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SYNTHESIS, CHARACTERIZATION, AND PHARMACOLOGICAL EVALUATION OF SOME NOVEL HYDRAZONE DERIVATIVES DERIVED FROM 3-((4-FORMYL-2-METHOXYPHENOXY) METHYL) BENZONITRILE

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Key words:

Vanillin, Benzonitrile, Hydrazone, Antiinflammatory, Analgesic, Antibacterial

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ABSTRACT: Hydrazones are an important classe of biologically active compounds found in many synthetic compounds. In view of their importance in synthetic chemistry, the present article reported that a new series of novel hydrazone derivatives **(4a-e)** were synthesized by condensation of 3-((4-formyl-2-methoxyphenoxy)methyl)benzonitrile(3) with different benzohydrazides and confirmed by their IR, 1H NMR, and Mass spectral data. Further these synthesized derivatives **(4a-e)** were evaluated for their biological activities such as antiinflammatory, analgesic, and antibacterial activities. All the derivatives were showing the pharmacological activities mainly due to the presence of pharmacophore, azomethine group (CONH- N=CH) and were modified with various substituents. Among all the compounds **4a, 4d,** and **4e** incorporated with 4-methoxy, 4-chloro and 2,4-dichloro moieties exhibited more antiinflammatory activity and the remaining compounds **4b** and **4c** incorporated with 4-bromo and 2-bromo substituents showed moderate activity when compared with standard reference, indomethacin. The compounds **4d, 4e** and **4b** showed good analgesic activity and remaining compounds **4a** and **4c** showed moderate activity comparable to that of standard drug diclofenac. The compounds **4a** and **4e** exhibited excellent antibacterial activity and the compounds **4b, 4c** and **4d** showed less activity when compared with standard drug, Gentamycin.

INTRODUCTION: Hydrazones constitute biologically active drug molecules. Hydrazone derivatives are containing highly reactive azomethine group (CONH- N=CH) and thus useful in new drug development [1].Recently, a lot of biologically important hydrazone derivatives with a number of functional groups have been synthesized from aromatic and aliphatic compounds [2].

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New compounds are being synthesized as drugs in order to combat diseases with maximal therapeutic effects and minimal toxicity. Hydrazones are used for the synthesis of novel heterocyclic compounds [3]. Hydrazones have attracted a considerable attention of medicinal chemists due to their wide range of biological importance in medicinal chemistry. Many studies have confirmed that hydrazone derivatives exhibit a wide spectrum of biological activities including anti-inflammatory [4, 5] analgesic [6, 7] antibacterial [8, 9] antifungal[10, 11], anticancer [12], antioxidant[13, 14] antidepressant [15], antitubercular [16], cytotoxicity [17], antiamoebic [18], antitumor [19], antiplatelet [20], anticonvulsant [21], antimycobacterial [22], antihypertensive [23] and antinociceptive [24] activities. Encouraged by the

biological applications of hydrazones, the present research work is aspired to describe synthesis, characterization and antiinflammatory, analgesic and antibacterial activities of novel hydrazone derivatives **4a-e** derived from vanillin.

MATERIALS AND METHODS:

Chemicals and solvents used were purchased from Fluka and Merck. All the reagents used were of analytical grade. For thin-layer chromatography (TLC) analysis, Merck precoated silica gel 60 F254 Plates were used and spots were visualized with UV light. Melting point determinations were performed by using Mel-temp apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts were reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The Mass spectra were recorded on Agilent ion trap MS.

Preparation of 3-((4-formyl-2-methoxyphenoxy) methyl)benzonitrile(3) from vanillin(1) with 3-(bromomethyl) benzonitrile(2):

Vanillin was used as a starting material for the preparation of hydrazones. K_2CO_3 (0.905g, 6.55mmol) was added to the DMF solution containing vanillin(1) (1g, 6.57mmol), and then added 3-(bromomethyl) benzonitrile **(2)** (1.41g, 7.23mmol). The reaction mixture was stirred at 80 ^{o}C, for 2h. After the reaction reached completion, the mixture was cooled to room temperature and the precipitate obtained was filtered and washed with petroleum ether, to obtain the pure compound**(3)**. The 3-((4-formyl – 2 - methoxy phenoxy) methyl)benzonitrile**(3)** was synthesized and the quantified data along with the spectral data has been presented.

