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The Green Synthesis, Characterization, and Molecular Docking Study of Tetralone-Linked Pyrazole Chalcones

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ABSTRACT

In the present investigation, the tetralone-linked pyrazole chalcones have been prepared by the Claisen-Schmidt condensation of α-tetralone with various substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes using sodium hydroxides in PEG-400 as green solvent. The tetralone moiety plays an important role in diverse pharmacological activities like anticancer, antidepressants, anti-Parkinson, COX-2 inhibitors, and anticonvulsants. On the other hand, heterocycles containing the pyrazole ring also played an important role in anticancer agents. The substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes were prepared by the Vilsmeier-Haack reaction of various substituted aryl hydrazones from various substituted acetophenones. All the compounds were obtained in good to excellent yields. A molecular docking study was performed with PDB: 3LN1.

INTRODUCTION:

Aim: The Green Synthesis, Characterization, And Molecular Docking Study of Tetralone Linked Pyrazole Chalcones

Objective: The tetralone moiety plays an important role in diverse pharmacological activities like anticancer, antidepressants, anti-Parkinson, COX-2 inhibitors, and anticonvulsants. On the other hand, heterocycles containing the pyrazole ring also played an important role in anticancer agents. The chalcones exert their anticancer action through different mechanisms by acting through various targets.

Introduction of Chalcone:

Kostanecki and **Tambor** coined the term **Chalcone**. Chalcones are *1,3-diphenyl-2-propene-1-one*, in which two aromatic rings are linked by a three-carbon α-β unsaturated carbonyl system. These compounds are also known as *benzalacetophenone* or *benzylidene acetophenone* [1]. Chalcones are widely spread in nature (fruits, vegetables, spices, tea, and soya-based foodstuff) and some of their derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase and protein tyrosine kinase.

Many methods are reported in the literature for the synthesis of chalcones; the most convenient method is Claisen-Schmidt condensation. In Claisen-Schmidt condensation, chalcones were synthesized by equimolar quantities of acetophenone and aldehyde in the presence of alkali chalcone [2,3]. Chalcones and their derivatives have been reported to have therapeutic potential including **anti-inflammatory and antibacterial activities**.

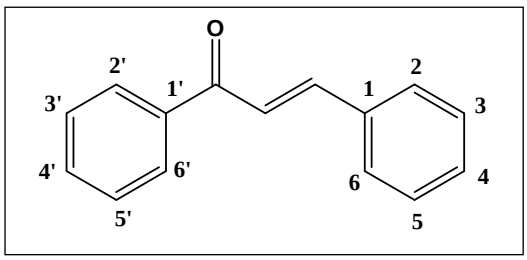

Fig. 1: General structure of chalcone derivatives

Introduction of PEG:

In recent years ecofriendly chemical processes have attracted much attention both in the academic and industrial fields. There has been an increasing emphasis among researchers to

design synthetic strategies keeping in view the principles of **'Green Chemistry'.** The use of PEG as a recyclable solvent system for the metal-mediated radical polymerization of methyl methacrylate and styrene has also been reported [4-6].

Introduction of Pyrazole:

In medicine, derivatives of pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamine oxidase inhibiting, antidiabetic, and antibacterial activities [7].

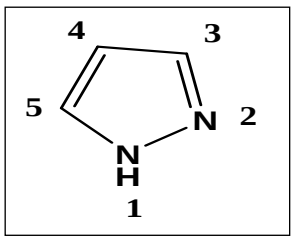

Fig. 2: Structure of pyrazole

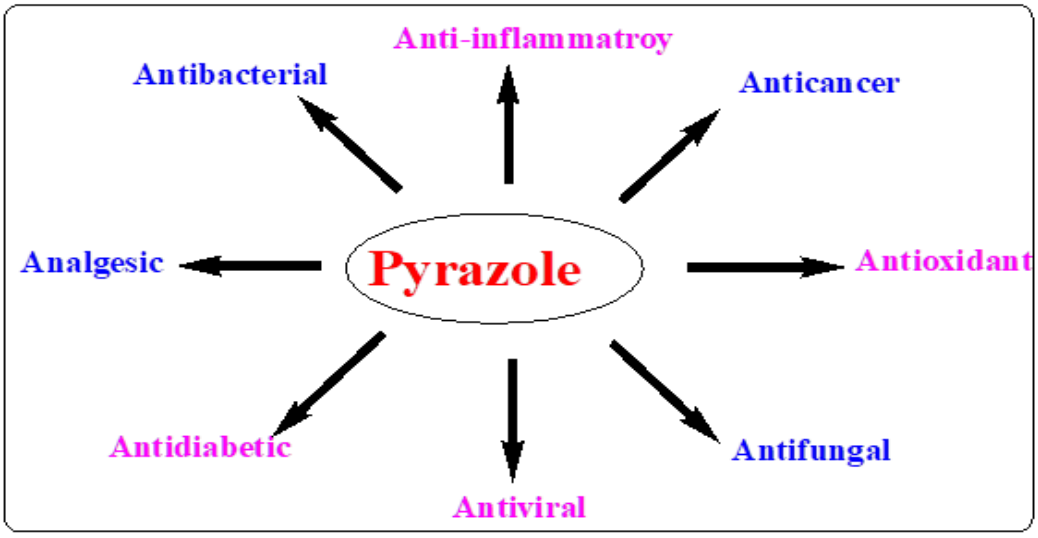

Fig. 3: **Biological Activity of Pyrazole**

MATERIALS AND METHODS:

Chemicals: Acetophenone (LR.), α-tetralone (LR.), PEG-400 (LR.), Phenyl hydrazine (LR.), DMF (LR.), $POCl_3$ (LR.), H_2SO_4 (LR.), Sodium hydroxide (LR.), Ethanol (LR.) all the chemicals are purchased from Vijay chemicals, Solapur.

