Med Chem Res (2011) 20:152–157
DOI 10.1007/s00044-010-9300-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and analgesic effects of 2-(2-carboxyphenylsulfanyl)-*N*-(4-substitutedphenyl)acetamide derivatives

Ümide Demir Özkay · Yusuf Özkay · Özgür Devrim Can

Received: 9 May 2009 / Accepted: 12 January 2010 / Published online: 2 February 2010

Abstract This present study was undertaken to synthesize and investigate possible analgesic activities of some 2-(2-carboxyphenylsulfanyl)-*N*-(4-substitutedphenyl)acetamide derivatives that were designed by combining an analgesic drug thiosalicylic acid and the main pharmacophore group of paracetamol, *N*-(4-substitutedphenylacetamide). Chemical structures of synthesized compounds were elucidated by IR, ^{1}H-NMR, and Mass spectral data. Paracetamol, thiosalicylic acid and some of the synthesized compounds in the series exhibited significant analgesic activities in hot-plate, tail-clip, and acetic acid-induced writhing tests. Compound **2d** showed more potent analgesic activity than both paracetamol and thiosalicylic acid. None of the compounds changed the responses of animals recorded in Rota-Rod or activity cage tests with respect to control values. Therefore, analgesic activities of the synthesized compounds evaluated in this study were not caused by motor impairments or neurosedative effects.

Keywords Paracetamol · Thiosalicylic acid · Hot-plate · Tail-clip · Writhing test

Introduction

Analgesic drugs are crucial therapeutic agents for the treatment of acute and chronic pain. They act in various neurological pathways on the central nervous system (CNS) and peripheral nervous system (PNS) (Collina *et al.*, 2003).

Narcotic analgesic drugs, acting mainly by influencing μ-opioid receptors, are used for the treatment of severe pain. For the treatment of inflammatory pain, several non-steroidal anti-inflammatory drugs (NSAIDs) are used. NSAIDs block cyclooxygenase (COX) enzyme and thus inhibit the synthesis of prostaglandins. While these main groups of analgesic drugs are commonly used to treat pain, a significant proportion of patients do not achieve full pain relief (Sałat *et al.*, 2009).

On the other hand, both opioid analgesics and NSAIDs can cause serious adverse side effects. Therapeutic uses of narcotic analgesics are limited by the common side effects, such as sedation, respiratory depression, constipation, and physical dependence etc. (Benyamin *et al.*, 2008). Besides, long-term clinical usage of NSAIDs is associated with several significant side effects including gastrointestinal lesions, bleeding, nephrotoxicity, and heart stroke (Habeeb *et al.*, 2001; Simon, 2001; Bertolini *et al.*, 2002). Therefore, discovery and development of more potent and safer analgesic compounds remains a major challenge in pharmaceutical field.

Salicylic acid derivatives such as thiosalicylic acid, acetylsalicylic acid, gentisic acid, and diflunisal are well known analgesic drugs that include free carboxyl group (Fig. 1). They act via inhibition of prostaglandin synthesis and preventing inflammation, pain, rise in temperature, and related diseases (Vane, 1978; Meade *et al.*, 1993; Wu and Ercal, 2004). Paracetamol and phenacetine which contain *N*-(4-substitutedphenyl)acetamide moiety on their scaffold are also frequently used as safe analgesics (Fig. 1). The mechanism by which paracetamol reduces fever and pain is debated because unlike salicylic acid derivatives, it works

Ü. Demir Özkay · Ö. D. Can (✉)
Faculty of Pharmacy, Department of Pharmacology, Anadolu University, 26470 Eskişehir, Turkey
e-mail: ozgurdt@anadolu.edu.tr