A white solid was obtained in 95% yield. mp 88 ^{o}C; FT-IR (KBr): υ_{max} 3448, 3348, 2973, 2824, 2739, 2229, 1680, 1590, 1517, 1451, 1425, 1386, 1341, 1318, 1275, 1244, 1177, 1125, 1029, 887, 870, 816, 796, 785, 683, 639, 619, 551 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 5.28 (s, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.55 (dd, J = 2.0, 8.4 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.94 (s, 1H), 9.85 (s, 1H); MS (ESI) m/z 267.8 $(M+H)^+$.

Synthesis of Hydrazone Derivatives (4a-e) from 3-((4-formyl - 2 - methoxy phenoxy) methyl) benzonitrile (3) reacting with different Benzohydrazide derivatives (a – e):

The hydrazone derivatives **(4a-e)** were synthesized by addition of benzohydrazide derivatives (a-e) to the solution of ethanol containing the 3-((4-formyl-2-methoxyphenoxy) methyl) benzonitrile **(3)**, and refluxed for 1h. The reaction mixture was cooled to room temperature and the precipitate obtained was filtered and washed with petroleum ether, to obtain the pure compounds **4a-e**. The yield of products varied from 89 – 97%. The hydrazone derivatives **4a-e** were synthesized and the quantified data along with the spectral data was presented.

(E)-*N′*-(4-(3-cyanobenzyloxy) - 3 - methoxy benzylidene)-4-methoxybenzohydrazide(4a):
White solid; Yield: 96%; mp 198-206 ^{o}C; FT- IR (KBr): υ_{max} 3435, 3232, 2939, 2838, 2230, 1644, 1605, 1576, 1542, 1507, 1462, 1417, 1377, 1295, 1269, 1256, 1232, 1178, 1139, 1052, 1030, 1010, 971, 899, 839, 810, 793, 760, 690, 627, 537 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 3.85 (s, 3H), 5.21 (s, 2H), 7.20-7.05 (m, 4H), 7.37 (s, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.92-7.80 (m, 5H), 8.38 (s, 1H), 11.64 (s, 1H); MS (ESI) m/z, 416 (M+1).

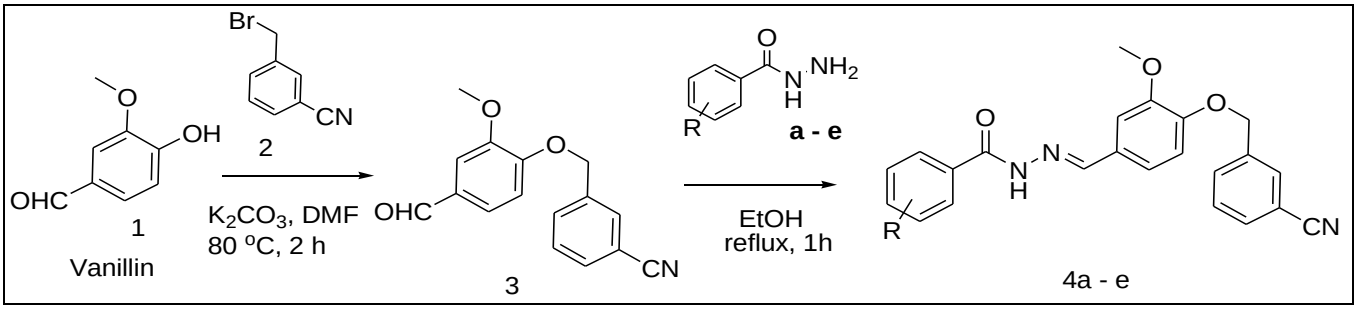
(E)-*N* - (4-(3-cyanobenzyloxy) – 3 - methoxy benzylidene)-4-bromobenzohydrazide(4b):
White solid; Yield: 92%; mp 195-200 ^{o}C; FT- IR (KBr): υ_{max} 3431, 3221, 3064, 2936, 2234, 1649, 1605, 1544, 1510, 1483, 1453, 1418, 1376, 1270, 1233, 1198, 1166, 1138, 1034, 1009, 970, 895, 867, 795, 754, 687, 623, 535 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s. 3H), 5.22 (s, 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.93-7.74 (m, 7H), 8.38 (s, 1H), 11.83 (s, 1H); MS (ESI) m/z, 463.9 (M-1).

