Acta Poloniae Pharmaceutica – Drug Research, Vol. 68 No. 3 pp. 381–386, 2011 ISSN 0001-6837
Polish Pharmaceutical Society

SYNTHESIS OF SOME NEW 2-(SUBSTITUTED-PHENYL)-5-(N,N-DIPHENYLAMINOMETHYL)-1,3,4-OXADIAZOLES: A SAFER ANTI-INFLAMMATORY AND ANALGESIC AGENTS

ADITYA KUMAR KATARIA[1], SUROOR AHMAD KHAN[1], MOHAMMAD MUMTAZ ALAM[1], ASIF HUSAIN[1], MYMOONA AKHTAR[1], SURUCHI KHANNA[2], RASHID HAIDER[3] and MOHAMMAD SHAQUIQUZZAMAN[1]*

[1]Department of Pharmaceutical Chemistry, [2]Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi-110062, India
[3]Al-Hafeez Degree College, Veer Kunwar Singh University, Arrah-802301, India

Abstract: A series of 2-(substituted-phenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazoles (**3-15**) were synthesized. The compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation actions. The percentage inhibition in edema at different time intervals indicated that compounds **8**, **11**, **12**, **14** and **15** exhibited good anti-inflammatory potential. The results illustrate that 2-(2-acetoxyphenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazole (**15**) and 2-(3,4-dimethoxyphenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazole (**12**) showed best anti-inflammatory activity among the series tested. Furthermore, activity is higher in case of chloro substitution as compared to methyl substitution. The compounds synthesized were also evaluated for their ulcerogenic and lipid peroxidation action and showed superior GI safety profile along with reduction in lipid peroxidation as compared to that of ibuprofen.

Keywords: oxadiazole, anti-inflammatory, analgesic

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been recognized as important class of therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions. However, long term use of NSAIDs has been associated with several side effects such as gastrointestinal mucosal damage, bleeding, intolerance and renal toxicity (1, 2) due to the presence of free carboxylic group and non-selective COX-inhibitor. The search for safer NSAIDs continues with the failure of the anticipated "ideal" anti-inflammatory agents, the coxibs, on long-term usage (3, 4). Synthetic approaches based upon chemical modification have been taken with the aim of improving safety profile of the molecule. Among the derivatives of 1,3,4-oxadiazole there is a large amount of compounds exhibiting anti-inflammatory activity (5–7). 1,3,4-Oxadiazoles are an important class of heterocyclic compound with broad spectrum of biological activities in addition to anti-inflammatory activity such as hypoglycemic (8), antimicrobial (9, 10), antimycobacterial (11), analgesic (7, 12), anticonvulsant (13), anticancer (14), antimalarial (15) etc. In our attempt to discover safer agents for the treatment of inflammatory conditions, we report the synthesis, spectral characterization and pharmacological evaluation of a series of 1,3,4-oxadiazoles (**3-15**). The newly synthesized compounds have been found to possess potential anti-inflammatory and analgesic activities with lesser ulcerogenic effects. We made an attempt to ascertain the dependence of anti-inflammatory activity on the nature of various substituents, introduced into phenyl ring at the 5th position of oxadiazole nucleus.

EXPERIMENTAL

Chemicals were purchased from Merck and Sigma-Aldrich as 'synthesis grade' and used without further purification. Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates (Merck No. 5544) using toluene : ethyl acetate : formic acid (5:4:1, v/v/v) as solvent system and the spots were localized either under UV light or through exposure to iodine vapors. The IR spectra were measured in potassium bromide pellets using a Perkin-Elmer

* Corresponding author: e-mail: shaqiq@rediffmail.com; phone: +91-9990663405

1725X spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker Avance-400 MHz in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal standard; chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS. ^{13}C-NMR has been recorded at 100 MHz for compound **3**. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70eV. Elemental analyses were performed on a Perkin-Elmer model 240 analyzer (C, H, N) and found within range of ± 0.4% of theoretical values.

