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SHORT COMMUNICATION

MICROWAVE ASSISTED FACILE ONE POT SYNTHESIS OF NOVEL 5-CARBOXAMIDO SUBSTITUTED ANALOGUES OF 1,4-BENZODIAZEPIN-2-ONE OF MEDICINAL INTEREST

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ABSTRACT. A novel synthetic approach developed by the use of a microwave (MW) assisted one pot protocol to the synthesis of methyl-1,4-benzodiazepin-2-one-5-carboxylate (**2**) derivatives for which *N*-chloroacetylisatin was employed with an elegant success to afford the formation of 5-methyl carboxylate derivatives of 1,4-benzodiazepines from its reaction with methanolic hexamine. We have utilized MW technique in the present work in conducting the reaction of carboxylate ester derivative (**2**) with several selected primary and secondary amines **3**, **4**, **5**, **6**, **7**, and **8** which had the previous history of being biologically active in the literature, to generate the corresponding carboxamide derivatives (**9-14**).

KEY WORDS: Morpholine, Piperidine, Piperazine, Pyridine, Pyrimidine

INTRODUCTION

1,4-Bezodiazepines belong to the class of privileged structures [1-2]. Development of methodologies to facilitate the preparation of compound libraries based on the privileged structures is an intense area of research. Due to the vast commercial success and medicinal utility of the heterocyclic scaffolds such as pyridines, morpholines, piperazines, 2-amino (pyridines, pyrimidines, benzothiazoles), etc. in drug design and synthesis, various methods to incorporate these pharmacophores in 1,4-benzodiazepines (mostly on 2-position) has been developed. [3-4]

Analysis of the literature on this reveals that most of the published approaches involved a multistep sequence and led to produce compounds which invariably contained a 5-aryl (or heteroaryl) substituent in the 1,4-benzodiazepine nucleus, leaving no scope for the utilization of this position for further functionalization or incorporation of potentially useful pharmacophores on this position. In view of generality which the carboxylic acid ester groups provide to an easy access of the corresponding carboxamido substituted derivatives, we envisioned that the goal which we have in our mind to develop 5-carboxamido substituted analogues of 1,4-benzodiazepines could only be achieved through the corresponding carboxylic acid ester functionality present at C_5 position [5]. A novel synthetic approach developed, based on this concept, has made use of MW assisted one pot protocol to the synthesis of methyl-1,4-benzodiazepin-2-one-5-carboxylate derivatives. N-chloroacetylisatin (**1**) was employed with an elegant success to afford the formation of 5-methyl carboxylate derivatives of 1,4-benzodiazepines from its reaction with methanolic hexamine (Scheme 1). [6-10].

Amides are important synthons in the preparation of a wide variety of heterocycles and fused heterocycles, so much so that number of applications of these materials in the synthesis of heterocycles had grown exponentially in the last few decades. Based on the earlier precedence in the literature, on the widespread pharmacological activity of morpholine, piperidine,

