Synthesis and evaluation of 2,6-piperidinedione derivatives as potentially novel compounds with analgesic and other CNS activities

ARTICLE *in* INFLAMMOPHARMACOLOGY · APRIL 2006

DOI: 10.1007/s10787-006-1498-4 · Source: PubMed

4 AUTHORS, INCLUDING:

Seham El-Batran
National Research Center, Egypt
17 PUBLICATIONS **150** CITATIONS
SEE PROFILE

Magda M. F. Ismail
Faculty of Pharmacy,Azhar University
49 PUBLICATIONS **346** CITATIONS
SEE PROFILE

Inflammopharmacology 14 (2006) 62–71
0925-4692/06/020062-10
DOI 10.1007/s10787-006-1498-4

Inflammopharmacology

Short Communication

Synthesis and evaluation of 2,6-piperidinedione derivatives as potentially novel compounds with analgesic and other CNS activities

S. A. El Batran[*1], A. E. N. Osman[2], M. M. Ismail[3] and A. M. El Sayed[3]

[1] Pharmacology Department, National Research Center, Dokki, Cairo, Egypt, Fax +20-2337-0931, e-mail: sehamelbatran@yahoo.com.
[2] Department of Organic Chemistry, Faculty of Pharmacy, Cairo University, Egypt
[3] Department of Pharmaceutical Chemistry, Faculty of Pharmacy (Girls), Al-Azhar University Nasr City, Cairo, Egypt

Received 12 March 2005; accepted 14 November 2005

Abstract. New 2,6-piperidinediones $2_{a–g}$ and $4_{a–d}$ were prepared by initial condensation of aromatic aldehydes or cycloalkanones with cyanoacetamide to give α-cyanocinnamides $l_{a–g}$ or cycloalkylidenes $3_{a,b}$ which underwent Michae1 addition with ethyl cyanoacetate or diethylmalonate. Compounds $4_{a–d}$ were alkylated by various alkyl halides to produce the N-alkylated 2,6-piperidinedione derivatives $5_{a–m}$.

Some new selected compounds $2_{a–c,f}$, $4_{a–d}$ & $5_{e,h,j}$ were pharmacologically evaluated for potential anticonvulsant, sedative and analgesic activities. These compounds exhibited significant anticonvulsant and analgesic effects after a single I.P. administration 100 mg/kg b.wt. . On the other hand all the investigated compounds induced hypnotic activity and prolonged the phenobarbital sodium- induced sleep as compared with the control group and the most potent compound was found to be 2_f.

Key words: *Carbamazepine; Phenobarbital sodium; Novalgine; Anticonvulsant; Sedative; Analgesic*

Introduction

2,6-Piperidinedione derivatives have been reported to exhibit anticonvulsant (Marshall and Vallance 1954; Jochheim and Gerberding,1955 ; Danuta et al.,1975; Wong et al.,1986; Yuji et al.,1988; Richard et al.,1990), and sedative-hypnotic activities (Jochheim and Gerberding,1955 ; Somers ,1956; Yao-Hua et al.,1969; Yuji et al., 1988; Fischer and Ambre ,1976; Osman et al.2003). Others have been shown to possess analgesic action (Stiz et al.,2000). Consequently, it was decided to synthesize certain new 2,6-piperidinedione derivatives by changing the substituents in P-4, P-l and /or P-3 to exhibit their pharmacological activities.

* *Corresponding author*

Experimental

Pharmacological experiments

Animals

Rats of both sexes weighing 150–200 g and mice weighing 18–20g were used in the experiments. Food and water was provided *ad libitum*. Rats and mice were obtained from the animal house colony, National Research Center, Dokki, Cairo, Egypt. All animal procedures were performed after approval from the Ethics Committee of the National Research Center and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

Anticonvulsant test

This effect was assessed according to the method reported by Rizzo et al.(1971) . Electrical stimulation was applied to the rat ear by using 515 Master shoker (Laffayette Inst. Co.) internal resistance is set to 400 kg. Percent increase in voltage required to induce an electric shock in treated animals is taken as a measure of anticonvulsant activity. The anticonvulsant effect of an intraperitoneal single dose of the tested compounds (100mg/kg b.wt.) and was compared to that of carbamazepine (Tegretol) (100 mg/kg b.wt.) as a reference

anticonvulsant drug . The reaction time was measured at 1, 3 and 24 hours after administration of tested compounds or carbamazepine.

Sedative test "potentiation of phenobarbital sleeping time"

Male mice weighing 20–25g were divided into 12 groups, each consisted of six animals and were injected i.p. according to the following:

Group 1 received 100 mg/kg b.wt of phenobarbital sodium and served as control group. The other groups received 100 mg/kg b.wt of the tested compounds. After 60 min., the treated groups were injected with 100 mg/kg b.wt of phenobarbital sodium.

The animals were observed in order to determine the onset and the duration of sleep as evidenced by loss of righting reflex. The mean onset and duration of sleep produced by the compounds were compared statistically with those of the positive control values using Students t-test (Karli et al.,1998).

Analgesic test

This effect was evaluated according to the method of Charlier et al. (1961) , by using electric current as a noxious stimulus applied to the rat tail by means of 515 Master shocker (Laffayette Inst. Co.) using alternative current of 50 cycles/sec. for 0.2 second. The minimum voltage required for the animal to emit a cry was recorded for the negative control group and the treated groups. The tested compounds were injected intraperitonealy at a dose level of 100mg/kg b.wt. The last group was injected with dipyrone (Novalgin) (50mg/kg b.wt. ,i.p.) . The reaction time was measured after one and two hours after the administration of the tested compounds or dipyrone.

Statistical analysis

The data are presented as (means $\pm$ standard error) using the Students t-test for determination of the level of significance $p<0.05$ was considered significant (Kapure and Saxena, 1972).