Reagents: 10% NaOH, 50% Ethanol.

Method:

Our goal in this project was to incorporate these two independently biologically active moieties into one molecule to generate compounds with synergistic in Vitro biological activities. Thus, we plan to synthesize a new series of tetralone-linked pyrazole chalcones by Claisen-Schmidt condensation reaction and expect them to show additive medicinal/ pharmacological properties.

Scheme-1

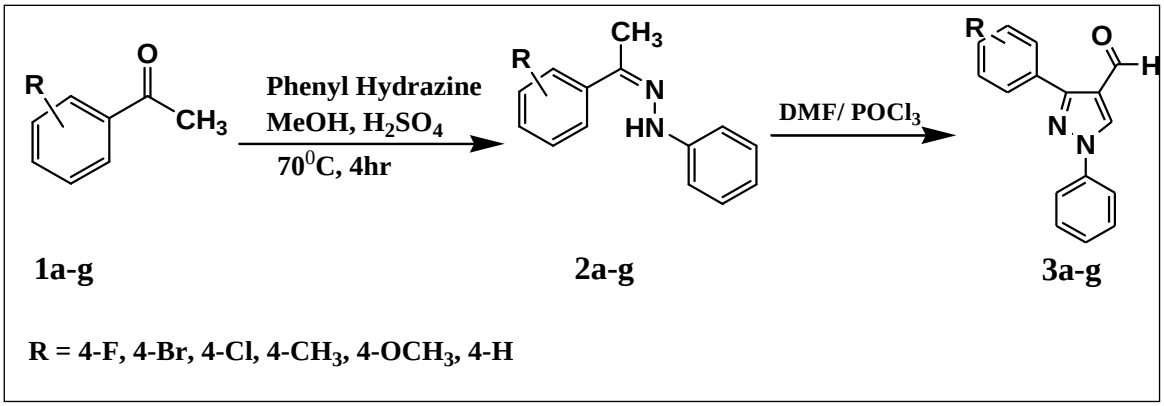

Fig. 4: Schematic representation of the reaction

The required substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes (3a-g) were prepared by the Vilsmeier-Haack reaction (scheme-1) on acetophenone hydrazones (2a-g) obtained from various substituted acetophenones (1a-g) according to literature method and confirmed IR, ^{1}H NMR, and LCMS.

Scheme -2

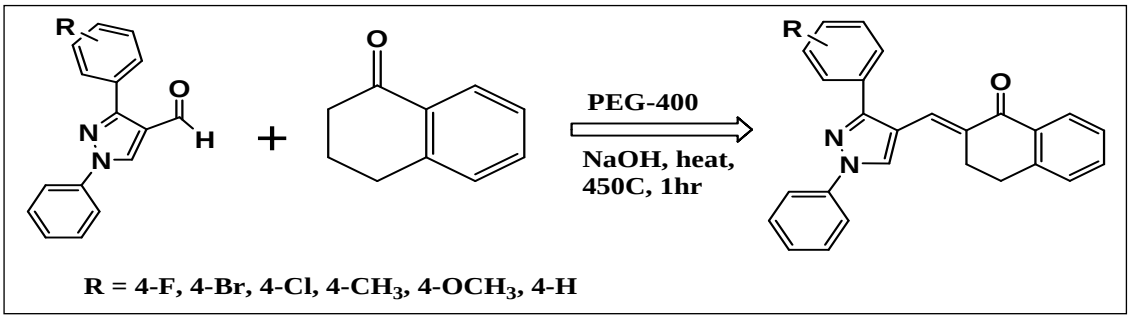

Fig. 5: Schematic representation of the reaction

Then, we treated differently substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (3a-g) (1mM) with α-tetralone (1mM) in 10% NaOH (2ml) and 15ml of PEG-400. On stirring the reaction mixture at 40-50^{0}C temperature for 1hr, we isolated the tetralone-linked pyrazole

chalcones (Scheme-2) with good yield and purity after the usual workup followed by recrystallization. All the synthesized compounds will be confirmed by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data.

2-[(3-(4-Fluoro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

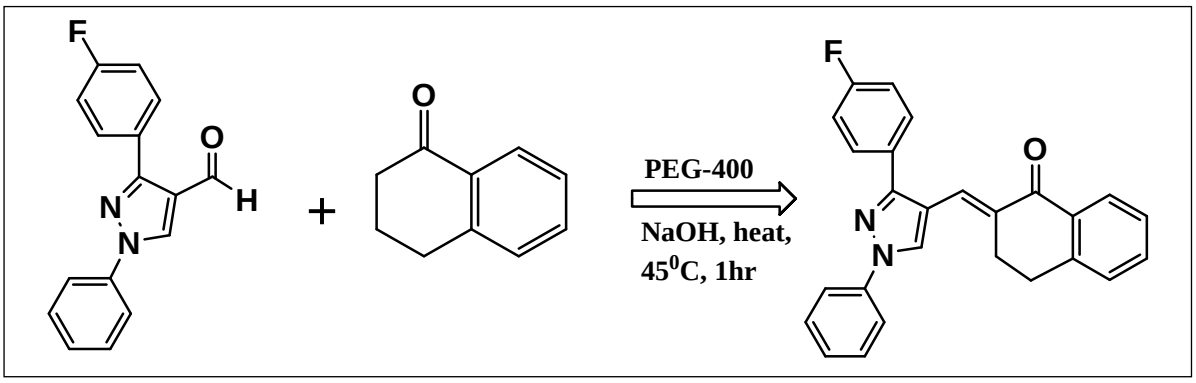

Fig. 6: Schematic representation of reaction

A mixture of 3-(4-fluorophenyl)-1-phenyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, it was filtered, washed with water, and dried it. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