Y. Özkay
Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Anadolu University, 26470 Eskişehir, Turkey

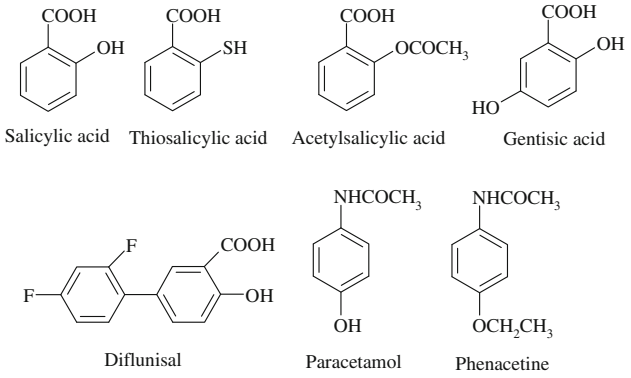

Fig. 1 Analgesic agents derived from salicylic acid and N-phenylacetamide

as a weak prostaglandin biosynthesis inhibitor on PNS and shows very low anti-inflammatory activity (Jackson *et al.*, 1984). In addition, paracetamol can offer a significant additive analgesic effect to the opiates in severe pain. It has been reported that paracetamol selectively inhibits prostaglandin production in the CNS, which could be responsible of its analgesic action (Ramwell, 1981; Jackson *et al.*, 1984; Cranswick and Coghlan, 2000).

Pharmacological evaluation of newly synthesized compounds containing one or more pharmacophore groups is the most popular strategy in new drug development avenue. From this point, our research group focused on structural attributes of analgesic drugs mentioned above, so thiosalicylic acid and *N*-(4-substitutedphenyl)acetamide were combined on the same chemical skeleton. Thus, we obtained six compounds bearing two different analgesic agents residues. No pharmacologic observation including the title compounds in back studies prompted us to investigate their probable central or peripheral analgesic activities.

Materials and methods

Chemistry

All chemicals used for the synthesis of the compounds were supplied from Merck (Germany). Melting points (m.p) of target compounds were determined in open capillaries on an Electrothermal 9001 Digital Melting Point Apparatus and were uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck). IR spectra were recorded on Shimadzu, 8400 FTIR spectrometer as KBr pellets (ν, cm^{-1}). ^{1}H-NMR spectra were obtained from a Brucker UltraShield 500 MHz spectrometer in deutoro dimethylsulfoxide (DMSO-d_6). Mass analysis was carried out within an Agilent 1100 Series LC/MSD Trap VL&SL spectrometer.

2-Chloro-*N*-(4-phenylacetamide) derivatives (**1a–1f**) were prepared according to literature procedures demonstrating acetylation reaction between aromatic amines and chloroacetyl chloride (Kaplancikli *et al.*, 2004; Turan-Zitouni *et al.*, 2004).

General synthesis procedure for the title compounds (**2a–2f**)

For synthesis of the each title compounds, appropriate 2-chloro-*N*-(4-substitutedphenyl)acetamide derivative (0.025 mol), thiosalicylic acid (0.025 mol), and triethylamine (0.025 mol) were dissolved in acetone. Reaction mixture was stirred for 3 h at room temperature. Acetone was removed then residue was washed with cold water and dried. Products were recrystallized from absolute ethanol. Synthesis procedure for the compounds was outlined in Fig. 2.

*2-(2-Carboxyphenylsulfanyl)-N-phenylacetamide (**2a**)*

m.p: 221°C. Yield: 74%. IR (KBr) ν_{maks}(cm^{-1}): 3352 (N–H st), 3227 (O–H st), 1728 (C=O st, carboxyl), 1674 (C=O st, amide), 1612–1445 (C=C st and C=N st), 836–753 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 4.22 (2H; s; –CH_2), 6.82–7.38 (8H; m; Ar–H), 8.17 (H; d; *thiosaliyclic acid* C_6–H), 10.66 (H; br, N–H), 12.19 (H; s; –COOH). ES-MS (m/e): M + 1: 288.2, M + 2: 289.3.

*2-(2-Carboxyphenylsulfanyl)-N-(4-chlorophenyl)acetamide (**2b**)*

m.p: 195°C. Yield: 81%. IR (KBr) ν_{maks}(cm^{-1}): 3359 (N–H st), 3223 (O–H st), 1716 (C=O st, carboxyl), 1679 (C=O st, amide), 1608–1446 (C=C st and C=N st), 832–758 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 4.23 (2H; s; –CH_2), 6.75–7.39 (7H; m; Ar–H), 8.18 (H; d; *thiosaliyclic acid* C_6–H), 10.62 (H; br, N–H), 12.13 (H; s; –COOH). ES-MS (m/e): M + 1: 322.6, M + 2: 323.7.