Chemical experiments

All melting points were recorded using on Electrothermal LA 9000 SERIS, Digital Melting Point Apparatus and were uncorrected. IR Spectra have been carried out on Pye Unicam SP 1000 IR spectrophotometer at Microanalytical Center, Cairo University and Ain Shames University.The ^{1}H-NMR Spectra were recorded on Varian Gemini EM-300 MHz NMR spectrometer at Research 'Services Unit, Faculty of Science, Cairo university. DMSO-d_6 and $CDC1_3$ were used as solvents, chemical shifts were, measured in δ ppm, relative to TMS as internal standard. Mass Spectra were recorded on Hewlrtt Packard 5988 spectrometer at Microanalytical Unit, Cairo University and Ain Shams University. Microanalyses were carried out at Microanalytical Center, Cairo University.

Cyanoacetamide (Vogel 1956), substituted α-cyanocinnamides $l_{a–l}$ (Manro et al.1995 and Karras et al.1998), cyc1opentylidene $3_{a,b}$ (Foucaud et al.1964) and cyc1ohexylidene-acetamides $3_{c,d}$ (Foucaud et al.1964)were prepared by known procedures. The α-cyanocinnamides $1_{b,e,h,I}$ are new compounds and their data are given in (table 4).

4-Aryl-3,5-dicyano-2,6-piperidinediones $2_{a–g}$
General procedure

A mixture of substituted α-cyanocinnamides $l_{a–g}$ (0.01 mol) and ethyl cyanoacetate (0.01mol) in an ethano1ic solution of sodium ethoxide was refluxed for 2 hrs., concentrated and poured into ice-cold water (50ml) containing hydrochloric acid (10ml). The separated solid was filtered off and crystallized ftom benzene/ethanol (1:1) mixture, (tables 5 and 6).

8-Azaspiro [4,5] decane-7.9-dione derivatives $4_{a,b}$, and 3-Azaspiro [5,5] undecane-2,4-dione derivatives $4_{c,d}$
General procedure

A mixture of 2-cyano-2-cyclopentylidene-acetamide $3_{a,b}$ or 2-cyano-2cyclohexylidene-acetamide $3_{c,d}$ (0.013 mol) and diethyl malonate or ethyl cyanoacetate (0.013 mol) each in an ethanolic solution of sodium ethoxide was stirred at room temperature for 12 hrs.The mixture was then acidified by hydrochloric acid (10ml in 50ml water). The separated solid was filtered off and crystallized from the appropriate solvent, (tables 6,7).

8-Alkyl-8-Azaspiro[4,5]decane- 7,9-dione derivatives $5_{a,c}$, and 3- Alkyl-3-Azaspiro [5,5] undecane-2,4-dione derivatives $5_{d–m}$
General procedure

$4_{a,b}$ or $4_{c,d}$ were initaly converted into their potassium salts by reaction with ethano1ic potassium hydroxide, then the appropriate dry salt [0.003 mo1.] and the suitable alkylhalide [0.003 mol] in dimethylformamide (10ml) was refluxed on a water bath for 2 hrs. The mixture was left to cool and poured into ice-cold water. The separated solid was filtered off and crystallized from the suitable solvent,(tables 6 and 7).

Results

Pharmacological part

Anticonvulsant effect (Table 1)

All the investigated compounds showed significant anticonvulsant effects and all of them exhibited their highest potency 3 hours after a single intraperitoneal (I.P.) dose of 100 mg/kg b.wt of the compound. Comparative study between the chemical structure of the tested compounds and their

Table 1. Anticonvulsant effect of the tested compounds compared to carbamazepine in rats at a dose of 100 mg/kg b.wt.

Comp. No.	Volts needed before treatment		Volts needed after single dose administration								
	Zero time		1 hr			3 hrs			24 hrs		
	Mean ± S.E.	% of change	Mean ± S.E.	% of change	# potency	Mean ± S.E.	% of change	# potency	Mean ± S.E.	% of change	# potency
Control	77.5 ± 3.1	0.00	74.17 ± 3.0	–4.3	0.11	79.17 ± 3.0	2.2	0.02	81.67 ± 3.33	5.4	0.08
2_a	70.0 ± 2.58	0.00	**83.0 ± 2.94	18.6	0.47	***95.0 ± 2.24	35.7	0.33	***97.5 ± 1.71	39.3	0.58
2_b	74.17 ± 1.5	0.00	78.33 ± 2.79	5.6	0.14	***106.67 ± 4.0	43.8	0.41	***100.0 ± 2.24	34.8	0.51
2_c	70.0 ± 1.83	0.00	***86.67 ± 2.11	23.8	0.6	***99.17 ± 2.39	41.7	0.39	***109.17 ± 6.63	56.0	0.82
2_f	71.67 ± 2.47	0.00	***100.0 ± 4.28	39.5	0.99	***103.3 ± 4.0	44.1	0.41	***105 ± 3.65	46.5	0.68
4_a	67.5 ± 2.8	0.00	***90.3 ± 2.79	33.8	0.85	***133.33 ± 4.01	97.5	0.91	***110 ± 2.9	63.0	0.92
4_b	65.83 ± 2.39	0.00	***88.17 ± 2.02	33.9	0.85	***14.33 ± 3.33	117.7	1.1	***125.5 ± 3.3	90.6	1.3
4_c	70.0 ± 1.83	0.00	**82.5 ± 2.5	17.9	0.43	***90.83 ± 2.39	29.8	0.28	***85.83 ± 3.5	22.6	0.33
4_d	70.8 ± 2.39	0.00	**87.5 ± 4.03	23.6	0.59	***121.67 ± 3.33	71.9	0.67	***119.17 ± 3.0	68.3	1.0
5_e	68.33 ± 2.47	0.00	***90.33 ± 3.8	32.2	0.81	***111.67 ± 4.22	63.4	0.59	***106.17 ± 4.97	55.4	0.81
5_h	67.5 ± 2.14	0.00	***99.5 ± 2.3	47.4	1.2	***114.17 ± 4.55	69.1	0.65	***105.0 ± 5.77	55.6	0.81
5_j	65.83 ± 2.39	0.00	***89.5 ± 2.29	36.0	0.9	***124.17 ± 2.39	88.6	0.83	***119.17 ± 4.36	81.0	1.2
Carbam azepine	70.83 ± 2.39	0.00	***99.17 ± 2.39	40.0	1.0	***146.7 ± 4.94	107.1	1.0	***119.17 ± 4.17	68.3	1.0

