

Synthesis of Some Imidazo[1,2-a]pyrazine Derivatives and Evaluation of Their Antinociceptive Activity

Bazı İmidazo[1,2-a]pirazin Türevlerinin Sentezi ve Antinosiseptif Aktivitelerinin Değerlendirilmeleri

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Abstract

Objective: The imidazopyrazine ring is a biologically active heterocyclic ring. Many hydrazide-hydrazone-possessing compounds have been reported to have interesting bioactivity, such as antibacterial, antifungal, anticonvulsant, anti-inflammatory, antituberculosis, and analgesic activities. In particular, aroyl hydrazides/hydrazone-containing hetero-rings, such as indole, pyridine, and imidazo[2,1-b]pyridine, and imidazo[1,2-a]pyrazine, have attracted special attention. We designed and synthesized N-(4-substitutedbenzylidene)imidazo[1,2-a]pyrazine-2-carbohydrazide (2a-j) derivatives using the two aforementioned pharmacophoric units based on the synthetic procedure indicated in our previous study.

Methods: The structures of the compounds were elucidated using ¹H-NMR, ¹³C-NMR, and mass spectroscopy. Ten final compounds were screened for their possible *in vivo* antinociceptive activity using a hot plate and acetic acid-induced writhing tests. In addition, the potential anticonvulsant activities of these compounds were evaluated using the PTZ-induced seizure test. A rotarod test was performed to examine probable neurological deficits because of the test compounds.

Results: In the hot plate tests, none of the test compounds in the series demonstrated a significant effect. However, compound 2f, which was administered at 100 mg/kg, significantly decreased the number of writhing behaviors in the acetic acid-induced writhing tests, indicating the antinociceptive activity of this compound. The rotarod latencies of mice were not changed by the test compounds. Furthermore, the tested compounds were ineffective in the PTZ-induced seizure tests.

Conclusion: Compound 2f bearing 5-benzylidene moiety was determined as the most active compound.

Keywords: Antinociceptive, hydrazone, imidazopyrazine, hot plate, writhing test

Öz

Amaç: İmidazopyrazin halkası biyolojik olarak aktif bir heterosiklik halkadır. Bir dizi hidrazid-hidrazon türevi bileşiğin antibakteryal-antifungal, anti-konvülzan, antiinflamatuar, anti-tüberkülotik ve analjezik aktiviteye sahip olduğu belirtilmiştir. Aroylhidrazid-hidrazon yapısını içeren piridin, indol, imidazo [2,1-b]piridin ve imidazo[1,2-a]pirazin gibi hetero halkalar özel ilgi çekmektedir. N-(4-Süstitüe benziliden)imidazo[1,2-a]pirazin-2-karbohidrazit (2a-j) türevi bileşikler daha önce belirtilen iki farmakoforik grup kullanılarak önceki çalışmamızda yapılan sentez prosedürüne göre tasarlanmış ve elde edilmiştir. Bütün sonuç bileşiklerinin antinosiseptif aktiviteleri incelenmiştir.

Yöntemler: Bileşiklerin yapıları ¹H-NMR, ¹³C-NMR ve Kütle spektroskopisi gibi spektroskopik metodlarla aydınlatılmıştır. On adet sonuç bileşiği potansiyel *in vivo* antinosiseptif aktiviteleri sıcak taban ve asetik asitle indüklenmiş kıvrınma testi kullanılarak araştırılmıştır. Ayrıca bu bileşiklerin potansiyel anti-konvülzan aktiviteleri Pentilentetrazol (PTZ) ile uyarılmış nöbetlere karşı değerlendirilmiştir. Rota-Rod testi bileşiklerin muhtemel nörolojik hasarlarını incelemek amacıyla yapılmıştır.

Bulgular: Serideki bileşiklerden hiçbiri sıcak tabaka testinde belirgin bir etki gösterememiştir. Bununla birlikte 2f bileşiği asetik asitle indüklenmiş kıvrınma testinde 100 mg/kg dozla bileşiğin antinosiseptif etkisini gösteren bir biçimde kıvrınma davranışının sayısında göze çarpan bir düşüşe neden olmuştur. Farelerin Rota-Rod gecikme süreleri test bileşikleri tarafından değiştirilememiştir. Ayrıca, test bileşikleri PTZ ile indüklenen nöbet testlerinde de etkisizdir.