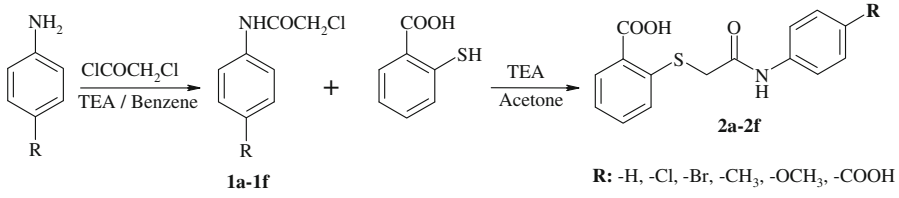

Fig. 2 Synthesis of the compounds **2a–2f**

*2-(2-Carboxyphenylsulfanyl)-N-(4-bromophenyl)acetamide (**2c**)*

m.p: 208°C. Yield: 83%. IR (KBr) $\nu_{maks}(cm^{-1})$: 3348 (N–H st), 3231 (O–H st), 1725 (C=O st, carboxyl), 1684 (C=O st, amide), 1610–1452 (C=C st and C=N st), 837–755 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 4.20 (2H; s; –CH_2), 6.79–7.38 (7H; m; Ar–H), 8.21 (H; d; *thiosaliyclic acid* C_6–H), 10.65 (H; br, N–H), 12.11 (H; s; –COOH). ES-MS (m/e): M + 1: 367.3, M + 2: 368.1.

*2-(2-Carboxyphenylsulfanyl)-N-(4-methylphenyl)acetamide (**2d**)*

m.p: 146°C. Yield: 76%. IR (KBr) $\nu_{maks}(cm^{-1})$: 3361 (N–H st), 3247 (O–H st), 1712 (C=O st, carboxyl), 1674 (C=O st, amide), 1609–1453 (C=C st and C=N st), 841–746 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 2.28 (3H; s; –CH_3), 4.21 (2H; s; –CH_2), 6.74–7.35 (7H; m; Ar–H), 8.20 (H; d; *thiosaliyclic acid* C_6–H), 10.63 (H; br, N–H), 12.23 (H; s; –COOH). ES-MS (m/e): M + 1: 302.5, M + 2: 303.4.

*2-(2-Carboxyphenylsulfanyl)-N-(4-methoxyphenyl)acetamide (**2e**)*

m.p: 171°C. Yield: 79%. IR (KBr) $\nu_{maks}(cm^{-1})$: 3352 (N–H st), 3227 (O–H st), 1728 (C=O st, carboxyl), 1674 (C=O st, amide), 1612–1445 (C=C st and C=N st), 836–753 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 3.86 (3H; s; –OCH_3), 4.19 (2H; s; –CH_2), 6.73–7.39 (7H; m; Ar–H), 8.16 (H; d; *thiosaliyclic acid* C_6–H), 10.74 (H; br, N–H), 12.20 (H; s; –COOH). ES-MS (m/e): M + 1: 318.2, M + 2: 319.3.

*2-(2-Carboxyphenylsulfanyl)-N-(4-carboxyphenyl)acetamide (**2f**)*

m.p: 264°C. Yield: 72%. IR (KBr) $\nu_{maks}(cm^{-1})$: 3366 (N–H st), 3228 (O–H st), 1719 (C=O st, carboxyl), 1671 (C=O st, amide), 1610–1448 (C=C st and C=N st), 836–753 (Ph deformation bands). ^{1}H-NMR (DMSO-d_6) δ(ppm): 4.18 (2H; s; –CH_2), 6.79–7.48 (5H; m; Ar–H), 8.08 (2H; d; *N-(4-carboxyphenyl)acetamide* $C_{3,5}$), 8.18 (H; d; *thiosaliyclic acid* C_6–H), 10.70 (H; br, N–H), 12.17 (2H; s; 2 x–COOH). Ms (Es) (m/e): M + 1: 332.2, M + 2: 333.4.

