Clinical and Experimental Health Sciences

Original Article / *Özgün Araştırma*

# *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 $^{1}$H-NMR, $^{13}$C-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 administrated 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:** İmidazopirazin halkası biyolojik olarak aktif bir heterosiklik halkadır. Bir dizi hidrazid-hidrazon türevi bileşiğin antibakteryial-antifungal, antikonvülzan, antiinflamatuvar, antitüberkülotik ve analjezik aktiviteye sahip olduğu belirtilmiştir. Aroilhidrazid-hidrazon yapısını içeren piridin, indol, imidazo [2,1-b]piridin ve imidazo[1,2-a]pirazin gibi hetero halkalar özel ilgi çekmektedir. N-(4-Sübstitüe 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 $^{1}$H-NMR, $^{13}$C-NMR ve Kütle spektroskopisi gibi spektroskopik metodlarla aydınlatılmıştır. On adet sonuç bileşiği potansiyel *in vivo* antinosiseptif aktiviteleri sıcak taban ve asetik asitle indüklenmiş kıvranma testi kullanılarak araştırılmıştır. Ayrıca bu bileşiklerin potansiyel antikonvülzan 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 kıvranma testinde 100 mg/kg dozla bileşiğin antinosiseptif etkisini gösteren bir biçimde kıvranma 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, imidazopirazin, sıcak taban testi, kıvranma 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, cardiotonic, 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).

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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); $^1$H-NMR, Bruker 400 MHz spectrometer; $^{13}$C-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$^{-1}$): $\nu_{max}$ 3215 (NH), 1659 (C=O), 1602–1422 (C=N) and (C=C), and 1235–1015 (C-O). $^1$H-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). $^{13}$C-NMR (100 MHz, DMSO-$d_6$, 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 $C_{15}H_{10}N_6O$: 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$^{-1}$): $\nu_{max}$ 3210 (NH), 1662 (C=O), 1603–1410 (C=N) and (C=C), and 1251–1018 (C-O). $^1$H-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). $^{13}$C-NMR (100 MHz, DMSO-$d_6$, 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 $C_{14}H_{10}BrN_5O$: 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$^{-1}$): $\nu_{max}$ 3221 (NH), 1645 (C=O), 1584–1442 (C=N) and (C=C), and 1247–1020 (C-O). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.31 (3H, s, $CH_3$), 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). $^{13}$C-NMR (100 MHz, DMSO-$d_6$, ppm): δ 21.05 ($CH_3$), 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 $C_{15}H_{12}BrN_5O$: 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$^{-1}$): $\nu_{max}$ 3222 (NH), 1642 (C=O), 1603–1429 (C=N) and (C=C), and 1212–1054 (C-O). $^1$H-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). $^{13}$C-NMR (100 MHz, DMSO-$d_6$, 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 $C_{14}H_9BrClN_5O$: 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$^{-1}$): $\nu_{max}$ 3217 (NH), 1654 (C=O), 1603–1438 (C=N) and (C=C), and 1232–1019 (C-O). $^1$H-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). $^{13}$C-NMR (100 MHz, DMSO-$d_6$, 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 $C_{14}H_9BrN_6O_3$: 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$^{-1}$): $\nu_{max}$ 3220 (NH), 1661 (C=O), 1598–1445 (C=N) and (C=C), and 1254–1023 (C-O). $^1$H-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±1°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±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, $^1$H 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 $^1$H-NMR spectra data were also consistent with the assigned structures. In the 400-MHz $^1$H-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

