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DESIGN, SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF SOME N^2-SUBSTITUTED NALIDIXIC ACID HYDRAZIDES AND THEIR CYCLIZED ANALOGUES

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تم فى هذا البحث تحضير مجموعة من مشتقات هيدرازيد حمض النااليدكسيك وكذلك بعض نظيراتها التى تم فيها استبدال مجموعة الهيدرازيد بحلقة ٤،٣،١-أوكساديازول الخماسية بهدف اختبار فاعليتها كمضادات للاكتئاب وقد تم تحضير هذه المركبات من خلال تفاعل هيدرازيد حمض النااليدكسيك مع العديد من المركبات المحتوية على مجموعة الكربونيل من الالدهيدات والكيتونات الاليفاتية والعطرية ، أما مشتقات ٤،٣،١-اوكساديازول فقد تم تحضيرها بواسطة تفاعل الهيدرازيد مع مشتقات الايزوثيوسيانات لينتج مركبات الثيوكارباموبل هيدرازيدات الوسيطة. وبإجراء تفاعل نزع الكبريت الحلقى تتحول هذه الأخيرة إلى مركبات ٤،٣،١-اوكساديازول المطلوبة. وقد تم التحقق من التركيب البنائى ودرجة النقاوة للمركبات المحضرة بإستعمال وسائل عديد منها الرنين النووى المغناطيسى ومطياف الكتلة وكذلك التحليل الدقيق للعناصر المكونة.

تم أختبار فاعلية احدى عشر مركبا من المركبات المحضرة بالمقارنة مع عقار ايزوكاربوكسازيد كمضادات للاكتئاب فى الجرزان عند ثلاث جرعات مختلفة وذلك بقياس مقدرتها على تقليل فترة استسلام الجرزان عند وضعها فى حوض به كمية من الماء. وقد تبين أن سبعة مركبات بالإضافة إلى المركب الوسيط (هيدرازيد حمض النااليدكسيك) لها فاعلية واضحة بالمقارنة بمجموعة الجرزان التى لم تحقن إلا بالمذيب كما ثبت أيضا أن مشتق الاسيتوفينيلدين هيدرازيد حمض النااليدكسيك له فاعلية تكاد تكون متساوية مع المركب القياسى (ايزوكاربوكسازيد) وفى نفس الوقت أثبتت التجربة أن استبدال مجموعة الهيدرازيد بنظيرتها خماسية الحقلة (٤،٣،١-اوكساديازول) قد أدى إلى ضعف فاعلية المشتقات بدرجة كبيرة.

*A series of N^2-substituted nalidixic acid hydrazides **7-26** and some of their rigid analogues **29-31** in which the hydrazinocarbonyl moiety has been replaced by the corresponding 1,3,4-oxadiazole nucleus were synthesized as potential antidepressant agents. The preparation of the aforementioned compounds was achieved by reaction of nalidixic acid hydrazide **6** with the appropriate carbonyl compound or isothiocyanate derivative to afford the corresponding N-alkylidenes **7-11**; N-arylidenes **12-26** or the thiocarbamoylhydrazinocarbonyl derivatives **27** and **28** respectively. Cyclodesulfurization of the latter derivatives yielded the corresponding 5-substituted amino-1,3,4-oxadiazoles **29** and **30**. The unsubstituted 5-amino-1,3,4-oxadiazol-2-yl derivative **31** was synthesized by interaction of the hydrazide **6** with cyanogen bromide. The structures of the synthesized compounds were confirmed by IR-; ^{1}H-NMR and MS and their purity was assessed by TLC and elemental analyses.*

*Eleven of the synthesized compounds and isocarboxazide as a reference drug were tested at three dose levels (0.5; 1.0 and 1.5 mg/kg) for antidepressant activity in mice. Reduction in the duration of immobility in forced swimming test was taken as a measure for antidepressant activity. Seven of the tested substituted compounds and the unsubstituted hydrazide **6** exhibited highly significant difference from the control group at a dose level of 1.5 mg/kg. The acetophenonylidene derivative **18** showed antidepressant activity comparable to that of the reference drug. The rigid substituted hydrazide analogues represented by compound **29** were*

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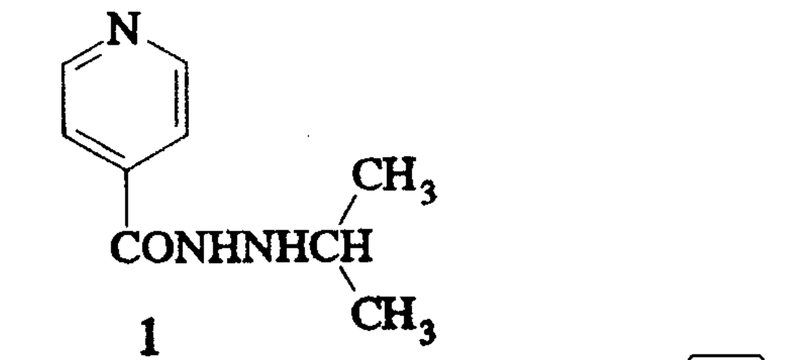
found to be inactive at the lower dose level and showed moderately significant difference than the control group at the higher dose level. This indicates that, cyclization of the hydrazide moiety to the corresponding 1,3,4-oxadiazole derivatives greatly reduced the antidepressant activity.

