Studies on Some 3(2*H*)-Pyridazinone Derivatives with Antinociceptive Activity

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Key Words *: 3(2H)-Pyridazinone; antinociceptive activity; molecular connectivity*

Summary

Nineteen new [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]-acetamide (**1–10**) and 3-[6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]propanamide (**11–19**) derivatives have been synthesized in this study. The structures of the compounds have been elucidated by their IR and NMR spectral data and elemental analysis. Antinociceptive activity of the compounds has been investigated by modified Koster's Test in mice, using aspirin as a reference. All the compounds (at 100 mg/kg dose) except **1** and **9** have been found more potent than aspirin. Compound **6** in the group of acetamide derivatives and compound **15** in the group of propanamides exhibited the highest antinociceptive activity. In addition, the propanamides have generally been found more potent than acetamides. In addition to these studies, the quantitative relationships between some structural parameters (such as log *P*, parachor, molar refractivity, and molecular connectivity indices) and antinociceptive activity of the compounds have been investigated. Statistical regression analysis has shown a close relationship to exist between the first-order molecular connectivity index ($^1\chi$) and the antinociceptive activity.

Introduction

Commonly used nonsteroidal antiinflammatory drugs (NSAIDs) have significant side effects such as gastrointestinal disorders and kidney damage. Therefore, the design of new compounds with analgesic activity has attracted the attention of medicinal chemists. As a result, there are many studies in progress on analgesic-antiinflammatory compounds.

It was previously reported that various derivatives of 2-benzoxazolinone, 2-benzothiazolinone, and oxazolopyridinone show significant analgesic activity[1–5]. A common characteristic of these compounds is the *N*-substituted lactam functional group. Another heterocyclic moiety which has this functional group is the pyridazinone ring system. Many authors previously reported that benzoxazolinone, oxazolopyridinone, and pyridazinone derivatives bearing an arylpiperazine moiety at the side chain on the lactam nitrogen of the rings have significant analgesic activity, and stressed the significance of this structural feature[1,5,6]. In addition, some authors claimed that these compounds exhibit better analgesic activity if they have a three carbon chain between the nitrogen of the lactam and the amine component on the side chain [5,6].

We have recently synthesized several benzoxazolinones and benzothiazolinones carrying acetamide moieties at position 3. We previously reported that *N*-[2-(4-methylpyridinyl)]-2-[2(3*H*)-benzazolone-3-yl]acetamide and 4-[2-(6-benzoyl-2-benzoxazolone-3-yl)acetyl]morpholine had significant antinociceptive activity in comparison with the others compounds synthesized[7,8]. In addition, we found that 3-[3-(4-phenylpiperazine-1-yl)propyl)]-2(3*H*)-benzothiazolone was more active as antinociceptive than the other synthesized compounds [9].

In addition, various compounds incorporating a 3(2*H*)-pyridazinone ring have been synthesized and their pharmacological activities have been reported[10–12]. Recently it was reported that a considerable number of 3(2*H*)-pyridazinone derivatives have analgesic activity [6,13–18]. Among these compounds, one of the 3(2*H*)-pyridazinone derivatives, 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (emorfazone) is a well-known analgesic and antiinflammatory agent (Figure 1) [13,14].

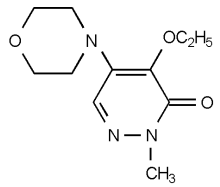

Figure 1. Emorfazone.

Dal Piaz et al. subsequently synthesized 4-amino-2-methyl-6-phenyl-5-vinyl-3(2*H*)-pyridazinone and discovered that this compound is almost seven-fold more potent than emorfazone[15]. Rohet and co-workers also synthesized some 4,6-diphenyl-2-[3-(4-arylpiperazin-1-yl)propyl]-3(2*H*)-pyridazinone derivatives and showed that these compounds have trazodone-like analgesic activity[6]. Santagati and co-workers claimed that 2-substituted 4,5-dihalo-3(2*H*)-pyridazinone derivatives have high analgesic activity. Additionally, all the compounds that they synthesized exhibited almost no ulcerogenic side effect[16]. Rubat and co-workers stated that *N*-substituted 5-benzylidene-6-methyl-3-pyridazinone derivatives also show analgesic activity[17,18].

Consequently we have decided to change the heterocyclic core of the compounds synthesized in our laboratory. Therefore, the 3(2*H*)-pyridazinone ring has been chosen and 3(2*H*)-pyridazinone derivatives carrying acetamide and propanamide moieties at position 2 of the pyridazinone ring have been synthesized.