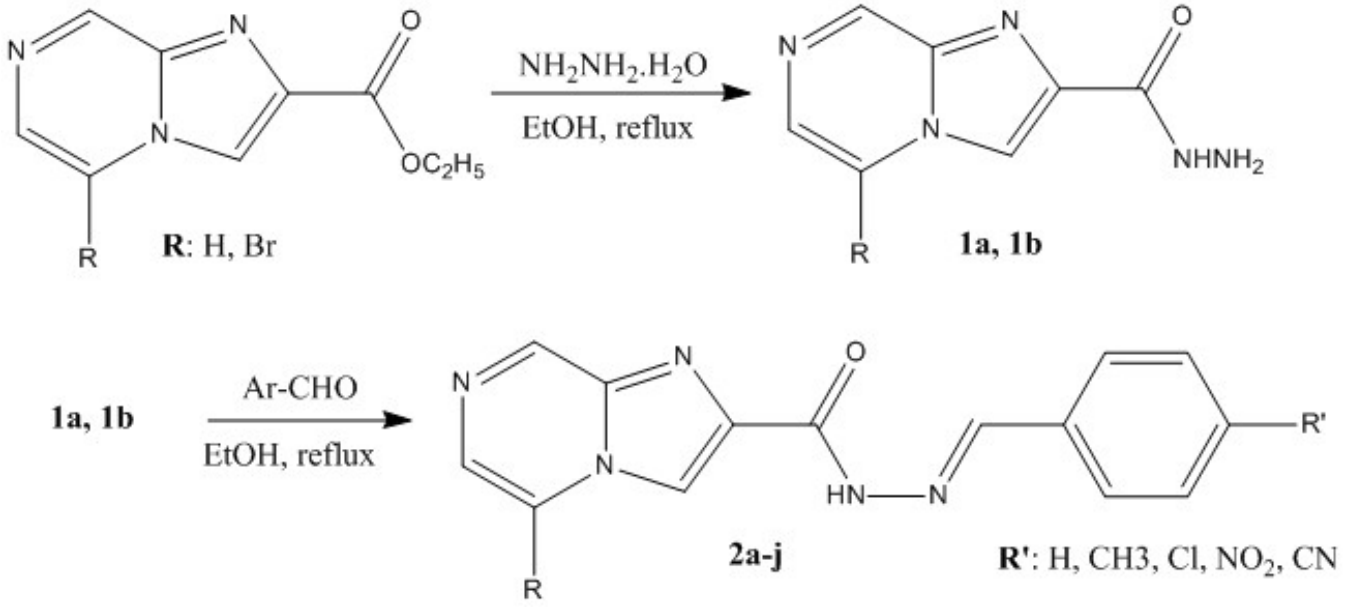


Figure 1. The synthesis scheme of the compounds (2a-j)

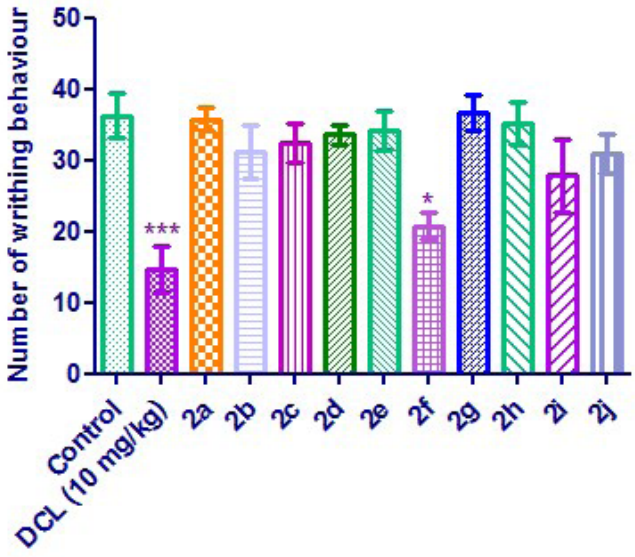


Figure 2. The effect of diclofenac sodium (DCL, 10 mg/kg) and the test compounds (100 mg/kg) on acetic acid–induced abdominal contractions and stretches of the mice in the writhing tests. Significant differences relative to "the control group" *p<0.05, ***p<0.001. Values are given as the mean ± SEM. 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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## REFERENCES

1. Hemasrilatha S, Sruthi K, Manjula A, Harinadha Babu V, Vittal Rao B. Synthesis and anti-inflammatory activity of imidazol[1,2-a]pyridnyl/pyrazinyl benzamides and acetamides. Indian J Chem 2012; 51B: 981-7.
2. Rimoli MG, Avallone L, De Caprariis P, Luraschil E, Abignente E, Filippelli W, et al. Research on heterocyclic compounds. XXXVII. Synthesis and antiinflammatory activity of methyl-substituted imidazo[1,2-a]pyrazine derivatives. Eur J Med Chem 1997; 32: 195-203. [CrossRef]
3. Ozdemir A, Turan-Zitouni G, Kaplancikli ZA, Tunali Y. Synthesis and biological activities of new hydrazide derivatives. J Enzym Inhib Med Chem 2009; 24: 825-31. [CrossRef]
4. Ozdemir A, Turan-Zitouni G, Asim Kaplancikli Z, Işcan G, Khan S, Demirci F. Synthesis and the selective antifungal activity of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine derivatives. Eur J Med Chem 2010; 45: 2080-4. [CrossRef]
5. Ulloora S, Shabaraya R, Adhikari AV. New 6-bromoimidazo[1,2-a]pyridine-2-carbohydrazide derivatives: synthesis and anticonvulsant studies. Med Chem Res 2014; 23: 3019-28. [CrossRef]
6. Tomczuk BE, Taylor CR Jr, Moses LM, Sutherland DB, Lo YS, Johnson DN, et al. 2-Phenyl-3H-imidazo[4,5-b]pyridine-3-acetamides as nonbenzodiazepine anticonvulsants and anxiolytics. J Med Chem 1991; 34: 2993-3006. [CrossRef]
7. Basiuk VA. Imidazo[1,2-a]pyrazines. Russ Chem Rev 1997; 66; 187-204. [CrossRef]
8. Sablayrolles C, Cros GH, Milhavet JC, Rechenq E, Chapat JP, Boucard M, et al. Synthesis of imidazo[ 1,2-a Ipyrazine derivatives with uterine-relaxing, antibronchospastic, and cardiac-stimulating properties. J Med Chem 1984; 27: 206-12. [CrossRef]
9. Laurent F, Michel A, Bonnet P A, Chapat JP, Boucard M. Evaluation of the relaxant effects of SCA40, a novel charybdotoxin-sensitive potassium