Ethyl-2-diphenylamino acetate (**1**)

Diphenylamine (0.01 mol) was dissolved in dry acetone (20 mL). To this ethyl chloroacetate (0.01 mol) and potassium carbonate (0.03 mol) were added and then reaction mixture was refluxed for 10 h. The solvent was concentrated and the mixture was poured into ice cold water with stirring. The precipitate separated was filtered and recrystallized from ethanol. Yield: 80%; m.p.: 156°C; R_f: 0.68; IR (KBr, cm^{-1}): 1684; ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.26 (t, 3H, CH_3), 4.22 (q, 2H, OCH_2), 4.87 (s, 2H, NCH_2), 7.05–7.34 (m, 10H, ArH).

2-Diphenylamino ethanohydrazide (**2**)

Compound **1** (0.01 mol) was dissolved in absolute ethanol and hydrazine hydrate (99%; 0.01 mol) was added to it and refluxed for 6–8 h. Then, an excess of alcohol was distilled off. The reaction mixture was then poured onto crushed ice and stirred for 15 min. The precipitated product was filtered and washed with water. It was recrystallized with ethanol. IR (KBr, cm^{-1}): 3355, 3281, 3110, 1665; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.42 (s, 2H, NCH_2), 4.86 (s, 2H, NH_2), 9.35 (s, 1H, NH), 7.11–7.36 (m, 10H, ArH).

General procedure for the synthesis of 2-(N,N-diphenyl-aminomethyl)-5-(substituted-phenyl)-1,3,4-oxadiazoles (3–15)

A mixture of compound **2** (0.01 mol) and substituted aromatic acid (0.01 mol) was refluxed in phosphorus oxychloride for 6–10 h. The solution was then poured onto crushed ice with continuous stirring for 10 min and neutralized with 20% sodium bicarbonate. The precipitate obtained was filtered, washed with water and recrystallized from methanol.

2-(N,N-diphenylaminomethyl)-5-phenyl-1,3,4-oxadiazole (**3**)

IR (KBr, cm^{-1}): 1615, 1252, 1090; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.49 (s, 2H, CH_2), 6.92–7.25 (m, 10H, ArH), 7.34 (m, 3H, 3',4',5'-H), 7.62 (m, 2H, 2',6'-H); ^{13}C-NMR ($CDCl_3$, δ, ppm): 53.1, 114.2, 117.2, 119.3, 125.2, 162.3, 166.2; MS (m/z): 327 (M^+).

2-(N,N-diphenylaminomethyl)-5-(2'-bromophenyl)-1,3,4-oxadiazole (**4**)

IR (KBr, cm^{-1}): 1616, 1240, 1092; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.56 (s, 2H, CH_2), 7.06–7.28 (m, 10H, ArH), 7.40 (d, 1H, H-3'), 7.52 (t, 1H, H-5'), 7.64 (d, 1H, H-6'), 7.84 (t, 1H, H-4'); MS (m/z): 406 (M^+).

2-(N,N-diphenylaminomethyl)-5-(4'-bromophenyl)-1,3,4-oxadiazole (**5**)

IR (KBr, cm^{-1}): 1618, 1252, 1096; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.59 (s, 2H, CH_2), 7.26–7.48 (m, 10H, ArH), 7.57 and 7.76 (d each, 2×A_2B_2, p-substituted phenyl); MS (m/z): 406 (M^+).

2-(N,N-diphenyl-aminomethyl)-5-(4'-chloro-phenyl)-1,3,4-oxadiazole (**6**)

IR (KBr, cm^{-1}): 1620, 1258, 1098; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.58 (s, 2H, CH_2), 7.16–7.42 (m, 10H, ArH), 7.70 and 8.05 (d each, 2xA_2B_2, p-substituted phenyl); MS (m/z): 362(M^+), 364 (M^++2).