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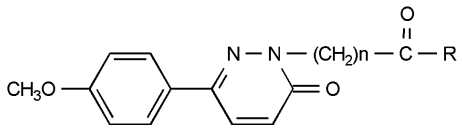


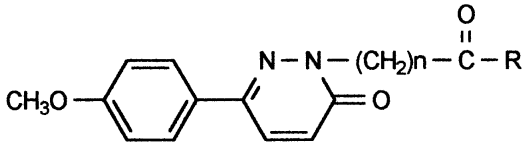
R = piperazines, piperidines

Figure 2. The chemical structure of the compounds synthesized.

The general structure of the compounds synthesized is shown in Figure 2.

In addition, the quantitative relationships between some physicochemical parameters (such as log *P*, parachor, molar refractivity, and molecular connectivity indices) and antinociceptive activity of the compounds have been investigated. A good relationship has been found between the first-order molecular connectivity index ($^1\chi$) and antinociceptive activity by performing statistical regression analysis.

Table 1. Physical and chemical data of the compounds **1–19**.



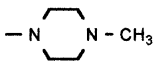
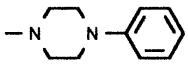
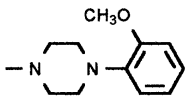
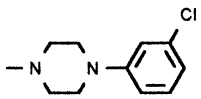
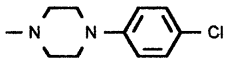
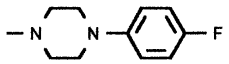
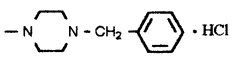
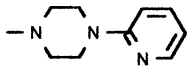
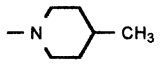
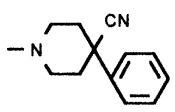
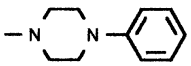
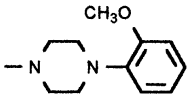
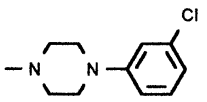
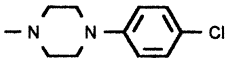
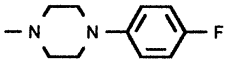
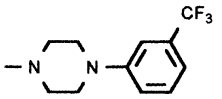
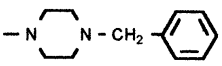
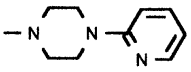
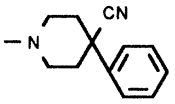
Compound	R	n	Cryst. Solvents	Mp. ^{0}C	Yield (%)
1		1	Dichloroethane-hexane	170-171	37.87
2		1	Ethanol	214-215	38.46
3		1	Methanol	192	53.89
4		1	Methanol	189-190	50.29
5		1	Methanol	224	47.33
6		1	Toluene	158	27.77
7		1	Ethanol	267-268	31.42
8		1	Methanol	199-200	51.28
9		1	Dichloroethane-hexane	156-157	34.35
10		1	2-propanol	192-193	36.36

Table 1. *Continued*

Compound	R	n	Cryst. Solvents	Mp. ^{0}C	Yield (%)
11		2	Ethanol	169	55.55
12		2	Methanol	144	51.82
13		2	Ethanol-water	139-141	22.00
14		2	Ethanol	175-176	39.40
15		2	2-propanol	153-155	34.60
16		2	Ethanol	131	31.07
17		2	Dichloroethane-cyclohexane	142	47.46
18		2	Ethanol	145-146	49.00
19		2	Ethanol	143	40.12

Result and Discussion

Chemistry

The title compounds were synthesized by the reaction of appropriate amine derivatives with mixed anhydride structures which were obtained by reacting [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]acetic acid or [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]propanoic acid in dichloromethane at 0 °C (ice-bath) with triethylamine and ethyl chloroformate (Scheme 1). Analytical data are given in Table 1.

The synthesis of **I**, **II**, **III**, **IV**, **V** has already been reported in the literature[19–22]. [6-(4-Methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]propanenitrile and the corresponding acid (**VI**, **VII**) were prepared for the first time in this study.

In the IR spectra of acetamide derivatives, carbonyl stretching bands of the amide function and pyridazinone ring were seen at about 1665–1655 cm^{-1}. However propanamide derivatives carbonyl stretching bands of the pyridazinone ring was seen at about 1670–1653 cm^{-1}, carbonyl stretching of amide appeared at around 1644–1631 cm^{-1}. ^{1}H-NMR spectral data of the compounds which were synthesized are presented in Table 2.

