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TETRALONE LINKED PYRAZOLECHALCONES: GREEN SYNTHESIS, CHARACTERISATION AND MOLECULAR DOCKING STUDY

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ABSTRACT

The new series of Tetralone linked pyrazolechalcones were synthesized by using polyethylene glycol (PEG-400) as a green as well as alternative reaction medium and molecular docking study was performed with PDB: 2J5F. All the synthesized compounds were characterized by using IR, ^{1}HNMR, ^{13}CNMR and DEPT spectroscopic methods. Compounds have shown significant interactions at the binding site and found interacting with some common amino acids interacting with co-crystallized ligand.

KEYWORDS: *Tetralone linked pyrazolechalcones, PEG-400, Molecular docking study.*

INTRODUCTION

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 chalcones analogues.

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[1]. Many tetralonesare pharmacologically active[3], functioning as anticancer[2], antidepressants, anti-parkinson[4], COX-2 inhibitors[5], antimicrobials[6], and anticonvulsants. On the other hand, heterocycles containing the pyrazole ring are important targets in the 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 acting as a anti-inflammatory as well as analgesic agents.

In present work, we plan 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 pyrazolechalcones by Claisen-Schmidt condensation using polyethylene glycol (PEG-400)[7,8] as a green solvent and molecular docking study was performed.

METHODS AND MATERIALS

Instrumentation

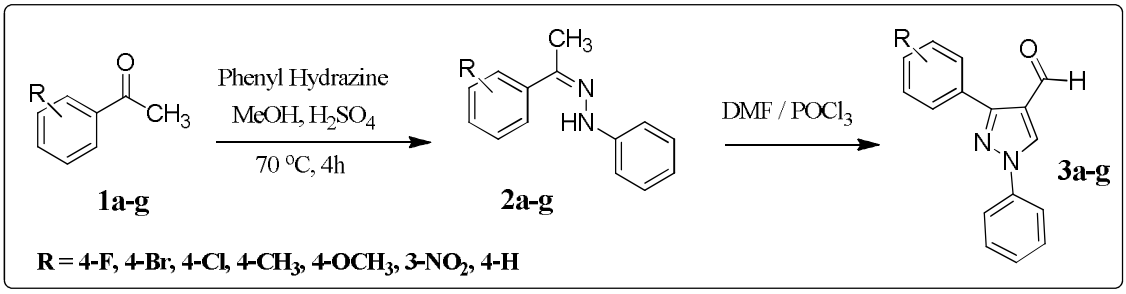
Melting points were recorded on a Superfit (India) capillary melting point apparatus and were uncorrected. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. ^{1}H NMR and ^{13}C NMR (400 MHz, 500 MHz) spectra

were recorded on a Brucker-AVANCE spectrometer in deuterochloroform (CDCl3) with tetramethylsilane (TMS, δ = 0 ppm) as an internal standard for ^{1}H NMR and chloroform-d middle peak of the triplet (δ = 77.10 ppm) as an internal standard for ^{13}C NMR.

Chemistry

The required substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes **3a-g** were prepared by Vilsmeier-Haack[9] reaction (**Scheme 1**) on acetophenonehydrazones**2** obtained from various substituted acetophenones**1** according to literature method and confirmed IR, ^{1}H NMR and ^{13}C NMR, DEPT etc.

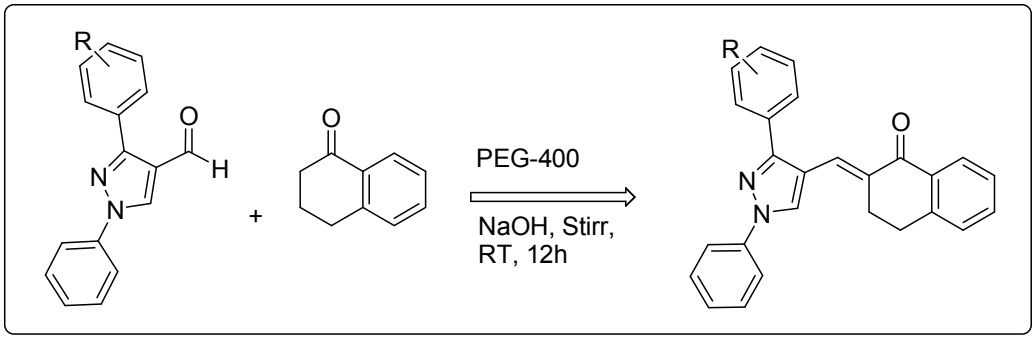
Scheme 1:



General procedure for the preparation of tetralone linked pyrazolechalcones (4a-g)

Then, we treated differently substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3a-g** (1 mM) with α-Tetralone (1 mM) in 40% KOH (2ml) and PEG-400. On stirring the reaction mixture at room temperature for 12 h, we have isolated the tetralone linked pyrazolechalcones(**Scheme 2**) with good yield and purity after usual workup followed by recrystallization. All the synthesized compounds will be confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data.