Sonuç: Benziliden kalıntısı taşıyan 2f bileşiği en aktif türev olarak belirlendi.

Anahtar kelimeler: Antinosiseptif, hidrazon, imidazopyrazin, sıcak taban testi, kıvrınma testi

INTRODUCTION

The imidazo[1,2-a]pyrazine nucleus has been reported with a broad range of bioactivities, such as antimicrobial, antiviral, anticancer, antiulcer, anticonvulsant, anti-inflammatory, analgesic, and hypoglycemic activities (1-4). The heterocyclic ring system is also an analog ring of the imidazo[1,2-a]pyridine structure (5), which exists in the structure of the anticonvulsant drugs zolpidem, alpidem, and saripidem (6). Moreover, the imidazo[1,2-a]pyrazine derivative compounds have exhibited theophylline-like pharmacological properties, such as muscle relaxant, cardiostimulant, and antibronchospasm activity, because of their similarity to the theophylline molecule, which includes an imidazo[1,2-a]pyrimidine ring in its structure (7-9). According to the literature (10), imidazo[1,2-a]pyrazine-3-(7H)-on derivative compounds were designed as a prodrug of ibuprofen, which is a strong non-steroidal anti-inflammatory drug, and is reported to have a high anti-inflammatory activity. Furthermore, there are many studies regarding the effect of imidazopyrazines on the central nervous system (CNS) (11-13).

Hydrazone groups, which are derived from the carboxylic acid structure, have analgesic effects and have similar effects as carboxylic acid derivatives on CNS (14). Moreover, *N*-acylhydrazone has come to prominence and has acquired an important place in medicinal chemistry as an effective pharmacophoric group (15-17).

In this study, we designed and synthesized *N'*-(4-substitutedbenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2a-j) derivatives using the aforementioned two pharmacophoric units according to the synthetic procedure indicated. Ten final compounds were screened for their *in vivo* antinociceptive activity.

METHODS

General

The melting point (mp) was determined using the Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded with the following instruments: IR, Shimadzu 8400S spectrophotometer (Shimadzu, Tokyo, Japan); ¹H-NMR, Bruker 400 MHz spectrometer; ¹³C-NMR, Bruker 100 MHz spectrometer; and MS-FAB VG Quattro Mass spectrometer.

General procedure for the synthesis of compounds

Imidazo[1,2-*a*]pyrazine-2-carboxylic acid hydrazides (1a, 1b):

A mixture of ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (0.1 mol) and hydrazine hydrate (0.2 mol) in ethanol was refluxed for 12 h. At the end of the reaction (observed by TLC), the mixture was cooled down, and the precipitated product was isolated by filtration to afford the intermediate compounds 1a and 1b.

N'-(4-substitutedbenzylidene)-5-substitutedimidazo[1,2-*a*]pyrazine-2-carbohydrazide (2a-2j):

Equimolar quantities of acid hydrazide intermediates (30 mmol) and various benzaldehydes in 30 mL ethanol were refluxed for 8–10 h. After TLC, the reaction mixture was cooled, and the solid precipitate was filtered and washed with ethanol.

N'-Benzylideneimidazo[1,2-*a*]pyrazine-2-carbohydrazide (2a)

Mp: 255°C (3)

N'-(4-Methylbenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2b)

Mp: 257°C, Lit: 256–258°C (3).

N'-(4-Chlorobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2c)

Mp: 238°C (3).

N'-(4-Nitrobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2d)

Mp: 275°C (decomp) (3).