INTRODUCTION

Since the discovery that the antidepressant activity of iproniazide **1** is due to its high monoamine oxidase inhibition *in vivo*,[1] many compounds embodying amine or hydrazine moieties in their structure have been synthesized. The popularity of MAO inhibitors has diminished in the recent years due to some unpredictable and notorious side effects as hypertensive crises and hepatotoxicity.[2] In spite of these side effects, MAO inhibitors still have particular indications for their use in certain resistant or recurrent depressions.[3] Moreover, MAO inhibitors are devoid of addicting properties and their effects are dose dependent and cease immediately on interruption of treatment.[4] Consequently, the synthesis of new generations of more selective MAOIs with reversible, rapid onset of action and at the same time having greater therapeutic safety is still inquired.[5] Isocarboxazide **2**, is a well-known antidepressant agent of the MAOIs series, with less pronounced side effects.[6] Moreover, hydrazone derivative **3** has been reported as long acting brain MAO inhibitor *in vivo*.[7] Also, it is known that the nature of the heterocyclic residue present could increase the potency of the inhibitors[8] and often endow a hydrazine with a particular tissue specificity.[9,10]

The newly introduced generations of the quinolone antibacterials rendered their prototype, nalidixic acid, as an outdated chemotherapeutic agent. This prompted us to investigate additional possible pharmacological potentialities resulting from structural modification of nalidixic acid. The integrated 1,4-dihydronicotinoyl moiety rationalizes our objective on basis of its utility as a good carrier for the site-specific delivery of several drugs to the brain.[11-13] In this article we report the synthesis of some N-substituted hydrazides of nalidixic acid **7-26** and some of their cyclic analogues **29-31** to be tested for possible antidepressant activity as selective brain MAOIs.



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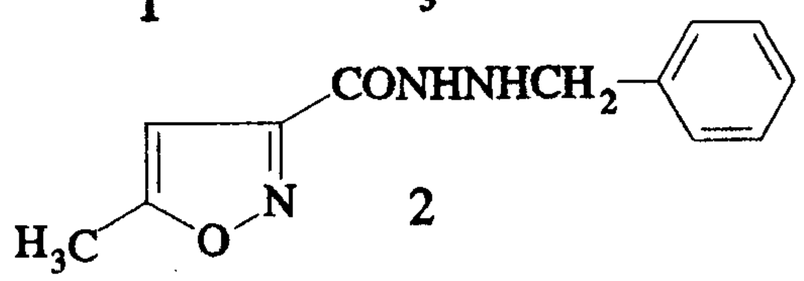

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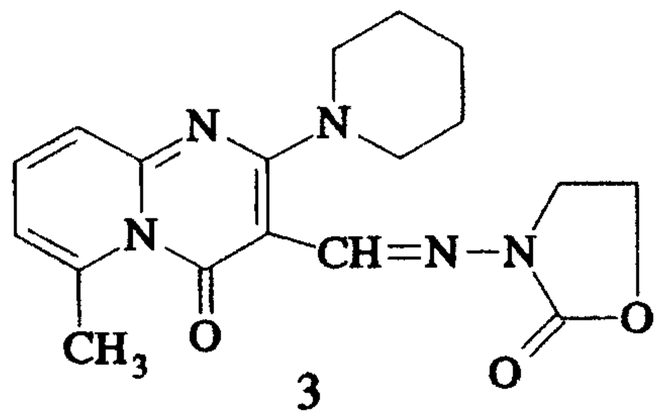

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EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infra red spectra were recorded as KBr compressed disks on a schimadzu IR 200-91527 spectrophotometer. The ^{1}H-NMR spectra were measured on Varian EM-60L NMR spectrometer (Varian, USA), TMS was used as internal standard and chemical shifts are expressed in δ (ppm). For TLC the DC-Alufolien 5554, kieselgel 60 F254 precoated plates were used (E. Merck, Darmstadt, Germany). Elemental analyses were carried out on a Perkin-Elmer 240 C elemental analyzer at Faculty of science, Assiut University. Nalidixic acid was offered by El-Nasr Chemical industry Co (Cairo/Egypt). Isocarboxazide was kindly supplied by the department of analytical chemistry, Faculty of Pharmacy, Assiut

University. All other chemicals, reagents and solvents are of reagent grades. The purity of the prepared compounds was monitored by thin layer chromatography.

3-(N-Alkylidenehydrazinocarbonyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-napthyridines (7-11)

The appropriate aliphatic aldehyde or ketone (0.01 mole) was added to a solution of nalidixic acid hydrazide (0.01 mole) in methanol (50 ml). After addition of few drops of glacial acetic acid the reaction mixture was heated on a steam bath for 4-10 hr. The solvent was removed under reduced pressure and the resulting product was filtered, dried and crystallized from a suitable solvent (Table 1).

3-(N-Arylidenehydrazinocarbonyl)-1-ethyl-1, 4-dihydro-7-methyl-4-oxo-1,8-naphthyridines (12-26)

Equimolar amounts of nalidixic acid hydrazide (0.01 mole) and the appropriate aromatic aldehyde or ketone (0.01 mole) were refluxed in 50 ml dioxan until the hydrazide completely disappeared as monitored by TLC (eluent: chloroform : acetone 1:1). The solvent was removed under reduced pressure and the product that precipitated on cooling was separated and recrystallized from the appropriate solvent (Table 1), or purified by column chromatography.

3-(N-Substituted-thiocarbamoylhydrazino-carbonyl)-1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine (27,28)

Equimolar quantities of nalidixic acid hydrazide (0.01 mole) and the appropriate isothiocyanate (0.01 mole) were heated under reflux in ethanol (50 ml) for two hours. The solvent was then removed under reduced pressure and the separated crystalline product was crystallized from the appropriate solvent (Table 2).