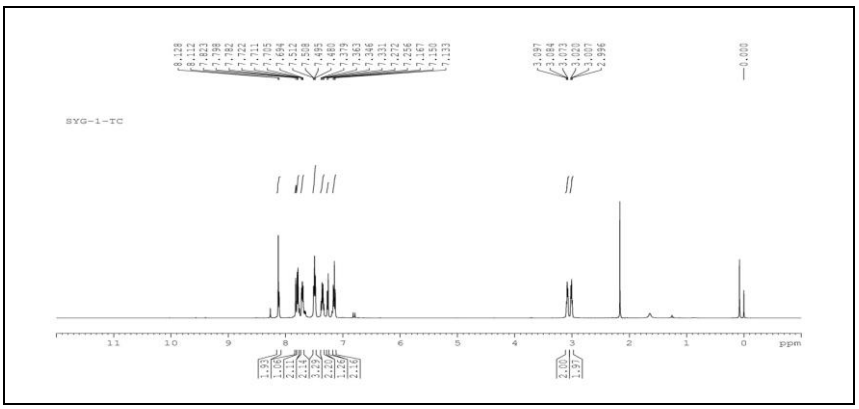

Fig. 7: ^{1}H-NMR Spectrum

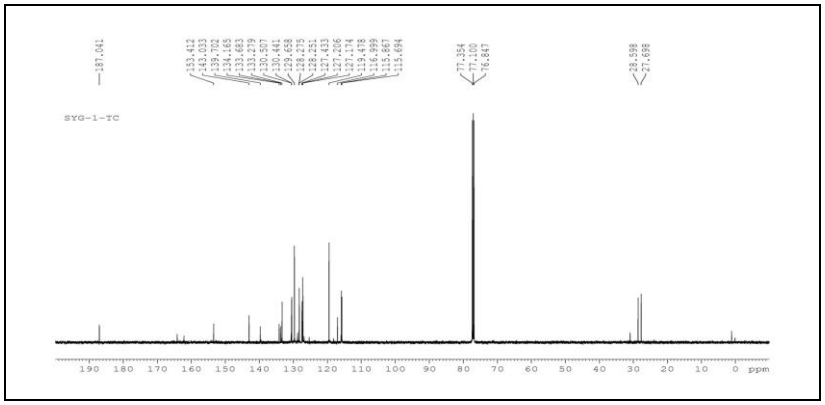

Fig. 8: ^{13}C-NMR Spectrum

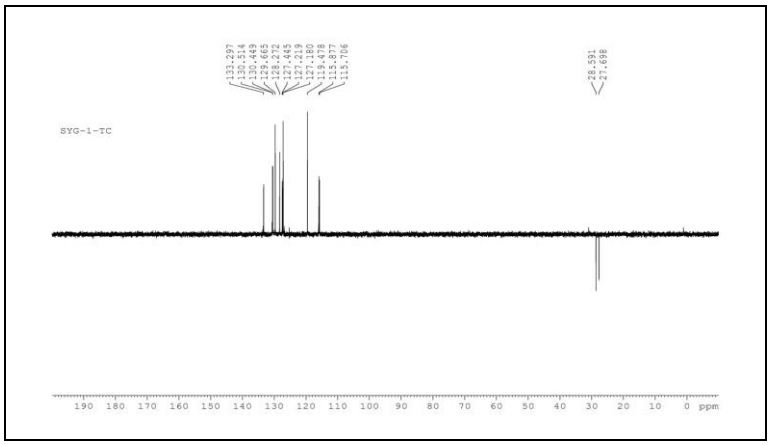

Fig. 9: DEPT Spectrum

Yield: 85%

Molecular formula: $C_{26}H_{19}N_2OF$

IR (neat): v 2953, 1658,1591,1533 cm^{-1}.

^{1}H NMR (500MHz): δ 3.0 (t, 2H), 3.08 (t, 2H), 7.13-7.82 (m, 13H, Ar-H),

8.11(s, 1H, pyrazole-H), 8.12 (s, 1H, -CH=C-);

^{13}C NMR (100MHz): δ 27.69, 28.59, 115.69, 119.47, 127.20, 128.27,

130.50, 133.68, 139.70

DEPT : δ 27.69, 28.59, 115.70, 119.47, 127.18, 127.44, 129.66, 130.51,133.29

2-[(3-(4-bromo-phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

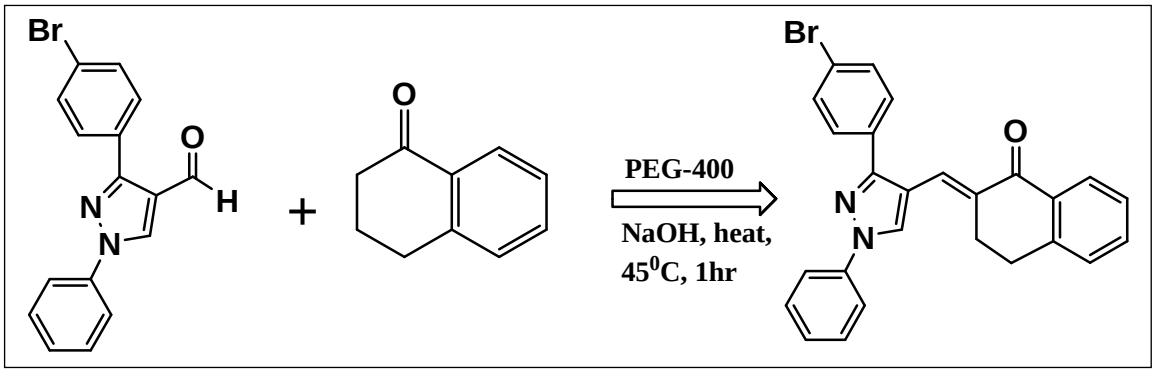

Fig. 10: Schematic representation of reaction

A mixture of 3-(4-bromophenyl)-1-phenyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, it was filtered, washed with water and dried. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

