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SYNTHESIS, CHARACTERIZATION, AND ANTIOXIDANT ACTIVITY OF NEW PYRAZOLES

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ABSTRACT: Pyrazole and its derivatives are pharmacologically active and are being used in various disorders and diseases with a few side effects. The wide distribution of pyrazole compounds in nature with fascinating pharmacological action is key in the application of this development of newer derivatives. The main structure has a great variety of compounds that have essential pharmaceutical and agrochemical activities in addition to biological activity like anti-inflammatory, antifungal, antitumor, antiviral, antibacterial, anti-tubercular, and antiphrastic. Protection against various substances that causes oxidative stress in the body is needed in the modernizing world in this direction intermediate obtained from the Vilsmeier Haack reaction (4) was treated with aromatic amines to obtain N-[3-(naphthalen-1-yl)-1-phenyl-1H-pyrazol-4-yl] methylene) derivatives (5a-5l). The *in-vitro* antioxidant activity of newly synthesized compounds was determined by the Nitric oxide scavenging method.

INTRODUCTION: As most of the naturally available compounds are heterocyclic by their chemical structure, the search for medicinally active molecules in these classes of compounds is comparatively higher than in other classes. The first medicinally used pyrazole derivative was antipyrine (phenazone) discovered by Ludwig Knorr in 1883. Pyrazoles are five-membered aromatic systems with adjacent nitrogen atoms in the heterocyclic ring; the lone pair of electrons in the ring due to delocalization impart the basic properties [1]. Half of the known organic compounds distributed in nature are well known to contain pyrazole derivatives (alkaloids such as Withasomnine, 4-Hydroxywithasomnine which exhibit antioxidant activity; nucleoside analogues such as Pyrazofurin, Pyrazofurin B are related to ribavirin extracted from *Streptomyces candidus*; Formycin (Formycin A), Formycin B, Oxoformycin B, which have antineoplastic activity found in streptomyces Lavendula; Fluviol A from Pseudomonas fluorescens) which has a marked antitumor activity) [2–6].

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Many synthetic compounds of pyrazole are used in the treatment of several clinical manifestations, derivatives such as Celecoxib, Deracoxib, Ramifenazone and Famprofazone (anti-inflammatory) [7], Sulfaphenazole (antibacterial which competitively inhibits dihydropteroate synthase enzyme), Rimonabant (anti-obesity), Sildenafil (vasodilator) and Fezolamide (antidepressant) [8], Phenylbutazone (anti-inflammatory, antipyretic mainly used in osteoarthritis, rheumatoid arthritis, spondylitis, Reiter's disease), Sulfinpyrazone (chronic gout), and Oxyphenbutazone (antipyretic, analgesic, anti-inflammatory, mild uricosuric) [9], pyrazole and fused pyrazole systems, such as pyranopyrazole and pyrazolpyrimidines are promising scaffolds for

many anticancer agents [10] Veliparib, Pracinostat, Bendamustine, Selumetinib, Galeterone (anticancer activity), Niraparib (ovarian cancer), Darolutamide (Prostate cancer), Pictilisib [11–13] **Fig. 1** . Pyrazoles among the azole derivatives are gaining attention for decades due to their potent activity.

Free radicals such as Superoxide ($O_2 \cdot -$), Oxygen radical ($O_2 \cdot \cdot$), Hydroxyl (OH·), Alkoxyradical (RO·), Peroxyl radical (ROO·), Nitric oxide (nitrogen monoxide) (NO·) and nitrogen dioxide ($NO_2 \cdot$) which are metabolic products and have an important role. Such as Nitric Oxide metabolites stimulate and inhibit lipid peroxidation reactions, modulate enzymatically catalyzed lipid oxidation, complex with lipid-reactive metals, and alter proinflammatory gene expression in the presence of an excess of oxidants.

In contrast, depleted condition oxidants produce a secondary oxidizing species causing proatherogenic effect, neurodegenerative diseases, stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer [14–16]. Many novel molecules have shown potent activity as an antioxidant molecules scavenging the oxidants [17–19]. Some of the natural compounds consisting of pyrazole ring.