* P< 0.05, ** P < 0.01 and *** P < 0.001 vs the corresponding zero time. # potency is considered as the percent of change of the different treatments divided by the percent of change of carbamazepine. The % of change was calculated as regards the effect at zero time.

pharmacological effects, revealed that 4-arylpiperidine-2,6-dione, (4_c) exhibited strong anticonvulsant activity compared to carbamazepine (potency 0.8:1.0,respectively). The potent anticonvulsant effect of (4_c) is probably due to the presence of 4-phenyl substituent bearing -Cl atom at the ortho para position. Most of the tested spiroglutarimides demonstrated higher activity than the 4-arylpiperidine-2,6-diones e.g. 4_b and 5_j have higher anticonvulsant activity (1.3 and 1.2 potencies respectively) relative to carbamazepine, while 4_d was equipotent to carbamazepine. In addition, when comparing the following pairs of compounds: [4_a & 4_b], [4_c & 4_d] and [5_e & 5_j], it was observed that the CN group at P-3 imparts higher activity than – COOEt. Also by comparison between [4_a & 4_c] and [4_b& 4_d], it was found that 8-azaspiro [4,5]-decane7,9-diones are more potent than 3-azaspiro [5,5]-undecane2,4-diones. Moreover, when comparing [4_d & 5_j] and [4_c,5_e & 5_h], it was clear that N-alkylation imparts higher anticonvulsant activity. Almost all the tested compounds exhibited their highest potency 24 hr. after I.P. administration (see Table 1).

Sedative Effect (Table 2)

The tested compounds significantly decreased the onset time of sleep induced by phenobarbital sodium, and increased its duration as well. Compounds 2_b,2_c,2_f,5_e and 5_j were the highly potent ones in onset and duration of sleep at P<0.001 where 2_f demonstrated the shortest onset and longest duration of sleep after phenobarbital administration.

Table 2. Effect of the tested compounds on the onset and duration of sleep induced by phenobarbital sodium (100 mg/kg b.wt.) in mice.

Compound No.	Onset of sleep 'min' mean ± S.E.	% effect relative to control	Duration of sleep 'min' mean ± S.E.	% effect relative to control
2_a	***33.2 ± 2.6	60.0	**95.0 ± 4.3	128.0
2_b	***30.8 ± 2.4	55.7	***121.7 ± 4.8	164.0
2_c	***24.2 ± 1.6	44.0	***106.7 ± 4.9	143.8
2_f	***19.7 ± 1.2	36	***128.3 ± 6.0	172.9
4_a	***25.8 ± 1.4	46.7	**94.2 ± 4.2	127.0
4_b	**38.0 ± 3.1	68.7	***133.3 ± 4.9	179.7
4_c	**38.3 ± 2.8	69.3	***112.5 ± 4.4	151.6
4_d	**39.2 ± 3.3	70.9	*92.2 ± 5.4	124.3
5_e	***25.0 ± 1.8	45.2	***117.5 ± 4.4	158.4
5_h	***27.0 ± 2.0	48.8	*94.2 ± 5.2	127.0
5_j	***34.2 ± 3.0	61.8	***119.2 ± 5.8	160.7
Phenobarbital sodium (control)	55.3 ± 2.5	100	74.2 ± 4.2	100

* P< 0.05, ** P < 0.01 and *** P < 0.001 vs control.

Table 3. Analgesic effect of the tested compounds (100 mg/ kg b.wt.) compared to that of dipyrone in rats .

Comp. No.	Dose mg/ 100g b.wt	After one hour			After two hour		
		Volts needed mean ± S.E.	% of change	# Potency	Volts needed mean ± S.E.	% of change	# Potency
Control	Saline	76.67 ± 2.11	–	–	79.17 ± 3.0	–	–
2_a	10	***113.33 ± 3.33	47.82	0.54	***104.17 ± 3.0	31.58	0.41
2_b	10	***108.33 ± 2.79	41.3	0.46	**100.83 ± 3.75	27.36	0.35
2_c	10	***115.83 ± 3.52	51.08	0.57	**99.17 ± 3.52	25.26	0.32
2_f	10	***121.67 ± 4.22	58.7	0.66	***127.5 ± 2.81	61.05	0.78
4_a	10	***135.83 ± 3.0	77.16	0.87	***125.83 ± 3.0	58.94	0.76
4_b	10	***130.83 ± 4.73	70.64	0.79	***134.17 ± 3.0	69.47	0.89
4_c	10	***116.67 ± 3.07	52.17	0.59	***103.17 ± 3.18	30.31	0.39
4_d	10	***115.0 ± 2.89	50.0	0.56	***111.67 ± 3.33	41.05	0.53
5_e	10	***111.67 ± 3.33	45.65	0.51	***105.3 ± 2.73	33.0	0.42
5_h	10	***113.33 ± 4.01	47.82	0.54	***110.0 ± 3.87	38.94	0.5
5_j	10	***115.0 ± 3.65	50.0	0.56	***134 ± 2.66	69.26	0.89
Dipyrone	5	***145.0 ± 4.83	89.12	1.0	***140.83 ± 4.17	77.88	1.0

* P< 0.05, ** P < 0.01 and *** P < 0.001 vs control. # potency is considered as the percent of change of the different treatments to the percent of change of dipyrone . The % change denotes change from saline control group.

Analgesic effect (Table 3):

There was significant increase in analgesic effect one and two hours after administration of all compounds as compared to the control value. Compounds 2_f (4-arylpiperidine-2,6-dione), 4_a, 4_b and 5_j (spiroglutarimide) were found to be the most potent ones (0.8–0.9 potency relative to that of dipyrone , two hours after administration).