Yield: 90%

Molecular formula: $C_{26}H_{19}N_2OBr$

IR (neat): v 2960, 1660, 1595,1538 cm^{-1}.

^{1}H NMR (500MHz): δ 3.01 (t, 2H), 3.08 (t, 2H), 7.17-7.19 (m, 13H, Ar-H),

8.13(s, 1H, pyrazole-H), 8.135 (s, 1H, -CH=C-);

^{13}C NMR (100MHz): δ 27.69, 28.63, 116.60, 120.40, 128.50, 128.68,

131.00, 133.82, 139.78, 143.09, 153.46, 187.05.

2-[(3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

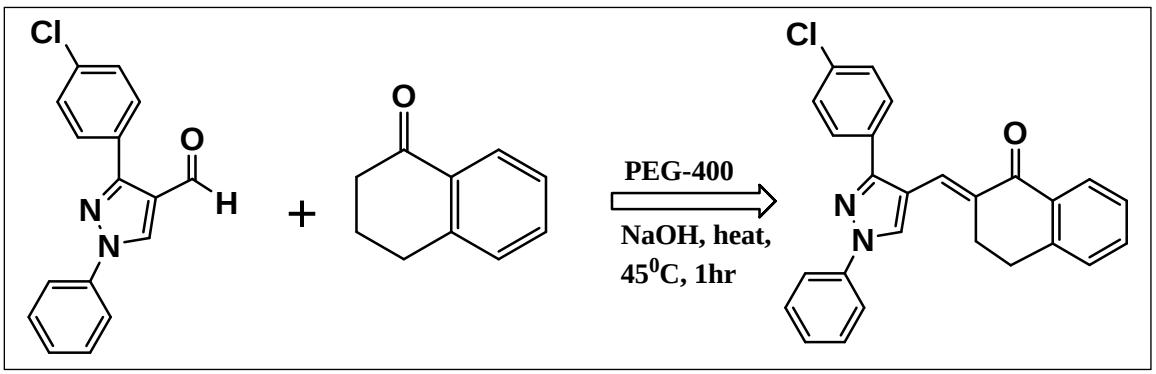

Fig. 11: Schematic representation of reaction

A mixture of 3-(4-chlorohenyl)-1-phenyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, filtered, washed with water, and dried it. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

Yield: 90%

Molecular formula: $C_{26}H_{19}N_2OCl$

IR (neat): v 2960, 1659,15931530 cm^{-1} .

^{1}H NMR (500MHz): δ 3.0 (t, 2H), 3.07 (t, 2H), 7.15-7.19 (m, 13H, Ar-H),

8.12(s, 1H, pyrazole-H), 8.13 (s, 1H, -CH=C-);

^{13}C NMR (100MHz): δ 27.67, 28.61, 115.60, 119.40, 128.20, 128.29,

130.00, 133.60, 139.75, 143.07, 153.43, 187.03.

2-[(1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

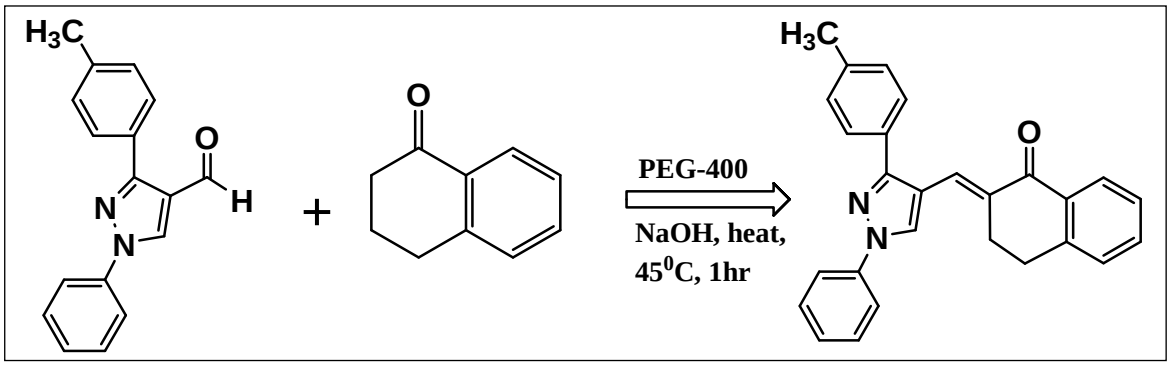

Fig. 12: Schematic representation of reaction

A mixture of 1-phenyl-3-p-tolyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, filtered, washed with water, and dried it. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

