Arylidene Carbazole Carbohydrazides: Synthesis and Characterization

Ariliden Karbazol Hidrazitler: Sentezi ve Karakterizasyonu

Research Article

Cevher Gündoğdu Hızlıateş
Department of Chemistry, Faculty of Sciences, Dokuz Eylul University, Buca, Izmir, Turkey.

ABSTRACT

Because of the wide range of pharmacological activities and their distinctive structural features hydrazones and carbazole alkaloids have attracted considerable attention in medicinal chemistry. In this study, new carbazole acyl hydrozones (3a-k) which may have high biological activity potential, were synthesized with condensation reaction between carbazole hydrazide and benzaldehyde derivatives. After determination of the melting points of all synthesized derivatives, their structures were identified by FT-IR and ^{1}H-NMR spectroscopic methods.

Key Words
Carbazole, carbohydrazide, hydrazide-hydrazone, biological activity.

ÖZ

Geniş farmakolojik etkinlikleri ve kendine özgü yapısal özellikleri nedeniyle, hidrazonlar ve karbazol alkaloitleri tıbbi kimyada büyük ilgi görmektedir. Bu çalışmada, karbazol hidrazit bileşiği ile benzaldehit türevleri arasındaki kondenzasyon reaksiyonu ile yüksek biyolojik aktiflik potansiyeline sahip olabilecek yeni karbazol açil hidrazon türevleri (3a-k) sentezlenmiştir. Sentezlenen türevlerin erime noktaları belirlendikten sonra, yapıları FT-IR ve 1H-NMR spektroskopik yöntemleri ile aydınlatılmıştır.

Anahtar Kelimeler
Karbazol, karbohidrazit, hidrazit-hidrazon, biyolojik aktiflik.

Article History: Dec 13, 2017; Revised: Feb 27, 2018; Accepted: Feb 28, 2018; Available Online: Mar 26, 2018.

DOI: 10.15671/HJBC.2018.226

Correspondence to: C. Gündoğdu Hızlıateş, Department of Chemistry, Faculty of Sciences, Dokuz Eylul University, Izmir, Turkey.
Tel: +90 232 301 79 09 Fax: +90 0232 453 41 88 E-Mail: cevher.gundogdu@deu.edu.tr

INTRODUCTION

Studies on the diagnosis and treatment of cancer, which is one of the most common diseases of our age, are increasing day by day. The discovery of new medicines and agents in cancer treatment is very important because the number of drugs used in the treatment of cancer disease is insufficient and the side effects are too high.

Hydrazide-hydrazone derivatives are important compounds for pharmaceutical chemistry. The biological activity associated with these compounds was attributed to the presence of the (–CONHN=CH–) moiety. Because of their broad spectrum of biological activities such as anticonvulsant [1,2], antidepressant [3], analgesic and antiinflammatory [4], antiplatelet [5], antimalarial [6], antimicrobial [4,7,8], anti tuberculosis [9-14], antitumoral [15,16] activities, there are lots of study about hydrazides. Especially antitumor activity researches about hydrazide derivatives are important for breast [17,18], ovarian [19], renal [20], prostate [16] cancer.

Carbazole alkaloids have been had significant pharmacological activities such as anti-microbial [21], anti-tumor [22,23], anti-HIV [24], anti-oxidant [25] activity since their discovery and the attention on carbazole alkaloids has increased rapidly. The studies until today show that carbazole alkaloids and it's synthetic derivatives have cytotoxic, apoptosis inducing and antiproliferating activities on pancreatic [26], leukemia [27,28], prostate [29] and lung [30] cancer.

In this study, by combining these two biologically active groups, carbazole bearing new arylidene carbohydrazide derivatives were synthesized. After determination of the melting points of all synthesized derivatives, their structures were identified by FT-IR and ^{1}H-NMR spectroscopic methods.