Discussion

Obtained results revealed that administration of a single dose of the tested compounds in rats and mice induced significant anticonvulsant, analgesic and sedative effects which are in harmony with many published results (Yao-Hua et al.,1972; Tateoka et al.,1988; Karli et al.,1998; Stiz et al., 2000). The anticonvulsant, sedative and analgesic activities of the tested com-

Table 4. Physicochemical data of $1_{b,e,h,i.}$

1	M. p, °C (solvent of crystallization)	Yield % (Reported)	Molecular Formula (M.W.)	Analysis %	
				Calcd	Found
b	135 (ethanol)	67.8	$C_{10}H_7BrN_2O$ (251.08)	C 47.83 H 2.81 N 11.15 Br 31.82	47.80 3.48 10.62 29.28
e	160 (benzene)	87	$C_{10}H_6Cl_2N_2O$ (241.07)	C 49.82 H 2.51 N 11.61 Cl 29.41	50.29 3.17 11.50 29.36
h	185 (ethanol)	70.9	$C_{12}H_{12}N_2O_3$ (232.24)	C 62.06 H 5.21 N 12.06	62.20 4.40 11.95
i	195 (ethanol)	67.3	$C_{12}H_{12}N_2O_3$ (232.24)	C 62.06 H 5.21 N 12.06	62.00 5.66 11.95

IR spectra (KBr) Cm^{-1}
3419-3326 cm^{-1} (NH_2); 2276-2214cm^{-1} (C ≡ N); 1693-1670 cm^{-1} (C = O).

Table 5. Physicochemical data of $2_{a,g}$

2	m.p.	Yield %	Molecular Formula (M.W.)	Micro analysis	
				Calcd	Found
a	255	51.9	$C_{13}H_9N_3O_2$ (239.23)	C 65.27 H 3.79 N 17.56	65.55 4.20 16.94
b	165	61.5	$C_{13}H_8BrN_3O_2$ (318.13)	C 49.08 H 2.53 N 13.21 Br 25.12	48.92 2.70 12.74 24.06
c	288	60	$C_{13}H_8ClN_3O_2$ (273.67)	C 57.05 H 2.95 N 15.35 Cl 12.95	56.90 2.50 15.26 12.95
d	235	14.6	$C_{13}H_8ClN_3O_2$ (273.67)	C 57.05 H 2.95 N 15.35 Cl 12.95	56.82 2.70 15.30 12.95
e	285	57.7	$C_{13}H_7Cl_2N_3O_2$ (308.12)	C 50.67 H 2.28 N 13.63 Cl 23.01	50.30 2.50 13.15 23.94
f	255	35.7	$C_{13}H_8FN_3O_2$ (257.22)	C 60.70 H 3.13 N 16.33	60.43 4.12 16.25
g	325	20	$C_{14}H_{11}N_3O_3$ (269.255)	C 62.45 H 4.12 N 15.61	62.00 4.00 15.35

pounds may be attributed to an effect on the CNS enzyme (5-hydroxytryptophan (5-HTP) decarboxylase), monoamine oxidase (MAO) (Karli et al.,1998). The biological screening data of a series of N-(4-phenyl-1-piperazinyl–alkyl)-substituted cyclic imides. These compounds were shown to possess in – varying degrees –, psychotropic properties typical

Table 6. Physicochemical data of $4_{a,d}$ and $_{am}$

Compd.	m.p. (solvent of crystalization)	Yield %	Molecular Formula (M.W.)	Analysis %	
				Calcd	Found
4_a	145 (ethanol)	51.4	$C_{13}H_{16}N_2O_4$ (264.27)	C 59.08 H 6.10 N 10.60	59.76 6.46 11.05
4_b	166 (ethanol)	55.5	$C_{11}H_{11}N_3O_2$ (217.22)	C 60.82 H 5.10 N 19.34	60.88 5.60 19.00
4_c	167.170 (methanol)	98	$C_{14}H_{18}N_2O_4$ (278.30)	C 62.33 H 6.52 N 10.07	60.20 6.50 10.40
4_d	200 (chloroform)	87	$C_{12}H_{13}N_3O_2$ (231.25)	C 60.42 H 5.67 N 18.17	62.20 5.90 18.20
5_a	95 (ethanol)	52	$C_{14}H_{18}N_2O_4$ (278.30)	C 60.42 H 6.52 N 10.07	60.42 6.79 9.99
5_b	55 (ethanol)	40	$C_{16}H_{22}N_2O_4$ (306.35)	C 62.72 H 7.23 N 9.14	62.50 7.00 9.34
5_c	130 (ethanol)	32.3	$C_{13}H_{15}N_3O_2$ (245.27)	C 63.66 H 6.16 N 17.13	63.04 6.40 17.10
5_d	115 (hexane)	70	$C_{15}H_{20}N_2O_4$ (292.33)	C 61.63 H 6.9 N 9.58	61.80 7.00 9.70
5_e	80 (hexane)	65.6	$C_{16}H_{22}N_2O_4$ (306.35)	C 62.72 H 7.23 N 9.14	62.70 7.40 9.42
5_f	60 (hexane)	35	$C_{17}H_{24}N_2O_4$ (320.38)	C 63.73 H 7.55 N 8.74	63.35 6.20 8.50
5_g	47 (hexane)	76	$C_{18}H_{26}N_2O_4$ (334.41)	C 64.65 H 7.84 N 8.38	64.90 7.70 8.40
5_h	100 (methanol)	73.9	$C_{21}H_{24}N_2O_4$ (368.43)	C 68.46 H 6.57 N 7.6	68.60 6.60 7.50
5_i	135 (ethanol)	63.6	$C_{13}H_{15}N_3O_2$ (245.27)	C 63.66 H 6.16 N 17.13	64.00 5.60 17.10
5_j	100 (ethanol)	21	$C_{14}H_{17}N_3O_2$ (259.30)	C 64.85 H 6.61 N 16.2	65.00 5.60 16.40
5_k	90 (hexane)	2	$C_{15}H_{19}N_3O_2$ (273.33)	C 65.91 H 7.01 N 15.37	65.50 7.40 15.00
5_i	85-90 (methanol)	18.9	$C_{16}H_{21}N_3O_2$ (287.36)	C 66.88 H 7.37 N 14.62	67.00 6.10 14.85
5_m	140 (methanol)	30.8	$C_{19}H_{19}N_3O_2$ (321.37)	C 71.01 H 5.96 N 13.07	71.50 5.30 13.20