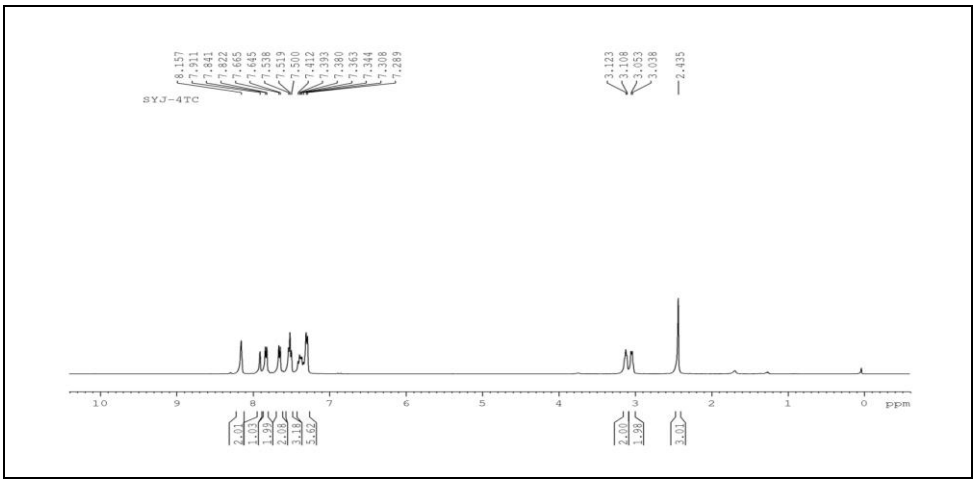

Fig. 13: ^{1}H-NMR Spectrum

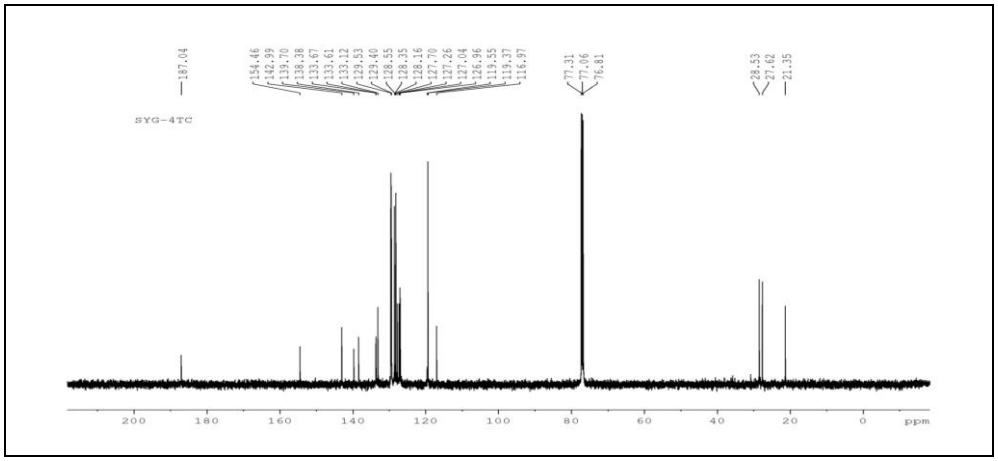

Fig. 14: ^{13}C-NMR Spectrum

Yield: 85%

Molecular formula: $C_{26}H_{19}N_2OCH_3$

IR (neat): v 2953, 1660,1594,1534cm^{-1}.

^{1}H NMR (500MHz): δ 2.43 (s, 3H), 3.04 (t, 2H), 3.11 (t, 2H), 7.28-8.0 (m, 13H, Ar-H), 8.15 (s, 1H, pyrazole-H), 7.91(s, 1H, -CH=C-);

^{13}C NMR (100MHz): δ 21.35, 27.62, 28.53, 116.97, 119.55, 126.96, 127.7, 128.35, 129.40, 133.12, 138.38, 154.46, 187.04.

2-[(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

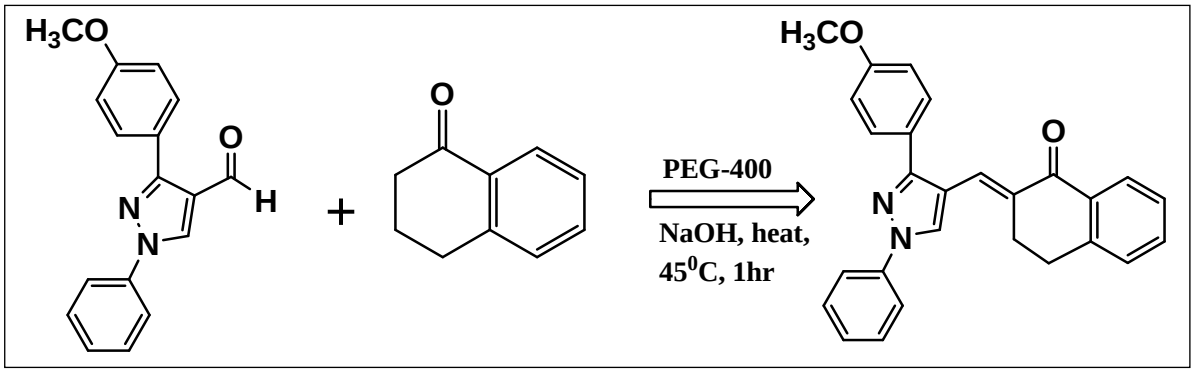

Fig. 15: Schematic representation of reaction

A mixture of 3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, filtered, washed with water, and dried it. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

Yield: 85%

Molecular formula: $C_{26}H_{19}N_2O_2CH_3$

IR (neat): v 2953, 1660,1595,1534 cm^{-1}.

^{1}H NMR (500MHz): δ 2.43 (S, 3H), 3.04 (t, 2H), 3.11 (t, 2H), 7.28-8.0 (m, 13H, Ar-H), 8.15 (s, 1H, pyrazole-H), 7.91 (s, 1H, -CH=C-);

^{13}C NMR (100MHz): δ 21.35, 27.62, 28.52, 116.97, 126.96, 127.7, 128.35, 129.40, 113.12, 138.38, 154.46, 187.04.

