"Synthesis of some novel Chromones, Pyrazoles and Pyrazolines by conventional method and evaluation of their biological activity"

Minor Research Project Report submitted

To

UNIVERSITY GRANTS COMMISSION

By

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CONTENTS

PART-I

Section A: Synthesis of (E)-4-(1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)but-3-en-2-one

Chalcones derivatives

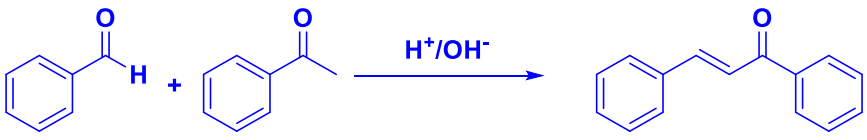
Chalcone shows a spread of fascinating biological actions as well as medication, antifungal, anti-mouse liver disease virus (MHV), inhibition of herpes simplex virus sort one (HSV-1), and animal virus, anti-cancer, antimosquito larvae and herbicidal activities. In agricultural chemistry, it's kenned that the presence of a chloro and chemical group moiety invariants of azomethine compounds will exhibit chemical activity. There area unit various biologically active molecules that contain sundry heteroatoms like N, sulfur, and oxygen, perpetually drawn the eye of chemist over the years in the main are subjected to in depth study within the recent years. There's growing interest within the medicine potential of natural merchandise is chalcones represent a overriding cluster of natural merchandise. The presence of a reactive α, β unsaturated keto perform in chalcones is found to be chargeable for their antimicrobial activity. In recent years a spread of chalcones are reviewed for his or her cytotoxic, anticancer, and agent yet as antiviral, insecticidal, and accelerator repressive properties. variety of chalcones having chemical group, alkoxy teams in several positions are reported to possess medication, antiulcer, antifungal, inhibitor, vasodilatory, antimitotic, antiprotozoal, antileishmanial and inhibition of chemical mediators unleash.

Cross condensation (Claisen -Schmidt)

The most standard and oftentimes certain route to synthesize chalcone is Claisen-Schmidt [1] condensation that entails condensation of natural compound and aldehydes, with token work-up and fewer aspect product [2].

Claisen condensation[1] is that the most dominating method using variety of catalysts like LiOH.H2O[3,4], K2CO3[5],NaOCH3 [6], OH[7], NaOH [8-11] AlCl3 [12], Ba(OH)2, HCl [13], component acid [14], CsOH-γAl2O3 [15], cesium salts of 12-tungstophosphoric acid [16], H5PMo10 V2O4O/SiO2 [17], SiO2-H3PO4 [18], B2O3-ZrO2 [19] and silica- H2SO4[20]. Amino-acetophenone with substituted benzaldehyde in the presence of hydroxide delivered 4-aminochalcone that extra reacted with maleic chemical compound inside the presence of NEt3 in dissolver to bring 80-84% yield of 1-(4-(3-aryl)acryloyl)phenyl)-1H-pyrrole-2,5-dione derivatives, that have the undertaking to modify human metabolism[21].

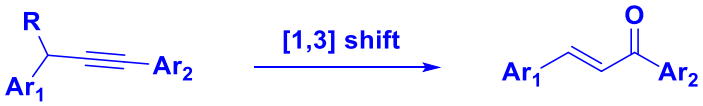
1- (2-Hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)phenyl)ethanone was once reacted with Associate in Nursing fragrant natural compound beneath methanolic, KOH, tetrahydropyranyl chalcones, extra dealt with with ethanolic acidic media to make dihydroxychalcones in 70-86% yield[22]. Scientists have conjointly in accordance on victimization inexperienced stipulations and ecofriendly catalysts like ash (65% yield) [23], poly(N-vinylimidazole) (71% yield)[24], acidic resins amberlite-200 and amberlyst-15 C (98% yield) [25], nanocrystalline mineral (MgONPs) eighty one yield[26]. Many energetic heterocyclic catalysts like graphene chemical compound [27], KF/Al2O3 in glycerine [28], nano-TiO2-SO3H [29], clay montmorillonite KSF[30], C/Co, DMAN [31], and deep combination solvent (DES) [32], media have conjointly been utilised in Claisen-Schmidt condensation response to get high-quality yield of chalcone [33].