Pharmacology

The antinociceptive activity of the compounds has been investigated by modified Koster's Test in mice, using aspirin as a reference[23]. All the compounds (at 100 mg/kg dose) except **1** and **9** have been found more potent than aspirin. Compound **6** in the group of acetamide derivatives and compound **15** in the group of propanamides have exhibited the highest antinociceptive activity among the others. Both of the compounds have the 4-fluorophenylpiperazine moiety as

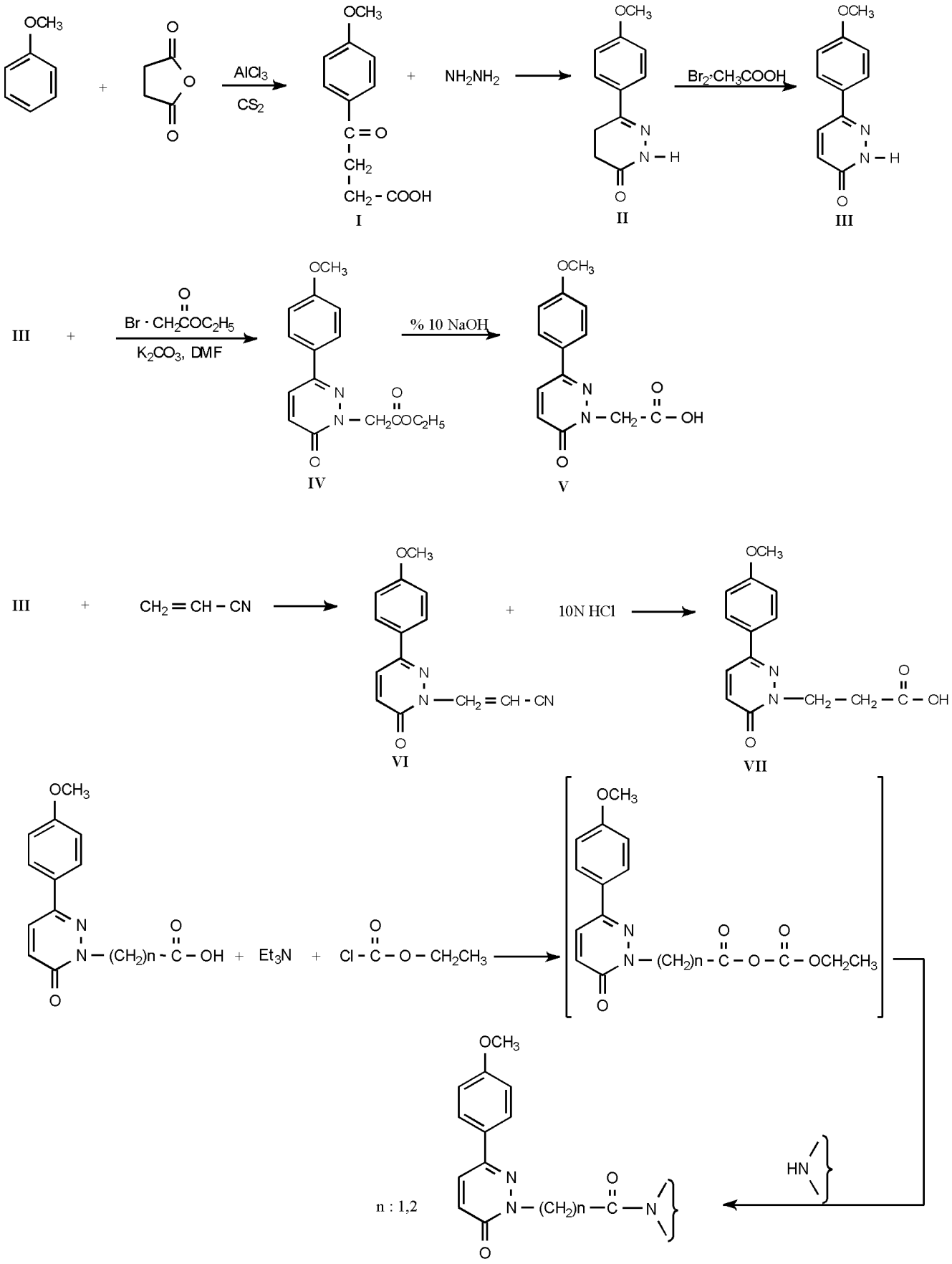

OCH3
AlCl3
CS2
NH2NH2
Br2·CH3COOH
I
II
III
Br · CH2COC2H5
K2CO3, DMF
% 10 NaOH
IV
V
CH2 = CH - CN
10N HCl
VI
VII
Et3N
Cl - C - O - CH2CH3
n : 1,2
HN

Table 2. ^{1}H-NMR spectroscopic data of the compounds **1–19**.

