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Original Article

Synthesis and evaluation of pyrazole containing aromatic and heterocyclic derivatives as anti-inflammatory agents

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ABSTRACT

Series of new compounds containing heterocyclic rings were synthesized and evaluated for their anti-inflammatory activities. 1,3-Diphenyl-1H-pyrazole-4-carbaldehyde **(III)** was synthesized from 1-phenyl-2-(1-phenylethylidene) hydrazine **(II)** through Vilsmier-Haack reaction. The compound **(III)** was reacted with appropriate aromatic/ heteroaromatic amines to generate the corresponding pyrazole derivatives (**IV a-f)**. The structures of synthesized compounds were confirmed using elemental and spectral methods. The anti-inflammatory activity of the synthesized compounds was evaluated using the carrageenan-induced rat paw edema assay compared with ibuprofen as a reference. The synthesized compounds **(IV a-f)** showed moderate activity with % inhibition of edema ranges (45.58-67.32%) when compared to the reference standard ibuprofen (76.45% inhibition).

Keywords: Anti-inflammatory, Carrageenan, Pyrazole, Ibuprofen

INTRODUCTION

Pyrazole is an aromatic heterocyclic diazole alkaloid characterized by a5-membered aromatic ring structure composed of three carbon and two nitrogen atoms in adjacent position in which one nitrogen is basic and nitrogen is neutral in nature. Pyrazole derivatives are categorized in a higher position as the other heterocyclic compound possesses in the heterocyclic chemistry. A great deal of research is carried out to prepare novel heterocyclic molecules having therapeutic uses and also so many heterocyclic derivatives are synthesized till now having desired

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pharmacological effect. Being so composed and having pharmacological effects on human, pyrazoles have a significant value in the field of medicinal chemistry. [1-11]

A Celecoxib has a central pyrazole ring and two adjacent phenyl substituent which reported as selective COX-2 inhibitor anti-inflammatory agent but lack the toxic side effects associated with currently used NSAIDs.[12]

1,3,4-Thiadiazoleheterocyclic compounds exhibit a wide variety of pharmacological activities such as anticancer, anti-tubercular, antibacterial, antifungal, antimicrobial, anti-inflammatory, analgesic, anticonvulsant, diuretic and anti-secretory activities. [13] 1,2,4-Triazole and its derivatives are a major class of compounds which possess diverse agricultural, industrial and biological activities, including anti-microbial, sedative, anticonvulsant, anticancer, anti-inflammatory, diuretic, antibacterial, hypoglycemic, anti-tubercular and antifungal.[14]

Over 30 drugs containing sulfonamide are in clinical use, including antihypertensive agent, antibacterial, antiprotozoal, antifungal, anti-inflammatory, non-peptide vasopressin receptor antagonists and translation initiation inhibitors.[15]

A quinazolin-4-one derivative possessing abroad spectrum of biological and pharmacological activities such as antifungal, antimicrobial, bronchodilator,antihistaminic, anti-inflammatory, antifungal and anti-inflammatory activities. [16]

From the above finding and in our seeking to develop new anti-inflammatory agents, we have synthesized novel pyrazole containing aromatic andheterocyclic derivatives.

MATERIALS AND METHODS

General: Melting points were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK) and are uncorrected. The IR spectra (KBr, cm^{-1}) were recorded on Shimadzu IR 110 spectrophotometer (Shimadzu, Koyoto, Japan). 1H-NMR spectra were recorded on a Bruker proton NMR-300 (300 MHz) (Bruker, Munuch, Germany), in DMSO-d6 as a solvent, using tetramethylsilane (TMS) as internal standard (chemical shift in ppm).

Mass spectra were determined using a GC/MS Mat 112 S at 70ev spectrometer. Elemental analysis (C, H, N) were performed on Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the microanalytical laboratories of the Faculty of Science, Cairo University.

All reactions were monitored by thin layer chromatography (TLC) using precoated Aluminium sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Darmstadt, Germany).