channel opener, in guinea-pig isolated trachealis. Br J Pharmacol 1993; 108: 622-6. [CrossRef]
10. De Wael F, Muccioli GG, Lambert DM, Sergent T, Schneider YJ, Rees JF, et al. Chemistry around imidazopyrazine and ibuprofen: Discovery of novel fatty acid amide hydrolase (FAAH) inhibitors. Eur J Med Chem 2010; 45: 3564-74. [CrossRef]
11. Barlin GB, Davies LP, Ireland SJ, Ngu MML, Zhang JK. Imidazo[1,2-b]pyridazines. XII. Syntheses and central nervous system activities of some substituted imidazo[1,2-b]pyridazines and related imidazo[1,2-a]pyridines, Imidazo[1,2-a]pyrimidines and imidazo[1,2-a]pyrazines. Aust J Chem 1992; 45: 877-88. [CrossRef]
12. Abignente E, De Caprariis P, Rimoli MG, Capasso G, Autore F. Research on heterocyclic compounds, XXIX. Synthesis and antiinflammatory activity of imidazo[1,2-a]pyrazine derivatives. Farmaco 1992; 47: 919-30.
13. Michael A, Laurent F, Chapat JP, Boucard M, Bonnet PA. Pharmacological activities of imidazo[1,2-alpha]pyrazine derivatives. Arzneimittel-Forsch 1995; 45: 1288-93.
14. Rollas S, Küçükgüzel ŞG. Biological activities of hydrazone derivatives. Molecules 2007; 12: 1910-39. [CrossRef]
15. Congiu C, Onnis V. Synthesis and biological evaluation of novel acylhydrazone derivatives as potential antitumor agents. Bioorg Med Chem 2013; 21: 6592-9. [CrossRef]
16. Limaa PC, Limaa LM, da Silva KCM, Lédab PHO, de Mirandac AL, Fragac CA, et al. Synthesis and analgesic activity of novel N-acylarylhydrazones and isosters, derived from natural safrole. Eur J Med Chem 2000; 35: 187-203. [CrossRef]
17. Todeschini AR, de Miranda ALP, da Silva KCM, Parrini SC, Barreiro EJ. Synthesis and evaluation of analgesic, antiinflammatory and antiplatelet properties of new 2-pyridylarylhydrazone derivatives. Eur J Med Chem 1998; 33: 189-99. [CrossRef]
18. Asongalem EA, Foyet HS, Ngogang J, Folefoc GN, Dimo T, Kamtchouing P. Analgesic and antiinflammatory activities of Erigeron floribundus. J Ethnopharmacol 2004; 91: 301-8.[CrossRef]
19. Koster R, Anderson M, De Beer E. Acetic acid for analgesic screening. J Fed Proc 1959; 18: 412-8.
20. Adzu B, Amos S, Muazzam I, Inyang US, Gamaniel KS. Neuropharmacological screening of Diospyros mespiliformis in mice. J Ethnopharmacol 2002; 83: 139-43. [CrossRef]
21. Wilhelm EA, Jesse CR, Roman SS, Bortolatto CF, Nogueira CW. Anticonvulsant effect of (E)-2-benzylidene-4-phenyl-1,3-diselenole in a pilocarpine model in mice. Life Sci 2010; 87: 620-7. [CrossRef]
22. Silva FD, Silva MG, Feng D, de Freitas RM. Evaluation of central nervous system effects of iso-6-cassine isolated from Senna spectabilis var. excelsa (Schrad) in mice. Fitoterapia 2011; 82: 255-9. [CrossRef]
23. Ya'u J, Yaro AH, Abubakar MS, Anuka JA, Hussaini IM. Anticonvulsant activity of Carissa edulis (Vahl) (Apocynaceae) root bark extract. J Ethnopharmacol 2008; 120: 255-8. [CrossRef]