2-(N,N-diphenyl-aminomethyl)-5-(2'-chloro-phenyl)-1,3,4-oxadiazole (**7**)

IR (KBr, cm^{-1}): 1612, 1248, 1094; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.54 (s, 2H, CH_2), 7.08–7.30 (m, 10H, ArH), 7.36 (d, 1H, H-3'), 7.49 (t, 1H, H-5'), 7.58 (d, 1H, H-6'), 7.76 (t, 1H, H-4'); MS (m/z): 362 (M^+), 364 (M^++2).

2-(N,N-diphenyl-aminomethyl)-5-(4'-fluorophenyl)-1,3,4-oxadiazole (**8**)

IR (KBr, cm^{-1}): 1608, 1246, 1088; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.57 (s, 2H, CH_2), 7.05–7.31 (m, 10H, ArH), 7.88 and 8.10 (d each, 2xA_2B_2, p-substituted phenyl); MS (m/z): 345 (M^+).

2-(N,N-diphenyl-aminomethyl)-5-(2'-methylphenyl)-1,3,4-oxadiazole (**9**)

IR (KBr, cm^{-1}): 1620, 1258, 1098; ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.51 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.13–7.37 (m, 11H, ArH and H-3'), 7.44–7.56 (m, 2H, H-4',5'), 7.61 (d, 1H, H-6'); MS (m/z): 341 (M^+).

2-(N,N-diphenyl-aminomethyl)-5-(4'-methylphenyl)-1,3,4-oxadiazole (**10**)

IR (KBr, cm^{-1}): 1606, 1242, 1086; ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.44 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 7.10–7.36 (m, 12H, ArH & H-3',5'), 7.48 (d, 2H, H-2',6'); MS (m/z): 341 (M^+).

2-(N,N-diphenyl-aminomethyl)-5-(4'-methoxy-phenyl)-1,3,4-oxadiazole (**11**)

R (KBr, cm^{-1}): 1612, 1256, 1092; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.53 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 7.12–7.40 (m, 12H, ArH & H-3',5'), 7.75 (d, 2H, H-2',6'); MS (m/z): 357 (M^+).

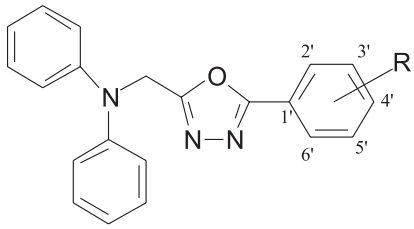
2-(N,N-diphenyl-aminomethyl)-5-(2',4'-dimeth-oxyphenyl)-1,3,4-oxadiazole (**12**)

IR (KBr, cm^{-1}): 1618, 1258, 1098; ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.72 & 3.76 (s, 6H, 2xOCH_3), 4.56 (s, 2H, CH_2), 6.85 (s, 1H, H-2'), 6.98 (d, 1H, H-5'), 7.20–7.41 (m, 11H, ArH & H-6'); MS (m/z): 387 (M^+).

2-(N,N-diphenyl-aminomethyl)-5-(4'-aminophen-yl)-1,3,4-oxadiazole (**13**)

IR (KBr, cm^{-1}): 1616, 1252, 1090; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.52 (s, 2H, CH_2), 5.19 (bs, 2H, NH_2), 6.84 (d, 2H, H-3',5'), 7.02–7.28 (m, 10H, ArH), 7.47 (d, 2H, H-2',6'); MS (m/z): 342 (M^+).