Experimental

Synthesis of 1-phenyl-2-(1-phenylethylidene) hydrazine (II): Phenyl hydrazine (1.49g, 13.78mmol, 1.0 eq) was added to a solution of acetophenone (1.35g, 11.23 mmol, 1.1 eq) in ethanol (37.5 mL) at 0^oC followed by the slow addition of glacial acetic acid (1.12 mL). The reaction mixture was then refluxed for 2h and cooled to room temperature. The precipitated product was filtered, washed with cold ethanol (20 mL) and dried under vacuum to obtain pure yellow solid. Yield =88% M.P 104 ^oC as reported.[17]

Synthesis of 1,3-diphenyl-1H-Pyrazole-4-Carbaldehyde (III): Vilsmeier-Haack reagent was prepared from separately cooled dimethylformamide (2.58g, 35.3mmol) and $POCl_3$(5.4g, 35.5 mmol) at 0°C and stirred at 0°C.A solution of compound **(II)** (3 g,11.76 mmol) in DMF (3ml)was added drop wise to Vilsmeier-Haack reagent, which was then warmed to room temperature and refluxed at70- 80 °C for 4-5 h. After cooling, the mixture was basified with a cool saturated K_2CO_3 solution. The precipitate obtained was filtered, strongly washed with water and recrystallized from ethanol. Yield =81% M.P 142 ^oC as reported.[18]

General procedure for synthesis of 5-[(1,3-Diphenyl-1H-pyrazol-4-ylmethylene)-amino derivatives (IVa-f): A mixture of compound **(III)** (2.48g,0.01 mol) and amino substituted compound (0.01 mol) was taken in absolute ethanol (30 mL) and few drops of glacial acetic acid were added. Then the mixture was refluxed for 6h on water bath. The excess solvent was distilled off, then poured into ice cold water. The separated solid was filtered, washed and recrystallized from ethanol. The physicochemical properties compounds **(IVa-f)** are shown in table 1.