Pharmacology

Animals

Adult Swiss albino female mice weighing 30–35 g were used for the experiments. The animals were housed in a room with controlled temperature (24 ± 1°C) for 12 h light/12 h dark cycle. All animals were acclimatized to the laboratory environment at least 48 h before the experimental session. Twelve hours before each experiment animals received only water in order to avoid food interference with substance absorption. The experimental protocols have been approved by the Local Ethical Committee on Animal Experimentation of Eskişehir Osmangazi University, Turkey (Approval No: 07.35.35-1)

Administration of test compounds

All administrations to mice ($n = 6$ in each group) were made by single injections via intraperitoneal (i.p) route. Response latencies were measured 30 min after the applications. Physiological saline was injected to control group, as all compounds were dissolved in it. Thiosalicylic acid, paracetamol, and synthesized compounds were applied at 100 mg/kg doses.

Assessment of analgesic activity

Hot-plate test The supraspinal component of antinociceptive action in mice was evaluated by hot-plate test as described previously (Kaplancikli *et al.*, 2008). Mouse was placed in a glass beaker, which was set at a fixed temperature of 55 ± 0.5°C in a water bath and the latency time for paw licking or jumping was determined by a stopwatch (De Fátima Arrigoni-Blank *et al.*, 2004). A sensitivity test was carried out before the experiments and only the animals reacting within 15 s were chosen for the tests (Shinde *et al.*, 1999). Maximum cut-off time was established as 30 s to prevent tissue damage (De Fátima Arrigoni-Blank *et al.*, 2004). Effects of the synthesized compounds on the nociception were calculated by converting hot-plate latencies to percentage analgesic activity according to the following equation (Asongalem *et al.*, 2004):

$$\text{Analgesic activity } \% = [(\text{postdrug latency} - \text{predrug latency})/\text{predrug latency}] \times 100$$

Tail-clip test The mechanical antinociceptive activities of the compounds were measured by tail-clip test in mice as described elsewhere (D'Amour and Smith, 1941; Aydin *et al.*, 2003). Animals that did not response to the clamp within 10 s were discarded from the experiments before the experimental session (Adeyemi *et al.*, 2004). Cut-off time for the tail-clip tests was chosen as 10 s to avoid possible tissue damage (Ozturk *et al.*, 2002). Analgesia was expressed as a percentage of the maximum possible effect (MPE %), according the following equation (Gabra and Sirois, 2003):

$$\text{MPE } \% = [(\text{postdrug latency} - \text{predrug latency})/(\text{cut-off time} - \text{predrug latency})] \times 100$$

Acetic acid-induced writhing responses Acetic acid-induced writhing test was applied for the investigation of peripheral component of analgesic activity (Koster *et al.*, 1959). Mice were treated with an aqueous solution of acetic acid (0.6% v/v, i.p) at a dose of 10 ml/kg to induce contractions. Five minutes after the injection of acetic acid solution, the number of abdominal contractions and stretches during the following 10 min was recorded. After pretreatment with reference or synthesized compounds, significant reduction in the number of writhing was considered as positive analgesic response. The percentage protection against writhing was calculated according to following equation (Gülçin *et al.*, 2004):

$$\text{Protection } \% = [(\text{control mean} - \text{treated mean})/\text{control mean}] \times 100$$

Assessment of neurosedative activity

For examining possible sedative activity due to the compounds **2a–f**, which may interfere with the test results to give false positives, activity cage test was performed. The horizontal and vertical locomotor activities of the mice were recorded by the activity cage apparatus (Ugo Basile, No.7420, Varese, Italy). Interruptions of light beams to the photocells during horizontal and vertical movements of the animals were automatically recorded for 4 min (Votava *et al.*, 2005).