Meyer-Schuster arrangement

Mayer-Schuster arranging has acquired first-rate activity inside the previous a long time to synthesize chalcones from definitely one-of-a-kind reactants like propargyl alcohol [34], propargyl acetate [35], and siloxypropyne [36], with absolutely distinctive mechanistic arrangements.

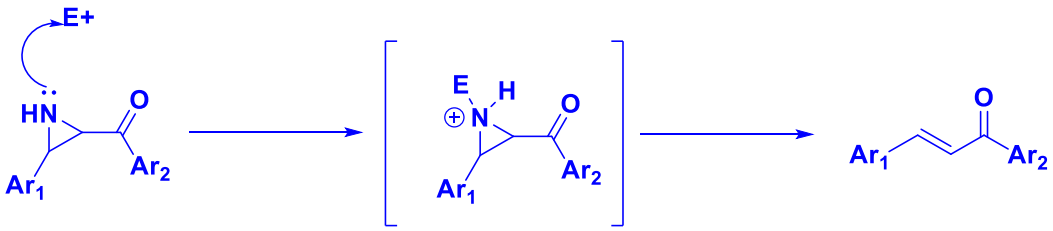
The convenient one, 3-shift of cluster hydroxyl radical chemical team purposeful team in propargylic alcohols is variety of completely extraordinary from Rupe arranging. It used several bases especially trimethylamine[37], KOH[38], catalyst was once additionally used like 1,2,3-triazole coordinated, PPh3Au(TAAu)[39], metallic superior [ReOCl3(OPPh3)(SMe2)][40], Ir/Pd superior and Au (III)Cl2 superior [41]. Propargyl alcohols vicinity unit definitely out there, lower priced and clever chelating companions with N-phenoxyacetamides having monodentate -ONHAc ODG, consequently it is with N-phenoxyacetamide beneath [Cp*RhCl2]2 and CsOAc to synthesize (81-84 %) yield of chalcones [42].



Deamination of Aziridine

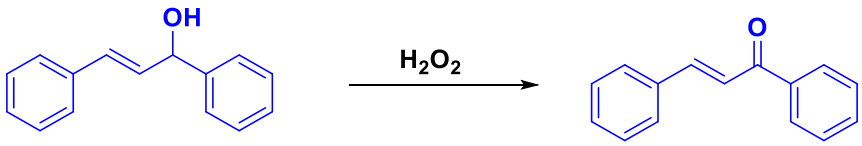
The elimination of aminoalkane groups from phenyl(3- phenylaziridin-2-yl)methanone (aziridine). Aziridine is Associate in Nursing natural three-membered chemical compound, having one aminoalkane cluster (-NH-) and two team groups(-CH2-). chemical motion of various aziridines was once executed under N2O4, iodine[43], PPh3/iodine, organosilyllithium, n-butyl group, N-nitroso-3-nitrocarbazole, nitrosyl chloride (NOCl) and alkyl radical team [44], to find the money for chalcone in clever yield. This approach has risks like highly-priced reagents,

excessive expenses of preparations, tedious work-up approaches and nitrosation agents. Novel a range of catalysts added through researchers to cope its drawbacks region unit DEG (diethylene glycol)/ I2 [45], N-bromosuccinimide (NBS)/ cerium(IV) nitrate (CAN) [46], Fe(NO3)3, I2, AgNO3 and RuCl3 [47] .



Oxidation

The synthesis of chalcone used to be conjointly investigated through conversion of chemical crew alcohols into the corresponding natural compound inside the presence of Associate in Nursing oxidizer like oxide. Novel chemical exchange amendment was once accomplished by using response of chemical crew alcohols i.e. 9-azabicyclo[3.3.1]nonane- N-oxyl (ABNO) furnished ninety fifth yield, KBrO3, TEMPO ninety 9 yield [48], PhI(OAc)2 ninetieth yield [49], iron(III)-based Lewis acidic ionic beverages (IBLAILs) [50], Mn(OTf)2, H2O2 ninety two yield [51], and anatase TiO2(TiO2-A) photocatalyst (60% yield) [52]. Poor yield in accordance with few catalysts for the response of chemical team alcohol used to be thanks to the formation of a combine of product, beneath Rh2(Msip)4 5 hundredth yield , and TEMPO@PMO-IL (37% yield).