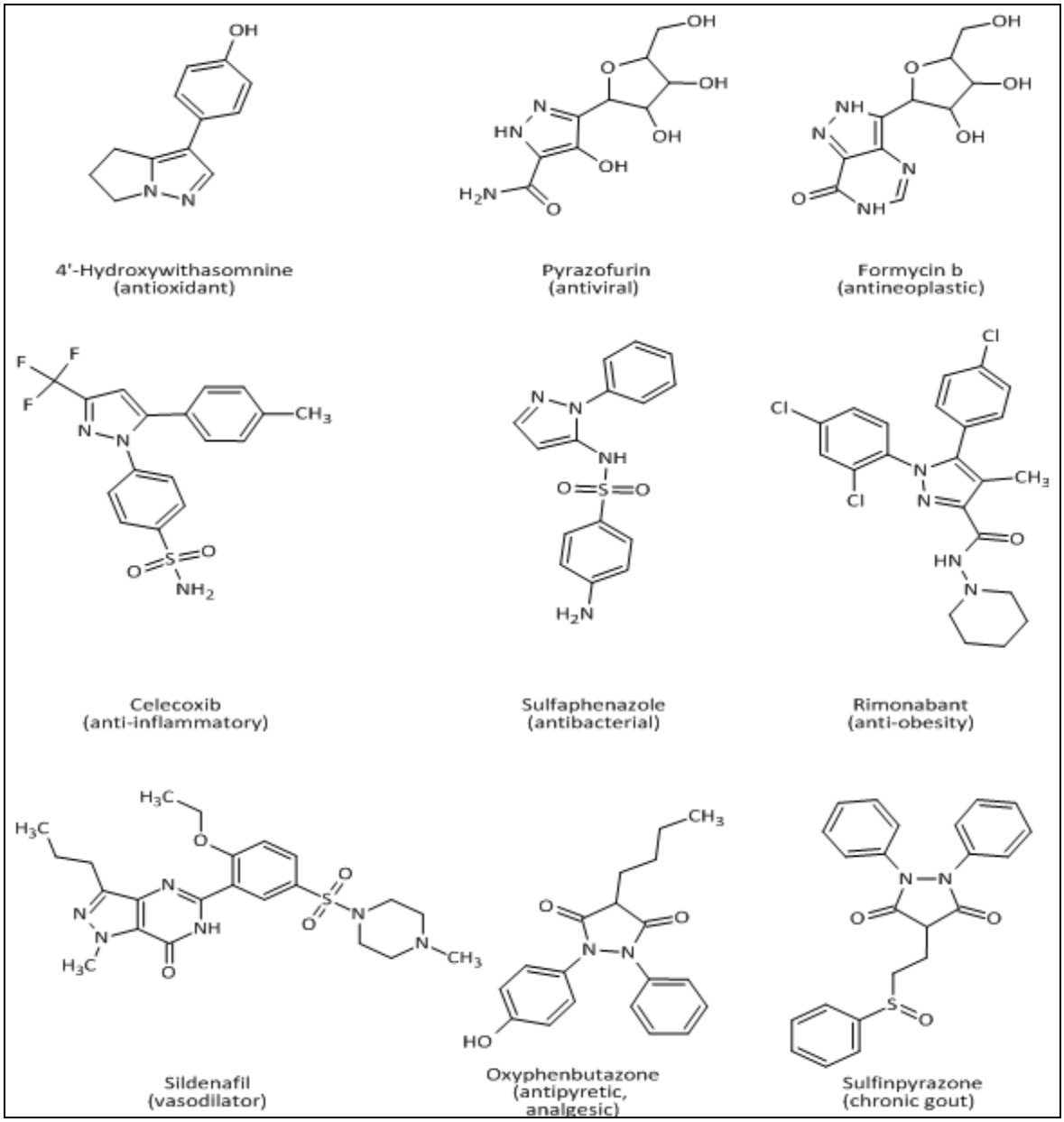