Comp.	^{1}H-NMR (DMSO-d_6): δ (ppm)
1	8.03 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.04 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 5.01 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.52 (t, 2H, piperazine 2-H); 3.45 (t, 2H, piperazine 6-H); 2.35 (t, 2H, piperazine 3-H); 2.26 (t, 2H, piperazine 5-H); 2.20 (s, 3H, -NCH_3).
2	8.04 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.24 (t, 2H, phenyl 3-H, 5-H), 7.05 (d, 1H, pyridazine 4-H); 7.03 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 6.98 (d, 2H, phenyl 2-H, 6-H); 6.83 (t, 1H, phenyl 4-H); 5.10 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.70 (t, 2H, piperazine 2-H); 3.61 (t, 2H, piperazine 6-H); 3.25 (t, 2H, piperazine 3-H); 3.15 (t, 2H, piperazine 5-H).
3	8.05 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.05 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 6.91 (m, 4H, phenyl 3-H, 4-H, 5-H, 6-H) 5.10 (s, 2H, -CH_2CO); 3.80 (two separate singlets, 6H, -OCH_3); 3.69 (t, 2H, piperazine 2-H); 3.60 (t, 2H, piperazine 6-H); 3.05 (t, 2H, piperazine 3-H); 2.95 (t, 2H, piperazine 5-H).
4	8.04 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.24 (t, 1H, phenyl 5-H), 7.04 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 6.99 (dd, 1H, phenyl 2-H); 6.94 (dd, 1H, phenyl 4-H); 6.82 (dd, 1H, phenyl 6-H); 5.10 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.70 (t, 2H, piperazine 2-H); 3.60 (t, 2H, piperazine 6-H); 3.30 (t, 2H, piperazine 3-H); 3.20 (t, 2H, piperazine 5-H).
5	8.04 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.25 (t, 2H, *p*-methoxyphenyl 3-H, 5-H); 7.00 (m, 5H, pyridazine 4-H , phenyl protons); 5.10 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.70 (t, 2H, piperazine 2-H); 3.60 (t, 2H, piperazine 6-H); 3.25 (t, 2H, piperazine 3-H); 3.15 (t, 2H, piperazine 5-H).
6	8.05 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.05 (m, 7H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H, phenyl protons), 5.10 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.71 (t, 2H, piperazine 2-H); 3.62 (t, 2H, piperazine 6-H); 3.18 (t, 2H, piperazine 3-H); 3.08 (t, 2H, piperazine 5-H).
7	11.7 (s, 1H,amine salt); 8.04 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.66 (m, 2H, phenyl 3-H, 5-H); 7.47 (m, 3H, phenyl 2-H, 4-H, 6-H); 7.04 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 5.20–5.02 (two separate doublet, 2H, -CH_2CO); 4.38 (m, 3H, piperazine 2e-H, CH_2); 4.16 (m, 1H, piperazine 6e-H); 3.80 (s, 3H, -OCH_3); 3.47–2.90 (m, 6H, piperazine protons).
8	8.14 (m, 1H, pyridine 6-H); 8.03 (d, 1H, pyridazine 5-H); 7.81 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.57 (m, 1H, pyridine 4-H), 7.04 (d, 1H, pyridazine 4-H); 7.03 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 6.87 (d, 1H, pyridine 3-H); 6.68 (m, 1H, pyridine 5-H); 5.10 (s, 2H, -CH_2CO); 3.80 (s, 3H, -OCH_3); 3.60 (m, 8H, piperazine protons).
9	8.03 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.04 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 7.03 (d, 1H, pyridazine 4-H); 5.05–4.95 (two separate doublet, 2H, -CH_2CO); 4.27 (m,1H, piperidine 2e-H); 3.87 (m, 1H, piperidine 6e-H); 3.80 (s, 3H, -OCH_3); 3.07 (m, 1H, piperidine 6a-H); 2.60 (m, 1H, piperidine 2a-H); 1.65 (m, 3H, piperidine 5e-H, 3e-H, 4-H); 1.15 (m, 1H, piperidine 5a-H); 0.90 (m, 1H, piperidine 3a-H) 0.80 (d, 3H, -CH_3).
10	8.05 (d, 1H, pyridazine 5-H); 7.80 (d, 2H,*p*-methoxyphenyl 2-H, 6-H); 7.50 (m, 5H, phenyl protons); 7.02 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 5.20–5.08 (two separate doublet, 2H, -CH_2CO); 4.55 (m, 1H, piperidine 2e-H); 4.18 (m, 1H, piperidine 6e-H); 3.80 (s, 3H, -OCH_3); 3.42 (m, 1H, piperidine 6a-H); 2.92 (m, 1H, piperidine 2a-H); 2.20 (m, 3H, piperidine 5e-H, 5a-H, 3e-H); 1.93 (m, 1H, piperidine 3a-H).