Table 1. Elemental analyses and physical constants of 1,3,4-oxadiazoles **3-15**



Compd.	R	R_f value*	Yield (%)	M.p. (°C)	Molecular formula#	Found (calcd.) (%)		
						C	H	N
3	H	0.78	54	146–148	$C_{21}H_{17}N_3O$ (327.37)	77.04 (77.26)	5.23 (5.22)	12.84 (12.82)
4	2-Br	0.80	64	171–172	$C_{21}H_{16}BrN_3O$ (406.27)	62.08 (61.88)	3.97 (3.96)	10.34 (10.35)
5	4-Br	0.74	56	163–164	$C_{21}H_{16}BrN_3O$ (406.27)	62.08 (62.18)	3.97 (3.96)	10.34 (10.32)
6	4-Cl	0.80	54	148–150	$C_{21}H_{19}ClN_3O$ (361.82)	69.71 (69.98)	4.46 (4.47)	11.61 (11.60)
7	2-Cl	0.82	58	158–160	$C_{21}H_{19}ClN_3O$ (361.82)	69.71 (69.58)	4.46 (4.45)	11.61 (11.62)
8	4-F	0.82	62	149–150	$C_{21}H_{19}FN_3O$ (345.36)	73.03 (72.95)	4.67 (4.65)	12.17 (12.18)
9	2-CH_3	0.82	58	159–160	$C_{22}H_{19}N_3O$ (341.40)	77.40 (77.38)	5.61 (5.60)	12.31 (12.30)
10	4-CH_3	0.80	54	150–152	$C_{22}H_{19}N_3O$ (341.40)	77.40 (77.22)	5.61 (5.61)	12.31 (12.33)
11	4-OCH_3	0.76	60	161–162	$C_{22}H_{19}N_3O_2$ (357.40)	73.93 (73.98)	5.36 (5.37)	11.76 (11.73)
12	2,4-$(OCH_3)_2$	0.68	52	163–164	$C_{22}H_{19}N_3O$ (387.43)	71.30 (71.38)	5.46 (5.48)	10.85 (10.83)
13	4-NH_2	0.68	54	181–182	$C_{21}H_{18}N_4O$ (342.39)	73.67 (73.63)	5.30 (5.29)	16.36 (16.34)
14	2,4-Cl_2	0.80	48	128–130	$C_{21}H_{15}Cl_2N_3O$ (396.26)	63.65 (63.53)	3.82 (3.80)	10.60 (10.58)
15	2-$OCOCH_3$	0.76	48	138–140	$C_{23}H_{19}N_3O_3$ (385.41)	71.67 (71.72)	4.97 (4.96)	10.90 (10.93)

* R_f values for compounds **3**–**15** in solvent system (toluene : ethyl acetate : formic acid, 5:4:1 v/v/v). #The microanalysis values for C, H and N were within ± 4% of the theoretical values.

Table 2. Anti-inflammatory and analgesic activity along with ulcerogenic and lipid peroxidation effect of the synthesized compounds **3-15**.

Compd.	% Inhibition ± SEM[b]		Severity index[a]	Lipid peroxidation[†]	Analgesic activity (writhing test)
	After 2 h	After 3 h			% Protection
Control	-	-	0.00 ± 0.00	0.238 ± 0.002[b,***]	-
Ibu.	70.95 ± 1.26	80.48 ± 1.18	0.9 ± 0.36*	0.608 ± 0.001[a,***]	61.03
3	26.90 ± 1.44***	40.24 ± 1.61***	-	-	-
4	30.71 ± 3.25***	45.32 ± 2.07***	-	-	-
5	34.76 ± 1.71***	50.61 ± 1.63***	-	-	-
6	35.47 ± 2.69***	51.62 ± 2.47***	-	-	-
7	33.57 ± 1.87**	46.75 ± 1.65***	-	-	-
8	42.85 ± 2.18***	59.95 ± 1.24***	0.3 ± 0.12*	0.424 ± 0.002[ab,***]	51.39
9	20.71 ± 2.11***	34.14 ± 1.86***	-	-	-
10	24.52 ± 1.89***	38.41 ± 1.75***	-	-	-
11	44.76 ± 1.14***	61.99 ± 1.15***	0.1 ± 0.10	0.318 ± 0.001[ab,***]	53.13
12	46.19 ± 1.55***	63.82 ± 1.07***	0.2 ± 0.12	0.412 ± 0.002[ab,***]	55.17
13	18.57 ± 1.52***	32.92 ± 1.47***	-	-	-
14	41.19 ± 3.89***	58.54 ± 2.85***	0.1 ± 0.1	0.364 ± 0.002[ab,***]	49.34
15	48.81 ± 1.01***	66.46 ± 1.43***	0.2 ± 0.12	0.406 ± 0.014[ab,***]	56.17