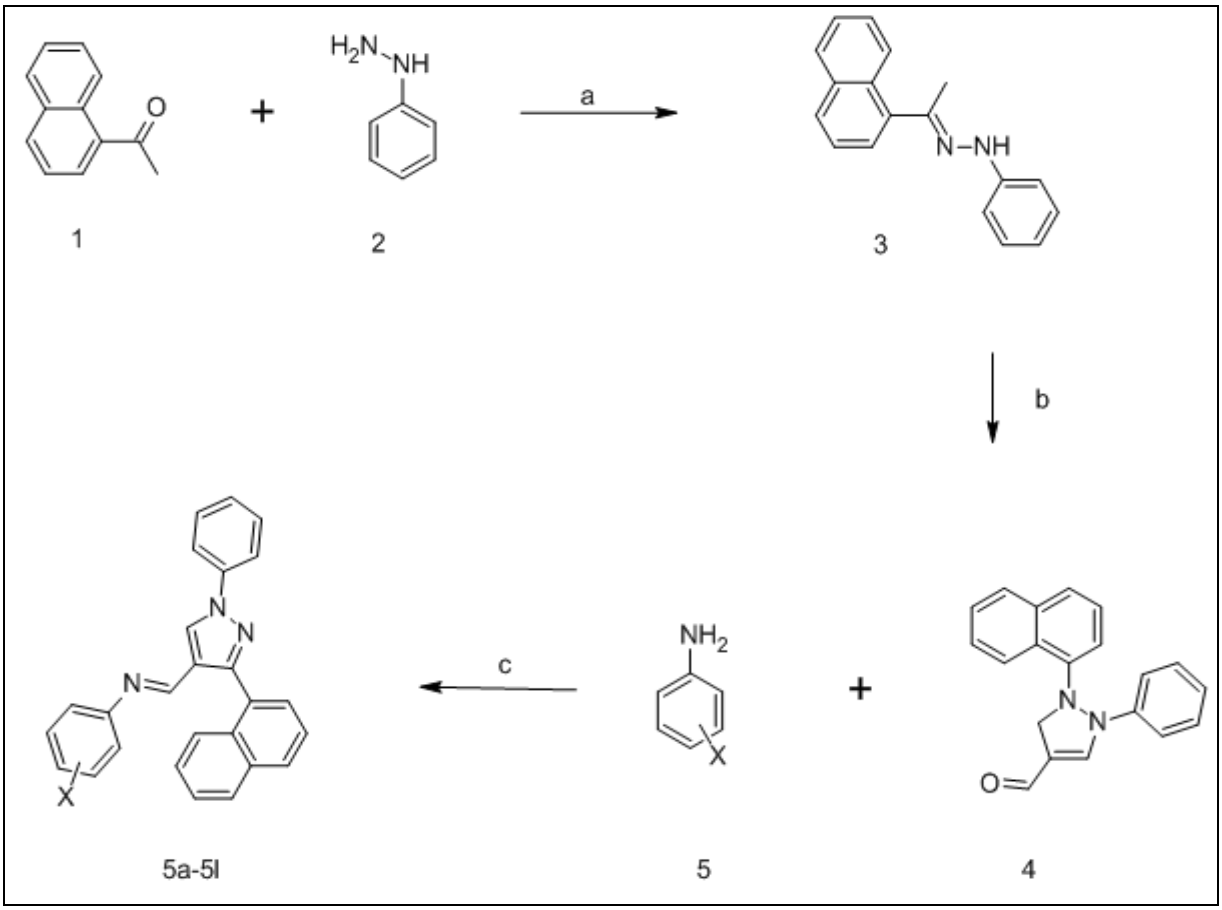