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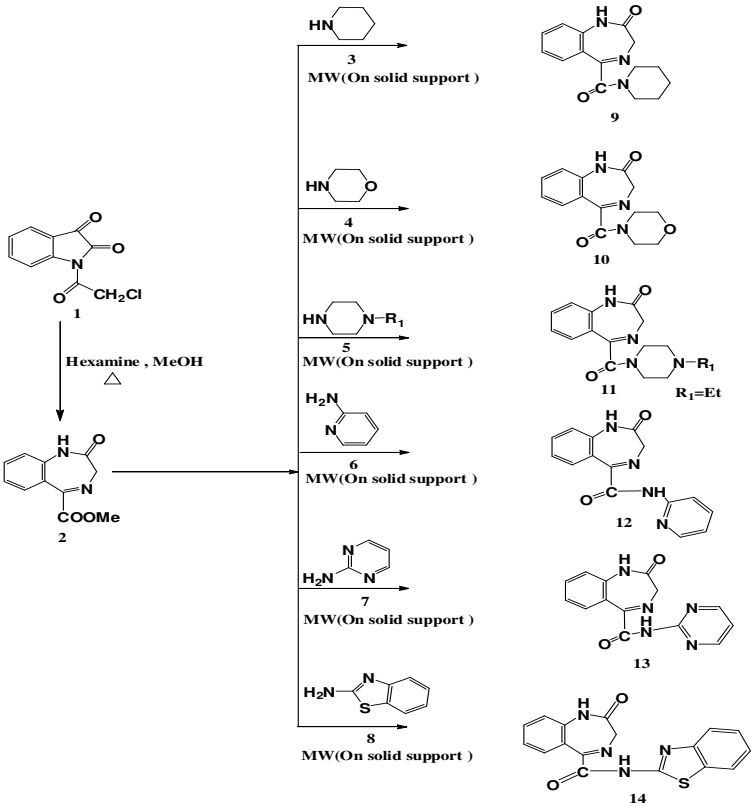
piperazine, pyridine, and pyrimidine, it was assumed that incorporation of these secondary amines to 1,4-benzodiazepine nucleus through the carboxylic ester group could produce interesting series of amide derivatives with enhanced biological activities [11-16]. This aroused our interest in these bioactive molecules and prompted us to undertake a study to seek structural modifications by incorporating secondary amine to 1,4-benzodiazepine molecules to generate novel carboxamide derivatives of 1,4-benzodiazepines. With this idea in mind, the present investigation was undertaken with a view to incorporate secondary amines fragment as a part of carboxamide fuction in to 1,4-benzodiazepine molecules.



Scheme 1

In view of the wide applicability of the microwave irradiation technique in chemical reaction rate enhancements, facilitating the reactions to take place in an environment friendly atmosphere, in a single pot, in less time, with higher yields, allowing the saving of time and energy both, we utilized this technique in the present work [17].

EXPERIMENTAL

All melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 intrachord. ^{1}H NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400 MHz spectrophotometer with TMS as internal standard

(chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1). Microwave activation coupled with dry media technique (using the solid supports) was applied in the synthesis of compounds **9-14.**

*Preparation of N-chloroacetyl isatin **1***

Solution phase microwave assisted method. A solution of isatin (0.068 mol) and chloroacetyl chloride (0.090 mol) was taken in a borosil conical flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a microwave oven at 180 ºC for 10 min (completion of reaction was checked by TLC) with short interval of 30 s to avoid the excessive evaporation of reactant. After the completion of reaction, the mixture was cooled for 2 h in an ice-bath. The precipitate was filtered, washed with 20 mL portions of ether, then air-dried and was recrystallised with ethyl acetate to give 1, yield: 95%, m.p. 210-212 °C. Other compounds were prepared from following the same procedure.

Solid phase microwave assisted method. Microwave irradiation of the mixture of isatin and chloroacetyl chloride over the basic alumina support produced chloroacetyl isatins in an excellent yield. In a typical run, slurry of isatin (0.068 mol) and chloroacetyl chloride (0.090 mol) and basic alumina (2.0 g) was prepared. The dried slurry was powdered and the free flowing powder was placed in a 100 mL borosil conical flask, in an alumina bath and irradiated at 180 ºC for 10 min. The completion of the reaction was checked by TLC. The organic product was extracted from the inorganic solid support with chloroform, evaporation of chloroform gave product.

*Preparation of methyl-1,3-dihydro-2H-[1,4]-benzodiazepin-2-one-5-carboxylate (2) from N-chloroacetyl isatin (**1**)*

Solution phase microwave assisted method. The equimolar quantities of *N*-chloroacetyl isatin (**1**), (0.218 g, 0.001 mol) and hexamethylenetetramine (hexamine) (0.14 g, 0.001 mol) in dry methanol (20 mL) was taken in a borosil conical flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a microwave oven at 180 ºC for 8 min with short interval of 30 s to avoid the excessive evaporation of solvent (completion of reaction was checked by TLC). After completion of reaction, solvent was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in C_6H_6:MeOH (9.5:0.5) as the eluant. The product obtained was recrystallised from benzene to give **2**, 0.247 g (yield 69%) m.p. 172-75 °C.