11	8.00 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.23 (t, 2H, phenyl 3-H, 5-H), 7.01 (d, 1H, pyridazine 4-H); 6.98 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 6.94 (d, 2H, phenyl 2-H, 6-H); 6.82 (t, 1H, phenyl 4-H); 4.34 (t, 2H, -NC*H*$_2$$CH_2$); 3.78 (s, 3H, -$OCH_3$); 3.61 (m, 4H, piperazine 2-H, 6-H); 3.14 (t, 2H, piperazine 3-H); 3.07 (t, 2H, piperazine 5-H); 2.92 (t, 2H, -CH_2C*H*$_2$CO).
12	8.00 (d, 1H, pyridazine 5-H); 7.84 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 6.93 (m, 7H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H, phenyl protons); 4.38 (t, 2H, -NC*H*$_2$$CH_2$); 3.80 (two separate singlets, 6H, -OCH_3); 3.60 (m, 4H, piperazine 2-H, 6-H); 2.90 (m, 6H, piperazine 3-H, 5-H, -CH_2C*H*$_2$CO).
13	8.00 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.20 (t, 1H, phenyl, 5-H); 7.01 (d, 1H, pyridazine 4-H); 6.98 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 6.94 (dd, 1H, phenyl 2-H,); 6.89 (dd, 1H, phenyl 4-H); 6.82 (dd, 1H, phenyl 6-H); 4.38 (t, 2H -NC*H*$_2$$CH_2$); 3.78 (s, 3H, -$OCH_3$); 3.58 (m, 4H, piperazine 2-H, 6-H); 3.20 (t, 2H, piperazine 3-H); 3.13 (t, 2H, piperazine 5-H); 2.92 (t, 2H, -CH_2C*H*$_2$CO).
14	8.00 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.24 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 7.01 (t, 1H, pyridazine 4-H); 6.98 (d, 2H, phenyl 3-H, 5-H); 6.94 (d, 2H, phenyl 2-H, 6-H); 4.34 (t, 2H, -NC*H*$_2$$CH_2$); 3.78 (s, 3H, -$OCH_3$); 3.60 (m, 4H, piperazine 2-H, 6-H); 3.14 (t, 2H, piperazine 3-H); 3.07 (t, 2H, piperazine 5-H); 2.92 (t, 2H, -CH_2C*H*$_2$CO).
15	8.00 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.00 (m, 7H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H, phenyl protons); 4.38 (t, 2H, -NC*H*$_2$$CH_2$); 3.80 (s, 3H, -$OCH_3$); 3.60 (m, 4H, piperazine 2-H, 6-H); 3.04 (t, 2H, piperazine 3-H); 3.01 (t, 2H, piperazine 5-H); 2.91 (t, 2H, -CH_2C*H*$_2$CO).
16	8.00 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.43 (t, 1H, phenyl 5-H); 7.22 (dd, 1H, phenyl 2-H); 7.18 (dd, 1H, phenyl 4-H); 7.10 (dd, 1H, phenyl 6-H); 7.02 (d,1H, pyridazine 4-H); 6.98 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 4.35 (t, 2H, -NC*H*$_2$$CH_2$); 3.78 (s, 3H, -$OCH_3$); 3.62 (m, 4H, piperazine 2-H, 6-H); 3.28 (t, 2H, piperazine 3-H); 3.20 (t, 2H, piperazine 5-H); 2.92 (t, 2H, -CH_2C*H*$_2$CO).
17	7.98 (d, 1H, pyridazine 5-H); 7.82 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.30 (m, 5H, phenyl protons); 7.05 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 7.00 (d, 1H, pyridazine 4-H); 4.30 (t, 2H, -NC*H*$_2$$CH_2$); 3.80 (s, 3H, -$OCH_3$); 3.45 (m, 4H, piperazine 2-H, 6-H); 3.30 (s, 2H, -CH_2-); 2.85 (t, 2H, -CH_2C*H*$_2$CO); 2.30 (m, 4H, piperazine 3-H, 5-H).
18	8.12 (m, 1H, pyridine 6-H) 8.00 (d, 1H, pyridazine 5-H); 7.80 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.55 (m, 1H, pyridine 4-H); 7.02 (d, 1H, pyridazine 4-H); 6.98 (d, 2H, *p*-methoxyphenyl 3-H, 5-H); 6.83 (d, 1H, pyridine 3-H); 6.67 (m, 1H, pyridine 5-H) 4.37 (t, 2H, -NC*H*$_2$$CH_2$); 3.78 (s, 3H, -$OCH_3$); 3.50 (m, 8H, piperazine protons); 2.92 (t, 2H, -CH_2C*H*$_2$CO).
19	8.00 (d, 1H, pyridazine 5-H); 7.83 (d, 2H, *p*-methoxyphenyl 2-H, 6-H); 7.42 (m, 5H, phenyl protons), 7.00 (m, 3H, pyridazine 4-H, *p*-methoxyphenyl 3-H, 5-H); 4.61 (m, 1H, piperidine 2e-H); 4.35 (t, 2H, -NC*H*$_2$$CH_2$); 4.12 (m, 1H, piperidine 6e-H) 3.80 (s, 3H, -OCH_3); 3.32 (m, 1H, piperidine 6a-H); 2.95 (m, 2H, -CH_2C*H*$_2$CO); 2.85 (m, 1H, piperidine 2a-H); 2.10 (m, 3H, piperidine 5e-H, 5a-H, 3e-H); 1.85 (m, 1H, piperidine, 3a-H).