FIG. 1: COMPOUNDS CONTAINING PYRAZOLE RINGS WHICH EXHIBIT VARIOUS PHYSIOLOGICAL ACTIVITIES

MATERIALS AND METHODS: All the chemicals and solvents were procured locally from Merck, Sigma Aldrich, and Finar. The synthesized compounds were preliminarily confirmed by thin-layer chromatography (TLC) and UV spectroscopy. The final derivatives were characterized by spectral methods such as Fourier transform infrared (FTIR), and 1H-NMR. Each compound's Melting points were determined from the digital melting point apparatus and were uncorrected.

General Procedure: The synthesis route involved three steps as mentioned in Scheme 1, starting from the conversion of acetyl naphthalene followed by the below-mentioned steps.

Step 1, Synthesis of (1E)-1-[1-(naphthalen-1-yl) Ethylidene]-2-phenylhydrazine (3): 4.25g (0.025 M) acetyl naphthalene (1) and 3ml (0.025 M) of phenylhydrazine (2) were dissolved in 50 ml of alcohol and heated to reflux for 5 h. The excess alcohol was distilled off after the completion of the reaction, and crushed ice was added to the reaction mass and set overnight in the refrigerator to precipitate the product 3. The precipitated product 1 was recrystallized from cyclohexane.



SCHEME 1: SYNTHETIC ROUTE FOLLOWED DURING THE SYNTHESIS OF THE PYRAZOLE DERIVATIVES

a) Ethanol, reflux 5 hours; b) Phosphorous oxychloride, DMF (Vilsmeier Haack reagent); c) ethanol, glacial acetic acid reflux 4 hours.X= aromatic amines.

Step 2, Synthesis 3-(naphthalen-1-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (4): A mixture of 3.12g (0.012 mol) compound 3 was taken in 10ml RBF along with 3 ml (0.025 mol) of Dimethyl formamide and 2.5ml (0.025 mol) phosphorous oxychloride and were refluxed on a water bath for 4 h, the reaction mass was cooled on an ice bath and is neutralized with sodium acetate. The precipitated solids are filtered and recrystallized by using DMF and water.

Step 3, Synthesis of N-[3-(naphthalen-1-yl)-1-phenyl-1H-pyrazol-4-yl] Methylene) Substituted Benzamine (5a-5l): A mixture (0.01 mol) of compound 4 with (0.01 mol) substituted aniline in 40ml of ethanol and a catalyst amount of 2ml glacial acetic acid were refluxed for 4 h.

The reaction mass was cooled to room temperature to precipitate the product (substituted Schiff base). The obtained solid precipitate was filtered and recrystallized with a mixture of DMF and water.

N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5a): Percentage yield 50%; melting point (mp) 117^0C, FT-IR 3355.74 cm^{-1} (aromatic, =C-H), 3200-3000 cm^{-1}(-NH stretch), 1600-1300 cm^{-1} (C=O), 1500-1300 cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.1 (2H, s, pyrazole-CH, H3, H5), 7.7(4H m, naphthalene ring H1, H2, H3, H4), 7.4(3H, s, naphthalene ring H5, H6), 7.2 (4H, d, aniline), 7.1(5H, m, phenyl); Mass spectra- [M+H]= 376.

2-fluoro-N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5b): Percentage yield 52%; melting point (mp) 125°C, FT-IR 3355.74 cm^{-1} (aromatic, =C-H), 3200-3000 cm^{-1}(-NH stretch), 1600-1300 cm^{-1} (C=O), 1500-1300 cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.32 (2H, s, pyrazole-CH, H3, H5), 7.63 (4H m, naphthalene ring H1, H2, H3, H4), 8.12 (3H, s, naphthalene ring H5, H6), 7.03 (4H, d, aniline), 7.56(5H, m, phenyl); Mass spectra[M–H] $^+$= 394.

4-fluoro-N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5c): Percentage yield 58%; melting point (mp) 131^0C, FT-IR 800-700 cm^{-1} (Fluorine), 3345.2cm^{-1} (aromatic, =C-H), 3200-3000cm^{-1}(-NH stretch), 1600-1300cm^{-1} (C=O), 1500-1300cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.1 (2H, s, pyrazole-CH, H3, H5), 7.7(4H m, naphthalene ring H1, H2, H3, H4), 7.4(3H, s, naphthalene ring H5, H6), 7.2 (4H, d, aniline), 7.1(5H, m, phenyl); Mass spectra- M+ 393.

2-methoxy-N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5d): Percentage yield 49%; melting point (mp) 129°C, FT-IR 2955.74 cm^{-1} (aromatic, =C-H), 3100-3000 cm^{-1}(-NH stretch), 1600-1300 cm^{-1} (C=O), 1500-1300 cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.1 (2H, s, pyrazole-CH, H3, H5), 7.7(4H m, naphthalene ring H1, H2, H3, H4), 7.4(3H, s, naphthalene ring H5, H6), 7.2 (4H, d, aniline), 7.1(5H, m, phenyl) 3.26(3H, d, 2-methoxy); Mass spectra- M+ 393.

4-methoxy-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5 - dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5e): Percentage yield 42%; melting point (mp) 118^0C, FT-IR 3382.74 cm^{-1} (aromatic, =C-H), 3174cm^{-1}(-NH stretch), 1600-1300 cm^{-1} (C=O), 1500-1300 cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.5 (2H, s, pyrazole-CH, H3, H5), 8.38 (4H m, naphthalene ring H1, H2, H3, H4), 7.9 (3H, s, naphthalene ring H5, H6), 6.99 (2H, d, aniline), 7.3 (5H, m, phenyl); Mass spectra- M+ 393.