Solid phase microwave assisted method. A slurry of equimolar quantities of *N*-chloroacetyl isatin (**1**) (0.218 g, 0.001 mol) and hexamethylenetetramine (hexamine) (0.14 g, 0.001 mol) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (2 mL). The dried slurry was powered and the free flowing powder was placed in a 100 mL borosil beaker and irradiated at 360 W microwave power for 5 min and then at 720 W for 2 min until completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethanol. The solvent was evaporated and the solid obtained was recrystallized from ethanol-chloroform mixture (1:9) and dried to give **2**, 0.257 (yield 72%), m.p. 172-175 ^{o}C.

*General solution and solid phase microwave assisted method for the preparation of (9-14) from (**2**)*

Solution phase microwave assisted method. 1,3-Dihydro-[2*H*]-[1,4]-benzodiazepin-2-one-5-methylcarboxylate (**2**) (0.218 g, 0.001 mol) and piperidine (0.0170 g, 0.001 mol)/morpholine (0.087 g, 0.001 mol)/N-ethyl piperazine (0.1 g, 0.001 mol)/2-aminopyridine (0.18 g, 0.001 mol)/2-amino pyrimidine (0.123 g, 0.001 mol)/2-aminobenzothiazol (0.336 g, 0.001 mol) was placed in a 100 mL borosil flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation, at 180 W microwave power for 2 min, 360 W for 5 min and then at 720 W for 2 min with short interval of 1 min to avoid the excessive evaporation of solvent. Overheating of the solution had to be avoided. The completion of the reaction was checked by TLC. The reaction mixture was cooled, and the resulting solid was filtered washed with dilute ethanol dried and recrystallized from ethanol-chloroform mixture (1:9), to give **9-14**, respectively.

1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-piperidinylcarboxamide (**9**), 0.345 g (yield 68.2%), m.p. 250-251 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-morpholinylcarboxamide (**10**), 0.226 g (yield 74.3%), m.p. 254-55 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(N-ethyl)-piperazinyl carboxamide (**11**), 0.237 g (yield 74.6%), m.p. 257-58 ^{o}C.1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-pyridinyl-carboxamide (**12**), 0.254 g (yield 64.0%), m.p. 252-53 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-pyrimidinyl-carboxamide (**13**), 0.293 g (yield 68.1%), m.p. 260-61 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-benzothiazolyl-carboxamide (**14**), 0.417 g (yield 75.3%), m.p. 253-54 ^{o}C.

Solid phase microwave assisted method. A slurry of equimolar quantities of 1,3-dihydro-[2*H*]-[1,4]-benzodiazepin-2-one-5-methylcarboxylate (0.218 g, 0.001 mol) and piperidine (0.0170 g, 0.001 mol)/morpholine (0.087 g, 0.001 mol)/*N*-ethyl piperazine (0.1 g, 0.001 mol)/2-aminopyridine (0.18 g, 0.001 mol)/2-amino pyrimidine (0.123 g, 0.001 mol)/2-aminobenzothiazol (0.336 g, 0.001 mol) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (2 mL). The dried slurry was powered and the free flowing powder was placed in a 100 mL borosil beaker and irradiated at 360 W microwave power for 5 min and then at 720 W for 2 min until completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethanol. The solvent was evaporated and the solid obtained was recrystallized from ethanol-chloroform mixture (1:9) and dried to give **9-14**, respectively.