*p < 0.05; **p < 0.01; ***p < 0.001. [a]Relative to their respective control and data were analyzed by one-way ANOVA followed by Tukey test for n = 6. [b]Relative to the standard (Ibuprofen = Ibu.) and data were analyzed by one-way ANOVA followed by Tukey test for n = 6. [†]Lipid peroxidation activity is expressed as nmoles of MDA/mg of protein.

2-(N,N-diphenyl-aminomethyl)-5-(2',4'-dichlorophenyl)-1,3,4-oxadiazole (**14**)

IR (KBr, cm^{-1}): 1622, 1262, 1096; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.62 (s, 2H, CH_2), 7.16–7.38 (m, 11H, ArH & H-3'), 7.47 (d, 1H, H-5'), 7.64 (d, 1H, H-6'); MS (m/z): 396 (M^+), 399 (M^++2).

2-(N,N-diphenyl-aminomethyl)-5-(2'-acetoxyphenyl)-1,3,4-oxadiazole (**15**)

IR (KBr, cm^{-1}): 1615, 1265, 1090; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.36 (s, 3H, $OCOCH_3$), 4.49 (s, 2H, CH_2), 7.10–7.36 (m, 11H, ArH & H-3'), 7.41 (t, 1H, H-5'), 7.52 (t, 1H, H-4'), 7.68 (d, 1H, H-6'); MS (m/z): 385 (M^+).

Animals

Wistar rats and albino mice used in the present study were housed and kept in accordance with the Hamdard University Animal Care Unit, which applies the guidelines and rules laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Wistar rats and albino mice of either sex weighing 120–150 g and 22–25 g, were used. The animals were housed in groups of six and acclimatized to room conditions for at least 2 days before the experiments. Food and water were freely available up to the time of experiments. The food was withdrawn 12/24 h before the start of experiment, but free access to water was allowed.

Anti-inflammatory activity

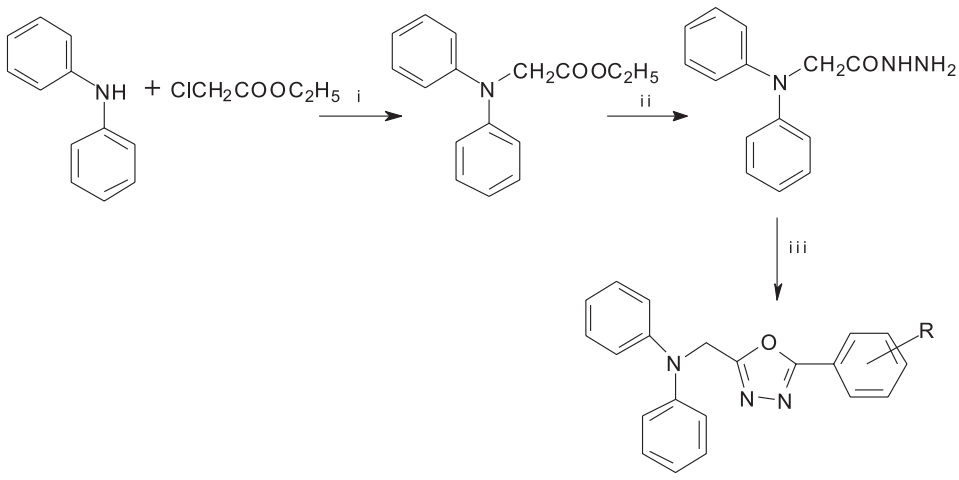
The synthesized compounds were evaluated for their anti-inflammatory activity using carrageenan-induced paw edema method of Winter et al. (16) using ibuprofen as standard drug at 20 mg/kg *p.o*. The paw volume was measured using Ugo Basile plethysmometer.