Table 3. Antinociceptive activity of the compounds **1–19**.

Compd	% Anti-nociceptive Activity	Compound	% Anti-nociceptive Activity
1	35	**11**	51*
2	42	**12**	65*
3	50	**13**	70*
4	61*	**14**	59*
5	47	**15**	84*
6	67*	**16**	76*
7	60*	**17**	70*
8	62*	**18**	68*
9	33	**19**	64*
10	59*	**Aspirin**	41

*$p<0.05$ (in comparison with control group).

amine component at the side chain. In addition, the propanamides have generally been found more potent than acetamides (Table 3).

Structure-Activity Relationships

Quantitative structure-activity relationships (QSARs) are mathematical models which aim to predict the properties of molecules from their structures. There are two basic kinds of molecular predictors used in QSAR. One of them involves parameters that bear a relation to free energy and usually represent some important physicochemical properties of molecules, e.g., hydrophobic, electronic, and steric parameters. The other category of molecular descriptor is the topological index or numerical graph invariant which is produced directly from molecular structure[24].

Molecular connectivity is a topological method used to describe the structure of a molecule by means of connectivity indices ($^{m}\chi_t$) that is known as a numerical descriptor. The molecular connectivity index for a molecule is calculated from the hydrogen-suppressed graph. The molecular connectivity method is used to investigate the relationship between the experimental values of physical or biological properties and calculated connectivity indices[25,26]. In recent studies the usefulness of molecular connectivity has been demonstrated in the design of analgesics[27,28]. In this paper, some structural parameters (such as log *P*, parachor, molar refractivity, and molecular connectivity indices) were studied for possible correlation with antinociceptive activity of some 3(2*H*)-pyridazinone derivatives (Table 4 and Table 5). A good collinearity between all parameters was found, and the $^{1}\chi$ parameter had the best correlation with antinociceptive activity. Therefore, the linear regression analysis was performed between the $^{1}\chi$ parameter and antinociceptive activity. The following relationships were found between $^{1}\chi$ and antinociceptive activity as the result of statistical regression analysis.

$$\text{Activity} = (8.73 \pm 1.81)^{1}\chi - (72.27 \pm 27.27)\ r^2 = 0.58$$

$$\log \text{Activity} = (0.076 \pm 0.013)\ ^{1}\chi + (0.616 \pm 0.197)\ r^2 = 0.67$$

Table 4. Molecular connectivity indices of the compound **1–19**.