N'-(4-Cyanobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2e)

Yield: 74%, mp: 297°C (decomp). IR (cm⁻¹): ν_{\max} 3215 (NH), 1659 (C=O), 1602–1422 (C=N) and (C=C), and 1235–1015 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.82–7.89 (4H, m, phenyl protons), 7.96 (1H, d, *J* = 4.48 Hz, aromatic proton), 8.60–8.67 (3H, m, N=CH and aromatic protons), 9.15 (1H, s, aromatic proton), and 11.29 (1H, s, N-NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): δ 111.92 (C), 117.01 (CH), 118.62 (C), 120.76 (CH), 127.66 (2CH), 129.80 (C), 132.76 (2CH), 138.83 (C), 139.33 (CH), 139.69 (C), 144.07 (CH), 146.58 (CH), and 158.22 (C). MS (FAB) (*m/z*): [M]⁺ 290. Anal. Calcd. for C₁₅H₁₀N₆O: C, 62.06; H, 3.47; and N, 28.95. Found: C, 62.08; H, 3.48; and N, 28.94.

5-Bromo-*N'*-benzylidene-imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2f)

Yield: 69%. mp: 265°C (decomp). IR (cm⁻¹): ν_{\max} 3210 (NH), 1662 (C=O), 1603–1410 (C=N) and (C=C), and 1251–1018 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.42–7.47 (3H, m, phenyl protons), 7.67–7.70 (2H, m, phenyl protons), 8.26 (1H, s, aromatic proton), 8.59 (2H, s, N=CH and aromatic protons), 9.18 (1H, s, aromatic proton), and 11.29 (1H, s, N-NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): δ 112.46 (C), 116.76 (CH), 127.18 (2CH), 128.85 (2CH), 130.20 (CH), 131.75 (C), 134.27 (CH), 139.94 (C), 140.11 (C), 142.35 (CH), 148.83 (CH), and 157.49 (C). MS (FAB) (*m/z*): [M]⁺ 358, [M+1]⁺ 359. Anal. Calcd. for C₁₄H₁₀BrN₅O: C, 48.86; H, 2.93; and N, 20.35. Found: C, 48.87; H, 2.92; and N, 20.34

5-Bromo-*N'*-(4-methylbenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2g)

Yield: 68%. mp: 271°C (decomp). IR (cm⁻¹): ν_{\max} 3221 (NH), 1645 (C=O), 1584–1442 (C=N) and (C=C), and 1247–1020 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 2.31 (3H, s, CH₃), 7.24 (2H, d, *J* = 8.02 Hz, phenyl protons), 7.58 (2H, d, *J* = 8.06 Hz, phenyl protons), 8.27 (1H, s, aromatic proton), 8.54 (1H, s, N=CH), 8.58 (1H, s, aromatic proton), 9.17 (1H, s, aromatic proton), and 11.30 (1H, s, N-NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): δ 21.05 (CH₃), 112.46 (C), 116.70 (CH), 127.17 (2CH), 129.47 (2CH), 131.57 (CH), 131.74 (C), 139.94 (C), 140.05 (C), 140.19 (C), 142.33 (CH), 148.86 (CH), and 157.38 (C). MS (FAB) (*m/z*): [M]⁺ 358, [M+1]⁺ 359. Anal. Calcd. for C₁₅H₁₂BrN₅O: C, 50.30; H, 3.38; and N, 19.55. Found: C, 50.31; H, 3.38; and N, 19.53.

5-Bromo-*N'*-(4-chlorobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2h)

Yield: 72%. mp: 287°C (decomp). IR (cm⁻¹): ν_{\max} 3222 (NH), 1642 (C=O), 1603–1429 (C=N) and (C=C), and 1212–1054 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.49 (2H, d, *J* = 8.48 Hz, phenyl protons), 7.70 (2H, d, *J* = 8.54 Hz, phenyl protons), 8.27 (1H, s, aromatic proton), 8.57 (1H, s, N=CH), 8.59 (1H, s, aromatic proton), 9.18 (1H, s, aromatic proton), and 11.29 (1H, s, N-NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): δ 112.47 (C), 116.84 (CH), 128.81 (2CH), 128.98 (2CH), 131.78 (CH), 133.22 (C), 134.63 (C), 139.96 (C), 140.00 (C), 142.37 (CH), 147.49 (CH), and 157.55 (C). MS (FAB) (*m/z*): [M]⁺ 378, [M+1]⁺ 379, [M+2]⁺ 380. Anal. Calcd. for C₁₄H₉BrClN₅O: C, 44.41; H, 2.40; and N, 18.50. Found: C, 44.41; H, 2.39; and N, 18.50.