2-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]-3,4-dihydro-2*H*-naphthalene-1-one

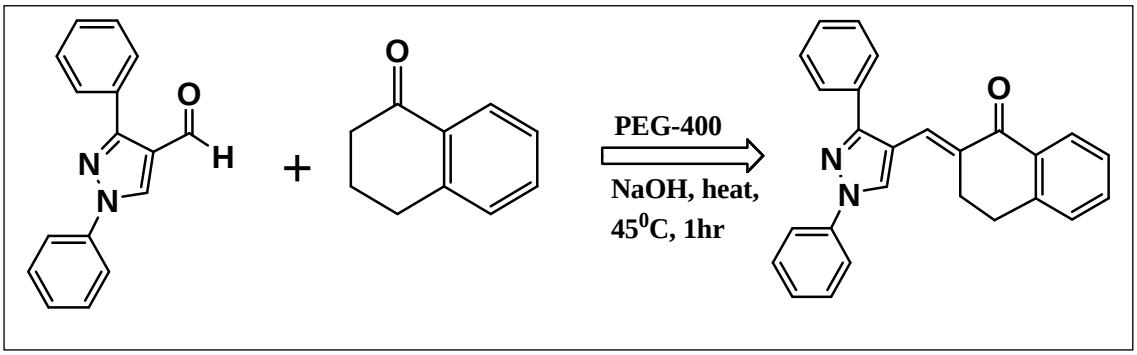

Fig. 16: Schematic representation of reaction

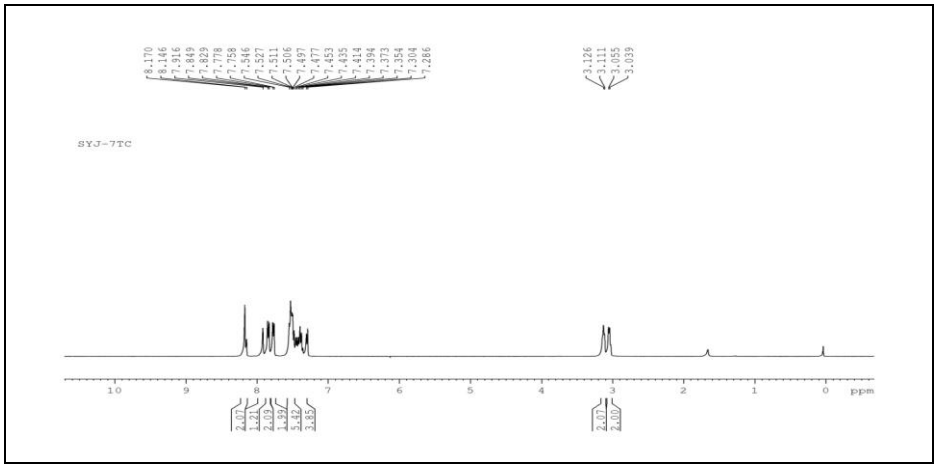

***Fig. 17:* ^{1}*H-NMR* Spectrum**

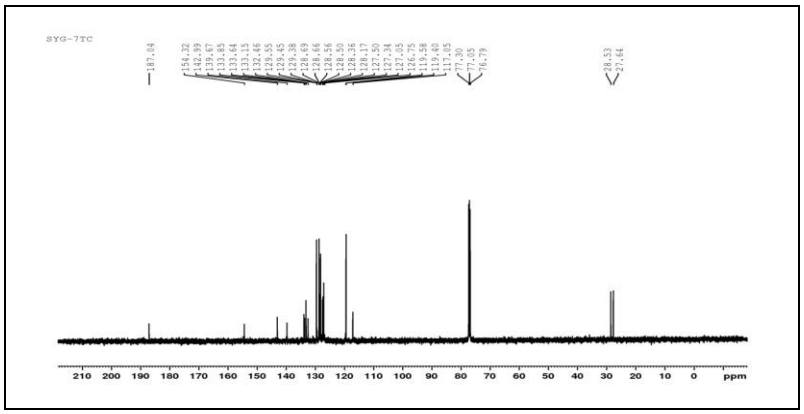

Fig. 18:* ^{13}*C-NMR Spectrum

A mixture of 1,3-diphenyl-1H-pyrazole-4- carbaldehyde (1mM) and α-Tetralone (1mM) was dissolved in 15ml PEG-400. To this mixture sodium hydroxide (10%, 2ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 1hr. After completion of the reaction (TLC). The reaction mixture was then poured into 100ml ice-cold water. The product was separated, filtered, washed with water, and dried. The product obtained was purified by recrystallization using 50% ethanol to afford a pure compound as a yellow solid.

Yield: 90%

Molecular formula : $C_{26}H_{20}N_2O$

IR (neat): v 3134, 3046, 1654, 1600, 1567, 1495 cm^{-1}.