Compd	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$
1	12,062	8,253	14,220	7,942
2	14,634	9,937	16,154	8,958
3	15,582	10,469	18,081	9,966
4	15,025	10.210	17,729	10,088
5	15,025	10,210	17,836	10,111
6	15,025	10,038	17,836	9,676
7	15,117	10,383	15,894	8,982
8	14,634	9,800	16,154	8,824
9	12,062	8,566	14,220	8,322
10	15,539	10,514	17,047	9,887
11	15,134	10,437	16,260	9,115
12	16,082	10,969	18,187	10,123
13	15,525	10,510	17,835	10,245
14	15,525	10,510	17,942	10,268
15	15,525	10,538	17,942	9,833
16	16,735	11,154	21.067	10,92
17	15,617	10,883	16,000	9,139
18	15,134	10,300	16,260	8,931
19	16,039	10,014	17,153	10,044

Table 5. Log *P*, parachor, and molar refractivity values of the compounds **1–19**.

Compd	log *P*	Parachor (cm^3)	Molar refractivity (cm^3)
1	1.69 ± 0.73	722.5 ± 8.0	95.49 ± 0.5
2	3.00 ± 0.75	868.3 ± 8.0	116.18 ± 0.5
3	3.72 ± 0.77	918.5 ± 8.0	121.99 ± 0.5
4	3.96 ± 0.76	897.1 ± 8.0	120.78 ± 0.5
5	3.84 ± 0.75	897.1 ± 8.0	120.78 ± 0.5
6	3.29 ± 0.79	868.4 ± 8.0	116.05 ± 0.5
7	3.58 ± 0.74	906.9 ± 8.0	120.79 ± 0.5
8	2.09 ± 0.76	849.4 ± 8.0	114.62 ± 0.5
9	3.30 ± 0.69	727.0 ± 8.0	96.15 ± 0.5
10	3.43 ± 0.72	933.4 ± 8.0	123.89 ± 0.5
11	3.17 ± 0.73	906.9 ± 8.0	120.79 ± 0.5
12	3.89 ± 0.75	957.1 ± 8.0	126.60 ± 0.5
13	4.13 ± 0.74	935.7 ± 8.0	125.39 ± 0.5
14	4.01 ± 0.74	935.7 ± 8.0	125.39 ± 0.5
15	3.46 ± 0.78	907.1 ± 8.0	120.66 ± 0.5
16	4.49 ± 0.77	960.9 ± 8.0	125.54 ± 0.5
17	3.74 ± 0.72	945.5 ± 8.0	125.39 ± 0.5
18	2.25 ± 0.74	888.0 ± 8.0	119.23 ± 0.5
19	3.60 ± 0.70	972.0 ± 8.0	128.50 ± 0.5

Acknowledgment

This study is financially sopported by Gazi University Research Fund (Project No. 11/98–07).

Experimental Part

Chemistry

All chemicals including piperazine and piperidine derivatives were obtained from Aldrich Chemical Co. (Steinheim, Germany). Melting points were determined with Electrothermal-9200 digital melting point apparatus (Southend, Great Britain) and are uncorrected. IR spectra (KBr) of the compounds were recorded on Bruker Vector 22 IR spectrometer. The ^{1}H-NMR spectra were recorded on Jeol 500 MHz-NMR spectrometer and a Bruker 200 FT-NMR spectrometer using TMS as internal standard and DMSO-d_6. All chemical shifts were recorded as δ (ppm). Elemental analyses were performed with Leco-932 (C,H,N,S-Elemental analyzer, St. Joseph, USA) at Scientific and Technical Research Council of Turkey, Instrumental Analysis Center (Ankara, Turkey), and the results were within the range of ± 0.4 % of calculated values.

Synthesis of [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetamides and 3-[6-(4-Methoxyphenyl)-3(2H)-pyridazinone-2-yl]propanamides

0.01 Mol of [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]acetic acid or 3-[6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]propanoic acid in 40 ml dichloromethane at 0 °C (ice-bath) was treated with triethylamine (3 ml) and 0.01 mol of ethyl chloroformate. After stirring the reaction mixture at 0 °C for 15 min, 0.011 mol of an appropriate amine derivative was added to this solution. The final mixture was stirred at 0–25 °C for 24 h and evaporated to dryness then treated with either acetone or acetone-hexane mixture. All solid materials thus obtained were dried and crystallized from appropriate solvents illustrated in Table 1.

6-(4-Methoxyphenyl)-4,5-dihydro-3(2H)-pyridazinone[20]

0.01 Mol of 4-(4-methoxyphenyl)-4-oxobutanoic acid and 0.015 mol of hydrazine hydrate (0.85 ml; 55 %) in 30 ml ethanol were refluxed for 4 h. The reaction mixture was cooled and the precipitate thus formed was collected by filtration, dried, and crystallized from ethanol. Mp: 155–156 °C. (Lit. mp: 151 °C).