1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-piperidinylcarboxamide (**9**), 0.430 g (yield 90.2%), m.p. 250-251 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-morpholinylcarboxamide (**10**), 0.278 g, (yield 91.3%), m.p. 254-55 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(N-ethyl)-piperazinyl carboxamide (**11**), 0.285 g, (yield 89.7%), m.p. 257-58 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-pyridinyl-carboxamide (**12**), 0.370 g, (yield 93.2%), m.p. 252-53 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-pyrimidinyl-carboxamide (**13**), 0.394 g, (yield 91.6%), m.p. 260-61 ^{o}C. 1,3-Dihydro-[2H]-[1,4]-benzodiazepin-2-one-5-(2-amino)-benzothiazolyl-carboxamide (**14**), 0.511 g, (yield 92.3%), m.p. 253-54 ^{o}C.

Biological activity. The novel compounds (**9-14**) were screened for their antibacterial activity against *Escherichia coli* (MTCC 119) and *Bacillus subtilis* (MTCC 619) and antifungal activity against *Aspergillus niger* (MTCC 282) and *Aspergillus flavus* (MTCC 871). The zone of inhibition and activity index were determined in comparison of the standard drugs

'ciprofloxacin' and 'fluconazol'. The outcome of this study is presented in tabular from in Table 3.

Table 1. Physical and analytical data of the compounds **9-14**.

S. No.	Comp-ound	Molecular formula	MW	M.P. (°C)	Yield (%)		Elemental analysis			
					MW solvent phase	MW solid phase	Cald./found C	Cald./found H	Cald./found N	Cald./found S
1.	9	$C_{15}H_{17}N_3O_2$	271	250-51	68.2	90.2	66.40/66.22	6.32/6.34	15.49/15.42	-
2.	10	$C_{14}H_{15}N_3O_3$	273	254-55	74.3	91.3	61.53/61.32	5.53/5.55	15.38/15.32	-
3.	11	$C_{16}H_{20}N_4O_2$	300	257-58	74.6	89.7	63.93/63.72	6.71/6.73	18.65/18.72	-
4.	12	$C_{15}H_{12}N_4O_2$	280	252-53	64.0	93.2	64.28/64.09	4.32/4.30	19.99/20.07	-
5.	13	$C_{14}H_{11}N_5O_2$	281	260-61	68.1	91.6	59.78/59.57	3.94/3.97	24.90/24.79	-
6.	14	$C_{17}H_{12}N_4O_2S$	336	253-54	75.3	92.3	60.70/60.48	3.60/3.62	16.66/16.74	9.53/9.55

Table 2. Spectral data of compounds **9-14**.

S. No.	Compound	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$+DMSO-d_6) δ (ppm)
1.	**9**	3360, 1690, 1640, 1532	8.01 (s, 1H, NH), 7.67-7.03 (m, 4H, ArH, *J* = 7.1 Hz), 4.49 (s, 2H, CH_2), 3.34 (t, 4H, CH_2, *J* = 7.5 Hz), 1.50 (m, 6H, CH_2, *J* = 7.2 Hz).
2.	**10**	3355, 1695, 1648, 1536	8.05 (s, 1H, NH), 7.80-7.50 (m, 4H, ArH, *J* = 7.1 Hz), 4.50 (s, 2H, CH_2), 3.67 (t, 4H, CH_2, *J* = 7.6 Hz), 3.47 (t, 4H, CH_2, *J* = 7.5 Hz).
3.	**11**	3350, 1685, 1655, 1534	8.02 (s, 1H, NH), 7.69-7.08 (m, 4H, ArH, *J* = 7.2 Hz), 4.42 (s, 2H, CH_2), 3.08 (t, 4H, CH_2, *J* = 7.5 Hz), 2.81(t, 4H, CH_2, *J* = 7.6 Hz), 2.50 (q, 2H, CH_2, *J* = 7.4 Hz), 1.20 (t, 3H, CH_3, *J* = 7.5 Hz).
4.	**12**	3360, 1680, 1645, 1532	8.20 (s, 1H, NH), 8.05 (s, 1H, NH), 8.11-7.65 (m, 4H, py-H, *J* = 7.2 Hz), 7.62-7.05 (m, 4H, Ar-H, *J* = 7.1 Hz), 4.48 (s, 2H, CH_2).
5.	**13**	3356, 1680, 1650, 1534	8.50 (s, 1H, NH), 8.38 (s, 1H, NH), 8.22-8.01 (m, 3H, pyrim-H, *J* = 7.2 Hz),7.69-7.06 (m, 4H, ArH, *J* = 7.1 Hz), 4.49 (s, 2H, CH_2).
6.	**14**	3365, 1685, 1648, 1536	8.20 (s, 1H, NH), 8.10 (s, 1H, NH), 7.82-7.08 (m, 8H, ArH, *J* = 7.1 Hz), 4.47 (s, 2H, CH_2).