Table 7. Spectral data of newly synthesized compounds:

Compd.	Spectral data
2_{a-g}	IR: 3390-3207 (NH); 2275-2210 (CN); 1752-1700 (C=O) and 1700-1643(C=O)
2_a	^{1}HNMR(DMSO-d_6): 4.30 (t, 1H, proton attached to C_4 in 2,6-piperidinedione ring); 4.91 (d,2H, protons attached to C_3 and C_5 in 2,6-peridinedione ring); 7.45 (s, 5H aromatic protons); 12.00 (s, 1H, NH exchangeable by D_2O).
	MS: m/z 239 ($C_{13}H_9N_3O_2$, 19.65% M); m/z 156 ($C_{10}H_6NO$, 73.21%); m/z 129 (C_9H_5O, 97.90 %); m/z 102 (C_8H_6 11.90%); m/z 67 (C_3HNO, 100% Base)
2_b	^{1}HNMR(DMSO-d_6): 4.35 (t, 1H, proton attached to C_4 in 2,6-piperidinedione ring); 4.98 (d,2H, protons attached to C_3 and C_5 in 2,6-peridinedione ring); 7.45-7.70 (m, 4H aromatic protons); 12.05 (s, 1H, NH exchangeable by D_2O).
	MS: m/z 317.319 ($C_{13}H_8BrN_3O_2$, 16.51%, 17.65%, M,M^{+2}); m/z 234.236 ($C_{10}H_5BrNO$, 93.24%, 90.21%); m/z 207,209 (C_9H_4BrO, 72.31%, 95.23%); m/z 129 (C_9H_5O, 100% Base); m/z 101 (C_8H_5, 53.77%); m/z 55 (C_2HNO, 99.46%).
2_c	MS: m/z 273,275 ($C_{13}H_8ClN_3O_2$, 37.31%, 13.45%, M,M^{+2}); m/z 190,192 ($C_{10}H_5ClNO$, 100%, 33.7% Base); m/z 163, 165 (C_9H_4ClO, 37.09%, 19.32%); m/z 128 (C_9H_4O, 32.56%); m/z 101 (C_8H_5, 11.59%); m/z 67 (C_3HNO, 25.14%).
2_d	MS: m/z 273,275 ($C_{13}H_8ClN_3O_2$, 65.03%, 22.73%, M,M^{+2}); m/z 238 ($C_{13}H_8N_3O_2$, 15.41%); m/z 190, 192 ($C_{10}H_5ClNO$, 97.40%, 33.60%); m/z 163, 165 (C_9H_4ClO, 100%, 43% Base); m/z 129 (C_9H_5O, 10.91%); m/z 101(C_8H_5, 25.10 %); m/z 67 (C_3HNO, 31.77%)
2_e	MS: m/z 307, 309 ($C_{13}H_7Cl_2N_3O_2$, 40.09%, 25.30%, M,M^{+2}); m/z 124, 126, 128 ($C_{10}H_4Cl_2NO$, 100%, 65.70%, 7.91% Base); m/z 197, 199, 201($C_9H_3Cl_2O$, 49.94%, 19.02%, 9.95%); m/z 67 (C_3HNO, 29.53%).
2_f	MS: m/z 257 ($C_{13}H_8FN_3O_2$, 33.33%, M); m/z 174 ($C_{10}H_5FNO$, 100% Base); m/z 147 (C_9H_4FO, 56.21%); m/z 120 (C_8H_5F, 7.19%); m/z 67 (C_3HNO, 16.30%).
2_g	MS: m/z 269 ($C_{14}H_{11}N_3O_3$, 24.93 5, M); m/z 186 ($C_{11}H_8NO_2$, 100 5, Base); m/z 159 ($C_{10}H_7O_2$, 10.41%); m/z 67 (C_3HNO, 11.90%).
4_a	IR: 3197 (NH); 2251 (CN); 1706; 1756 (C=O)
	^{1}HNMR (DMSO-d_6): 1.22 (m, 7H, protons attached to C_2, C_3 and CH_3 in ester group); 1.63 (m, 4H, protons attached to C_1 and C_4): 3.70 (s, 1 H, proton attached to C_{10}); 4.18 (q, 2H, CH_2jn ester group); 4.71 (s, 1H, proton attached to C_6); 11.78 (s 1H, NH exchangeable by D_2O).
	MS: m/z 265, 264 ($C_{13}H_{16}N_2O_4$, 100% Base, M +H; 9.61%M); m/z 236 ($C_{11}H_{12}N_2O_4$ 3.34%); m/z 191 ($C_{10}H_{11}N_2O_2$, 27.61%); m/z 107 ($C_7H_9N_6$, 6.64%); m/z 67 (C_5H_7 3.47%).
4_b	IR: 3203 (NH); 2259 (CN); 1703, 1740 (C=O).
	^{1}HNMR (DMSO-d_6): 1.79 (m, 8H, protons of cyclopentane ring) 3.80 (s, 2H, protons attached to C_6 and C_{10}); 12.02 (s, 1H, NH exchangeable by D_2O).
	MS: m/z 217 ($C_{11}H_{11}N_3O_2$, 0.30%M); m/z 189 ($C_{10}H_{11}N_3O$, 1.32%); m/z 107 (C_7H_9N, 100% Base); m/z 67 (C_5H_7 78.15%); m/z 51 (C_4H_3 35.257%).
4_c	IR: 3276 (NH); 2254 (CN); 1716, 1740 (C=O).
	^{1}HNMR ($CDCl_3$): 1.31 (t, 7H, protons attached to C_7, C_{11} in cyclohexyl moiety and CH_3 in ester group); 1.60 (m, 4H, protons attached to C_8 and C_{10} in cyclohexyl moiety); 1.79 (m, 2H, protons attached to C_9 in cyclohexyl moiety); 4.09 (s, 1H, proton attached to C_5); 4.26 (q, 2H, CH_2 in ester group); 4.52 (s, 1H, proton attached to C_1); 8.46 (s, 1H, NH).
	MS: m/z 218 ($C_{14}H_{18}N_2O_4$, 2.93%M); m/z 233 ($C_{12}H_{13}N_2O_3$, 6.48%); m/z 205 ($C_{11}H_{13}N_2O_2$, 16.46%); m/z 121 (C_8H_{11}N, 33.53%); m/z 87 ($C_4H_7O_2$, 100% Base); m/z 67 (C_3HNO, 77.34%)
4_d	IR: 3206 (NH); 2251 (CN); 1718, 1730 (C=O).
	^{1}HNMR (DMSO-d_6): 1.41 (m, 4H, protons attached to C_7, and C_{11} in cyclohexyl moiety); 1.56 (m, 4H, protons attached to C_8 and C_{10} in cyclohexyl moiety); 1.69 (m, 2H, protons attached to C_9) C_{11} in cyclohexyl moiety); 4.85 (s, 2H, proton attached to C_1 and C_5); 12.12 (s, 1H, NH exchangeable by D_2O).
	MS: m/z 231 ($C_{12}H_{13}N_3O_2$, 0.35%M); m/z 163 ($C_9H_{11}N_2O$, 11.53%); m/z 121 ($C_8H_{11}N$, 100% Base); m/z 81 (C_6H_9 87047%); m/z 55 (C_4H_7 97%).
$5_{a,b}$	IR: 2245-2245 (CN); 1735-1677 (C=O).
5_a	MS: m/z 278 ($C_{14}H_{18}N_2O_4$, 0.25%M); m/z 264 ($C_{13}H_{16}N_2O_4$, 9.03%); m/z 232 ($C_{11}H_8N_2O_4$, 29.01%); m/z 107 (C_7H_9N 100% Base); m/z 77 (C_6H_5 99.91%).
5_c	IR: 2255 (CN); 1673, 1718 (C=O).
	^{1}HNMR ($CDCl_3$) 1.20 (t, 3H,-CH_2-CH_3); 1.60-2.20 (m, 8H, protons of cyclopentane ring); 3.60 (m, 4H, protons at C_6, C_{10} and CH_2 –CH_3).
5_{d-m}	IR: 2255 (CN); 1763-1680 (C=O); NH bands are absent.