Assessment of motor coordination

For examining possible motor coordination deficits due to synthesized compounds, which may interfere with the test results, Rota-Rod test was performed. Before the experimental session, three trials were given for three consecutive days on the Rota-Rod apparatus (Ugo Basile 7560, Milano, Italy) set at a rate of 16 revolutions per minute. Mice that were able to remain on the rod longer than 180 s were selected for the test. Latency to fall from the rotating mill was recorded (Adzu *et al.*, 2002; Tabarelli *et al.*, 2004).

Statistical analyses

The data used in statistical analyses were obtained from six animals for each of the groups. Experimental data of all tests were analyzed by one-way ANOVA, following by Tukey's test. Statistical analyses of the experimental data were performed using GraphPad Prism 3.0 software (GraphPad Software, San Diego, CA, USA). The results were expressed as mean ± standard error of mean (S.E.M). Differences between data sets were considered as significant when p-value was less than 0.05.

Results and discussion

Chemistry

In this study, some 2-(2-carboxyphenylsulfanyl)-*N*-(4-substitutedphenyl)acetamide derivatives were synthesized (Fig. 2). Structure elucidations of the final compounds were performed with IR, ^{1}H-NMR, and ES-MS methods.

Literature surveys demonstrated that treatment of thiosaliyclic acid with alkyl halides under basic conditions gives *S*-alkylation reaction. Thus, in final reaction step, esterification of carboxyl group of thiosalicylic with 2-chloro-*N*-phenyl acetamide derivatives is unexpected (Mironov *et al.*, 2004; Volonterio and Zanda, 2005). Besides, spectral data are in accordance with the chemical structure of the compounds **2a–f**.

Characteristic stretching absorption of amide and carboxylic acid carbonyl (C=O) groups were observed at 1671–1684 cm^{-1} and 1712–1728 cm^{-1}, respectively. The stretching absorption at about 3348–3366 cm^{-1} and 3223–3257 cm^{-1} were recorded for amide N–H and carboxylic acid O–H bonds, respectively. Disappearance of stretching absorption for S–H bond at about 2550 cm^{-1} could be commented as evidence for target compounds.

In ^{1}H-NMR spectra, aromatic carboxyl group protons were observed at 12.11–12.23 ppm as a singlet. N–H and CH_2 protons of acetamide group gave peaks at 10.62–10.74 ppm as a broad and at 4.18–4.23 ppm as a singlet, respectively. Aromatic protons of phenyl groups were observed at 6.73–7.48 ppm as multiplet. Only the aromatic protons belong to 6th position of thiosalicylic acid and 3rd and 5th positions of *N*-(4-carboxyphenyl)acetamide moieties (for compound **2f**) could be separated from other aromatic protons and were observed at 8.16–8.21 ppm and 8.08 ppm as doublets, respectively.

M + 1 and M + 2 peaks in MS agreed well with the calculated molecular weight of the target compounds.

Pharmacology

As well as peripherally mediated analgesic actions, centrally mediated analgesic activities of NSAIDs have been reported previously (Vanegas, 2002; Anderson, 2008). Therefore, both central and peripheral analgesic action potentials of the synthesized compounds were studied in this present study. Hot-plate and tail-clip tests were performed for examining centrally mediated, whereas acetic acid-induced writhing tests were applied for investigating peripherally mediated analgesic actions of the synthesized

Table 1 Effects of reference and synthesized compounds on response latencies of mice in hot-plate tests

Treatment	Analgesia %
Control	1.32 ± 3.47
Paracetamol (100 mg/kg)	51.61 ± 6.50***
Thiosalicylic acid (100 mg/kg)	62.49 ± 11.91***
2a (100 mg/kg)	79.98 ± 10.75***
2b (100 mg/kg)	65.73 ± 9.84***
2c (100 mg/kg)	8.48 ± 5.91
2d (100 mg/kg)	89.37 ± 11.58***, [a,b]
2e (100 mg/kg)	35.12 ± 11.57
2f (100 mg/kg)	18.07 ± 13.82

Values are given as mean ± S.E.M. Significance against control values, *** $p < 0.001$; Significance against thiosalicylic acid, [a] $p < 0.05$; Significance against paracetamol, [b] $p < 0.01$. One-way ANOVA, post-hoc Tukey test, $n = 6$