MATERIALS and METHODS

Chemicals and Instrument

All solvents and chemicals were used as purchased without further purification. Thin-layer chromatography (TLC) was conducted on aluminium sheets coated with silica gel 60 F_{254}, obtained from Merck (Darmstadt, Germany)., with visualisation by UV lamp (254 or 360 nm). Column chromatography was carried out with silica gel 60 (particle size 0.040-0.063 mm, 230-400 mesh; (Merck, Darmstadt, Germany) and commercially available solvents. All melting points were measured on a Gallenkamp melting-point apparatus in open capillaries and are uncorrected. For characterization of synthesized molecules, Fourier transform infrared spectroscopy (FTIR) analysis was studied with PerkinElmer Spectrum BX-II Model FTIR spectrophotometer. The samples within KBr pellets were measured in the range of 4000 and 400 cm^{-1}. Proton (^{1}H) NMR spectra was obtained on a Varian AS-400 NMR spectrometer with tetramethylsilane as an internal standard.

Synthesis of 4-Methyl-9H-carbazole-3-carbohydrazide (2)

Ethyl 4-methyl-9H-carbazole-3-carboxylate, (10 g, 39.5 mmol) was refluxed with hydrazine hydrate (25 mL, 80%) in ethanol (50 mL) for 6 h (Scheme 1). After cooling the separated solid was filtered. The compound was obtained as white needles (8.5 g, 90%), mp: 290-292ºC. IR (KBr, ν_{max}, cm^{-1}): 3159 (NH), 3280 (NH), 2974 (CH), 1684 (C=O). ^{1}H NMR (DMSO-d_6): 2.85 (s, 3H, CH_3), 4.47 (s, 2H, NH_2), 7.20 (t, 1H, J= 8.0 Hz, ArH), 7.31-7.37 (m, 2H, ArH), 7.41 (t, 1H, J= 8.0 Hz, ArH), 7.53 (d, 1H, J= 8.0 Hz, ArH), 8.18 (d, 1H, J= 7.6 Hz, ArH), 9.32 (s, 1H, CONH), 11.42 (s, 1H, NH).

General Procedure for the Synthesis of Carbazole Acyl Hydrazone Derivatives (3a-k)

Carbazole hydrazide 2 (5 mmol) was refluxed with benzaldehyde derivatives (5 mmol) in the presence of one drop of glacial acetic acid in ethanol (25 mL) for 4 h (Scheme 1). Then the reaction mixture was cooled and precipitate was filtered. The crude product was recrystallized from ethanol yielded carbazole acyl hydrazone derivatives.

N'-Benzylidene-4-methyl-9H-carbazole-3-carbohydrazide (3a)

Yield: 70%; mp: 312-314ºC. IR (KBr, ν_{max}, cm^{-1}): 3246 (NH), 3214 (NH), 3054 (CH), 1631 (C=O), 1540 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.92 (s, 3H, CH_3), 7.23 (t, 2H, J= 7.2 Hz, ArH), 7.41-7.57 (m, 6H, ArH), 7.74 (d, 2H, J= 7.2 Hz, ArH), 8.22 (d, 1H, J= 7.2 Hz, ArH), 8.37 (s, 1H, N=CH), 11.52 (s, 1H, CONH), 11.73 (s, 1H, NH).

N′-(4-Fluorobenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3b)

Yield: 67%; mp: 299-302ºC. IR (KBr, ν_{max}, cm^{-1}): 3222 (NH), 3068 (CH), 1636 (C=O), 1547 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (s, 3H, CH_3), 7.23 (t, 1H, J= 7.2 Hz, ArH), 7.30 (t, 2H, J= 8.4 Hz, ArH), 7.40-7.46 (m, 2H, ArH), 7.51 (d, 1H, J= 8.4 Hz, ArH), 7.55 (d, 1H, J= 8.0 Hz, ArH), 7.79 (t, 2H, J= 7.6 Hz, ArH), 8.21 (d, 1H, J= 8.0 Hz, ArH), 8.34 (s, 1H, N=CH), 11.52 (s, 1H, CONH), 11.73 (s, 1H, NH).