(E)-*N′*-(4-(3-cyanobenzyloxy) – 3 - methoxy benzylidene)-2-bromobenzohydrazide(4c):

White solid; Yield: 97%; mp 185-190 ^{o}C; FT- IR (KBr): υ_{max} 3448, 3185, 3047, 3008, 2230, 1657, 1600, 1557, 1509, 1463, 1420, 1390, 1375, 1301, 1268, 1226, 1171, 1138, 1068, 1029, 1004, 901, 863, 831, 808, 793, 757, 737, 693, 655, 555 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.85 (*3.63, s, 3H), 5.21 (*5.14, s, 2H), 7.00 (*6.95, *J* = 8.6 Hz, 1H), 7.20 (*7.10, d, *J* = 8.6 Hz, 1H), 7.55-7.35 (m, 4H), 7.76-7.52 (m, 3H), 7.93-7.80 (m, 2H), 8.19 (*7.95, s, 1H), 11.94 (*11.82, s, 1H); MS (ESI) m/z, 463.9 (M+H).

(E)-*N'*-(4-(3-cyanobenzyloxy) – 3 - methoxy benzylidene)-4-chlorobenzohydrazide(4d):
White solid; Yield: 94%; mp 185-190 ^{o}C; FT-IR (KBr): υ_{max} 3223, 3078, 3055, 2976, 2938, 2879, 2236, 1649, 1605, 1596, 1542, 1509, 1485, 1454, 1419, 1376, 1329, 1271, 1233, 1198, 1166, 1139,1093, 1033, 1006, 970, 896, 866, 841, 795, 755, 687, 624, 538 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.86 (s, 3H), 5.22(s, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.38 (s, 1H), 7.66 - 7.60 (m, 3H), 7.83 (t, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 3H), 8.38 (s, 1H), 11.83 (s, 1H); MS (ESI) m/z, 419.9 (M+H)$^{+}$.

(E)-*N'*-(4-(3-cyanobenzyloxy) - 3 - methoxy benzylidene)-2,4-dichlorobenzohydrazide(4e):
White solid; Yield: 89%; mp 185-190 ^{o}C; FT-IR (KBr): υ_{max} 3431, 3190, 3056, 2932, 2836, 2232, 1652, 1599, 1561, 1515, 1467, 1386, 1331, 1268, 1234, 1172, 1133, 1103, 1034, 1010, 943, 899, 854, 793, 689, 571, 534 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.85 (*3.66, s, 1H), 5.21 (*5.15, s, 1H), 7.03 (*6.98, d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 1.6 Hz, 1H), 7.66-7.48 (m, 3H), 7.93-7.74 (m, 3H), 8.18 (*7.95, s, 1H), 12.03 (*11.87, s, 1H); MS (ESI) m/z, 453.9 (M+1).



SCHEME: 1

4a; R= 4-Methoxy
4b; R= 4-Bromo
4c; R= 2-Bromo
4d; R= 4-Chloro
4e; R= 2,4-Dichloro

Animals and Instruments used:
Adult Wistar rats of either sex weighing between 150-200g were used for the study of anti-inflammatory activity. Adult Wistar mice of either sex (20-25 g) were used for the study of the analgesic activity. All experimental procedures were carried out according to the guidelines given by the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) and were approved by the Institutional Animal Ethics Committee with registration number. 1722/RO/ERe/S/13/CPCSEA.

All the synthesized compounds were tested for *in vivo* antiinflammatory activity [25] in adult wistar rats by paw edema method and edema was produced by using Carrageenan, foot volume measured by using plethysmometer. Analgesic activity [26] was carried in adult wistar mice by using Eddy's hot plate method. *In vitro* antibacterial activity [27] was done by the disk diffusion technique.

Pharmacological screening:
The synthesized compounds were screened for anti inflammatory, analgesic, and antimicrobial activities. The test dose for the synthesized compounds was fixed as 10 mg/kg for anti inflammatory and analgesic activities and fixed as 100 and 200 µg/mL for antimicrobial activity. Indomethacin was taken as the standard drug for

anti inflammatory activity and Diclofenac sodium was taken as the standard drug for analgesic activity. Gentamycin was used as standard drug for antimicrobial activity.