Scheme 1

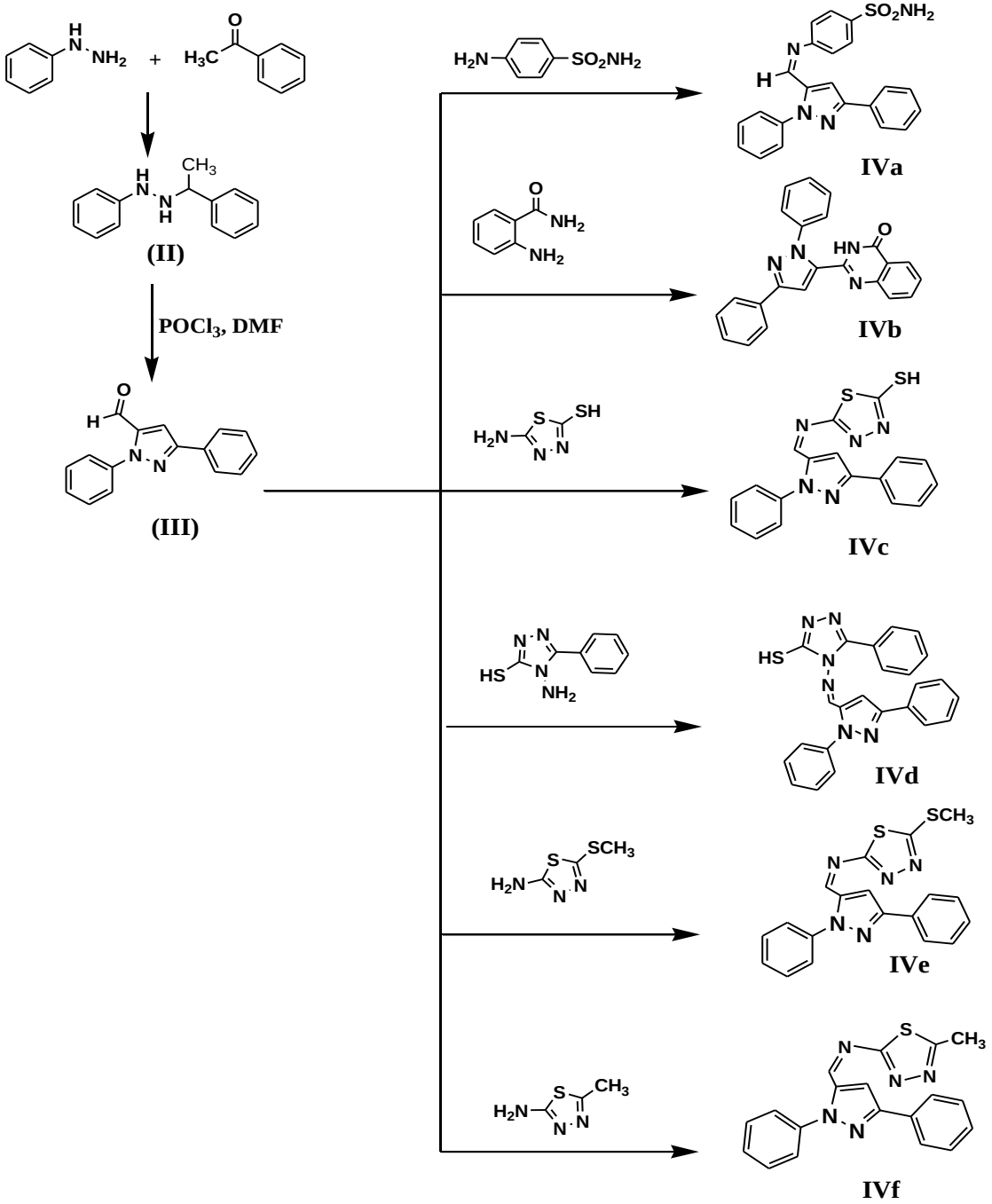

Table 1: Physicochemical properties of 5-[(1,3-diphenyl-1H-pyrazol-4-ylmethyl-ene)-amino derivatives IVa-f

Compound No	MF	M.Wt	M.p °C	Yield %
Iva	$C_{22}H_{18}N_4O_2S$	302.45	215-220	51.5
IVb	$C_{23}H_{16}N_4O$	364.40	212-214	37.8
IVc	$C_{18}H_{13}N_5S_2$	363.45	142-144	38
IVd	$C_{14}H_{18}N_6S$	422.50	199-202	47
IVe	$C_{19}H_{15}N_5S_2$	377.48	147-149	33
IVf	$C_{19}H_{15}N_5S$	345.42	146-148	38

4-{[(1,3-Diphenyl-1*H*-pyrazol-5-yl) methylidene] amino}benzene-1sulfonamide (IVa): IR (KBr, cm^{-1}): *v* = 3260 (NH), 3054-3005 (arom. CH), 2949, 2925 (aliph. CH),1600 (C=N),1413 (C=C), ^{1}HNMR (300 MHz, DMSO-d) ppm: 7.99-8.40 (m,18H, 14H ArH, 1H pyrazole H, 1H CH=N, 2H NH_2). Mass m/z: 378 (M^+). Anal.Calcd. For $C_{22}H_{18}N_4O_2S$ C 65.65%, H 4.51% and N13.92%. Found: C 65.42 %, H 4.73% and N 13.82%.

2-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-2,3-dihydroquinazolin-4(1*H*)-one (IVb):IR (KBr, cm^{-1}): *v* = 3054-3010 (arom. CH), 2948, 2922 (aliph. CH),1680 (C=O), 1620 (NH), 1604 (C=N), 1400 (C=C). ^{1}HNMR (300 MHz, DMSO-d) ppm: 6.87-7.98 (m,15H, 14H ArH, 1H pyrazole-H, 1H NH of 2,3-dihydroquinazolin-4(1*H*)-one).Mass m/z: 364 (M^+). Anal.Calcd. For $C_{23}H_{16}N_4O$ C 75.81%, H 4.43% and N15.38%. Found: C 75.92 %, H 4.65% and N 15.28%.