^{1}H NMR (500MHz) : δ 3.04 (t, 2H), 3.12 (t, 2H), 7.28-8.14 (m, 14H, Ar-H),

8.17 (s, 1H, pyrazole-H), 7.91 (s, 1H, -CH=C-);

^{13}C NMR (100MHz) : δ 27.64, 28.53, 117.05, 119.40, 126.70, 127.5,

128.36, 129.45, 133.15, 139.60, 154.32, 187.04

Molecular docking

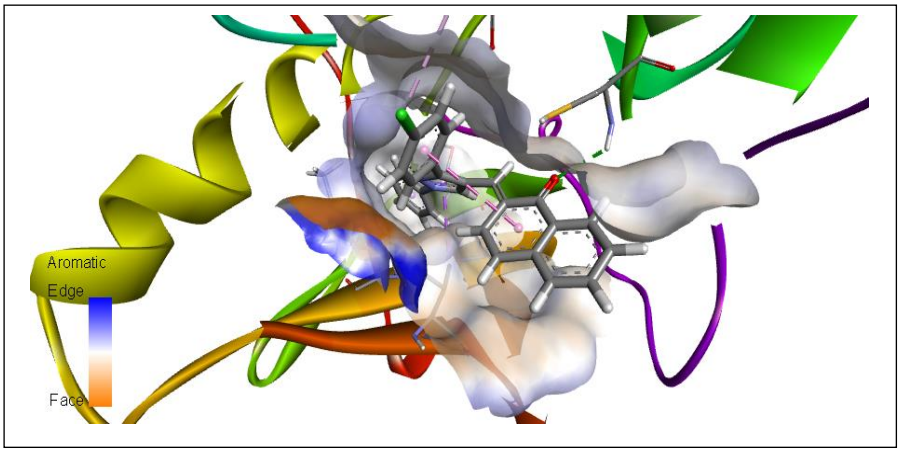

Fig. 19: Molecular docking studies-I

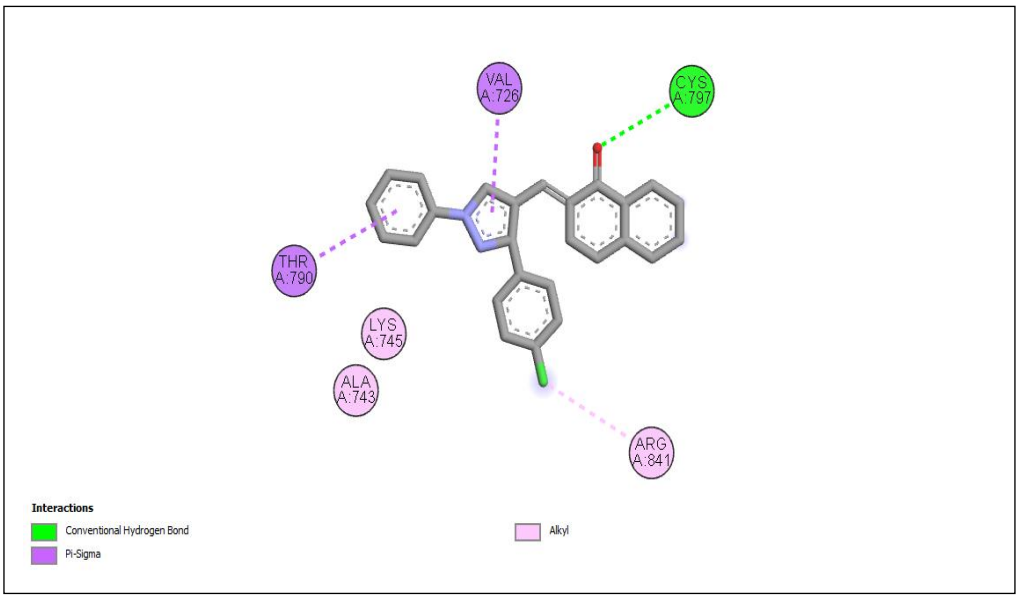

Fig. 20: Molecular docking studies-II

RESULTS AND DISCUSSION: -

Our goal in this project was to incorporate these two independently biologically active moieties into one molecule to generate compounds with synergistic in vitro biological activities. Thus, we plan to synthesize a new series of tetralone-linked pyrazole chalcones by Claisen-Schmidt condensation reaction and expect them to show additive medicinal/

pharmacological properties. A molecular docking study was performed with PDB: 2J5F.The required substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes 3a-g were prepared by Vilsmeier-Haack reaction (Scheme 1) on acetophenone hydrazones 2 obtained from various substituted acetophenones 1 according to the literature method and confirmed ^{1}H NMR & ^{13}C NMR. Chalcones as starting materials were successfully synthesized via Claisen–Italics Schmidt condensation using 15% KOH from the corresponding aldehydes with acetophenone in methanol [8]. Chalcones are well known as intermediates for the synthesis of various heterocyclic compounds, many of which have remarkable biological activities and play a principal role in medicinal chemistry. The presence of the α-β unsaturated carbonyl system in chalcones makes them biologically attractive. The growing interest in these compounds and their potential use in medicinal applications are proved by the growing number of publications concerning the synthesis and biological evaluation of chalcone analogs.

The tetralone moiety plays an important role in diverse biological activities and is a feature of some of the most interesting and important classes of compounds. Many tetralones are pharmacologically active, functioning as anticancer, antidepressants, anti-Parkinson, antimicrobials, COX-2 inhibitors, and anticonvulsants. On the other hand, heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this ring is the key moiety in numerous biologically active compounds. Some of them, such as Antipyrine, Phenylbutazone, Celecoxib, Deracoxib, etc. are prominent COX-2 inhibitors and act as anti-inflammatory as well as analgesic agents.

CONCLUSION: -

In conclusion, we have synthesized a new series of tetralone-linked pyrazole chalcones with excellent yields without the formation of any detectable side products and are expected to show pharmacological properties either similar or additive biological activities as compared to previously reported drugs. The synthesized compounds showed significant interaction with the Tyrosine Kinase enzyme and also showed significant interaction with some common amino acids and co-crystallized ligands. Hence, it can be concluded that the tested tetralone-linked pyrazole chalcones will be considered potential anticancer agents.