2-chloro-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5f): Percentage yield 60%; melting point (mp) 129°C, FT-IR 3382.74 cm^{-1} (aromatic, =C-H), 3156cm^{-1}(-NH stretch), 1526cm^{-1} (C=O), 1489cm^{-1} (C=N). 1H-NMR ($CDCl_3$); δ(ppm) 8.6 (2H, m, pyrazole-CH, H3, H5), 8.25 (4H d, naphthalene ring H1, H2, H3, H4), 7.43 (3H, d, naphthalene ring H5, H6), 7.25 (4H, d, aniline), 7.23 (5H, m, phenyl); Mass spectra- [M+H] =410.

4-chloro-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline(5g): Percentage yield 48%; melting point (mp) 130°C, FT-IR 3382.74 cm^{-1} (aromatic, =C-H), 3156cm^{-1}(-NH stretch), 1526cm^{-1} (C=O), 1489cm^{-1} (C=N) 852Cm^{-1}(-Cl). 1H-NMR (CDCl3); δ(ppm) 8.79 (2H, m, pyrazole-CH, H3, H5), 8.55 (4H d, naphthalene ring H1, H2, H3, H4), 7.86 (3H, d, naphthalene ring H5, H6), 7.55 (2H, m, aniline H2, H6), 7.16 (2H, d, aniline H3, H5), 7.17 (5H, m, phenyl); Mass spectra- [M+H] =410.

2-methyl-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5h): Percentage yield 62%; melting point (mp) 128°C, FT-IR 3390.65 cm^{-1} (aromatic, =C-H), 3156cm^{-1}(-NH stretch), 1526cm^{-1} (C=O), 1452cm^{-1} (C=N). 1H-NMR (CDCl3); δ(ppm) 8.62 (2H, m, pyrazole-CH, H3, H5), 8.28 (4H d, naphthalene ring H1, H2, H3, H4), 7.92 (3H, t, naphthalene ring H5, H6), 7.28 (3H, t, aniline H3, H5, H6), 6.99 (1H, s, aniline 3H), 7.17 (5H, m, phenyl), 2.65 (3H, s, methyl); Mass spectra- [M+H] =390.

3-methyl-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5i): Percentage yield 59%; melting point (mp) 113°C, FT-IR 3352.27 cm^{-1} (aromatic, =C-H), 3509cm^{-1}(-NH stretch), 1563cm^{-1} (C=O), 1489cm^{-1}

(C=N), 852Cm^{-1}(-Cl). 1H-NMR (CDCl3); δ(ppm) 8.75 (2H, m, pyrazole-CH, H3, H5), 8.35 (4H d, naphthalene ring H1, H2, H3, H4), 7.45 (3H, t, naphthalene ring H5, H6), 7.65 (2H, q, aniline H3, H5), 6.56 (2H, d, aniline H2, H6), 7.23 (5H, m, phenyl), 2.45 (3H, d, methyl); Mass spectra- [M+H] =390.

4-methyl-N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5j): Percentage yield 72%; melting point (mp) 112^{0}C, FT-IR 3381.31 cm^{-1} (aromatic, =C-H), 3145cm^{-1}(-NH stretch), 1592cm^{-1} (C=O), 1423cm^{-1} (C=N) 852Cm^{-1}(-Cl). 1H-NMR (CDCl3); δ(ppm) 8.75 (2H, m, pyrazole-CH, H3, H5), 8.35 (4H d, naphthalene ring H1, H2, H3, H4), 7.52 (3H, t, naphthalene ring H5, H6), 7.75 (2H, q, aniline H3, H5), 6.12 (2H, d, aniline H2, H6), 7.35 (5H, m, phenyl), 2.59 (3H, d, methyl); Mass spectra- [M+] =389.

2-nitro-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5k): Percentage yield 58%; melting point (mp) 115°C, FT-IR 3353.70 cm^{-1} (aromatic, =C-H), 3165cm^{-1}(-NH stretch), 1530cm^{-1} (C=O), 1489cm^{-1} (C=N) 852Cm^{-1}(-Cl).

1H-NMR (CDCl3); δ(ppm) 8.33 (2H, m, pyrazole-CH, H3, H5), 8.42 (4H m, naphthalene ring H1, H2, H3, H4), 7.62 (3H, q, naphthalene ring H5, H7), 7.80 (2H, d, aniline H3, H5), 6.06 (2H, m, aniline H4, H6), 7.52 (5H, t, phenyl); Mass spectra- [M+] =420.