Scheme 2:



RESULTS AND DISCUSSION

Spectral analysis

All the synthesized compounds were characterized by IR, ^{1}H NMR, and MS. The IR spectrum of the titled compounds showed absorption due to –carbonyl stretching at ~1658 cm^{-}1. ^{1}H NMR spectrum (400 and 500 MHz) recorded in $CDCl_3$ showed a typical triplet at δ ~ 3.0for $–CH_2$- proton in tetralone moiety and a typical 1H-1H coupling constant in between 12-16 Hz showing *trans* stereochemistry of the double bond.

(E)-2-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (1):

IR (neat): ν 2953, 1658, 1591, 1533 cm^{-1}; **^{1}H NMR** (500 MHz): 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**(100 MHz): δ 27.69, 28.59, 115.69, 119.47, 127.20, 128.27, 130.50, 133.68, 139.70, 143.03, 153.41, 187.04; **DEPT:** δ 27.69, 28.59, 115.70, 119.47, 127.18, 127.44, 129.66, 130.51, 133.29.

(E)-2-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (2):

IR (neat): ν 2960, 1659, 1593, 1530 cm^{-1}; **^{1}H NMR**(500 MHz): δ 3.0 (t, 2H), 3.07 (t, 2H), 7.15-7.18 (m, 13H, Ar-H),8.12 (s, 1H, Pyrazole-H), 8.13 (s, 1H, -CH=C-);**^{13}C NMR**(100 MHz) : 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.

(E)-2-((3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (3):

IR (neat): ν 2960, 1660, 1595, 1538 cm^{-1}; **^{1}H NMR**(500 MHz): 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**(100 MHz): 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.

(E)-2-((1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (4):

IR (neat): ν 2953, 1660, 1594, 1534 cm^{-1}; **^{1}H NMR**(400 MHz): δ 2.43 (s, 3H), 3.04 (t, 2H), 3.11 (t, 2H), 7.28-8.0 (m, 13H, Ar-H), 7.91 (s, 1H, -CH=C-), 8.15 (s, 1H, Pyrazole-H);**^{13}C NMR**(100 MHz): 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.

(E)-2-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (5):

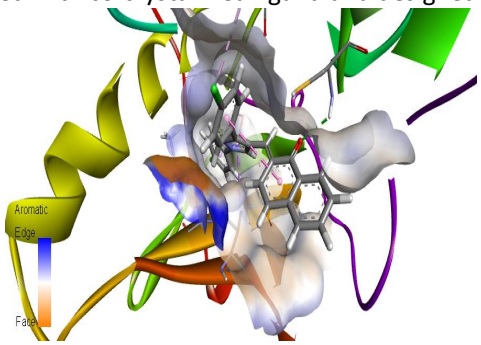
IR (neat): ν 2953, 1660, 1594, 1534 cm^{-1}; **^{1}H NMR** (400 MHz): δ 2.43 (s, 3H), 3.04 (t, 2H), 3.11 (t, 2H), 7.28-8.0 (m, 13H, Ar-H), 7.91 (s, 1H, -CH=C-), 8.15 (s, 1H, Pyrazole-H);**^{13}C NMR**(100 MHz): δ 21.35, 27.62, 28.53, 116.97, 119.55, 126.96, 127.7, 128.35, 129.40, 133.12, 138.38, 154.46, 187.04.

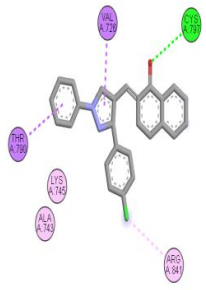
(E)-2-((1,3-diphenyl-1*H*-pyrazol-4-yl)mehtylene)-3,4-dihydronaphthalen-1(2*H*)-one (7):

IR (neat): ν 3134, 3046, 1654, 1600, 1567, 1495 cm^{-1};**^{1}H NMR**(400 MHz): δ 3.04 (t, 2H), 3.12 (t, 2H), 7.28-8.14 (m, 14H, Ar-H), 7.91(s, 1H, -CH=C-), 8.17 (s, 1H, Pyrazole-H);**^{13}C NMR**(100 MHz): 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 STUDY

Docking study was carried out on the Autodock software[10] with PDB: 2J5F that was taken from RCSB protein data bank (*https://www.rcsb.org*) developedbyX-RAY diffraction with resolution**:** 3 Å is used, which is a structure tyrosine kinase enzyme. The software generated binding affinity scores were obtained and analyzed. Grid for docking was selected where the co-crystallized ligand was attached. Interactions generated with co-crystallized ligand and designed molecules were studied.





Compounds have shown significant interactions at the binding site and found interacting with some common amino acids interacting with co-crystallized ligand. Binding site contains Leu 370, Tyr 371, Trp 373,

Phe 504, Ile 503, Gln 178, Gly 340, Tyr 341, his 75, Arg 499, Tyr 334, Val 335, Ala513, Arg 106, Val 102, Met 508, Val 509, Glu 510, Leu 345, Ser 339, Leu 517, Ala 502, Gly 512, Met 99, Ser 516, Leu 345 in the proximity of 5 Å.

CONCLUSION

In conclusion, we have synthesized a new series of tetralone linked pyrazolechalcones with excellent yields without 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. All the synthesized compounds were performed with molecular docking study. The results of molecular docking study reveals that all the compounds have shown significant interactions at the binding site and found interacting with some common amino acids interacting with co-crystallized ligand.

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Conflict of Interest

Authors have no conflict of interest.

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