Analgesic activity

Compounds which showed anti-inflammatory activity above 70% of ibuprofen inhibition were screened for analgesic activity. Analgesic activity was done by acetic acid induce writhing method (17) at 20 mg/kg using ibuprofen as reference drug.

Acute ulcerogenesis

Acute ulcerogenesis test was done according to method of Cioli et al. (18). Ulcerogenic activity evaluated after *p.o.* administration of test compounds or ibuprofen at the dose of 60 mg/kg.



Scheme 1. Synthesis of title compounds. i = dry acetone, potassium carbonate; ii = abs. ethanol, hydrazine hydrate; iii = aromatic acid, $POCl_3$

Lipid peroxidation

Lipid peroxidation studies were carried out as a measure of damage to gastric mucosa. It was determined according to the method of Ohkawa et al. (19).

Statistical analysis

Data were expressed as the mean ± standard error (S.E.) of the means. For a statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA) with *post hoc* analysis. The Tukey-Karmer test *post hoc* was applied to identify significance among groups; $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Chemistry

Thirteen new compounds (**3**-**15**) were synthesized as outlined in Scheme 1. The title compounds were synthesized by refluxing 2-diphenyl aminoacetohydrazide (**2**) with different substituted aromatic acids in phosphorus oxychloride. Physical data of compounds are presented in Table 1. In general, the IR spectral data of all the compounds showed characteristic peaks around 1615 cm^{-1} and 1255 cm^{-1} supporting the cyclization of compound **2** to oxadiazole.

In ^{1}H-NMR spectral data, all the compounds showed characteristic peak at appropriate δ-values. The structure of the compounds was further supported by mass spectral data. The synthesized compounds gave M^+ peak in reasonable intensities. The molecular ion or other related ions produced the appropriate isotopic abundances due to presence of chlorine atom(s).

Pharmacology

The pharmacological evaluation showed that the compounds exhibit anti-inflammatory and analgesic activity with lesser GI toxicity.

The results illustrate that 2-(3,4-dimethoxy-phenyl)-5-(N,N-diphenyl-aminomethyl)-1,3,4-oxadiazole (**12**) and 2-(2-acetoxy-phenyl)-5-(N,N-diphenyl-aminomethyl)-1,3,4-oxadiazole (**15**) showed best anti-inflammatory activity, having maximum percentage inhibition in edema at different time intervals, respectively. They showed 63.82% (compound **12**) and 66.46% (compound **15**) percentage inhibition in edema. In addition, three compounds **8**, **11** and **14** also showed 59.95, 61.99 and 58.54% inhibition, respectively. The remaining derivatives were less active anti-inflammatory agents.

The anti-inflammatory activity enhanced in the presence of acetoxy group and diminished in the presence of methyl indicating that the activity declines with replacement of electronegative group by electropositive group.

Test compounds which exhibited good anti-inflammatory activity **8**, **11**, **12**, **14** and **15** were further evaluated for their analgesic, ulcerogenic and LPO actions. The results of analgesic activity indicated that compounds **12** and **15** showed 55.17% and 56.17% protection against acetic acid-induced writhings and this percentage protection was comparable to ibuprofen (61.03%). Compounds **8**, **11** and **14** also showed good analgesic activity. According to structure activity relationship, it is

clear that 5-(4-fluorobenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**26**) and 5-(4-chlorobenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**20**) were found to be a good anti-inflammatory agent with analgesic activity.