5-{([(1,3-Diphenyl-1*H*-pyrazol-5-yl) methylidene]amino}-1,3,4-thiadiazole-2-thiol (IVc): IR (KBr, cm^{-1}): *v* = 3074-3010 (arom. CH), 2969, 2925 (aliph. CH),1600 (C=N),1400 (C=C). ^{1}HNMR (300 MHz, DMSO-d) ppm: 7.00-8.40 (m,13H, 10H ArH, 1H pyrazole-H, 1H CH=N, 1H NH).Mass m/z: 363 (M^+). Anal.Calcd. For $C_{18}H_{13}N_5S_2$ C 59.48%, H 3.61% and N19.27%. Found: C 59.34 %, H 3.83% and N 19.18%.

4-{[(1,3-Diphenyl-1*H*-pyrazol-5-yl) methylidene] amino}-5-phenyl-4*H*-1,2,4-triazole-3-thiol (IVd): IR (KBr, cm^{-1}): *v* = 3054-3005(arom. CH), 2949, 2925 (aliph. CH),1606 (C=N),1413 (C=C). ^{1}HNMR (300 MHz, DMSO-d) ppm: 6.91-8.20 (m,18H, 15H ArH, 1H pyrazole-H, 1H CH=N, 1H NH). Mass m/z: 422 (M^+). Anal.Calcd. For $C_{24}H_{18}N_6S$ C 68.23%, H 4.29% and N19.89%. Found: C 68.36 %, H 4.42% and N 19.87%.

1-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-*N*-[5-(methylsulfanyl)-1,3,4-thiadiazol-2-yl] methanimine(IVe): IR (KBr, cm^{-1}): *v* = 3054-3005(arom. CH), 2949, 2925 (aliph. CH),1605 (C=N), 1413 (C=C).^{1}HNMR (300 MHz, DMSO-d) ppm: 2.54 (s, 3H, SCH_3), 6.77-8.32 (m,12H, 10H ArH, 1H pyrazole-H, 1H CH=N). Mass m/z: 377 (M^+). Anal.Calcd. For $C_{19}H_{15}N_5S_2$ C 60.45%, H 4.01% and N18.55%. Found: C 60.56 %, H 4.21% and N 18.44%.

1-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-*N*-(5-methyl-1,3,4-thiadiazol2yl)methanimine (IVf):IR (KBr, cm^{-1}): *v* = 3054-3005(arom. CH), 2949, 2925 (aliph. CH),1600 (C=N), 1413 (C=C). ^{1}HNMR (300 MHz, DMSO-d) ppm 2.53 (s, 3H, CH_3), 6.90-8.10 (m,12H, 10H ArH, 1H pyrazole-H, 1H CH=N). Mass m/z: 345 (M^+). Anal.Calcd. For $C_{19}H_{15}N_5S$ C 66.07%, H 4.38% and N20.27%. Found: C 66.13 %, H 4.41% and N 20.30%.

Anti-inflammatory screening [20,21]

Adult albino rats of both sexes weighing between 125-140 g were used. Rats were uniformly hydrated by giving 3 ml water/rat through gastric inoculation to reduce variability to edema response. Animals were divided into 8 groups each of five animals. The control group was given saline solution containing few drops of Tween 80, ibuprofen (50 mg /kg) was taken as standard drug for comparison and compounds under examination (50mg/kg) were suspended in distilled water by the aid of few drops of Tween 80 and were given interaperitoneally one hour before induction of inflammation. Induction of inflammation was performed by subcutaneous injection of 0.1 ml of 1% carrageenan-sodium gel (Sigma-Aldrich, USA), into the sub-plantar region of the right hind paw. The dorso-ventral diameter (thickness) of the right of each rat was measured using a pair of dial thickness gauge calipers accurate to 0.001 cm3 1h, 2h, 3h and 4h after induction of inflammation. The percentage of anti-inflammatory activity (% inhibition of inflammation) was calculated after 4 hours according to the following equation:

% inhibition = $(L_c-L_t/ L_c) \times 100$

L_t is the mean increase in paw thickness in rats treated with the tested compounds. L_c is the mean increase in paw thickness in control group.