6-(4-Methoxyphenyl)-3(2H)-pyridazinone[20]

A solution of 0.043 mol bromine in 25 ml glacial acetic acid was added dropwise to a solution of 0.039 mol of 6-(4-methoxyphenyl)-4,5-dihydro-3(2*H*)-pyridazinone in 100 ml glacial acetic acid at 60–70 °C. Then, the reaction mixture was refluxed for 3 h. After cooling to 5 °C, it was poured into ice water and converted to the free base with ammonium hydroxide. The precipitate was collected by filtration, washed with water until neutral, dried, and crystallized from ethanol-water. Mp: 188 °C. (Lit. mp: 191 °C).

Ethyl [6-(4-Methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetate[21]

0.025 Mol of 6-(4-methoxyphenyl)-3(2*H*)-pyridazinone, 0.0375 mol of ethyl bromoacetate and 0.01 mol of anhydrous potassium carbonate in 25 ml anhydrous DMF were stirred at room temperature for 1 h. The reaction mixture was poured into ice water. The solid which separeted was collected by fitration, dried, and crystallized from ethanol-water. Mp: 101 °C.

[6-(4-Methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetic Acid[22]

0.035 Mol of ethyl [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]acetate in 150 ml 10 % NaOH was hydrolyzed for 4 h. After cooling to 5 °C, the reaction mixture was acidified 20 % HCl. The solid was collected by filtration and dissolved in $NaHCO_3$ and acidified with 20 % HCl. The precipitate was filtered, washed with water to neutral pH, and dried and crystallized from water. Mp: 207 °C.

3-[6-(4-Methoxyphenyl)-3(2H)-pyridazinone-2-yl]propanenitrile

0.25 Mol of 6-(4-methoxyphenyl)-3(2*H*)-pyridazinone, 0.3 mol of triethylamine, 0.3 mol of acrylonitrile were added in 500 ml of water, heated at 50–60 °C for 6 h and then stirred at the room temperature for 18 h. At the end of this time, the solid was collected by filtration, washed with water to neutral pH, dried, and crystallized from ethanol. Mp: 139 °C.

3-[6-(4-Methoxyphenyl)-3(2H)-pyridazinone-2-yl]propanoic Acid

0.01 Mol of 3-[6-(3-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl]propanenitrile, in 10 N hydrochloric acid (50 ml) was stirred at the room temperature for 2 h, then refluxed for 3 h. The reaction mixture was cooled and the precipitate was collected by filtration, washed with water, dried, and crystallized from ethanol-water. Mp: 173–174 °C.

Pharmacology

Local breed male albino mice (25.0 ± 5.0 g) were employed. All the animals were left for two days in the laboratory for acclimatization before the day of experiment and the last day they were given water only. Each group consisted of 6 mice.

Acetic acid (Merck AG), Carboxymethyl cellulose Sodium Salt (CMC Na) (Aldrich), aspirin (Bayer), Gauge Calipers (Peacock, Ozaki Co., Tokyo) were used.

Antinociceptive Activity[23]

A modified Koster's Test was used. Aspirin served as a reference. Test compounds and reference were administered orally at 100 mg/kg dose as a suspension in 0.2 ml of 0.5% CMC Na. Control animals received the same volume of vehicles. One hour after the drug administration, every mouse was treated with an aqueous acetic acid solution (3% w/v) injected intraperitoneally at a 300 mg/kg dose. Five minutes later, writhing movements were counted for a period of 10 min. The mean writhing counts for each group were used, in the antinociceptive activity calculation employing the following equation.

$$\text{Antinociceptive activity (writhing inhibition \%)} = \frac{n - n'}{n} \times 100$$

n = The mean writhing count of control group
n' = The mean writhing counts of test groups

Statistical Analysis

The differences between control and test groups were found statistically significant by Mann-Whitney *U* test.

Structure-Activity Relationships

Statistical analysis of the results was performed using the SPSS version-6 computer program. The values of molecular connectivity index and valence molecular connectivity index of nineteen compounds were calculated by our group. To calculate molecular connectivity indices of compounds that were synthesized, we used the values of connectivity delta (δ) and valence delta (δ^v) that were reported by Kier and Hall[29,30]. The log *P* values were calculated (determined) by ACD-log *P* version 1.0 computer program. The values of the parachor and the molecular refractivity were calculated by ACD-Chem Sketch version 2.51 computer program.

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Received: September 13, 1999 [FP424]