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Note

Microwave assisted synthesis and pharmacological screening of 3-(substituted phenyl)-5-methylquinolino [3,2-e]-1,2,4-triazines

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A series of quinolinotriazines have been synthesized by condensation of 2-hydrazino-4-methylquinoline **3** with aromatic aldehydes followed by nitrosation with sodium nitrite in acetic acid leading to ring closure under microwave irradiation.

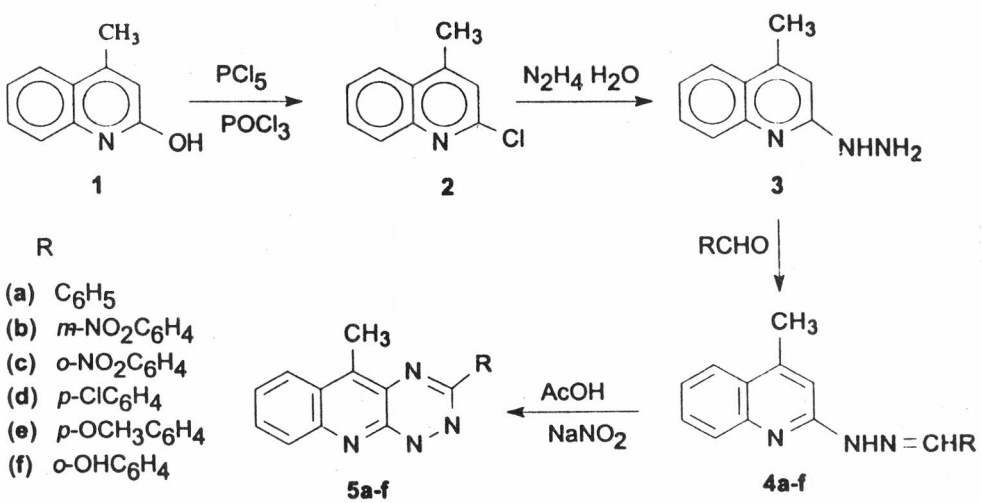
Recently reported studies on the use of domestic microwave oven for the synthesis of heterocycles[1-5] showed that it is a safe rapid and convenient methodology. Keeping in view the potential of microwave irradiation (MWI) in chemical synthesis and pharmacological importance of quinoline derivatives[6-8] it was of interest to prepare the title compounds.

2-Hydroxy-4-methylquinoline was obtained by cyclisation of acetoacetanilide[9] which on treatment with $POCl_3/PCl_5$ gave 2-chloro-4-methylquinoline[7] **2**. **2** on reaction with hydrazine hydrate (99%) afforded corresponding hydrazide[7] **3** which on condensation with aryl aldehydes under MWI yielded the corresponding 2-hydrazones **4a-f** (Scheme I). The IR spectra showed the presence of NH group in the region 3250-3350 cm^{-1}. Nitrosation of compounds **4a-f** with sodium nitrite in acetic acid under MWI led to the ring closure and formation of 3-(substituted phenyl)-5-methylquinolino [3,2-*e*] 1,2,4 triazines **5a-f** which was evidenced by the absence of NH group in IR and NMR spectra and peak at δ 8.20-8.42 due to C*H*=N.

Experimental Section

Melting points were taken on Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer using KBr discs and ^{1}HNMR were recorded on FT NMR Hitachi R-600 using Me_4Si as internal standard (chemical shifts in δ, ppm). The purity of the compounds were checked on silica gel coated Al plates (Merck).

Synthesis of 4-methylquinolinyl-2-hydrazones 4a-f. 2-Hydrazino-4-methylquinoline **3** (0.01 mole) and arylaldehyde (0.01 mole) were taken in



Scheme I

Table I—Characterization data of compounds **4a-f**

Compd	R	m.p. °C	Yield %	Found (Calcd) %			^{1}HNMR ($CDCl_3$ + DMSO- d_6 ,δ, ppm)
				C	H	N	
4a	C_6H_5	165-67	87	78.29 (78.16	5.72 5.75	16.15 16.09)	2.40 (s,3H, 4 CH_3), 6.6-7.9 (m,10H, Ar-H), 8.20 (s,1H, CH=N), 9.50 (brs, 1H, NH).
4b	3-NO_2 C_6H_4	210-13	89	66.50 (66.67	4.60 4.57	18.36 18.30)	2.38 (s,3H, 4CH_3), 6.7-8.2 (m, 9H, Ar-H), 8.40 (1H, CH =N), 9.70 (brs, 1H, NH)
4c	2-NO_2 C_6H_4	216-19	88	66.60 (66.67	4.59 4.57	18.25 18.30)	2.40 (s, 3H , 4 CH_3), 6.6-8.1 (m, 9H, Ar-H), 8.42 (s, 1H, CH=N), 9.60 (brs, 1H, NH)
4d	4-Cl C_6H_4	185-88	89	69.20 (69.03	4.72 4.74	14.35 14.21)	2.37 (s, 3H, 4 CH_3), 6.8-8.2 (m, 9H, Ar-H), 8.40 (s, 1H , CH=N), 9.60 (brs, 1H, NH)
4e	4-OCH_3 C_6H_4	213 -15	90	74.10 (74.23	5.82 5.84	14.35 14.43)	2.39 (s, 3H, 4CH_3), 3.80 (s,3H, OCH_3), 6.7 -8.2 (m, 9H, Ar -H), 8.40 (s, 1H, CH=N) 9.70 (brs, 1H, NH)
4f	4-OH C_6H_4	220	80	73.70 (73.64	5.51 5.4	15.22 15.16)	2.38 (s, 3H, 4 CH_3), 5.00 (brs, 1H, OH), 6.6-8.2 (m, 9H, Ar-H, 8.42 (s, 1H, CH=N), 9.60 (brs, 1H, NH)