5-Bromo-*N'*-(4-nitrobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2i)

Yield: 65%. mp: 301°C (decomp). IR (cm⁻¹): ν_{\max} 3217 (NH), 1654 (C=O), 1603–1438 (C=N) and (C=C), and 1232–1019 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.94 (2H, d, *J* = 8.80 Hz, phenyl protons), 8.26–8.29 (3H, m, aromatic proton), 8.63 (1H, s, aromatic proton), 8.69 (1H, s, N=CH), 9.19 (1H, s, aromatic proton), and 11.28 (1H, s, N-NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): δ 112.45 (C), 116.62 (CH), 128.55 (2CH), 128.18 (2CH), 130.98 (CH), 133.02 (C), 134.03 (C), 140.96 (C), 142.09 (C), 142.49 (CH), 147.69 (CH), and 157.95 (C). MS (FAB) (*m/z*): [M]⁺ 389, [M+1]⁺ 390. Anal. Calcd. for C₁₄H₉BrN₅O₂: C, 43.21; H, 2.33; and N, 21.60. Found: C, 43.19; H, 2.35; and N, 21.58.

5-Bromo-*N'*-(4-cyanobenzylidene)imidazo[1,2-*a*]pyrazine-2-carbohydrazide (2j)

Yield: 68%. mp: 288°C (decomp). IR (cm⁻¹): ν_{\max} 3220 (NH), 1661 (C=O), 1598–1445 (C=N) and (C=C), and 1254–1023 (C-O). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.85 (2H, d, *J* = 8.90 Hz, phenyl protons), 7.88 (2H, d, *J* = 9.01 Hz, phenyl protons), 8.27 (1H, s, aromatic proton), 8.61 (1H, s, N=CH), 8.63 (1H, s, aromatic proton), 9.18 (1H, s,

aromatic proton), and 11.30 (1H, s, N-NH). MS (FAB) (m/z): $[M]^+$ 369, $[M+1]^+$ 370. Anal. Calcd. for $C_{15}H_9BrN_6O$: C, 48.80; H, 2.46; and N, 22.76. Found: C, 48.79; H, 2.45; and N, 22.78. ^{13}C -NMR (100 MHz, $DMSO-d_6$, ppm): δ 112.27 (C), 116.54 (CH), 118.32 (C), 127.73 (2CH), 128.98 (C), 132.80 (2CH), 138.72 (C), 134.63 (CH), 139.96 (C), 140.01 (C), 141.86 (CH), 147.03 (CH), and 158.51 (C).

Pharmacology

Animals

Swiss albino mice, weighing 30 g to 40 g, were housed at a room temperature of $24 \pm 1^\circ C$ with a 12/12-h light/dark cycle. The animals received only water 12 h before the experiments, because of the need to avoid food interference with absorption of the compounds. The experimental protocols that were used were approved by the Local Ethical Committee on Animal Experimentation of the Anadolu University, Eskişehir, Turkey. Informed consent is not required for this study.

Nociceptive tests

The compounds were screened to determine their antinociceptive activity profiles ($n=6$). The central component of nociception was projected from the hot plate test (18). Furthermore, the acetic acid-induced writhing test was used to determine the potential antinociceptive activity against chemical noxious stimulus (19). Diclofenac sodium (DCL) was used as the standard drug.

Behavioral tests

The rotarod test was performed ($n=6$) to examine the possible neurological deficits caused by the test compounds, which could give rise to false positives, such as muscle relaxant or impairment of the motor coordination (20).

To evaluate the presence of anticonvulsant activity, PTZ-induced seizure tests were performed. PTZ at a dose of 80 mg/kg was applied to mice ($n=10$ in each group) to induce seizure (21). The time to the appearance of the first seizure (latency, min), percentage inhibition

of convulsions, and percentage inhibition of death were recorded (22). Mice were observed over a period of 30 min; the absence of an episode of clonic spasm of at least a 5-s interval pointed out a compound's ability to abolish the effect of PTZ on seizure threshold, and these animals were thus accepted as protected (23).