Table 2 Effects of reference and synthesized compounds on response latencies of mice in tail-clip tests

Treatment	MPE % (Maximum possible effect %)
Control	0.70 ± 3.38
Paracetamol (100 mg/kg)	32.02 ± 4.77**
Thiosalicylic acid (100 mg/kg)	40.37 ± 8.98***
2a (100 mg/kg)	52.10 ± 6.98***
2b (100 mg/kg)	43.94 ± 3.87***
2c (100 mg/kg)	13.71 ± 3.02
2d (100 mg/kg)	72.31 ± 4.85***,[b,c]
2e (100 mg/kg)	25.01 ± 6.32
2f (100 mg/kg)	17.05 ± 5.86

Values are given as mean ± S.E.M. Significance against control values, ** $p < 0.01$; *** $p < 0.001$; Significance against thiosalicylic acid, [b] $p < 0.01$; Significance against paracetamol, [c] $p < 0.001$; One-way ANOVA, post-hoc Tukey test, $n = 6$

compounds. In this study, paracetamol and thiosalicylic acid increased the reaction times of mice in hot-plate (Table 1) and tail-clip (Table 2) and decreased the numbers of abdominal contractions in acetic acid-induced writhing tests (Table 3), therefore these reference compounds were exhibited significant analgesic activities in all applied tests.

Among the synthesized compounds, **2a**, **2b,** and **2d** caused statistically significant increase in reaction times of mice in hot-plate (Table 1) and tail-clip (Table 2) tests. These compounds decreased the number of abdominal contractions in acetic acid-induced writhing tests (Table 3). Significant increase in reaction times of animals in hot-plate and tail-clip tests indicated the analgesic actions of the compounds against thermal and mechanical noxious stimuli, respectively. Besides, decrease in the number of

Table 3 Effects of synthesized compounds on response latencies of mice in acetic acid-induced writhing tests

Treatment	Number of writhing	Protection %
Control	29.50 ± 2.20	–
Paracetamol (100 mg/kg)	20.83 ± 0.60*	29.38
Thiosalicylic acid (100 mg/kg)	19.50 ± 1.73*	33.89
2a (100 mg/kg)	13.33 ± 1.28***	54.80
2b (100 mg/kg)	14.83 ± 1.19***	49.72
2c (100 mg/kg)	26.84 ± 2.12	9.04
2d (100 mg/kg)	7.00 ± 1.29***,[c]	76.27
2e (100 mg/kg)	21.34 ± 2.32	27.68
2f (100 mg/kg)	23.50 ± 2.88	20.34

Values are given as mean ± S.E.M. Significance against control values, * $p < 0.05$; *** $p < 0.001$; Significance against thiosalicylic acid and paracetamol, [c] $p < 0.001$; One-way ANOVA, post-hoc Tukey test, $n = 6$

abdominal contractions and stretches in acetic acid-induced writhing test pointed out the analgesic activities of the compounds against chemical noxious stimuli. Therefore, analgesic actions of compounds **2a**, **2b,** and **2d** in this study seem to be related with all thermal, mechanical, and chemical neuronal pathways.

Hot-plate test is known to predominantly measures responses organized supraspinally, while tail-clip test mainly measures spinal reflexes (Wong *et al.*, 1994; Gabra and Sirois, 2003). As the compounds **2a**, **2b**, and **2d** showed significant analgesic activities in both hot-plate and tail-clip tests (Tables 1, Table 2), it may be suggested that these analgesic activities may related to both supraspinal and spinal mechanisms. Furthermore, protections of animals from writhing behavior in the writhing tests (Table 3), indicating that peripheral mechanisms may also play a role in the analgesic actions.

On the other hand, none of the applied compounds significantly changed horizontal or vertical spontaneous locomotor activities in activity cage measurements or falling latencies in Rota-Rod tests (data not shown). None of the animals died at 100 mg/kg dose. Unchanged responses in activity cage and Rota-Rod tests exhibited the absence of neurosedative activity or motor coordination deficits, which may interfere with the test results to give false positives. Therefore, analgesic actions of paracetamol, thiosalicylic acid, and compounds **2a**, **2b**, and **2d** observed in this study were not caused by neurological deficits.