N′-(4-Chlorobenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3c)

Yield: 62%; mp: 271-273ºC. IR (KBr, ν_{max}, cm^{-1}): 3285 (NH), 3203 (NH), 3049 (CH), 1618 (C=O), 1535 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 2.88 (s, 3H, CH_3), 7.21 (d, 1H, J= 8.0 Hz, ArH), 7.34-7.55 (m, 6H, ArH), 7.74 (d, 2H, J= 8.4 Hz, ArH), 8.20 (d, 1H, J= 7.6 Hz, ArH), 8.31 (s, 1H, N=CH), 11.50 (s, 1H, CONH), 11.76 (s, 1H, NH).

N′-(4-Bromobenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3d)

Yield: 72%; mp: 281-283ºC. IR (KBr, ν_{max}, cm^{-1}): 3289 (NH), 3199 (NH), 3047 (CH), 1622 (C=O), 1537 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (s, 3H, CH_3), 7.22 (t, 1H, J= 7.6 Hz, ArH), 7.40-7.52 (m, 4H, ArH), 7.55 (d, 1H, J= 8.0 Hz, ArH), 7.65-7.74 (m, 3H, ArH), 8.21 (d, 1H, J= 8.0 Hz, ArH), 8.31 (s, 1H, N=CH), 11.52 (s, 1H, CONH), 11.78 (s, 1H, NH).

4-Methyl-N′-(4-methylbenzylidene)-9H-carbazole-3-carbohydrazide (3e)

Yield: 70%; mp: 339-340ºC. IR (KBr, ν_{max}, cm^{-1}): 3226 (NH), 3048 (CH), 1625 (C=O), 1542 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 2.35 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 7.22 (t, 1H, J= 7.2 Hz, ArH), 7.27 (d, 2H, J= 8.0 Hz, ArH), 7.38-7.46 (m, 2H, ArH), 7.50 (d, 1H, J= 8.4 Hz, ArH), 7.55 (d, 1H, J= 8.0 Hz, ArH), 7.62 (d, 2H, J= 8.4 Hz, ArH), 8.21 (d, 1H, J= 8.4 Hz, ArH), 8.30 (s, 1H, N=CH), 11.52 (s, 1H, CONH), 11.65 (s, 1H, NH).

N′-(4-tert-Butylbenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3f).

Yield: 65%; mp: 268-270ºC. IR (KBr, ν_{max}, cm^{-1}): 3402 (NH), 3212 (NH), 2960 (CH), 1632 (C=O), 1538 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 1.29 (s, 3H, $C(CH_3)_3$), 2.90 (s, 3H, CH_3), 7.20 (t, 1H, J= 8.4 Hz, ArH), 7.37-7.48 (m, 4H, ArH), 7.50 (d, 1H, J= 8.4 Hz, ArH), 7.54 (d, 1H, J= 8.4 Hz, ArH), 7.65 (d, 2H, J= 8.4 Hz, ArH), 8.19 (d, 1H, J= 8.0 Hz, ArH), 8.31 (s, 1H, N=CH), 11.53 (s, 1H, CONH), 11.69 (s, 1H, NH).

N′-(4-Hydroxybenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3g)

Yield: 64%; mp: 293-294ºC. IR (KBr, ν_{max}, cm^{-1}): 3582 (NH), 3260 (NH), 3200 (OH), 3070 (CH), 1635 (C=O), 1581 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 6.79 (d, 2H, J= 8.0 Hz, ArH), 7.19 (t, 1H, J= 7.6 Hz, ArH), 7.32-7.56 (m, 6H, ArH), 8.14-8.20 (m, 2H, ArH, N=CH), 11.49 (s, 1H, CONH), 11.67 (s, 1H, NH).

N′-(4-Methoxybenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3h)

Yield: 73%; mp: 319-321ºC. IR (KBr, ν_{max}, cm^{-1}): 3254 (NH), 3075 (CH), 1616 (C=O), 1547 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 2.89 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.01 (d, 2H, J= 7.6 Hz, CH_3O-ArH), 7.21 (t, 1H, J= 8.0 Hz, ArH), 7.35-7.44 (m, 2H, ArH), 7.48 (d, 1H, J= 8.0 Hz, ArH), 7.52 (d, 1H, J= 8.0 Hz, ArH), 7.67 (d, 2H, J= 7.6 Hz, ArH), 8.20 (d, 1H, J= 8.0 Hz, ArH), 8.26 (s, 1H, N=CH), 11.50 (s, 1H, CONH), 11.59 (s, 1H, NH).

