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Conventional and microwave assisted synthesis of small molecule based biologically active heterocyclic amidine derivatives

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ABSTRACT

Heterocyclic amidine derivatives have been synthesized by condensation of 2-cyanopyrazine, 4-cyanopyridine and 2-cyanopyridine with furfurylamine, histamine, 1-(3-aminopropyl)imidazole, 4-picolylamine, 2-picolylamine, and tryptamine respectively, in the presence of sodium methoxide as well as *via* microwave irradiation in good yields. All these compounds were screened for anti-inflammatory and anticancer activities. At a dose of 50 mg/kg *p.o.* compounds **3a** (36.6%), **3d** (32%), **4d** (31.0%) and **4e** (33.8%) exhibited good anti-inflammatory activity, comparable to standard drug ibuprofen which showed 39% activity at 50 mg/kg *p.o.*

1. Introduction

Amidine derivatives form an important class of compounds which are used clinically [1], and exhibit a wide variety of biological activities, thus amidine derivatives exhibiting anticancer [2–6], antiviral [7], antibacterial [8], anti-HIV [9] and anti-inflammatory [10–13] activities are well known in literature. Amidine derivatives also act as drug carrier [14]. Apart from biological activities, amidine derivatives are also used as starting material for synthesis of various heterocyclic molecules [15].

Amidine derivatives can be synthesized by condensation of amines with nitriles but in most of the cases activation of nitriles is required [16–22]. Microwave assisted synthesis of amidine derivatives have been reported in literature *via* (i) using heterocyclic amides in the presence of $TiCl_4$ [23], (ii) diamines with inorganic ammonium salts and orthoester [24], (iii) triethylorthoacetate with substituted anilines in the presence of acetic acid [25] and (iv) primary and secondary amines with imidoylbenzotriazoles in the presence of $AlCl_3$ [26].

In continuation of our work [27,28] in search for biologically active molecules, we have synthesized several amidine derivatives (i) by conventional method in the presence of sodium methoxide and (ii) under microwave irradiation using silica gel as solid support. All the amidine derivatives synthesized were screened for anti-inflammatory and anticancer activities, results of these screening are reported in this paper.

2. Chemistry

Direct condensation of various amines (**2a–f**) (Method-I; Scheme 1) with 2-cyanopyrazine (**1a**), 4-cyanopyridine (**1b**) and 2-cyanopyridine (**1c**) do not give amidine derivatives even after refluxing for two days. Instead of amidine derivatives most of the starting materials remain unchanged. In order to overcome this difficulty 2-cyanopyrazine (**1a**), 4-cyanopyridine (**1b**) and 2-cyanopyridine (**1c**) were first allowed to react with sodium methoxide by stirring at room temperature for 2–3 h, using absolute methanol as solvent of reaction to give insitu intermediate [29] **I′** (Scheme 1). Intermediate **I′** undergoes substitution reaction with various amines to give amidine derivatives in good yields. Condensation of 2-cyanopyrazine (**1a**), 4-cyanopyridine (**1b**) and 2-cyanopyridine (**1c**) with furfurylamine (**2a**), histamine (**2b**), 1-(3-aminopropyl)imidazole (**2c**), 4-picolylamine (**2d**), 2-picolylamine (**2e**) and tryptamine (**2f**) in the presence of sodium methoxide by refluxing for 6–8 h, using absolute methanol as solvent of reaction gave three series of amidine derivatives *i.e.* **3a–f**, **4a–f**, **5a–d** and **5f**. All these compounds were