Bromo, methoxy, and carboxy substituted derivatives (**2c**, **2e**, and **2f**, respectively) in the series did not show analgesic activities. Among the synthesized compounds, methyl substituted derivative **2d**, non-substituted derivative **2a**, and chloro substituted derivative **2b** exhibited statistically significant analgesic effects. Compound **2d** had the highest analgesia values (%) than other synthesized compounds and

was statistically more potent than both paracetamol and thiosalycilic acid in all analgesia tests (Tables 1, 2, 3).

Obtained results had shown that variation of substitution on the chemical structure caused significant difference on analgesic activity. Methyl substitution on para position of *N*-phenylacetamide may be suggested to increase the analgesic activity. It can be hypothesized that different alkyl substitution on phenyl ring at para position may also increase the analgesic activity of title compounds.

Conclusion

The results of this investigation pointed out that some derivatives of *N*-phenylacetamide and thiosalicylic acid combined compounds exhibit strong supraspinal, spinal, and peripheral analgesic activities. Compound **2d** carrying methyl substituted phenyl ring showed more potent analgesic action than both paracetamol and thiosalicylic acid.

References

Adeyemi OO, Okpo SO, Okpaka O (2004) The analgesic effect of the methanolic extract of *Acanthus montanus*. J Ethnopharmacol 90:45–48

Adzu B, Amos S, Muazzam I, Inyang US, Gamaniel KS (2002) Neuropharmacological screening of *Diospyros mespiliformis* in mice. J Ethnopharmacol 83:139–143

Anderson BJ (2008) Paracetamol (acetaminophen): mechanisms of action. Paediatr Anaesth 18:915–921

Asongalem EA, Foyet HS, Ngogang J, Folefoc GN, Dimo T, Kamtchouing P (2004) Analgesic and antiinflammatory activities of *Erigeron floribundus*. J Ethnopharmacol 91:301–308

Aydin S, Beis R, Can OD (2003) Analgesic and antispasmodic activities of 2-(2-nitrophenyl)-1H-benzimidazole 5-carboxylic acid: evidence for the importance of the 2-(o-substituted phenyl) group. Pharmazie 58:405–408

Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R (2008) Opioid complications and side effects. Pain Physician 11:S105–120

Bertolini A, Ottani A, Sandrini M (2002) Selective COX-2 inhibitors and dual acting anti-inflammatory drugs: critical remarks. Curr Med Chem 9:1033–1043

Collina S, Azzolina O, Vercesi D, Brusotti G, Rossi D, Barbieri A, Lanza E, Mennuni L, Alcaro S, Battaglia D, Linati L, Ghislandi V (2003) Synthesis and pharmacological evaluation of new *N*-methylarylpyrrolidinols with analgesic activity. Farmaco 58:939–946

Cranswick N, Coghlan D (2000) Paracetamol efficacy and safety in children: the first 40 years. Am J Ther 7:135–141

D'Amour FE, Smith DL (1941) A method for determining loss of pain sensation. J Pharmacol Exp Ther 72:74–79

De Fátima Arrigoni-Blank M, Dmitrieva EG, Franzotti EM, Antoniolli AR, Andrade MR, Marchioro M (2004) Anti-inflammatory and analgesic activity of *Peperomia pellucida* (L.) HBK (Piperaceae). J Ethnopharmacol 91:215–218

Gabra BH, Sirois P (2003) Beneficial effect of chronic treatment with the selective bradykinin B1 receptor antagonists, R-715 and R-954, in attenuating streptozotocin-diabetic thermal hyperalgesia in mice. Peptides 24:1131–1139

Gülçin I, Küfrevioglu OI, Oktay M, Büyükokuroglu ME (2004) Antioxidant, antimicrobial, antiulcer and analgesic activities of nettle (*Urtica dioica* L.). J Ethnopharmacol 90:205–215