Statistical analyses

The statistical analyses of the experimental data were determined by using GraphPad Prism 3.0 software (GraphPad Software, San Diego, CA, USA). One-way analysis of variance, followed by Tukey's test were used to specify significant differences between the groups. The results were expressed as the mean \pm standard error of the mean (SEM). Differences between data sets were considered as significant when the p value was <0.05 .

RESULTS

The present study was undertaken to synthesize ten imidazo[1,2-*a*]pyrazine-2-carboxylic acid arylidenehydrazide derivatives and to investigate their potential antinociceptive activity. According to the synthetic procedure as indicated in figure 1, ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate was used as the starting material. Imidazo[1,2-*a*]pyrazine-2-carboxylic acid hydrazides were obtained by the reaction of the ester compound and hydrazine hydrate in ethanol under reflux conditions. The condensation of the hydrazides 1a and 1b with aromatic aldehydes in ethanol in the presence of catalytic amounts of acetic acid gained acylhydrazone derivatives of the final compounds (2a-j) in 64-74% yields. All the final compounds were well characterized by IR, 1H NMR, ^{13}C NMR, and MS spectroscopic data. In the IR spectra of the final compounds, the significant stretching bands due to N-H, C=O, C-N and C-C, and C-O were at approximately 3225-3210 cm^{-1} , 1666-1642 cm^{-1} , 1610-1422 cm^{-1} , and 1254-1015 cm^{-1} , respectively. The 1H -NMR spectra data were also consistent with the assigned structures. In the 400-MHz 1H -NMR spectrum of the compounds, protons of the imidazo[1,2-*a*]pyrazine ring were resonated much further downfield according to the phenyl protons, which

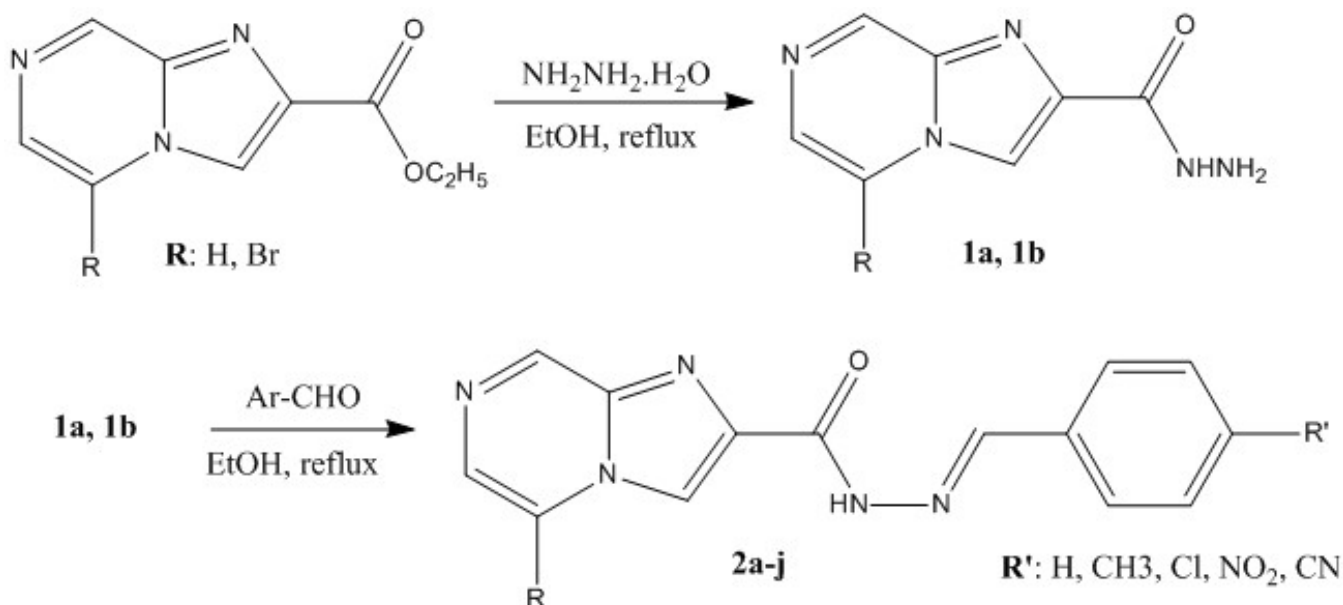


Figure 1. The synthesis scheme of the compounds (2a-j)