RESULTS AND DISCUSSION

As discussed in the preceding section the synthetic potentialities of 5-carboxylic acid ester derivative of 1,4-benzodiazepin-2-one has allowed this material to be used as a building block in the synthesis of a wide variety of carboxamide derivatives in the present work, from its reaction with several primary and secondary amines which have the previous history of being biologically active, to generate the corresponding products **9-14** from **2** (Scheme 1). The study which was undertaken in the present work on the synthesis of 5-carboxamido derivatives of 1,4-benzodiazepines too, was of an immense significance. Prompted in our mind, with this concept of the design of the above bioactive materials, we report here in the synthesis of the novel carboxamide derivatives **9-14** from the corresponding carbomethoxy derivative **2.**

MW assisted reactions were conducted in the solution phase as well as in the solid phase (using the basic alumina as a solid support), wherein the solid phase synthesis scored better over the solution phase synthesis in giving much higher yield of the products. Structures of these compounds were unambiguously established on the basis of their elemental and spectral analysis. The spectral data of all compounds were found to be consistent to the structures assigned to these molecules. The physical data, microanalyses, infrared, ^{1}H NMR spectral data of all the compounds are given in Table 2.

Table 3. Biological activity data of the compounds **9-14**.

Comp. no.	Conc. in (µg/mL)	*E. coli* zone of inhibition (mm)	% activity compared to the standard	*B. subtilis* zone of inhibition (mm)	% activity compared to the standard	*A. niger* zone of inhibition (mm)	% activity compared to the standard	*A. flavus* zone of inhibition (mm)	% activity compared to the standard
9	400	09.9	34.61	11.0	61.11	14.0	50.0	11.0	36.66
	200	08.0	30.76	10.6	59.44	13.6	48.57	10.5	35.33
	100	7.3	28.07	9.0	50.0	12.2	43.57	09.3	31.33
10	400	15.0	57.69	13.0	83.33	11.0	39.28	08.0	26.66
	200	14.2	54.61	12.6	80.0	10.6	37.28	07.5	25.0
	100	13.0	50.0	11.3	73.33	09.3	33.21	06.3	21.0.
11	400	14.0	53.84	15.0	72.22	17.0	60.71	13.0	43.33
	200	12.5	49.23	14.4	70.22	16.6	59.28	12.7	42.33
	100	11.6	44.61	13.2	62.77	15.2	54.28	11.4	38.0
12	400	13.0	50.0	11.0	61.11	16.0	57.14	16.0	53.33
	200	12.3	47.30	10.7	59.44	15.5	55.35	15.7	52.33
	100	12.0	46.15	9.0	50.0	14.4	51.42	14.4	48.0
13	400	11.0	42.30	17.0	94.44	24.0	85.71	24.0	80.0
	200	10.8	41.53	16.5	90.5	23.6	83.92	23.5	78.33
	100	10.0.	38.46	15.5	86.11	22.2	79.2 8	22.3	74.33
14	400	12.0	46.15	14.0	77.77	22.0	78.57	28.0	93.33
	200	11.7	45.0	13.5	75.0	21.5	76.78	27.6	92.0
	100	10.2	39.23	12.0	66.66	20.2	72.14	26.2	87.33

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