Habeeb AG, Rao PNP, Knaus EE (2001) Design and synthesis of 4, 5-diphenyl-4-isoxazolines: novel inhibitors of cyclooxygenase-2 with analgesic and antiinflammatory activity. J Med Chem 44:2921–2927

Jackson CH, MacDonald NC, Cornett JWD (1984) Acetaminophen. Can Med Assoc J 131:25–32

Kaplancikli ZA, Turan-Zitouni G, Revial G, Guven K (2004) Synthesis and study of antibacterial and antifungal activities of novel 2-[[(benzoxazole/benzimidazole-2-yl)sulfanyl] acetyl-amino]thiazoles. Arch Pharm Res 27:1081–1085

Kaplancikli ZA, Turan-Zitouni G, Ozdemir A, Devrim Can O, Chevallet P (2008) Synthesis and antinociceptive activities of some pyrazoline derivatives. Eur J Med Chem 44:2606–2610

Koster R, Anderson M, De Beer EJ (1959) Acetic acid and analgesic screening. Fed Am Soc Exp Biol 18:412–415

Meade EA, Smith WL, DeWitt DL (1993) Differential inhibition of prostaglandin endoperoxide synthetase (cyclooxygenase) isoenzymes by aspirin and other nonsteroidal anti-inflammatory drugs. J Biol Chem 268:6610–6614

Mironov MA, Ivantsova MN, Tokareva MI, Mokrushin VS (2004) New synthesis of 1,4-benzothiazepin-5-ones. Russ Chem Bull 53:1232–1236

Ozturk N, Baser KH, Aydin S, Ozturk Y, Calis I (2002) Effects of *Gentiana lutea* ssp. symphyandra on the central nervous system in mice. Phytother Res 16:627–631

Ramwell PW (1981) Biological importance of arachinodic acid. Arch Int Med 141:275–284

Sałat K, Filipek B, Wieckowski K, Malawska B (2009) Analgesic activity of 3-mono-substituted derivatives of dihydrofuran-2-one in experimental rodent models of pain. Pharmacol Rep 61:807–818

Shinde UA, Phadke AS, Nair AM, Mungantiwar AA, Dikshit VJ, Saraf MN (1999) Studies on the anti-inflammatory and analgesic activity of *Cedrus deodara* (Roxb.) Loud. wood oil. J Ethnopharmacol 65:21–27

Simon LS (2001) COX-2 inhibition: an advance or only pharmaceutical "hype"? Arthritis Rheum 45:209–215

Tabarelli Z, Rubin MA, Berlese DB, Sauzem PD, Missio TP, Teixeira MV, Sinhorin AP, Martins MAP, Zanatta N, Bonacorso HG, Mello CF (2004) Antinociceptive effect of novel pyrazolines in mice. Brazilian J Med Biol Res 37:1531–1540

Turan-Zitouni G, Kaplancikli ZA, Ucucu U, Ozdemir A, Chevallet P, Tunalı Y (2004) Synthesis of some 2-[(benzazole-2-yl)thio]-diphenylmethylacetamide derivatives and their antimicrobial activity. Phosphorus Sulfur Silicon Relat Elem 179:2183–2188

Vane JR (1978) The mode of action of aspirin-like drugs. Agents Actions 8:430–431

Vanegas H (2002) Bases for a spinal analgesic action of cyclooxygenase inhibitors. Proc West Pharmacol Soc 45:225–227

Volonterio A, Zanda M (2005) Synthesis of 1-aryl-tetralins and 4-aryl-benzopyrans by sulfoxide-mediated benzylic carbocation cyclizations. Tetrahedron Lett 46:8723–8726

Votava M, Hess L, Slíva J, Krsiak M, Agová V (2005) Dexmedetomidine selectively suppresses dominant behavior in aggressive and sociable mice. Eur J Pharmacol 523:79–85

Wong CH, Day P, Yarmush J, Wu W, Zbuzek UK (1994) Nifedipine-induced analgesic after epidural injections in rats. Anesth Anal 79:303–306

Wu W, Ercal N (2004) Determination of thiocyl in biological samples by liquid chromatography with ThioGlo 3 derivatization. J Chromatogr B 809:295–299