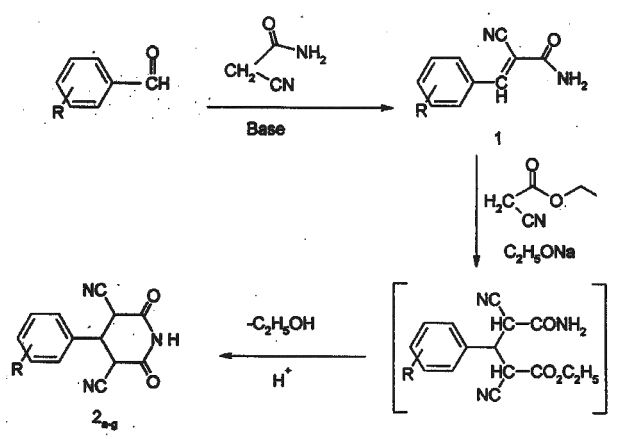
Table 7. continued

Compd.	Spectral data
5_e	MS: m/z 307, 306 ($C_{16}H_{22}N_2O_4$, 100% Base, M+H and 20.85 M); m/z 279 ($C_{14}H_{18}N_2O_4$, 6.62%); m/z 261 ($C_{14}H_{17}N_2O_3$, 14.09%); m/z 233 ($C_{12}H_{13}N_2O_3$ 30.59%); m/z 162 ($C_{10}H_{12}$ NO, 7.89%).
5_h	^{1}HNMR ($CDCl_3$) 1.25 (t, 7H, protons attached to C_7, C_{11} in cyclohexyl moiety and CH_3 in ester group); 1.44 (m, 4H, protons attached to C_8 and C_{10} in cyclohexyl moiety); 1.74 (m, 2H, 2H, protons attached to C_9 in cyclohexyl moiety); 4.15 (s, IH, Proton attached to C_5); 4.22 (q, 2H, CH_2 in ester group); 4.52 (s, 1H, proton attached to C_1); 5.00 (d,d, 2H, N-CH_2); 7.30 (m 5H aromatic protons).
5_i	MS: m/z 245 ($C_{13}H_{15}N_3O_2$, 0.29% M); m/z 148 ($C_9H_{10}NO$, 1.34%); m/z 121 ($C_8H_{11}N$, 15.92%); m/z 81 (C_6H_9 9.71%); m/z 77 (C_6H_5 9.07%); m/z 67 (C_5H_7, 100% Base); m/z 55 (C_4H_7, 9.33%)
5_j	^{1}HNMR ($CDCl_3$) 1.20 (t, 3H, CH_2-CH_3) 1.19 (m, 4H, protons attached to C_7 and C_{11} in cyclohexyl moiety); 1.57 (m, 4H, protons attached to C_8 and C_{10} in cyclohexyl moiety); 1.94 (m, 2H, protons attached to C_9 in cyclohexyl moiety); 3.90 (q, 2H, N-CH_2); 4.11 (s, 2H, proton attached to C_1 and C_5).

of major tranquilizers (Yao-Hua et al.,1972). These results indicate that the tested compounds possess some central depressant effect. Furthermore Stiz et al., (2000) demonstrated that some cyclic imides, including succinimides, maleimides, naphtalimides and related compounds, exhibited antinociceptive properties when tested against acetic acid-induced writhing in mice. From these data it is obvious that some of the newly synthesized compounds exhibited central depressant effects and are promising for treatment of epileptic seizures, insomnia and for the relief of pain.