N′-(4-(Dimethylamino)benzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3i)

Yield: 68%; mp: 313-315ºC. IR (KBr, ν_{max}, cm^{-1}): 3269 (NH), 2909 (CH), 1643 (C=O), 1552 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 2.88 (s, 3H, CH_3), 2.95 (s, 6H, $N(CH_3)_2$), 6.55 (d, 2H, J= 8.0 Hz, $(CH_3)_2$N-ArH), 7.18 (t, 1H, J= 7.6 Hz, ArH), 7.35-7.55 (m, 6H, ArH), 8.18-8.21 (m, 2H, ArH and N=CH), 11.42 (s, 1H, CONH), 11.50 (s, 1H, NH).

4-Methyl-N′-(4-nitrobenzylidene)-9H-carbazole-3-carbohydrazide (3j)

Yield: 73%; mp: 288-289ºC. IR (KBr, ν_{max}, cm^{-1}): 3267 (NH), 1654 (C=O), 1529 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 2.94 (s, 3H, CH_3), 7.23 (t, 1H, J= 7.6 Hz, ArH), 7.42-7.60 (m, 4H, ArH), 7.92-8.30 (m, 5H, ArH), 8.46 (s, 1H, N=CH), 11.55 (s, 1H, CONH), 12.05 (s, 1H, NH).

N′-(4-Cyanobenzylidene)-4-methyl-9H-carbazole-3-carbohydrazide (3k)

Yield: 67%; mp: 268-269ºC. IR (KBr, ν_{max}, cm^{-1}): 3374 (NH), 3207 (NH), 3053 (CH), 2232 (CN), 1647 (C=O), 1537 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (s, 3H, CH_3), 7.21 (d, 1H, J= 7.6 Hz, ArH), 7.39-

7.57 (m, 5H, ArH), 7.82-7.94 (m, 3H, ArH), 8.19 (d, 1H, J= 7.2 Hz, ArH), 8.38 (s, 1H, N=CH), 11.54 (s, 1H, CONH), 11.98 (s, 1H, NH).

RESULTS and DISCUSSION

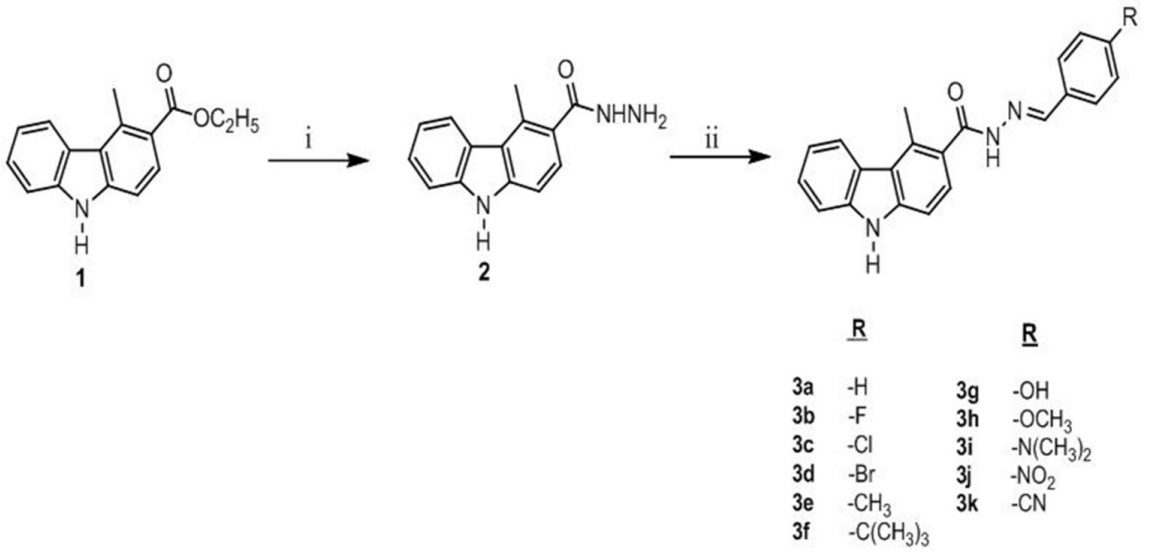
In this work, firstly carbazole carbohydrazide compound was synthesized. And then via condensation reaction with various benzaldehyde derivatives and carbazole carbohydrazide compound, arylidene carbazole carbohydrazide derivatives were obtained (Scheme 1). After determination of the melting points of all synthesized derivatives, their structures were identified by FT-IR and ^{1}H-NMR spectroscopic methods.