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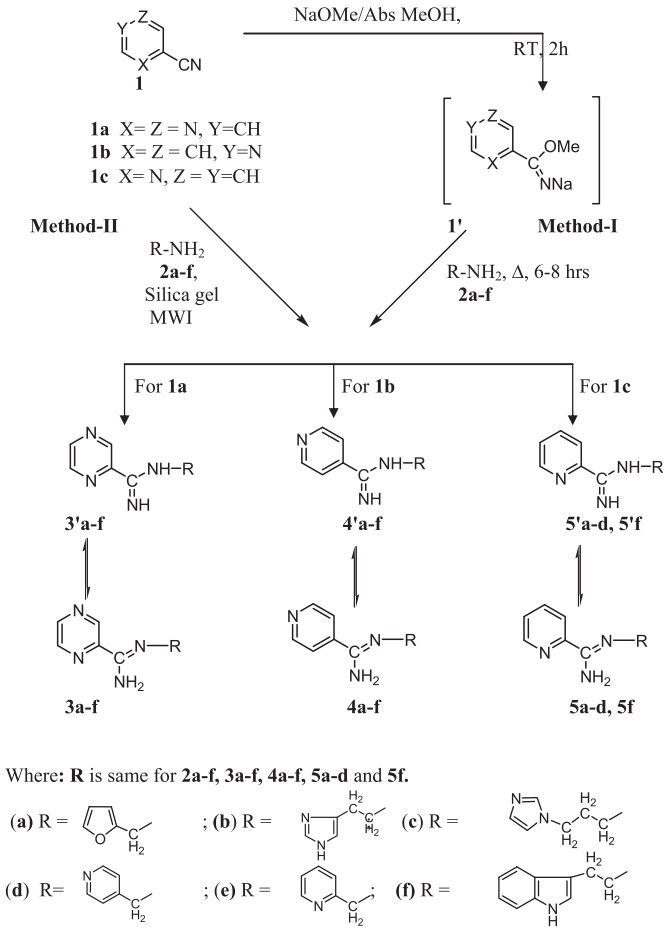


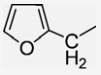
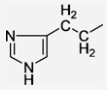
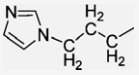
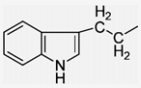
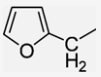
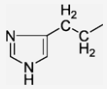
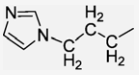
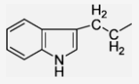
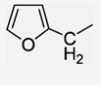
Scheme 1. Synthesis of amidine derivatives.

purified by crystallization and structures assigned to **3a–f**, **4a–f**, **5a–d** and **5f** are fully supported by spectral data *i.e.* ^{1}H NMR, IR, GC-MS and elemental analysis.

A solution of furfurylamine (0.202 g; 1 mmol) and 2-cyanopyrazine (0.105 g; 1 mmol) in methanol (5 mL) was prepared and to it was added silica gel G (5 g). Solvent from this mixture was removed under high vacuum to give dry silica gel on which furfurylamine and 2-cynopyrazine are adsorbed. Furfurylamine and 2-cynopyrazine adsorbed over silica gel were subjected to microwave irradiation for different time intervals and at different power levels. Irradiation for 2 min at a power level 100 Watt and 180 Watt do not give any product. Irradiation for 2 min at 300 Watt power level gave desired product in small amount. Irradiation for additional 2 min was carried out two times at 300 Watt power level but the reaction was not complete. At power level of 450 Watt and irradiation for 2 min, two times (*i.e.* total irradiation for 4 min) showed that the reaction is complete. So all the microwave assisted condensation of **3a–f** with **1a–c** was carried out at 450 Watt power level.

Optimum time of irradiation at 450 Watt power level for all the compounds *i.e.*, **3a–f**, **4a–f**, **5a–d** and **5f** is worked out and is reported in Table 1. Refluxing time & yield by conventional method and irradiation time & yield by microwave assisted method are reported in Table 1. A look at Table 1 indicates that the yields obtained by microwave assisted method are comparable with conventional method, but microwave assisted method is fast, simple to workwith and environmental friendly. All the compounds synthesized by method-1 and method-2 gave same physical

Table 1
Refluxing time, irradiation time & percentage yield of amidine derivatives synthesized by conventional and microwave assisted methods.

Compounds	R	Method-I		Method-II	
		Refluxing time (h)	% Yield	Irradiation time (min) at 450 W	% Yield
3a		6	95	4	93
3b		6	90	4	91
3c		7	85	4	80
3d		6	95	3	90
3e		6	95	3	96
3f		8	95	6	85
4a		7	85	3	90
4b		7	80	5	82
4c		8	85	4	80
4d		7	92	4	85
4e		8	90	3	93
4f		8	85	5	80
5a		7	80	2	85

(*continued on next page*)