3-(5-Substituted-amino-1,3,4-oxadiazol-2-yl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine (29,30)

To an ice cooled stirred solution of the appropriate thiocarbamoylhydrazinocarbonyl derivative (0.01 mole) in ethanol (100 ml) was added dropwise 2N sodium hydroxide solution until the mixture acquired pH = 9. Aqueous iodine solution in KI (5%) was added dropwise with stirring at room temperature until the yellow color of iodine persisted. The solvent was then removed under reduced pressure and the resulting aqueous suspension was cooled and neutralized with 10% acetic acid. The precipitated product was filtered triturated with 5% aqueous sodium thiosuphate solution, washed with water, dried and crystallized from the proper solvent (Table 2).

3-(5-Amino-1,3,4-oxadiazol-2-yl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine (31)

To a solution of nalidixic acid hydrazide (0.01 mole) in dioxan (20 ml), cyanogen bromide (0.93 g, 0.008 mole) and aqueous sodium hydrogen carbonate (15 ml; 10% solution) were added. The reaction mixture was stirred for two hours at room temperature and the precipitated product was filtered, washed with methanol, dried and crystallized from ethanol/DMF.

Measurement of immobility

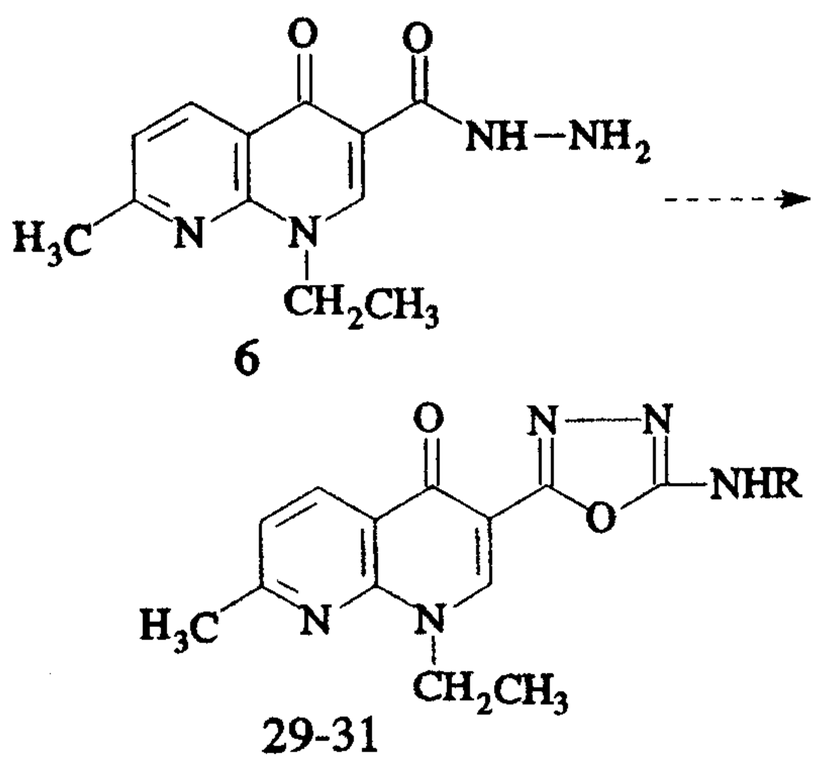
Groups of 6 mice weighing 20-25 g were used in the present study. Compounds were injected ip as suspensions in 0.5% sodium carboxymethyl cellulose solution at three dose levels ; 0.5, 1.0 and 1.5 mg/kg. The control group received only the vehicle. Isocarboxazide was used as reference and treated under the same dosage schedule.

Mice were individually placed in vertical glass cylinders (height 40 cm, diameter 10 cm) containing water (15 cm height) at 25°C. In the first day the mice were placed in water for 15 min, removed and then allowed to dry for 15 min in a 30°C drying room before being returned to their home cages. The next day, they were again put into the cylinder for 10 min after 45 min from drug administration and the total duration of immobility was measured. The mice were judged to be immobile whenever it remained floating in water, in an upright position, showing only the small amount of movement necessary to keep its head above water.

RESULTS AND DISCUSSION

Chemistry

The N-alkylidene or arylidene derivatives of nalidixic acid hydrazide **7-26** were synthesized as outlined in Scheme 1 by treatment of the latter with the appropriate aldehyde or ketone. The key intermediate, nalidixic acid hydrazide **6** was obtained in good yield by refluxing the corresponding methyl ester[14] with hydrazine hydrate in methanol. Physical constants, yields and elemental analyses of the N-substituted hydrazides **7-26** are listed in Table 1. In a trial to investigate the role of the hydrazide moiety in the observed antidepressant activity, it has been replaced by the rigid five membered structure of 1,3,4-oxadiazole ring. For synthesis of representative examples of this series, the hydrazide **6** was allowed to interact with isothiocyanate derivatives to give the corresponding thiocarbamoyl hydrazinocarbonyl derivatives **27** and **28**. Cyclization of the latter derivatives using iodine[15] at pH = 9 affords the 5-N-substituted-1,3,4-oxadiazole derivatives **29** and **30**. The unsusbtituted 5-amino analogue **31** was prepared by the interaction of the key intermediate **6** with cyanogen bromide in dioxan in presence of sodium hydrogen carbonate.[16] Table 2 summerizes the physical constants and elemental analyses of the compounds **27-31**.