Anti inflammatory activity by paw edema method:

Adult Wistar rats of either sex with a body weight between 150-200g were used to study anti inflammatory activity. The animals were starved overnight. The test drug and standard were suspended in 1%CMC (control) and given orally. Thirty minutes later, 0.05 ml of 1% solution of carrageenan was given by a subcutaneous injection into the plantar side of the left hind paw of all the rats. The paw volume was measured by using plethysmometer after injection. Then the paw volume was again measured after 1h, 2h, 3h and 4h time intervals. The results were summarized in **Table 1.**

Analgesic activity by Eddy's hot plate:

Adult Wistar mice of either sex (20-25 g) Were weighed and numbered, the basal reaction-time was noted by observing hind paw licking in animals when placed on the hot plate maintained at constant temperature (55ºC). Drug was given by oral route to animals and noted the reaction time of animals on the hot plate at 30, 60, 90, 120 and 180 min after the drug administration. The percent increase in reaction-time (as index of analgesia) was calculated at each time interval. The results were shown in **Table 2.**

Antibacterial activity by disk diffusion method:

The antibacterial activity of the synthesized compounds was determined by the standard disk diffusion method. The test organism chosen were *Escherichia coli and Bacillus subtillis*. The concentration of the sample compounds and the standard was prepared as 100 and 200 µg/mL in DMSO. Gentamycin was used as standard drug. The antimicrobial study was conducted for the determination of following parameters like, Zone of Inhibition and MIC (minimum inhibitory concentration), Different concentrations of synthetic chemical compounds were tested for anti-microbial activity by disc diffusion method. Nutrient agar medium was inoculated with different microorganisms and once the media was solidified, it was punched with a 6 mm diameter well. The tested compounds solutions were prepared in DMSO and evaluated them for their in vitro antibacterial activity against *Bacillus subtillis*, and *Escherichia coli* respectively. Agar plates containing bacteria and synthetic chemical compounds were incubated at 37ºC for 24 hrs. Antimicrobial activity was evaluated by measuring the inhibition zone. The zone of inhibition obtained by different synthesized compounds was compared with that of standard drug Gentamycin. The results were given in **Table 3.**

RESULTS AND DISCUSSION:

Chemistry:

The synthesized hydrazone derivatives 4a–e explained in this paper were prepared according to the synthetic **Scheme 1**. Vanillin 1 present in the solution mixture of K_2CO_3 and DMF was condensed with 3-(bromomethyl) benzonitrile **(2)** by stirring at 80^{o}c, for 2h to get the pure compounds **(3)** in 95% yield. To the solution of 3-((4-formyl - 2 - methoxyphenoxy) methyl) benzonitrile **(3)** in ethanol, add Benzohydrazide derivatives **(a-e)** and refluxed for 1h to obtain the pure compounds **4a-e**. The yield of the product varied from 89 – 97%. The structures of the synthesized hydrazone derivatives **4a-e** were confirmed by IR, ^{1}H NMR and Mass spectral data. The ^{1}H NMR data for the derivatives **4a–e** were in agreement with the assigned structures. All the aliphatic and aromatic protons were observed at expected regions. The mass spectra of compounds **4a-e** showed (M+1) peaks, in agreement with their molecular formula.

Biological evaluation:

Anti-inflammatory activity:

The newly prepared hydrazone derivatives **4a-e** were screened for anti-inflammatory activity at concentration 10 mg/kg by carrageenan paw edema method. Among all tested compounds, **4a**, **4d** and **4e** exhibited maximum activity, while compounds **4b** and **4c** showed moderate activity when compared with standard indomethacin, anti inflammatory agent. In general, it is observed from **Table 1** and that the compounds having 4-methoxy, 4-chloro, and 2, 4-dichloro exhibited excellent anti inflammatory activity and remaining compounds showed moderate activity. As all the tested

compounds emerged as active against inflammation, it indicates that this basic moiety can be a promising scaffold for anti inflammatory drugs.