Chemistry

In a recent work (Osman et al.,2003) prepared 4-aryl-2,6-piperidinedione derivatives by application of Michael addition of diethyl malonate to α-cyanocinnamides in presence of sodium ethoxide as a base catalyst. In the present investigation ethyl cyanoacetate was used as the Michael donnor while α-cyanocinnamides l_{a-g} (table 4) served as the Michael acceptor in presence of sodium ethoxide as the base catalyst to produce the target 2,6-piperidinedione derivatives 2_{a-g}, following the same reaction conditions reported earlier by Osman et al. 2003(Scheme 1).



2	R	2	R
a	H	e	2,4-diCI
b	3-Br	f	4-F
c	2-C1	g	4-OCH3
d	4-C1		

Scheme 1

Strcture of 2_{a-g} were confirmed by microanalytical and spectral data (IR, ^{1}HNMRand Ms) (Tables 5 and 7).

Experimentaly five α-cyanocinnamides I_{h-1} failed to act as the Michael acceptor and to react with ethyl cyanoacetate. This fact may be ascribed to the resonance electronic effects of the electron donating groups bearing unshared electron pairs in the o- or p-positions in benzene ring, which will decrease the electrophilic character of the carbon atom adjacent to the aromatic ring, thus inhibiting the ability of the nucleophilic carbon of the methylene group in ethyl cyanoacetate to attack the α,β-unsaturated-carboxamides 1_{h-1}.

1	h	I	j	k	l
2	2,3-OCH_3-	2,5-OCH_3-	3,4,5-OCH_3-	4-OH-	4-$N(CH_3)_2$-

The investigation has extended to the synthesis of spiro 2,6-piperidinediones 4_{a-d}. The latter have been synthesized by initial preparation of 2-cyano-cycloalkylidene – acetamides 3_{a-d}, which were cyc1ized with diethyl malonate or ethyl cyanoacetate in presence of sodium ethoxide.

Alkylation of 4_{a-d} produced the N-alkyl derivatives S_{a-m}, (scheme 2).

Structures 4_{a-d} and 5_{a-m} were confirmed by micro analytical and spectral data (IR, ^{1}HNMR and Ms (table 6 and 7).

References

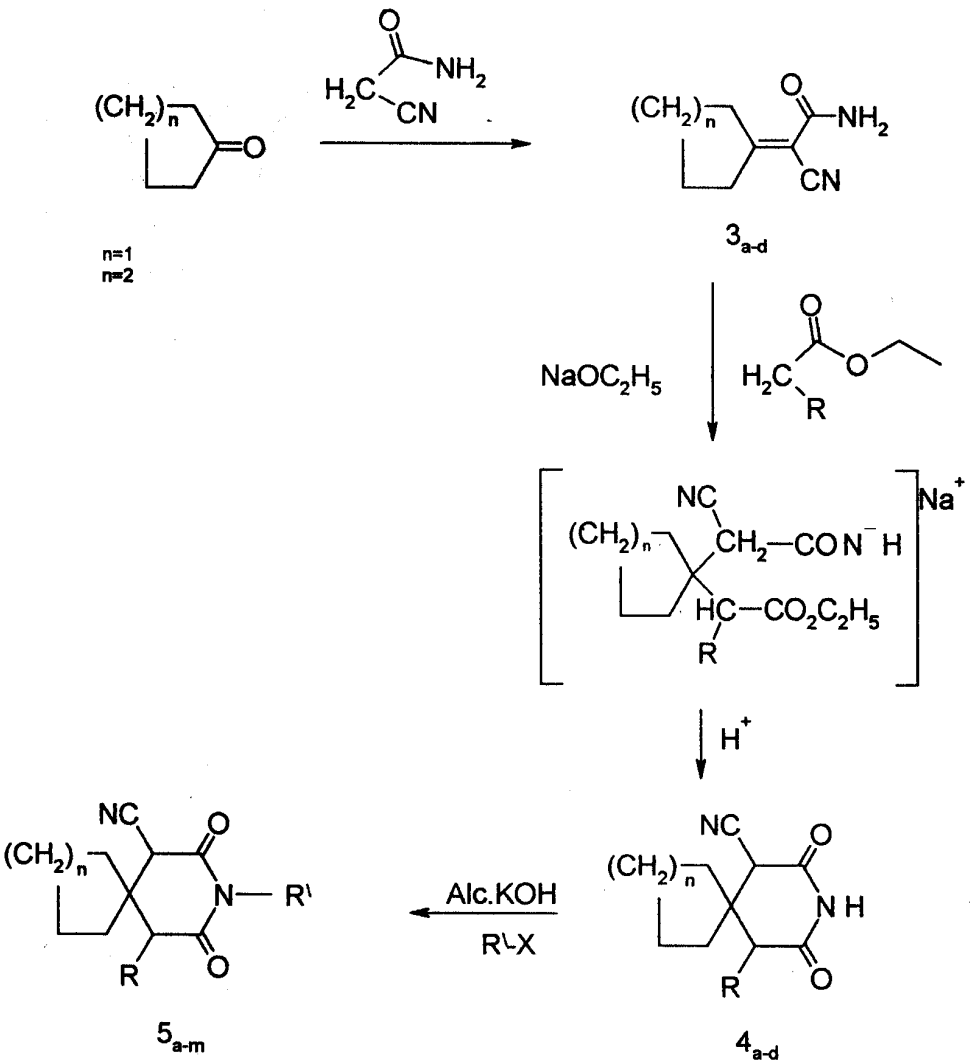
Charlier R., Prost M., Binon F and Deltour G. (1961): Pharmacology of an anti-1-phenethyl(-2-prepynyl)-4-propinoxypipridine acid glumarate. *Arch Intern Pharmacodynamic,* **134,** 306 .