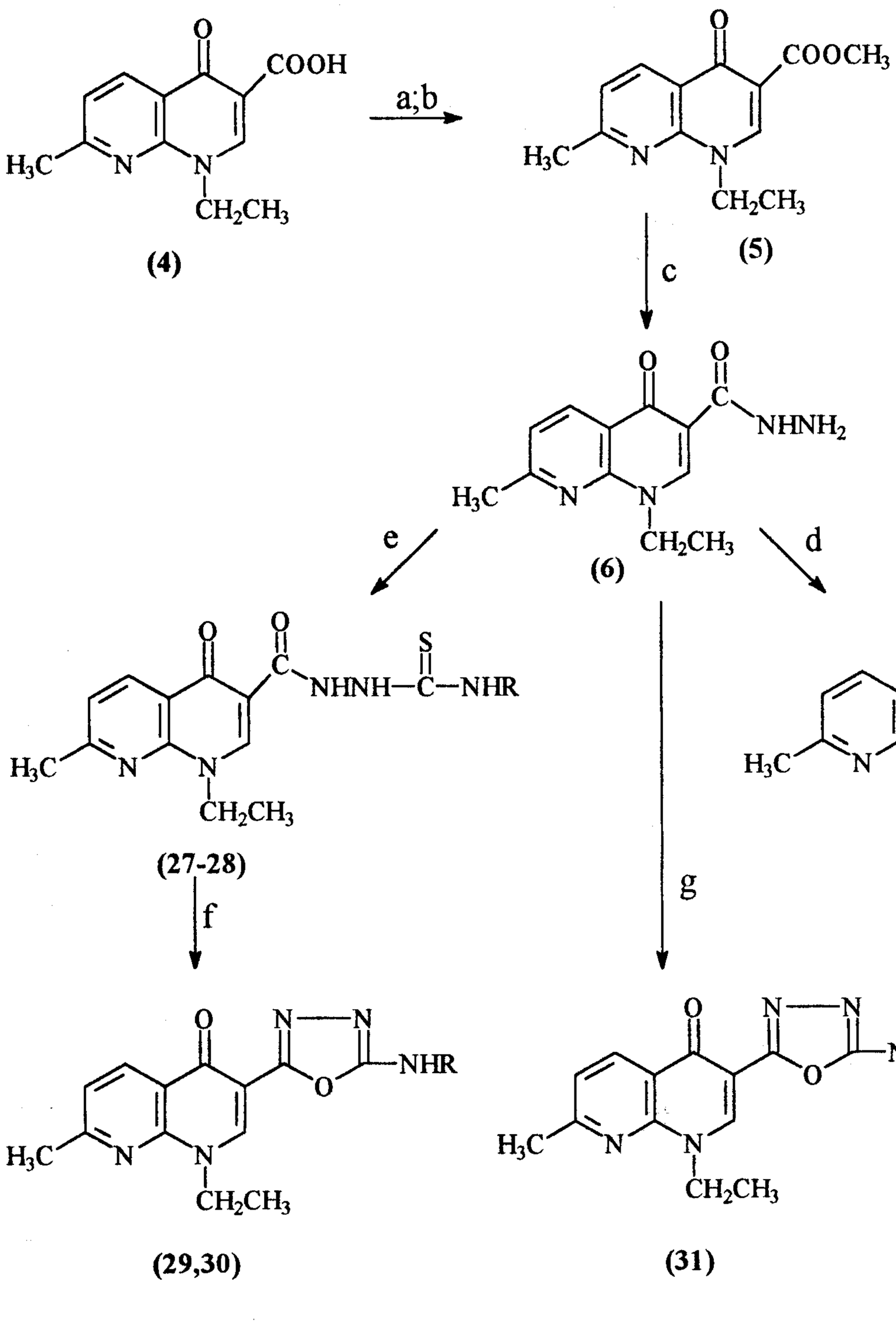


The structures of the synthesized derivatives were confirmed by IR-, ^{1}H-NMR. and mass spectra. The IR spectra showed the characteristic bands at 3200-3325 cm^{-1} (N-H str.), 1640-1670 cm^{-1} (amide I), 1585-1570 cm^{-1} (amide II), 1585-1600 and 1500-1510 cm^{-1}, (C=N-). In the ^{1}H-NMR spectra the signals corresponding to protons of the 1,4-dihydro-1,8-naphthyridine nucleus are not significantly affected by the type of the substituent on the hydrazide moiety and appeared at chemical shifts: $\delta \approx 7.2$ (1H, d, J = 5 Hz, H-6); 8.1- 9.1 (1H, s, H-2) and 8.5 (1H, d, J = 5 Hz, H-5). Similarly, the singlet characteristic for the C-7-CH_3- group at $\delta = 2.6$ ppm as well as the triplet-quartet system of the N^1-CH_2CH_3 appeared approximately at the same chemical shifts as in the spectrum of the parent compound at $\delta \approx 1.6$ and 4.6 ppm. In addition, the hydrazide moiety revealed characteristic bands at chemical shifts of $\delta = 4.1$ ppm for CONHN$\underline{H}_2$ and 10.5 for CON$\underline{H}$NH$_2$. Additional ^{1}H-NMR data of the alkylidene; arylidene as well as the thiocarbamoylhydrazinocarbonyl moieties for each of the synthesized derivatives are listed in Table 3.

It is noteworthy, that the formylidene protons in compound **7** appeared as a pair of doublets at $\delta = 6.8$ and 7.2 ppm. In such cases restricted rotation due to the C=N of the hydrazone moiety renders the two protons magnetically non equivalent and exhibited a geminal coupling of about 16 Hz.[17] The signals of α-hydrogens for the hydrazones derived from aliphatic aldehydes appeared at chemical shifts of $\delta \approx 5.9$-6.8, whereas those of the aromatic aldehydes are downfield shifted due to ring anisotropy to $\delta \approx 8.1$-8.6 ppm.