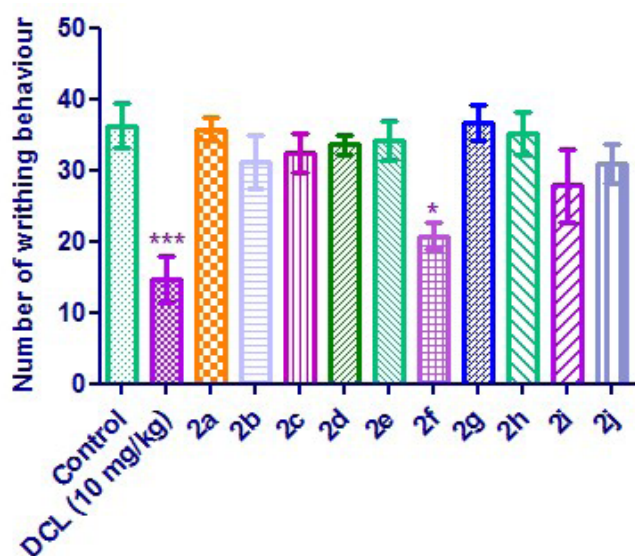


Figure 2. The effect of diclofenac sodium (DCL, 10 mg/kg) and the test compounds (100 mg/kg) on acetic acid-induced abdominal contractions and stretches of the mice in the writhing tests. Significant differences relative to "the control group" * $p < 0.05$, *** $p < 0.001$. Values are given as the mean \pm SEM. One-way ANOVA, post-hoc Tukey's test, $n = 6$

were approximately 8.26–9.19 ppm. In ^{13}C -NMR, carbonyl carbon was assigned at about 158 ppm and the other carbons were seen at the estimated areas. In the mass spectra of compounds $[M+1]$, the peaks were observed in agreement with their molecular formula.

According to the antinociceptive activity results, none of the test compounds in the series showed a significant antinociceptive effect in the hot plate tests (data not shown). On the other hand, compound 2f (100 mg/kg) significantly ($p < 0.05$) inhibited writhing behavior in the acetic acid-induced writhing tests (Figure 2).

DISCUSSION

According to activity results, the reduction in the number of writhes after 2f treatment suggests that the mechanism of this compound may be related with a decrease in the release of inflammatory mediators in peripheral tissues or by direct blockage of its receptors, which results in an antinociceptive effect. Furthermore, this activity could be caused by an augmentation of the nociceptive threshold or by interruption of the transmission of the pain stimulus to the nerve fiber.

In the rotarod tests, none of the tested compounds altered the latency to fall from the rotating mill (data not shown), indicating that the observed antinociception in this study is unlikely to be caused by motor abnormalities.

In the PTZ-induced seizure tests, none of the tested compounds significantly altered the onset of PTZ-induced tonic convulsions or prevented the animals from PTZ-induced convulsions.

CONCLUSION

In this study, ten imidazo[1,2-a]pyrazine-2-carboxylic acid arylidenehydrazide derivatives (2a-j) have been synthesized and evaluated for

their antinociceptive activity. Compound 2f bearing 5-benzylidene moiety was determined as the most active compound.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Anadolu University Ethics Committee on Animal Experiments.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - G.T.Z.; Design - G.T.Z.; Supervision - Z.A.K.; A.Ö.; Resource - G.T.Z.; Materials - G.T.Z.; Data Collection&/or Processing - L.Y.; Analysis&/or Interpretation - L.Y.; Literature Search - L.Y.; Writing - L.Y.; Critical Reviews - C.M.

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