Danuta M., Eliza F.and Zdzislaw K. (1975): Pharmacological properties of new derivatives of glutethimide. *Acta Pol. Pharm.,* **32(2),** 243 (1975); through *Chem. Abstr.,* **84,** 12451v.

Fischer L J. and Ambre J. J. (1976): Composition and methods for affecting sedation, (University of Iowa) U.S. 3,962,450 (Cl. 424–267; A61K31/445).

Foucaud P. A., Person H. and Robert A. (1964) : Preparation of B,B-disubstituted α-cyanoacylamides and spectroscopic investigation of their structure. *Bull. Soc. Chem. Fr.,* **8,** 1873–1876.

Jochheim K. A. and Gerberding 1. (1955): Anticonvulsive use of glutethimid. *Med. Monatsschr,* **9,** 808–811.



Compd.	n	R	R`	Comd.	n	R	R`
4_a	1	$-CO_2C_2H_5$	H	5f	2	$-CO_2C_2H_5$	$-C_3H_7(n)$
4_b	1	-CN	H	5g	2	$-C\ O_2C_2H_5$	$-C_4H_9(n)$
4_c	2	$-CO_2C_2H_5$	H	5h	2	$-C\ O_2C_2H_5$	$-CH_2$-Ph
4_d	2	-CN	H	5i	2	-CN	$-CH_3$
5_a	1	$-CO_2C_2H_5$	$-CH_3$	5j	2	-CN	$-C_2H_5$
5_b	1	$-CO_2C_2H_5$	$-C_3H_7(n)$	5k	2	-CN	$-C_3H_7(n)$
5_c	1	-CN	$-C_2H_5$	51	2	-CN	$-C_4H_9(n)$
5_d	2	$-CO_2C_2H_5$	$-CH_3$	5m	2	-CN	$-CH_2$-Ph
5_e	2	$-CO_2C_2H_5$	$-C_2H_5$				

Scheme 2

Kapure 1. N. and Saxena H. C (1972): Mathematical Statistics, S. Chand and Co Ltd., Ram Nagar, New Delhi.

Karli N., Gursoy A., Terzioglu U., Ozkirimli S., Ozer H. and Ekinci A.C. (1998): Synthesis and preliminary CNS depressant activity evaluation of new 3-[(3-substituted-5-methyl-4-thiazolidinon-2-ylidene)hydrazono]-1h-2-indolinones and 3-[(2-thioxo-3-substituted-4,5-imidazolidine-dion-1-ylimino]-1h-2-indolinones. *Arch. Pham. Pharm. Med. Chem.,* 254.

Karras J. W., Lindquist N. A., Camenisch D. R., Elam L., Hope N. ,Jencius M., Kaim M. and Kharas G. B. (1998): Novel copolymers of halogen ring substituted 2-cyano-3-phenyl-2-propenamides and styrene. *Pure Appl. Chem.,* **A35(2),** 395–400.

Manro M. R., Kanta C., Sharma R. C. and Kalsi P.S. (1995) : Reaction of active methylene compounds with 3,4,5-trimethoxybenzalanilines and antifungal activity of products, *J. Indian Counc.Chem.,* **11(1),** 35–38.

Marshall P. J. and ValIance D. K. (1954): Anticonvulsant activity derivatives of succinimide, glutarimide, thiazolidinedione methanol and miscellaneous compounds: *J. Pharm. and Pharmacol.,* **6,** 740 .

Osman A.N., Elgandy A., Kandel M.M, Ahmed E. M.and Abd Ellatif H.A. (2003): *Pul1. Fac. Pharm. Cairo University,* **41(1),** 51.

Richard G. R.,Greenwood T. D., Nwokogu G. C., Pisipati J. S., Rogers T G. and Wolfe J. F. (1990): Synthesis and anticonvulsant activity of 2-benzylglutarimides: *J. Med. Chem.,* **33(3),** 926 .

Rizzo M.,Morselli P.L. and Garattini S (1971): Further observation on the interaction between phenobarbitone and diphenylhydantoin drug,chronic treatment in the rat. *Biochem Pharmacol.,* **21:** 449–454.

Somers T. C. (1956): New analeptics and hypnotics related to the barbiturate antagonist,"Bemegride": *Nature,* **178,** 996.

Stiz D. S., Souza M. M.,Golin V. ,Neto R. A.S., Correa R., Nunes R. J., Ynnes R. A. and Cechinel-Filho, V. (2000): Antinociceptive properties N-aryl-glutaramic acid and N-aryl-glutarimides: *Pharmazie,* **55(12),** 942.

Tateoka Y, Kimura T, Kamiyama H, watanabe K, Yamamoto I. And HoIK (1988): Central effects of N-substituted derivativesof 2,6-dioxopiperidine in mice. *Res. Common Chem. Pathol Pharmacol,* **61(3),** 315–26.

Vogel A. I. (1956): Practical Organic Chemistry, Langmans, 3rd Edition, 434.

Wong M. G., Defina J. A. and Andrews P. R. (1986): Conformational analysis of clinically active anticonvulsant drugs: *J. Med. Chem.,* **29,** 562.

Yao-Hua Wu. Smiyh K. R. and Rayburn J W. (1969): Psychosedative agents N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides: *J. Med. Chem,* **12,** 876.

Yao-Hua Wu, Rayburn J.W., Allen L.E., Ferguson H.C. and Kisse J.W.(1972): Psychosedative8-(4-substituted1-piperazinyakyl)-8-azaspiro[4,5]decane-7,9diones. *J. Med, Chem,* **15,** 477.

Yuji T: Toshiyuki K., Hidehiro K., Kazuhito W., Ikuo Y. and Kang H. I. (1988): Central effect of N – substituted derivatives of 2,6-dloxopiperidine in mice. *Res. Commun. Chem. Pathol. Pharmacol.,* **61(3),** 315.