The mass spectra of the propylidene derivative **9**; 4-dimethylaminobenzylidene derivative **15** and 2-thienylidene derivative **26** showed signals characteristic for the molecular ion peaks at m/e; 286.1; 377.2 and 340.1 respectively. In addition several peaks characteristic for the naphthyridine fragmentation pattern were also identified.[18]

Scheme 1:



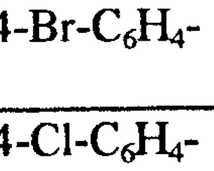
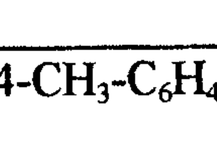
a: $ClCOOCH_2CH_3$; TEA; CH_2Cl_2; 0°C b: CH_3OH, c: $NH_2NH_2.H_2O$, CH_3OH

d: R_1COR_2, ethanol or dioxan e: RNCS, ethanol f: I_2/NaOH

g: CNBr, $NaHCO_3$ (10%), ethanol

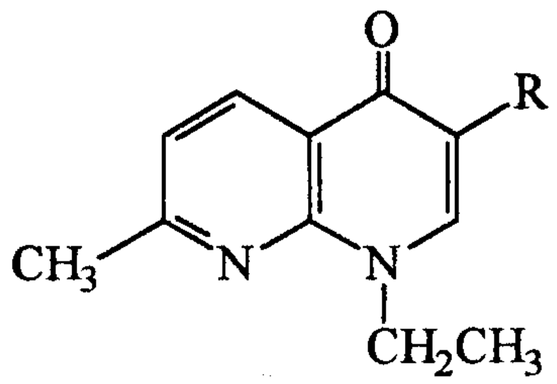
R_1, R_2: Table 1; R: Table 2

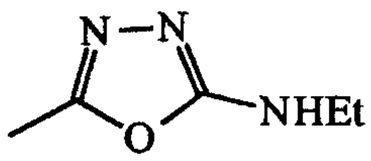
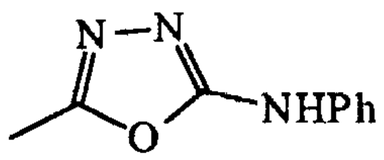
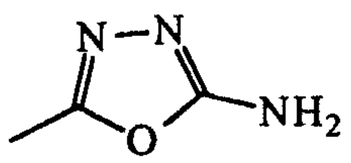
Table 1: Physical constants, Yields and Elemental analysis of The 3-(N-Substituted hydrazino-carbonyl)-1-ethyly-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridines (7-26).

NO.	R1	R2	yield (%)	MP* [°C]	Mol. formula (MW)	Anal. % ; calc / found C	H	N
7	H	H	70	250-1 (a)	$C_{13}H_{14}N_4O_2$ (258.11)	60.44 60.00	5.47 5.25	21.70 21.50
8	H	CH_3	81	220-2 (b)	$C_{14}H_{16}N_4O_2$ (272.13)	61.74 61.35	5.93 5.90	20.58 20.80
9	H	CH_3CH_2-	41	235-7 (b)	$C_{15}H_{18}N_4O_2$ (286.14)	62.91 62.57	6.34 6.65	19.57 19.28
10	CH_3	CH_3	95	250-1 (c)	$C_{15}H_{18}N_4O_2$ (286.14)	62.91 62.71	6.34 6.19	19.57 19.60
11	CH_3	-$CH_2CH(CH_3)_2$	58	196-8 (a)	$C_{18}H_{24}N_4O_2$ (328.59)	65.79 65.55	7.36 7.50	17.05 17.30
12	H	C_6H_5-	71	245-7 (d)	$C_{19}H_{18}N_4O_2$ (334.14)	68.23 68.00	5.43 5.76	16.76 16.36
13	H	4-Cl-C_6H_4-	67	212-3 (d)	$C_{19}H_{17}ClN_4O_2$ (368.10)	61.94 62.00	4.65 4.60	15.22 14.80
14	H	4-O_2N-C_6H_4-	66	345-7 (d)	$C_{19}H_{17}N_5O_4$ (379.13)	60.15 60.00	4.49 4.50	18.46 18.85
15	H	4-$(CH_3)_2N$-C_6H_4-	66	294-5 (e)	$C_{21}H_{23}N_5O_2$ (377.19)	66.81 66.68	6.15 6.40	18.56 18.47
16	H	4-CH_3O-C_6H_4-	80	258-60 (e)	$C_{20}H_{19}N_4O_3$ (363.51)	66.11 65.88	5.26 6.16	15.41 14.96
17	H	4-(OH)-3-(CH_3O)-C_6H_3-	89	250-2 (e)	$C_{20}H_{20}N_4O_4$ (380.14)	63.13 63.12	5.30 5.24	14.73 14.99
18	CH_3	C_6H_5-	65	287- 9 (d)	$C_{20}H_{20}N_4O_2$ (348.16)	68.93 68.72	5.79 5.75	16.09 15.81
19	CH_3	4-Br-C_6H_4-	61	339-41 (e)	$C_{20}H_{19}BrN_4O_2$ (426.07)	56.23 56.57	4.48 4.43	13.11 12.80
20	CH_3	4-Cl-C_6H_4-	87	234-5 (f)	$C_{20}H_{19}ClN_4O_2$ (382.11)	62.81 62.70	5.01 5.24	14.66 14.34
21	CH_3	4-CH_3-C_6H_4-	55	234-6 (e)	$C_{21}H_{22}N_4O_2$ (362.17)	69.58 69.90	6.01 5.90	15.47 15.67
22	CH_3	4-OH-C_6H_4-	59	334-6 (d)	$C_{20}H_{20}N_4O_3$ (364.51)	65.91 65.67	5.54 5.60	15.38 14.98
23	CH_3	4-CH_3O-C_6H_4-	58	307-9 (e)	$C_{21}H_{22}N_2O_3$ (378.17)	66.64 66.70	5.86 5.80	14.81 14.70
24	C_6H_5	C_6H_5-	25	287-8 (g)	$C_{25}H_{22}N_4O_2$ (410.48)	73.14 73.21	5.41 5.50	13.66 13.60
25	H		78	234-6 (e)	$C_{17}H_{16}N_4O_3$ (324.12)	62.95 63.65	4.97 5.00	17.28 17.50
26	H		71	224-6 (e)	$C_{17}H_{16}N_4O_2S$ (340.43)	59.98 59.92	4.74 4.71	16.47 16.32

* crystallization solvent: a = aq. methanol; b = aq. ethanol; c = methanol; d = dioxan; e = ethanol/chloroform, f = chloroform, g = ethanol.