The growing interest of synthetic organic, pharmacological, and medicinal chemists towards chalcones and their derivatives will continue in the future.

ACKNOWLEDGEMENT: -

I would like to express my special thanks of gratitude to my project supervisor Dr. S.Y. Jadhav, assistant professor, Department of Chemistry, D.B.F. Dayanand College of Arts and Science, Solapur for his guidance, inspiration, support and constant encouragement throughout the tenure of my project. I would like to express my gratitude to our principal Dr. Ubale V.P. and the Head of the Chemistry department Prof. Chavan S.K. and convey my senior thanks to my guide Dr. Jadhav S. Y. for the wholehearted cooperation, support, and guidance towards the successful completion of this project. In the present world of competition, there is a race of existence in which those have the will to come forward and succeed. A project is like a bridge between theoretical and practical working. With this willingness, I joined this particular project. I would like to thank the one who has always guided me to work on the right path in life. Thanks, to all other faculty members and non-teaching staff who directly or indirectly participate in my project work.

REFERENCES: -

1. Rudrapal M, et.al. Chalcone Scaffolds, Bio precursors of Flavonoids: Chemistry, Bioactivities, and Pharmacokinetics. Molecules. 2021 Nov 26;26(23):7177. doi: 10.3390/molecules26237177. PMID: 34885754; PMCID: PMC8659147.
2. Dhaliwal JS, Moshawih S, Goh KW, Loy MJ, Hossain MS, Hermansyah A, Kotra V, Kifli N, Goh HP, Dhaliwal SKS, Yassin H, Ming LC. Pharmacotherapeutics Applications and Chemistry of Chalcone Derivatives. Molecules. 2022 Oct 19;27(20):7062. doi: 10.3390/molecules27207062. PMID: 36296655; PMCID: PMC9607940.
3. Legoabe LJ, Petzer A, Petzer JP. α-Tetralone Derivatives as Inhibitors of Monoamine Oxidase. Bioorg Med Chem Lett. 2014 Jun 15;24(12):2758-63. doi: 10.1016/j.bmcl.2014.04.021. Epub. 2014 Apr 16. PMID: 24794105.
4. Shitole NV, Shelke KF, Sadaphal SA, Shingate BB, Shingare MS. PEG-400 Remarkably Efficient and Recyclable Media for One-pot Synthesis of Various 2-Amino-4H-chromenes, Green Chemistry Letters and Reviews. 2010 Jul 30;2(3):83-87. doi-10.1080/17518250903567246
5. Turkan F, Cetin A, Taslimi P, Karaman HS, Gulçin İ. Synthesis, Characterization, Molecular Docking and Biological Activities of Novel Pyrazoline Derivatives. Arch Pharm (Weinheim). 2019 Jun;352(6):e1800359. doi: 10.1002/ardp.201800359. Epub 2019 May 24. PMID: 31125504.
6. Salum KA, Murwih M, Khairuddean M, Kamal NNSNM, Muhammad M. Design, Synthesis, Characterization and Cytotoxicity Activity Evaluation of Mono-chalcones and New Pyrazolines Derivatives. J Appl Pharm Sci. 2020 Aug;10(08): 20–36. DOI: 10.7324/JAPS.2020.10803
7. Ouyang Y, Li J, Chen X, Fu X, Sun S, Wu Q. Chalcone Derivatives: Role in Anticancer Therapy. Biomolecules. 2021 Jun 16;11(6):894. doi: 10.3390/biom11060894. PMID: 34208562; PMCID: PMC8234180.
8. Bandgar BP, Gawande SS, Bodade RG, Totre JV, Khobragade CN. Synthesis and Biological Evaluation of Simple Methoxylated Chalcones as Anticancer, Anti-inflammatory and Antioxidant Agents. Bioorg Med Chem. 2010 Feb;18(3):1364-70. doi: 10.1016/j.bmc.2009.11.066. Epub 2009 Dec 6. PMID: 20064725.
9. Mantzanidou M, Pontiki E, Hadjipavlou-Litina D. Pyrazoles and Pyrazolines as Anti-Inflammatory Agents. Molecules. 2021 Jun 5;26(11):3439. doi: 10.3390/molecules26113439. PMID: 34198914; PMCID: PMC8201324.
10. Konstantinidou M, Gkermani A, Hadjipavlou-Litina D. Synthesis and Pharmacochemistry of New

Pleiotropic Pyrrolyl Derivatives. Molecules. 2015 Sep 10;20(9):16354-74. doi: 10.3390/molecules200916354. PMID: 26378503; PMCID: PMC6332026.
11. Costa RF, Turones LC, Cavalcante KVN, Rosa Júnior IA, Xavier CH, Rosseto LP, Napolitano HB, Castro PFDS, Neto MLF, Galvão GM, Menegatti R, Pedrino GR, Costa EA, Martins JLR, Fajemiroye JO. Heterocyclic Compounds: Pharmacology of Pyrazole Analogs from Rational Structural Considerations. Front Pharmacol. 2021 May 10; 12: 666725. doi: 10.3389/fphar.2021.666725. PMID: 34040529; PMCID: PMC8141747.
12. Abdellatif KRA, Fadaly WAA, Mostafa YA, Zaher DM, Omar HA. Thiohydantoin Derivatives Incorporating a Pyrazole Core: Design, Synthesis and Biological Evaluation as Dual Inhibitors of Topoisomerase-I and Cycloxygenase-2 With Anti-cancer and Anti-inflammatory Activities. Bioorg Chem. 2019 Oct;91:103132. doi: 10.1016/j.bioorg.2019.103132. Epub 2019 Jul 19. PMID: 31374529.

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