Data were collected, checked, revised and fed in the computer and then analyzed by one-way ANOVA (F test) followed by Dunnett's t test at $p<0.05$ was used to tabulate the results (table 2, 3).

Table 2: Edema thickness of control, ibuprofen and the tested compounds

Compound	Dose mg/Kg	Edema (mm)± S.E.M			
		1h	2h	3h	4h
Control	0	1.83 ± 0.432	3.54 ± 0.323	3.64 ± 0.195	3.87 ± 0.543
IVa	50	1.01 ± 0.213	1.71 ± 0.543	1.31 ± 0.643	1.26 ± 0.231
IVb	50	1.28 ± 0.342	2.07 ± 0.632	1.93 ± 0.324	1.79 ± 0.453
IVc	50	1.23 ± 0.634	1.94 ± 0.321	1.65 ± 0.287	1.48 ± 0.305
IVd	50	1.19 ± 0.231	2.13 ± 0.187	1.87 ± 0.232	1.98 ± 0.260
IVe	50	1.19 ± 0.145	1.57 ± 0.219	1.49 ± 0.122	1.32 ± 0.344
IVf	50	1.49 ± 0.244	2.17 ± 0.543	1.64 ± 0.543	2.11 ± 0.232
Ibuprofen	50	0.55 ± 0.078	0.98 ± 0.543	0.96± 0.084	0.91 ± 0.093

Results are means of five experiments ± S.E.

Table 3: % inhibition of edema of tested compounds and ibuprofen

Compound	Dose mg/Kg	% inhibition			
		1h	2h	3h	4h
Control	0	0	0	0	0
IVa	50	44.65	51.66	63.94	67.32
IVb	50	30.12	41.45	46.87	53.76
IVc	50	27.78	45.09	54.67	61.78
IVd	50	34.87	39.77	48.54	48.88
IVe	50	34.78	55.54	58.90	65.89
IVf	50	18.65	38.56	54.89	45.58
Ibuprofen	50	70.00	72.12	73.56	76.45

RESULTS AND DISCUSSION

Chemistry: The synthetic route for the synthesized compounds was depicted in scheme 1.1-Phenyl-2-(1-phenylethylidene) hydrazine **(II)** was prepared in good yield as reported. [17] 1,3-Diphenyl-1H-pyrazole-4-carbaldehyde **(III)** was synthesized from 1-phenyl-2-(1-phenylethylidene) hydrazine using DMF and $POCl_3$ (Vilsmier-Haack reaction) as reported.[18]

Compounds**(IVa-f)** were obtained by reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde **(III)** with amino derivatives (sulfanilamide, 2-aminobenzamide, 5-amino-1,3,4-thiadiazole-2-thiol, 4-amino-5-phenyl-4h-1,2,4-triazole-3-thiol, 2-amino-1,3,4-thiadiazole-5-methylthiol and 5-methyl 1,3,4-thiadiazole 2-amine) in refluxing absolute ethanol and in the presence of glacial acetic acid as catalyst.