From the spectroscopic studies, IR spectra of the target hydrazones showed NH (indol) stretching bands in the range 3222-3582; NH stretching bands in the range 3199-3269; C=O stretching bands in the range 1616–1654 and C=N stretching bands in the range 1529-1581 cm^{-1}, respectively. In the ^{1}H NMR spectra of the Arylidene Carbazole Carbohydrazide derivatives , the azomethine –N=CH- proton appeared at 8.20-8.46 ppm as a sharp singlet, and whereas characteristic of the –CONH- group at 11.42-11.55 ppm was a broad singlet. The singlet peaks which appeared at 11.50-12.05 ppm were indole NH protons. The other protons appeared at the expected chemical shifts and integral values.

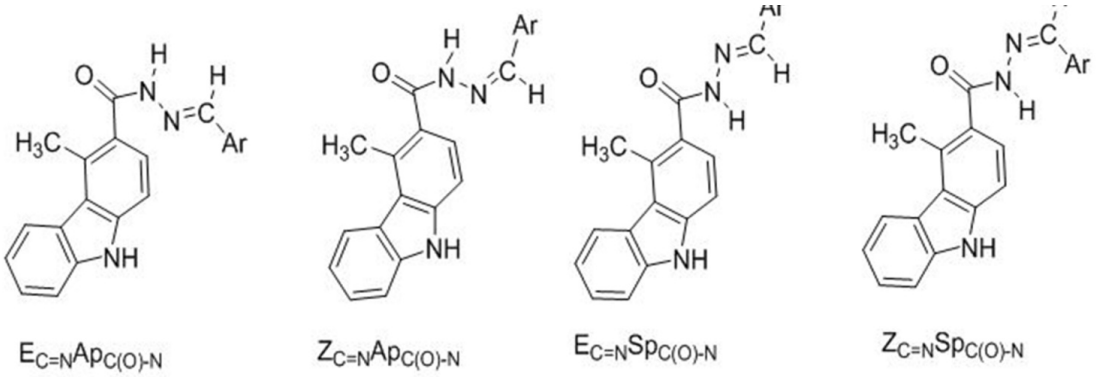
N-acylhydrazones can exist in four possible forms (Scheme 2). In respect to C=N two of them are geometrical isomers (E/Z) and the other two rotamers (antiperiplanar (*Ap*) and synperiplanar (Sp)) about amide N-CO (Figure 1). According to the literature, because of the steric hindrance $Z_{C=N}$ conformer is not reliazed [31,32]. Similarly, the existence of non-plannar form of C=N-NH moiety can be ruled out as it would disturb the n-π conjugation thereby the energy of stabilization [32]. So that N-acylhydrazones which are derived from aromatic aldehydes are expected in $E_{C=N}$ form according to the X-ray data of the Syakaev's study and the ratio of rotamers present in solution can be calculated from the ^{1}H NMR spectra of each compound [33]. In another previous study some tetrahydrocarbazole derivatives were synthesized and their conformer properties were studied by energetically calculations. And they had found that in solution two $E_{C=N}$ isomers are more stable than $Z_{C=N}$ and the most stable conformer is $E_{C=N}Ap_{C(O)-N}$ [34].

In former works it was suggested that when an aromatic structure was connected to the amide bond (ArCO-NH-), because of the sp^2 hybridizied C atoms a rotation around C(O)-N was not observed. So that this type of compounds can be in only one conformational structure that is $E_{C=N}$ which is the most stable conformer [35-38].