Table 2: Physical constants, Yields and Elemental Analysis of the compounds 27-31.



NO	R	yield (%)	M.P* [°C]	Mol. formula (M.W.)	Anal. %; calc/ found C	H	N
27	CONHNHCSNHEt	70	245-7 (a)	$C_{15}H_{19}N_5O_2S$ (333.13)	54.03 54.17	5.75 5.78	21.02 21.31
28	CONHNHCSNHPh	74	295-7 (b)	$C_{19}H_{19}N_5O_2S$ (381.13)	59.82 59.36	5.02 5.35	18.37 18.16
29		25	189-90 (c)	$C_{15}H_{17}N_5O_2$ (299.14)	60.17 60.49	5.73 5.80	23.41 23.73
30		50	249-50 (a)	$C_{19}H_{17}N_5O_2$ (347.14)	65.68 65.60	4.54 5.18	20.17 20.11
31		65	290-2 (d)	$C_{13}H_{13}N_5O_2$ (271.10)	57.54 57.40	4.83 4.75	25.83 25.90

* crystallization solvent: a = methanol; b = dioxan/methanol; c = ethanol /ethylacetate;
d =. ethanol/DMF

Table 3: ^{1}H-NMR data for the synthesized compounds (7-31).

Comp.	δ ppm; in $CDCl_3$; (R; R^1 and R^2)
7	6.8 (1H, d, J = 18Hz, N=C-H); 7.2(1H, d, J = 18Hz, N=C-H); 13.0(bs, 1H, -NH)
9	1.1(3H, t, J = 8 Hz, $-CH_2C\underline{H}_3$), 2.1(2H, m, N=C-$C\underline{H}_2CH_3$); 5.9(1H, t, J = 8 Hz, N=C<u>H</u>); 12.8(1H, bs, -NH)
10	2.0 (3H, s, $-C\underline{H}_3$); 2.05(3H, s, $-C\underline{H}_3$); 12.5(bs, 1H, -NH)
12	8.2(1H, s, N=C<u>H</u>); 7.2(6H, m, phenyl-H + naphthyridine C 6-<u>H</u>); 10.0(1H, bs, -NH)
13*	8.3(1H, s, N=C<u>H</u>); 7.2(2H, d, J = 7Hz, C2`-H, C6`-<u>H</u>); 7.7(2H, d, J = 7Hz, C3`-H, C5`-H)
14*	8.6(1H, s, N=C<u>H</u>); 8.1(2H, d, J = 9Hz, C2`-H, C6`-<u>H</u>); 8.5(2H, d, J = 9 Hz ,C3`-H, C5`-<u>H</u>)
15	8.1(1H, s, N=C<u>H</u>)); 3.0(6H, s, N[($C\underline{H}_3$)$_2$], 6.7(2H, d, J = 9Hz, C3`-H, C5`-<u>H</u>); 7.7(2H, d, J = Hz ,C2`,6-<u>H</u>); 13.0(1H, bs, -NH)
16	8.3(1H, s, NC<u>H</u>); 3.8(3H, s, $-OC\underline{H}_3$); 6.8(2H, d, J = 10Hz, C3-H, C5`-<u>H</u>); 7.7(2H, d, J = 10 Hz , C2`-H, C6`-<u>H</u>); 13.0(1H,bs, -NH)
17*	8.2(1H, s, N=C<u>H</u>); 3.8(3H, s, $-OC\underline{H}_3$), 6.8(1H, d, J = 9 Hz, C6`-<u>H</u>), 7.1(1H, d, J = 10 Hz, C5`<u>H</u>); 7.2(1H, d, J = 3Hz, C2′-H)
18	2.4(3H, s, N=C- $C\underline{H}_3$); 7.3(4H, m, naphthyridine-C6-<u>H</u> + phenyl-C-3`,4`,5`-<u>H</u>); 7.95 (2H, m, C-2`, 6`<u>H</u>).
19*	3.1(3H, s, N=C-$C\underline{H}_3$); 7.8(5H, bs, phenyl-H + naphthyridine-C-6-<u>H</u>)
21*	3.1(3H, s, N=C-$C\underline{H}_3$); 2.7(3H, s, p-tolyl-$C\underline{H}_3$); 7.8(4H, m, phenyl-<u>H</u>)
22*	3.1(3H, s, N=C-CH_3); 7.9(2H, d, J = 6Hz ,C2`-H, C6`-<u>H</u>); 8.2(2H, d, J = 7Hz, C3`-H, C5`-<u>H</u>).
23	2.4(3H, s, N=C-$C\underline{H}_3$); 3.8(3H, s, $-OCH_3$), 7.2(3H, m, phenyl-3`, 5`-H + naphthyridine-C6-H) 7.8(2H, d, J = 9Hz, C2`-H, C6`-<u>H</u>); 13.0(1H,bs, -NH)
24	7.3(11H, m, diphenyl-H + naphthyridine-C6-H); 12.7(1H,bs, -NH).
25	8.1(1H, s, N=C<u>H</u>); 6.5(1H, m, C3`-<u>H</u>), 6.9(1H, d. J = 3Hz, H-4′); 7.5(1H, d, J = 3Hz, H-2′).
26	7.3(3H, m, C2`, 3`,4` <u>H</u>); 8.6(1H, s, N=C<u>H</u>); 12.1(1H,bs, -NH)
27	1.4(3H, t, $-CH_2C\underline{H}_3$); 3.6(2H, q, -NHC$\underline{H}_2CH_3$); 10.1(1H, bs, -N<u>H</u>CS); 12.0(1H, bs, CON<u>H</u>)
28	7.5(6H, m, <u>phenyl protons</u> +C-6<u>H</u>); 9.8(1H, s ,-CSN<u>H</u>-); 10.1(1H, bs, -N<u>H</u>CS); 12.0(1H, bs, CON<u>H</u>-).
31	7.0(2H, bs, $-NH_2$)