Analgesic activity:

The newly prepared chalcone derivatives **4a-e** were screened for analgesic activity at concentration 10 mg/kg by using hot plate method. Among all tested compounds, **4d**, **4e** and **4b** showed maximum activity, while compounds **4a** and **4c** showed moderate activity when comparable with disease control. In general, it is observed from **Table-2** and that the compounds having 4-chloro, 2, 4-dichloro and 4-bromo, exhibited excellent analgesic activity and remaining compounds showed moderate activity. As all the tested compounds emerged as active against analgesia, it indicates that this basic moiety can be a promising nucleus for analgesic drugs. It may be suggested that this basic moiety can be a promising scaffold for analgesic drugs.

Anti- Bacterial Activity:

The anti-bacterial activity of **4a–e** compounds was determined by the disc diffusion method with Gentamycin (100 & 200µg/mL) as the reference standard. The synthesized compounds were screened against two Gram positive bacterial strains viz., *Escherichia coli,* and *Bacillus subtillis*. The outcome of the results are presented in the **Table-3**, it is evident from the results that, compounds **4a**, **4d** and **4e** exhibited high activity against the *Escherichia Coli* bacteria, the rest of the compounds were found to be moderately active (**4b** and **4c**) against the *Escherichia Coli*. The compound **4a** exhibited high activity against the *Bacillus subtilis* bacteria, the rest of the compounds were found to be moderately active (**4b**, **4c**, **4d** and **4e**) against the *Bacillus subtilis*. It is observed from the above anti-bacterial data that within the hydrazone derivatives **4a-e**, compounds incorporated with the substituents such as 4-methoxy, and 2, 4-dichloro exhibited excellent antibacterial activity.

TABLE 1: ANTIINFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS 4 a-e IN CARRAGEENAN-INDUCED RAT PAW EDEMA.

Compounds	R	Volume of paw edema (ml)*			
		After 1 hr	After 2hr	After3hr	After4hr
Control		0.63 ±0.021	0.70 ±0.036	0.80 ±0.000	0.80 ±0.000
Standard		0.55 ±0.034 ^{ns}	0.41 ±0.016 ***	0.30 ±0.044***	0.25±0.034***
4a	4-Methoxy	0.46 ±0.033*	0.40 ±0.044 ***	0.30 ±0.044***	0.26 ±0.033***
4b	4-Bromo	0.48 ±0.040^{ns}	0.38 ±0.060 ***	0.33 ±0.049***	0.32±0.042***
4c	2-Bromo	0.48 ±0.040^{ns}	0.36 ±0.055 ***	0.30 ±0.036***	0.31±0.040***
4d	4-Chloro	0.46 ±0.033*	0.38 ±0.016 ***	0.31 ±0.040***	0.28±0.040***
4e	2,4-Dichloro	0.53 ±0.033^{ns}	0.43 ±0.021***	0.35 ±0.050***	0.28±0.040***

All the values were expressed as mean ±SEM, n=6.

* p <0.05, **p <0.01, ***p <0.001, ns p>0.05 followed by Tukey's test when compared with Disease control (Carrageenan Treated).

TABLE 2: ANALGESIC ACTIVITY OF THE HYDRAZONE DERIVATIVES 4 a-e BY HOT PLATE METHOD IN ALBINO MICE.

Compound Name	Before admin (paw licking)	After administration(paw licking response)				
		30 min	60min	90min	120min	180min
Control	8.33±0.33ns	8.50 ±0.22**	8.33 ±0.33**	8.16±0.16**	8.17±0.30**	8.33±0.21**
Standard	8.33±0.33ns	23.16±0.30**	30.50±0.42**	41.50±0.76**	45.33±0.66**	42.66±0.80**
4a	8.16±0.30ns	17.83±0.30**	23.16±0.30**	32.66±0.49**	36.16±0.47**	33.33±0.61**
4b	8.00±0.36ns	15.16±0.30**	24.50±0.67**	36.83±0.79**	40.83±1.07**	38.16±0.90**
4c	7.83±0.47ns	14.83±0.30**	23.00±0.57**	34.00±0.73**	38.00±0.73**	35.16±0.65**
4d	8.33±0.33ns	18.33±0.21**	28.33±0.33**	37.50±0.42**	41.83±0.70**	39.00±0.57**
4e	8.50±0.22ns	17.16±0.47**	26.66±0.33**	38.16±0.30**	41.83±0.60**	38.33±0.33**

All the values were represented as MEAN ±SEM, n=6.