Table II—Characterization data of compounds **5a-f**

Compd	R	m.p. °C	Yield %	M^+ Observed (expected)	Time		Found (Calcd) %			^{1}HNMR ($CDCl_3$ + DMSO-d_6, δ, ppm)
					A (min)	B (hr)	C	H	N	
5a	C_6H_5	150	70	270 (272)	5.0	2.0	74.5 (75.0	4.40 4.41	20.60 20.58)	2.40 (s, 3H, 4 CH_3), 6.8-8.2 (m, 9H, Ar-H)
5b	3-NO_2 C_6H_4	>260	68	316 (317)	5.2	1.0	64.30 (64.35	3.52 3.47	22.10 22.08)	2. 38 (s, 3H, 4 CH_3) 6.9 -8.4 (m, 8H, Ar -H)
5c	2-NO_2 C_6H_4	210	80	316 (317)	6.0	1.0	64.38 (64.35	3.42 3.41	22.12 22.08)	2.40 (s,3H, 4 CH_3) 6.8-8.2 (m,8H Ar-H)
5d	4-ClC_6H_4	225	88	307 (306.5)	6.0	2.3	66.58 (66.55	3.60 3.58	18.30 18.27)	2.40 (s, 3 H, 4-CH_3) 6.8 -8.2 (m,8H Ar-H).
5e	4-OCH_3 C_6H_4	170-72	75	302 (302)	5.3	1.5	71.58 (71.52	4.69 4.63	18.60 18.54)	2.40 (s, 3H, 4 CH_3). 3.80 (s, 3H OCH_3) 6.7-8.1 (m,8H, Ar- H)
5f	2-OH C_6H_4	240	72	290 (288)	5.0	2.0	70.89 (70.83	4.20 4.16	19.48 19.44)	2.42 (s,3H,4 CH_3) 5.0 (s, 1H, br, OH) 6.9-8.5 (m 8H, Ar -H)

A—Using microwave irradiation.
B—Using conventional heating.

ethanol (15 mL) in a 100 mL beaker. The beaker was zapped inside a microwave oven for 1.5-2.0 min at 2450 Hz. The reaction mixture was cooled and the solid separated was filtered off, washed with water and recrystallized from ethanol. The characterization data of **4a-f** are given in Table I.

3-(Substituted phenyl)-5-methylquinolino-[3,2-e]-1,2,4 triazine 5a-f.

Method A

A solution of hydrazone **4a-f** (0.01 mole) in acetic acid (10 mL), and sodium nitrite (0.03 mole) in water (2 mL) was taken in a conical flask capped with a glass funnel and subjected to microwave irradiation for 5-6 min. A 500 mL beaker containing 200 mL was placed in the oven next to reaction flask to serve as "heat sink". The reaction mixture was cooled and the solid separated was filtered, washed with water and recrystallized from acetic acid to give **5a-f**. Their characterization data are given in Table II.

Method B

A solution of hydrazones **4a-f** (0.01 mole) in acetic acid (10 mL), and sodium nitrite (0.03 mole) in water (2 mL) was refluxed for an appropriate time, and worked-up as described in method-A.

Biological activity

The effect of compounds **5a-f** were observed on blood pressure, respiration and heart rate of pentobarbitone sodium (35 mg/kg, i.v) anaesthetized cats of either sex (weight 2.5 to 4.0 kg). Alterations in behaviour i.e. spontaneous motor activity, reactivity, lacrymation body temperature, etc. was studied in healthy albino mice (20-25 g). Anticon-

vulsant, antidepressant and analgesic effects were also studied at 100 mg doses in mice. Effect on blood pressure, heart rate and respiration were investigated at 1.0 and 5.0 mg/kg i.v. doses. However, the compounds did not show any significant effect on cardiovascular or central nervous system Paradigms studied.

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