Solvent: $CDCl_3$; * : TFA; s = singlet; d = doublet; t = triplet; q = quartet ; m = multiplett; bs = broad singlet

Table 4: Effect of the tested compounds and isocarboxazide on the duration of immobility of mice in forced swimming test.

Comp.	Duration of immobility (sec.); dose (mg/kg).		
	0.5	1.0	1.5
6	294.17 ± 20.5**	203.00 ±15.4 ***	178.33 ±25.7***
10	415.00 ± 10.8	225.83±16.9***	180.00 ±21.3***
12	394.00 ± 16.4	189.83 ±8.93 ***	174.47±10.4 ***
14	353.17 ±24.5	275.00 ±10.2 ***	230.83 ±21.1 ***
15	336.33 ± 5.7**	358.17 ±5.24 **	342.50±10.3 **
18	180.83 ±13.1***	85.33 ±12.6 ***	57.50 ±8.34 ***
19	378.17 ±12.9	375.83 ±14.00	367.5 ±11.5
23	335.83±8.98***	291.00 ±6.72 ***	275.83 ±9.44 ***
24	350.83 ±8.41*	281.33 ±10.6 ***	257.5 ±9.98 ***
25	358.33 ±11.7	319.00±31.3	255.83±33.7 **
29	400.67 ± 14	348.33 ±7.03**	333.33 ±9.37**
R.	55.00 ± 7.42 ***	50.00 ± 6.63 ***	40.00 ± 6.45 ***
C.	399.13 ±7.42	393.33 ±10.2	388.33 ±10.1

Compounds were intraperitoneally injected 45 min before the behavioral despair test. Results expressed as the duration of immobility in seconds within 10 min (mean ± S.E.). Significance of difference from the control using two tailed student's t-test;
* : $p< 0.05$; **: $p < 0.01$; ***: $P< 0.001$ R: reference drug; isocarboxazide; C: control.