4-nitro-N-((3-(naphthalen-1-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl) Methylene) Aniline (5l): Percentage yield 55%; melting point (mp) 122°C, FT-IR 3382.74 cm^{-1} (aromatic, =C-H), 3156cm^{-1}(-NH stretch), 1526cm^{-1} (C=O), 1493cm^{-1} (C=N) 852Cm-1(-Cl). 1H-NMR (CDCl3); δ(ppm) 8.42 (2H, q, pyrazole-CH, H3, H5), 8.65 (4H m, naphthalene ring H1, H2, H3, H4), 7.55 (3H, q, naphthalene ring H5, H7), 7.33 (2H, m, aniline H3, H5), 6.35 (2H, s, aniline H2, H6), 7.82 (5H, d, phenyl); Mass spectra- [M+] =420.

***In-Vitro* Antioxidant Activity:**

Nitric Oxide Scavenging Method [20–22]: Nitric oxide synthases (NOS) specifically generate relatively unstable, diatomic nitric oxide radical (NO-) in biological tissues. NOS metabolizes arginine to citrulline by producing a NO- through a five-electron oxidative reaction. This *in-vitro* method utilizes sodium nitroprusside compound, which produces NO after decomposition in an aqueous solution at physiological pH (7.2).

The NO- radicals in ideal conditions, i.e., aerobic conditions, react with molecular oxygen to yield stable products (nitrate and nitrite), which can be quantitatively analyzed by using the Griess reagent. All the synthesized compounds were tested for antioxidant activity along with ascorbic acid as a positive control at the concentration of 100µg, 200µg and 300µg.

RESULTS: Different novel pyrazole derivatives were successfully synthesized and peaks at the wavelength of 1489cm^{-1} (C=N), 3200-3000 cm-^{1} (NH stretch) indicate the presence of pyrazole nitrogen atoms and the absence of terminal keto peak at 1600cm^{-1} confirmed the substitutions.

The proton NMR data showed the presence of substituted aniline peaks at δ(ppm) 7.65 and 6.52. the mass spectroscopy of compounds established the mass of each compound. Compound 5g exhibited the highest antioxidant activity among the synthesized compounds, with 62.1% at a concentration of 300µg.

DISCUSSION: The route of reaction for synthesizing all compounds was as mentioned in Scheme 1. The starting compound acetyl naphthalene was condensed with phenyl hydrazine in presence of alcohol which yields (1E)-1-[1-(naphthalen-1-yl) ethylidene]-2-phenylhydrazine (1). Compound (1) on treating with Vilsmeier Haack reagent yield a pyrazole ring (2), further on reacting with substituted anilines yields substituted N-((3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)methylene)aniline.

All the synthesized compounds were screened for their antioxidant property by nitric oxide scavenging ability and tabulated in **Table 1,** where all the compounds exhibited mild to moderate activity. Among the substituted aniline derivatives, 4-substituted compounds showed a maximum percentage of inhibition. In the synthesized derivatives 2-fluoro and 4-nitro compounds showed the highest inhibition at the concentration of 200µg.

TABLE 1: PERCENTAGE INHIBITION NITRIC OXIDE BY NITRIC OXIDE SCAVENGING METHOD

Compound code	x	Percentage inhibition		
		100µg	200µg	300µg
5a	H	33.52	47.45	40.24
5b	2-fluoro	47.52	53.76	39.82
5c	4-fluoro	46.21	51.54	37.42
5d	2-methoxy	37.57	37.67	38.7
5e	4-methoxy	35.21	33.75	34.6
5f	2-chloro	33.43	43.22	61.11
5g	4-chloro	36.12	43.57	62.21
5h	2-methyl	34.6	51.34	43.82
5i	3-methyl	31.26	45.81	39.83
5j	4-methyl	35.51	48.71	41.24
5k	2-nitro	46.21	53.63	49.2
5l	4-nitro	48.53	57.51	54.22
Ascorbic acid	-	60.97	69.38	86.47

All the synthesized compounds exhibited mild to moderate scavenging activity against nitric acid.

CONCLUSION: A series of novel pyrazole derivatives were designed, synthesized and evaluated for their antioxidant activity. Among the synthesized compounds, compounds **5b** and **5l** showed promising activity.

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