P value *p<0.05, **p<0.01,***p<0.001, ^{ns} p>0.05 followed by Dunnet's test

Compare with normal control (treated with vehicle)

TABLE 3: RESULTS OF ANTIBACTERIAL BIOASSAY OF COMPOUNDS 4a-e (CONCENTRATION USED (100&200 µg/mL) OF DMSO)

Compound Code	R	*In vitro* antibacterial activity Zones of inhibition of compounds 4a-e in mm			
		Escherichia Coli		*Bacillus subtilis*	
		(100 µg/mL)	(200 µg/mL)	(100 µg/mL)	(200 µg/mL)
4a	4-Methoxy	15	28	18	27
4b	4-Bromo	12	16	10	19
4c	2-Bromo	13	18	9	17
4d	4-Chloro	10	22	10	16
4e	2,4-Dichloro	15	24	7	12
Standard Drug	Gentamycin (100&200µg/mL)	12	25	12	25

Zones of inhibition were measured in mm

CONCLUSION: In conclusion the new hydrazone derivatives were synthesized and the synthesized compounds were confirmed by spectral analysis such as IR, ^{1}HNMR and MS spectroscopy. However the newly synthesized compounds were screened for antiinflammatory and analgesic activities by *in vivo* methods. Antiinflammatory activity was found to be more for compound **4a**. The rest of the compounds were found to have moderate antiinflammatory activity. All the compounds exhibited analgesic activity and more activity was found in **4d**. The compounds were subjected to their antibacterial activity by *in vitro* method, and **4a** and **4e** were found to be more effective against gram positive bacteria and remaining compounds exhibited equipotent activity.

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REFERENCES:

1. Olayinka OA, Craig AO, Obinna CN and David AA: Microwave Assisted Synthesis and Antimicrobial Activity of 2-Quinoxalinone-3-Hydra-Zone Derivatives. Bioorg. Med. Chem 2010; 18:214-221.
2. Rollas S and Kucukguzel SG: Biological Activities of Hydrazone Derivatives. Molecules 2007; 12:1910-1939.
3. Brehme R, Enders D, Fernandez R and Lassaletta JM: "Aldehyde N,N- dialkylhydrazones as neutral acyl anion equivalents: umpolung of the imine reactivity". European Journal of Organic Chemistry 2007; 34:5629–5660.
4. Kaplancikli ZA, Altintop MD, Özdemir A, Zitouni GT, Khan SI and Tabanca N: Synthesis and Biological Evaluation of Some Hydrazone Derivatives as Anti-inflammatory Agents. Letters in Drug Design & Discovery 2012; 9:310-315.
5. Ali SMM, Jesmin M, Azad AK, Islam MK and Zahan R: Anti-inflammatory and analgesic activities of acetophenone semicarbazone and benzophenone semicarbazone. Asian Pacific Journal of Tropical Biomedicine 2012; S1036-S1039.
6. Hern´andez P, Cabrera M and Lavaggi ML et al: "Discovery of new orally effective analgesic and anti-inflammatory hybrid furoxanyl N-acylhydrazone derivatives". Bioorganic and Medicinal Chemistry 2012; 20:2158–2171.
7. Salgın-Göksen U, Gökhan-Kelekçi N, Göktas Ö, Köysal Y, Kılıç E, Isık S and Aktay G, Özalp M: 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: Synthesis, analgesic-antiinflammatory and antimicrobial activities. Bioorganic & Medicinal Chemistry. 2007; 15:5738-5751.
8. Rajasekhar N, Chandrasekhar KB, Mohanty S, Rao MR and Balram B: Synthesis and Antimicrobial Evaluation of Some Novel Hydrazone Derivatives of 2, 5-iflurobenzoic acid. Journal of Applicable Chemistry. 2013: 2:1489-1498.
9. Güzin Aslan H, Servet Özcan S and Nurcan Karacan: The antibacterial activity of some sulfonamides and sulfonyl hydrazones, and 2DQSAR study of a series of sulfonyl hydrazones. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2012; 98:329-336.
10. Özdemir A, Turan-Zitouni G, Asim Kaplancikli Z, Işcan G, Khan S and Demirci F: "Synthesis and the selective antifungal activity of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine derivatives". European Journal of Medicinal Chemistry 2010; 45:2080–2084.
11. Vikas N, Telvekar, Anirudh B, Vinod Kumar B and Kalpana S: Novel N′-benzylidene benzofuran-3-carbohydrazide derivatives as antitubercular and antifungal agents. Bioorganic & Medicinal Chemistry Letters 2012; 22:2343-2346.
12. Ali MM, Azad MAK, Jesmin M, Ahsan S and Rahman MM, et al: *In vivo* anticancer activity of vanillin semicarbazone. Asian Pacific Journal of Tropical Biomedicine 2012; S438-S442.
13. Belkheiri N, Bouguerne B and Bedos-Belval F et al: "Synthesis and antioxidant activity evaluation of a syringic hydrazones family". European Journal of Medicinal Chemistry 2010; 45:3019–3026.
14. Rajitha G, Saideepa N and Praneetha P: "Synthesis and evaluation of N-(α-benzamido cinnamoyl) aryl hydrazone derivatives for anti-inflammatory and antioxidant activities". Indian Journal of Chemistry B 2011; 50:729–733
15. Mohareb RM, El-Sharkawy KA, Hussein MM and El-Sehrawi HM: "Synthesis of hydrazide-hydrazone