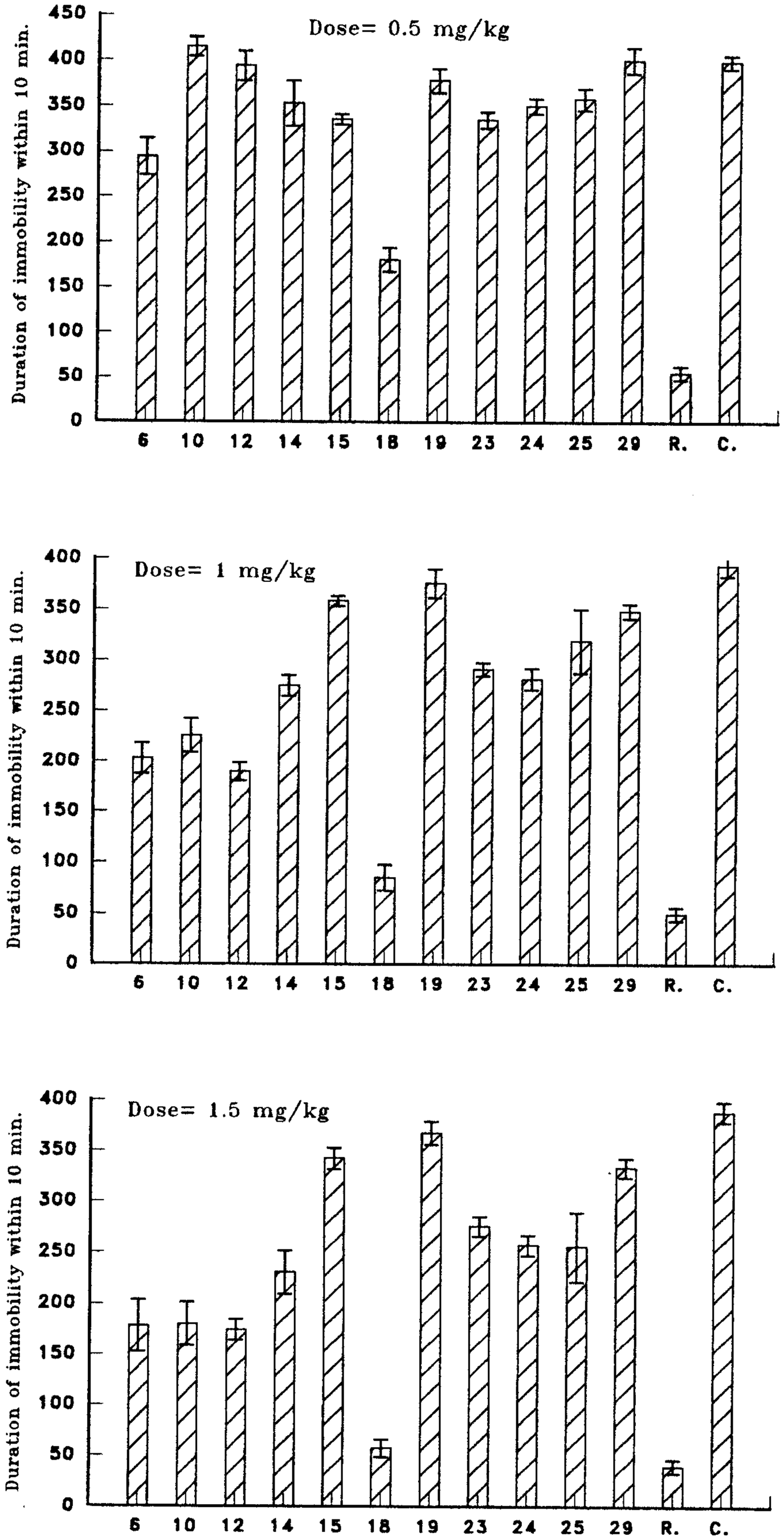


Fig. 1: Histogram showing the relationship between the dose and the reduction of the duration of immobility in mice using forced swimming test (mean ± S.E.).

Antidepressant activity

The behavioral despair test devised by Porsolt *et al.*[19-21] was applied for determination of the potential antidepressant activity of some of the synthesized hydrazones and oxadiazole derivatives. Depression state was induced by forcing mice to swim in a narrow cylinder from which they could not escape. After a brief period of vigorous activity, the animals adapted a characteristic immobile posture that was readily identifiable. The duration of immobility was reduced by the typical and atypical antidepressants.[22]

In the present work we adopted the recommendation of Kitada *et al.*,[23] whereby the duration of immobility only during the first 5-10 min of the 30 min test was considered as a measure for antidepressant activity. Reduction in duration of immobility of mice was measured 45 min after ip. injection of the tested compounds as well as isocarboxazide at three dose levels of 0.5; 1.0; and 1.5 mg/kg. The control group received equivalent amount of the vehicle. The data obtained were statistically analyzed for the significance of difference from the control groups using the two tailed student's-t test. The results are listed in Table 4 and illustrated in Fig. 1.

Generally all the tested compounds exhibited lower potency at the studied dose levels than the reference drug, isocarboxazide. The acetophenonylidene derivative 18 was found to be the most active of the series. Moreover it is nearly equipotent with the reference drug at a dose level of 1.5 mg/kg. Several other compounds showed variable significant reduction in the duration of immobility of mice specially at higher dose level. It is noteworthy that cyclization of the hydrazide moiety results in loss of the observed activity as illustrated by the oxadiazole derivative **29**. On the other hand, the electronic properties of the substituents on the phenyl moiety of the arylidene series **14**; **15**; **19** and **23** did not significantly affect the observed antidepressant activity. In contrary, The unsubstitued analogues **12** and **18** exhibited higher degree of reduction of the duration of immobility. This might be attributed to a steric rather than electronic requirements for the activity and needs further investigations. The results in Table 4 and Fig. 2 revealed that the tested compounds exhibited a dose-dependent activity.

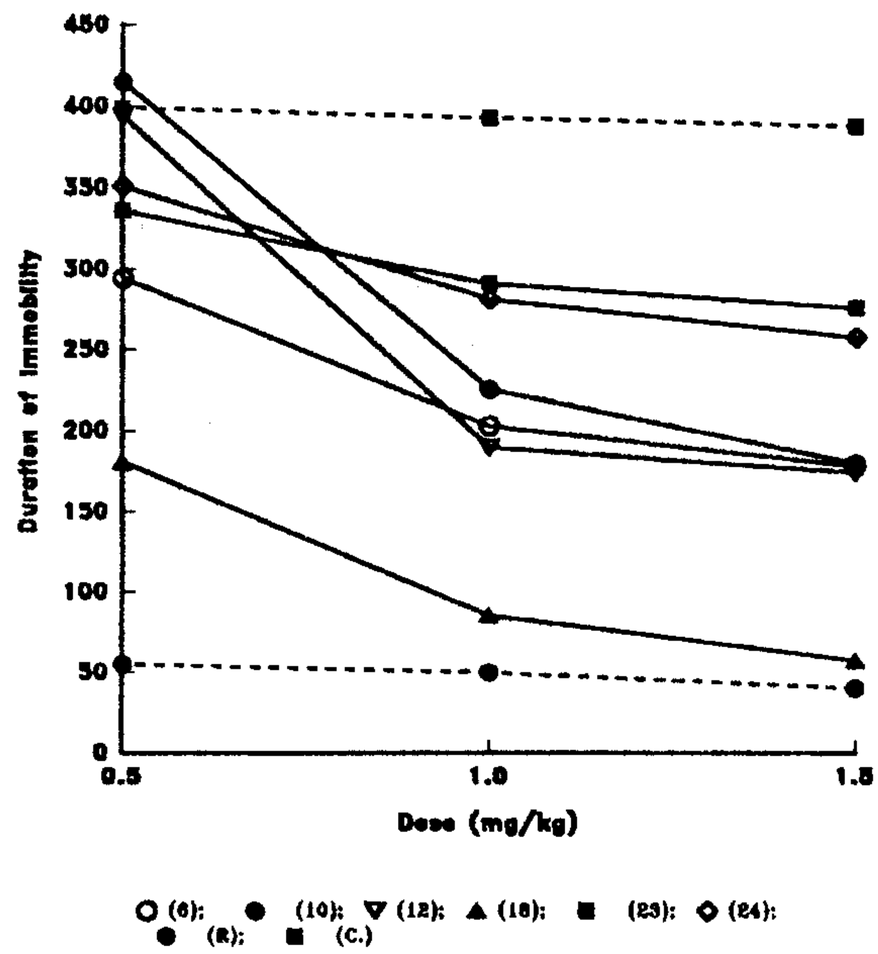


Fig. 2: Dose response curve of the tested compounds in comparison with isocarboxazide.

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