According to this results when we analyzed ^{1}H NMR spectras of the Arylidene Carbazole Carbohydrazide derivatives (for example Figure 2), only one set of signal was observed for all spesific groups such as –CO-NH- and –N=CH-.



Scheme 1. Synthesis route of Some Arylidene Carbazole Carbohydrazides. Reagent and Conditions: i) $NH_2NH_2.H_2O$, ethanol, reflux, 4h; ii) ArCHO, ethanol, AcOH, reflux, 6h.



Scheme 2. Possible structures for E and Z conformers of 3a-k.

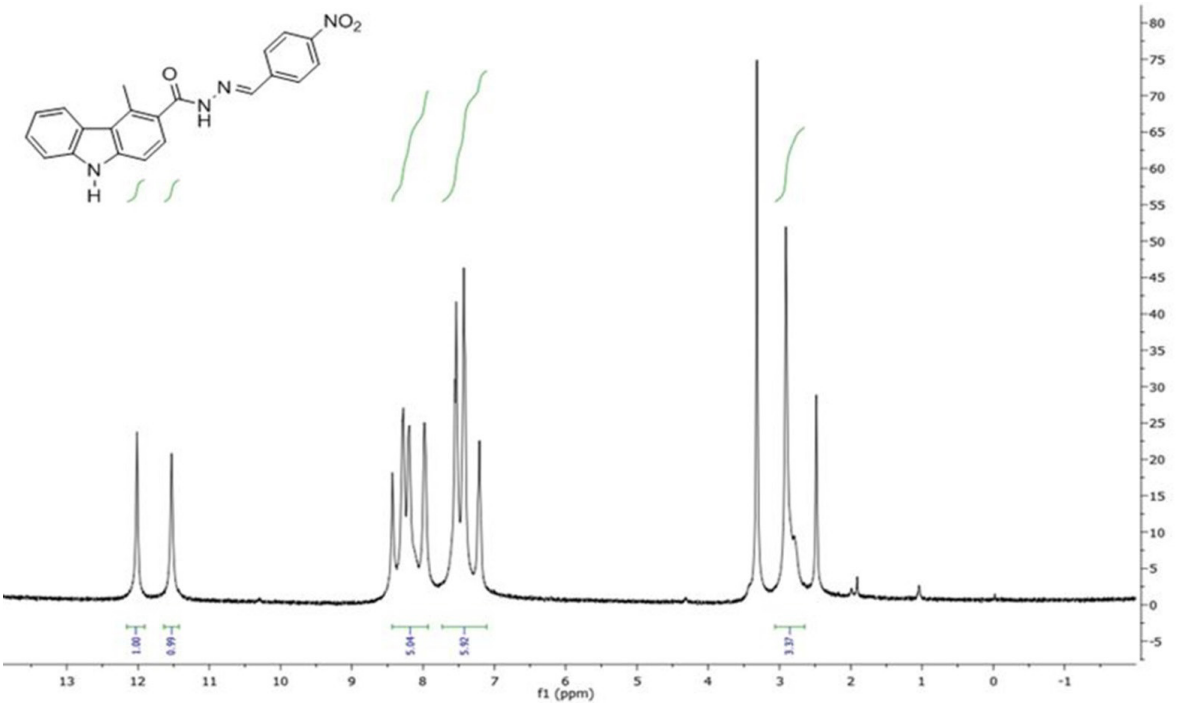


Figure 1. ^{1}H NMR spectrum of 4-Methyl-N'-(4-nitrobenzylidene)-9H-carbazole-3-carbohydrazide (3j) in DMSO-d_6.

Because of the aromatic carbazole moiety there is not a rotation around the C(O)-N bond and so there is only $E_{C=N}$ conformational structure in our solutions.

Because of the wide pharmacological activities of the hydrazide derivaties and carbazole alkaloids, the new synthesized Arylidene Carbazole Carbohydrazide derivatives whose yields are in the range 62-73%, may have high biological activity potential.

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