derivatives and their evaluation of antidepressant, sedative and analgesic agents". Journal of Pharmaceutical Sciences and Research 2010; 2: 185–196.
16. Gemma S, Savini L, Altarelli M, Tripaldi P, Chiasserini L and Coccone SS et al: Development of antitubercular compounds based on a 4-quinolylhydrazone scaffold: Further structure–activity relationship studies, Bioorganic & Medicinal Chemistry 2009; 17:6063-6072.
17. Nikolova-Mladenova B, Momekov G and Ivanov D: "Synthesis and physicochemical characterization of new salicylaldehyde benzoyl hydrazone derivative with high cytotoxic activity". Pharmacia 2011; 58:41-44.
18. Hayat F, Salahuddin A, Zargan J and Azam A: "Synthesis, characterization, antiamoebic activity and cytotoxicity of novel 2-(quinolin-8-yloxy) acetohydrazones and their cyclized products (1,2,3-thiadiazole and 1,2,3-selenadiazole derivatives)". European Journal of Medicinal Chemistry 2010; 45:6127–6134.
19. Rafat M, Daisy M H and Fleita: Novel Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor Activity. Molecules 2011; 16:16-27.
20. Mashayekhi V, Tehrani KHME, Amidi S and Kobarfard F: Synthesis of novel indole hydrazone derivatives and evaluation of their antiplatelet aggregation activity. Chemical and Pharmaceutical Bulletin 2013; 61:144–150.
21. Kumar S, Bawai S, Drabu S, Kumar R and Machwal L: "Chloroquinolinylhydrazone derivative as anticonvulsant," Acta Poloniae Pharmaceutica 2010; 67:567–563.
22. Ali Almasirad, Somayeh Samiee-Sadra and Abbas Shafiee: Synthesis and Antimycobacterial Activity of 2-(Phenylthio) benzoylarylhydrazone Derivatives. Iranian Journal of Pharmaceutical Research 2011; 10:727-731.
23. Longo JG and Laguna MDLS: Pyridazine derivatives. XI: Antihypertensive activity of 3-hydrazinocycloheptyl[1,2-c]pyridazine and its hydrazone derivatives. Journal of pharmaceutical science 1993; 82:286-290.
24. Miranda ASD, Júnior WB, Cupertino da Silva YK, Alexandre-Moreira MS, Castro RDP, Sabino JR, Lião LM, Lima LM and Barreiro EJ: Design, Synthesis, Antinociceptive and Anti-Inflammatory Activities of Novel Piroxicam Analogues. Molecules 2012; 17:14126-14145
25. Winter CA, Risely EA and Nuss EV: Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. Proceeding, Society for Experimental Biology and Medicine 1962; 111:544-547.
26. Eddy NB and Leimbach D: Synthetic analgesics. II. Dithienylbutenylamines and dithienylbutylamines. The Journal of Pharmacology and Experimental Therapeutics 1953; 107:385-393.
27. Rajasekhar N, Chandrasekhar KB, Sandeep M and Balram B: Synthesis of Novel Hydrazone Derivatives of 2, 5-difluorobenzoic Acid as Potential Antibacterial Agents. Letters in Drug Design & Discovery 2013; 10:620-624.

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