Structures of compounds **(IVa-f)** were established on the basis of elemental and spectral data. IR spectra of compounds **(IVa-f)** showed disappearance of sharp strong band inthe region (1700cm^{-1}) that represents the stretching vibration of carbonyl of aldehyde. Also, IR spectra showed disappearance of two absorption bands of C-H bond stretching vibration of an aldehyde at region (2730 cm^{-1}) and (2820 cm^{-1}). A strong intensity band is appeared in the IR spectra of Schiff bases **(IVa** and **IVc-f)** in the range of 1600 cm^{-1}which is attributed to C=N group. This provides strong evidence for the condensation of carbonyl compound **(III)** with the $–NH_2$ group of 3-amino derivatives. On the other hand, IR spectra of compound **(IVb)** showed the appearance of two band at 1620 cm^{-1} and 1680 cm^{-1} which are attributed to NH and C=O of 2,3-dihydroquinazolin-4(1*H*)-one.

All the mass spectra of the final synthesized compounds **(IVa-f)** exhibit parent peaks due to molecular ions (M^+). The proposed molecular formulae of these compounds were confirmed by comparing their molecular formula weight with m/z values. The molecular ion peaks at m/z (M^+) 378 (for compound **IVa**), 364 (for compound **IVb**), 363 (for compound **IVc**), 422 (for compound **IVd**), 377 (for compound **IVe**), 345 (for compound **IVf**). Massspectra support the molecular formula of all final compounds **(IVa-f)**. These values are in good agreement with the respective molecular formulae.

^{1}H NMR spectra of the synthesized compounds **(IVa-f)** showed disappearance of signal at 9.42 ppm that represents the CH of aldehyde. In addition, the singlet signal was appeared to CH=N protons of Schiff bases **(IVa** and **IVc-f)** in the range of 8.10-8.40 ppm. This supports the formation of a Schiff's bases by the condensation of acarbonyl compound with amino derivatives. On the other hand, ^{1}H NMR spectrum of the compound **(IVb)** showed the appearance of signal at 7.51 ppm which are attributed to NH and 2,3-dihydroquinazolin-4(1*H*)-one.

Anti-inflammatory screening

The anti-inflammatory activity of the newly synthesized compounds **IVa, IVb, IVc, IVd,** I**Ve** and **IVf** was evaluated using ibuprofen as standard drug and applying the method of "carrageenan rat paw edema" that had been described by Winter *et al*. [20]

Data represented in table 2 and 3 revealed that, the compounds **(IVa-f)** showed considerable anti-inflammatory activity with % inhibition of edema ranges (45.58-67.32%) in compared to the reference standard ibuprofen (76.45% inhibition). Most of theresults are significant difference from reference value at $p<0.05$.

Compounds **IVa, IVc** and **IVe** showed moderate activity with % inhibition of oedema of 67.32, 61.78, 65.89respectively,while the other compound **IVb, IVd**and **IVf** showed lower % of inhibition of edema (53.76, 48.88, 45.58 respectively).

CONCLUSION

It can be concluded that series of pyrazole containing aromatic and heterocyclic compounds **(IVa-f)** were synthesized and evaluated for their

anti-inflammatory activities. The pyrazole derivatives **(IVa-f)** were obtained from 1-phenyl-2-(1-phenylethylidene) hydrazine **(II)** through Vilsmier-Haack reaction to furnish (1,3-diphenyl-1H-pyrazole-4-carbaldehyde **(III)**, followed by condensation with appropriate aromatic/ heteroaromatic amines (sulfanilamide, 2-aminobenzamide, 5-amino-1,3,4-thiadiazole-2-thiol, 4-amino-5-phenyl-4h-1,2,4-triazole-3-thiol, 2-amino-1,3,4-thiadiaz-ole-5-methylthiol and 5-methyl-1,3,4-thiadiazole-2-amine).The structures of synthesized compounds were confirmed using elemental and spectral methods. The anti-inflammatory activity of the synthesized compounds was evaluated using carrageenan-induced rat paw edema assay in compared with ibuprofen as a reference. The synthesized compounds **(IVa-f)** showed moderate activity with % inhibition of edema ranges (45.58-67.32%) in compared to the reference standard ibuprofen (76.45% inhibition).

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