.04, 60.10.

6d: Pale yellow powder, Mp: 267–269 °C. ^{1}HNMR (300 MHz, DMSO-d_6) δ (ppm): 10.38 (s, 2H, benzamide), 7.93 (d, 4H, $J = 7.14$ Hz, Ar), 7.49–7.60 (m, 6H, Ar), 7.23 (s, 4H, Ar), 6.57 (s, 2H, C=CH), 3.50 (bs, 2H, CH aliphatic), 3.22 (bs, 6H, CH aliphatic), 1.40 (bm, 12H, CH aliphatic). ^{13}CNMR (75 MHz, DMSO-d_6) δ (ppm): 164.90, 164.41, 136.60, 135.72, 133.73, 132.40, 128.93, 128.19, 118.62, 115.32, 47.49, 41.86, 24.67–25.02. FTIR (KBr thin film) υ (cm^{-1}) 3,197, 2,938, 2,854, 1,668, 1,602, 1,530, 1,475, 1,445, 1,343, 1,279, 696, 562. Mass (*m/z*): *m/z* calcd for $C_{36}H_{38}N_4O_4$ (M^+) 590.29, Found 420.14 (M^+-170.2), 105, 77, 56. Anal Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20; H, 6.48; N, 9.48. Found: C, 72.98; H, 6.68; N, 8.95.

6e: Pale yellow powder, Mp: 287–290 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ (ppm): 10.17 (s, 2H, carbamoyl), 9.98 (s, 1H, benzamide), 7.87 (d, 4H, $J = 7.45$ Hz, Ar), 7.50–7.55 (m, 6H, Ar), 7.47 (t, 4H, $J = 7.40$ Hz, Ar), 7.21–7.31 (m, 8H, Ar), 7.18–7.20 (bs, 2H, C=CH), 2.19 (s,

6H, CH_3). ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 167.96, 167.01, 136.83, 135.23, 132.01, 131.76, 128.97, 127.93, 125.49, 124.87, 122.20, 122.18, 120.00, 118.98, 23.89. FTIR (KBr thin film) υ (cm^{-1}): 3,100–3,500 (b), 2,927, 1,610, 1,547, 1,449, 1,054, 1,028, 948, 671, 618, 469. Mass (*m/z*): *m/z* calcd for $C_{40}H_{34}N_4O_4$ (M^+) 634.26, Found 420.04, 166.94, 148.92, 104.94, 76.96, 56.91.

General method for the synthesis of Carbamoyl benzamide and imidazol-5(4H)-one 5:

To a mixture of 1 mmol of aldehyde, 1 mmol hippuric acid (0.179 g) and 0.1 mmol (0.285 g) of hydride catalyst that well ground in a mortar, was added 1 ml of fresh distilled acetic anhydride and then the mixture was submitted to microwave irradiation at 90 °C (850 W) using a micro-SYNTH lab station reactor for 9 min, In a high pressure Teflon reactor equipped with a magnetic stir bar and an IR sensor (for controlling the reaction temperature) (average temperature of the reaction 90 °C) for preferred time, the progress of the reaction was monitored by TLC of the reaction mixture, then after the completion of azlactone synthesis, 1 mmol of amine was added to the reaction vessel and irradiation continued until the amount of the imidazole-5(4*H*)-one reached to be highest level determined according to the TLC monitoring. For working up the reaction, the mixture was cooled down to the room temperature, after the addition of aqueous solution of sodium hydrogen carbonate, the mixture of catalyst and products were filtered off and with the dissolution in hot ethylacetate/ethanol, the catalyst is recovered and the mixture of products [carbamoyl-benzamide and imidazole-5(4*H*)-one] **5** obtained in this manner were isolated by column chromatography. The recovered catalyst can be used in the further reaction cycle with a simple treating in a vacuumed oven with temperature of 80 °C.

(4Z)-4-(4-chlorobenzylidene)-1-ethyl-2-phenyl-1H-imidazol-5(4H)-one: ***5b***

Yellow crystalline solid, Mp: 177–179 °C. FTIR (KBr thin film) υ (cm^{-1}): 2,968, 2,874, 1,734.66, 1,616, 1,594, 1,570.7, 1,490.7, 1,443, 1,089, 824, 697, 496; ^{1}HNMR(500 MHz, $CDCl_3$) δ (ppm): 8.17 (d, 2H, $J = 9.50$ Hz, Ar), 7.47 (d, 2H, $J = 8.30$ Hz, Ar), 7.38–7.42 (m, 2H, Ar), 7.33 (d, 2H, $J = 6.90$ Hz, Ar), 7.19 (d, 2H, $J = 8.30$ Hz, Ar), 3.50 (q, 2H, $J = 7.25$ Hz, CH_2 ethyl), 0.94 (t, 3H, $J = 7.25$ Hz, CH_3 ethyl); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 165.6, 150.1, 133.6, 131.6, 131.2, 131.1, 131.0, 129.9, 128.2, 127.8, 123.8, 121.4, 32.0, 13.0; Mass (*m/z*): *m/z* calcd for $C_{18}H_{15}ClN_2O$ (M^+), 310.09, Found, 310.06, 309.08, 131.94, 104.89, 103.86, 88.85, 76.56, 63.82.

(4Z)-4-(4-methoxybenzylidene)-2-phenyl-1-p-tolyl-1H-imidazol-5(4H)-one: ***5j***

Yellow crystalline solid, Mp: 198–200 °C. FTIR (KBr thin film) υ (cm^{-1}): 2,920, 2,844, 1,710, 1,638, 1,593, 1,509, 1,445, 1,377, 1,290, 1,260, 1,162, 1,021, 946, 905, 831, 785, 691, 508; ^{1}HNMR(500 MHz, $CDCl_3$) δ (ppm): 8.28 (d, 2H, $J = 8.70$ Hz, Ar), 7.59 (d, 2H, $J = 7.75$ Hz, Ar), 7.42 (t, 1H, $J = 7.70$ Hz, C=CH), 7.33 (t, 3H, $J = 7.75$ Hz, Ar), 7.22 (d, 2H, $J = 8.10$ Hz, Ar), 7.06 (d, 2H, $J = 8.10$ Hz, Ar), 6.98 (d, 2H, $J = 8.70$ Hz, Ar), 3.89 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3); ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm): 169.15, 164.98, 147.85, 135.27, 133.30, 132.83, 132.27, 131.73, 130.97, 128.83, 128.48, 128.30, 127.85, 126.47, 122.00, 114.13, 58.31, 20.41; Mass (*m/z*): *m/z* calcd for $C_{24}H_{20}N_2O_2$ (M^+), 368.15, Found, 368.17, 194.1, 146.06, 104.98, 90.99, 88.98, 76.98, 66.00.

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