The tested compounds showed low ulcerogenic activity ranging from 0.1 ± 0.1 to 0.3 ± 0.12 whereas the standard drug ibuprofen showed high severity index of 0.9 ± 0.36. The maximum reduction in ulcerogenic activity (0.1 ± 0.1) was found in the compounds **11** and **14**. The LPO was measured as nmoles of malondialdehyde (MDA)/mg of protein. Ibuprofen exhibited high lipid peroxidation 0.608 ± 0.007 whereas control group showed 0.238 ± 0.002. Thus, these compounds showed superior GI safety profile along with reduction in LPO in comparison with ibuprofen. The other tested compounds also exhibited better GI safety profile as compared to the standard drug ibuprofen. Results are presented in Table 2.

CONCLUSION

To sum up, 2-(2-acetoxyphenyl)-5-(N,N-diphenyl-aminomethyl)-1,3,4-oxadiazole (**15**) and 2-(3,4-dimethoxyphenyl)-5-(N,N-diphenyl-aminomethyl)-1,3,4-oxadiazole (**12**) were found to have dual functional i.e. anti-inflammatory and analgesic properties and hence, can be a promising class of compounds with an interesting pharmacological profile. It is conceivable that these derivatives could be further modified to develop potent and safer anti-inflammatory and analgesic agents. Further studies to acquire more information about quantitative structure-activity relationship (QSAR) are in progress in our laboratory.

REFERENCES

1. Allison M.C., Howatson A.G., Torrance C.J., Lee F.D., Russell R.I.: N. Engl. J. Med. 327, 749 (1992).
2. Flower R.J.: Nature Rev. Drug Discov. 2, 179 (2003).
3. Verrico M.M., Weber R.J., Mc Kaveney T.P., Ansani N.T., Towers A.L.: Ann. Pharmacother. 37, 1203 (2003).
4. Wollheim F.A. Lakartidningen 100, 2927 (2003).
5. Jakubkiene V., Burbuliene M.M., Mekuskiene G., Udrenaite E., Gaidelis P., Vainilavicius P.: Farmaco 58, 323 (2003).
6. Boschelli D.H., Connor D.T., Bornemeier D.A., Dyer F.D., Kennedy J.A., et al.: J. Med. Chem. 36, 1802 (1993).
7. Husain A., Ahmad F.J., Ajmal M., Ahuja P.: J. Serb. Chem. Soc. 73, 781 (2008).
8. Girges M.M.: Arzneimittelforschung 44, 490 (1994).
9. Sahin G., Palaska E., Ekizoglu M., Ozalp M.: Farmaco 57, 539 (2002).
10. Misra H.K.: Arch. Pharm. 316, 487 (1983).
11. Navarrete-Vazquez G., Molina-Salinas G.M., Duarte-Fajardo Z.V., Vargas-Villarreal J., Estrada-Soto S., et al.: Bioorg. Med. Chem. 15, 5502 (2007).
12. Bhandari S.V., Bothara K.G., Raut M.K., Patil A.A., Sarkate A.P., Mokale V.J.: Bioorg. Med. Chem. 16, 1822 (2008).
13. Zarghi A., Tabatabai S.A., Faizi M., Ahadian A., Navabi P., Zanganeh V., Shafiee A.: Bioorg. Med. Chem. 15, 1863 (2005).
14. Aboraia A.S., Abdel-Rahman H.M., Mahfouz N.M., EL-Gendy M.A.: Bioorg. Med. Chem. 14, 1236 (2006).
15. Zareef M., Rashid I., De Dominguez N.G., Rodrigues J., Javid H.Z., Arfan M., Supuran C.T.: J. Enz. Inh. Med. Chem. 22, 301 (2007).
16. Winter C.A., Risley E.A., Nus G.N.: Proc. Soc. Exp. Biol. 111, 544 (1962).
17. Seigmund E., Cadmus R., Lu G.: Proc. Soc. Exp. Biol. 95, 729 (1957).
18. Cioli V., Putzolu S., Rossi V. P.: Toxicol. Appl. Pharmacol. 50, 283 (1979).
19. Ohkawa H., Ohishi N., Yagi K.: Anal. Biochem. 95, 351 (1979).

Received: 31. 05. 2010