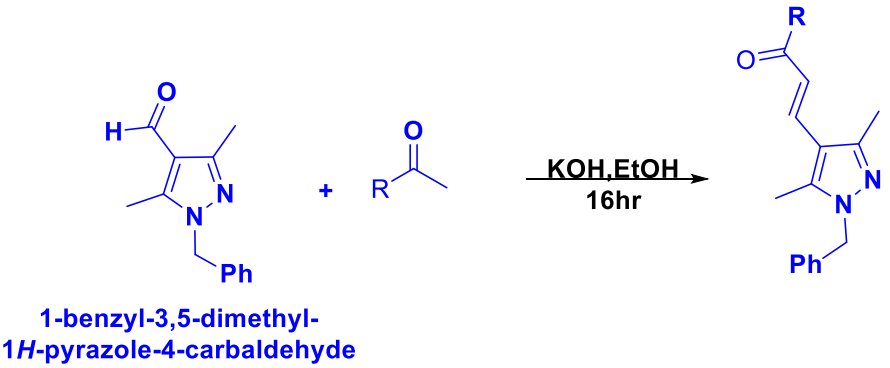


Present work:

Experimental: As Literature survey gone completed, we try to syntheses new series of chalcones from novel aldehyde. We gone through the condensation method just because of metal free, and easy path.

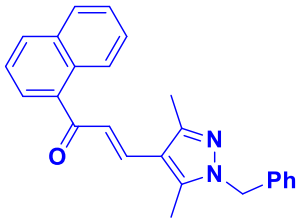
1-(2-ethoxyethyl)-1H-pyrazole-4-carbaldehyde reflex with acetophenones, it observe on TLC, no reaction proceed as with Potassium hydroxide, at 24 hr, so we try to varies the base as NaOH reaction was completed on TLC, but in NMR, desired compound was not observed. Again we varies the 1-(p-tolyl) ethan-1-one to 1-(3-nitrophenyl)ethan-1-one still we didn't get desired product from NMR, The reaction was failed.

From the below table we observed that electronegative acetophenones doesn't provided desirable product from NMR.



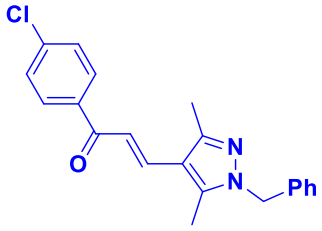
1-benzyl-3,5-dimethyl-
1*H*-pyrazole-4-carbaldehyde

entry	R	% yield
1a	Naphthalene	76
1b	Chlorobenzene	81
1c	Toluene	77
1d	o-phenol	54



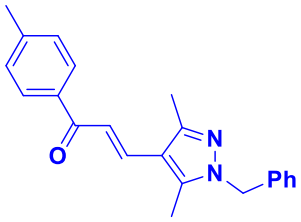
(*E*)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(naphthalen-1-yl)prop-2-en-1-one

1a



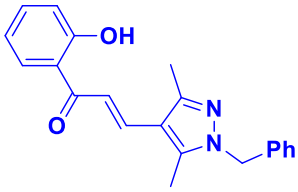
(*E*)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(4-chlorophenyl)prop-2-en-1-one

1b



(*E*)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(*p*-tolyl)prop-2-en-1-one

1c



(*E*)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one

1d

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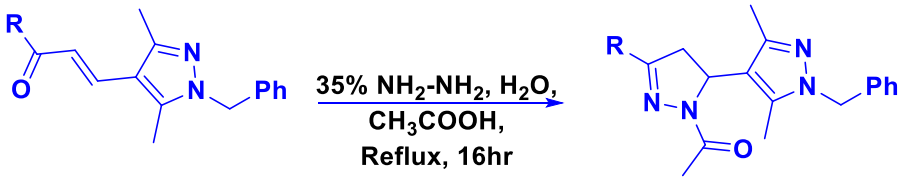
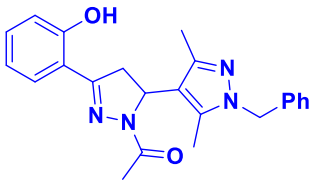
Section B : Synthesis of 1-(1'-benzyl-3',5,5'-trimethyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)ethan-1-one derivatives

Pyrazoles are well known nitrogen containing heterocyclic compounds. As per the literature, pyrazole and its derivatives represents one of the most desirable class of compounds with a wide variety of pharmacological activities *viz*., antitubercular,1,2 antifungal,3 antidepressant,4,5 antimicrobial,6 anti-angiogenic,7 analgesic,8 anticancer9 and anticonvulsant.10 Moreover, pyrazole containing pyrazoline derivatives are important drug molecules and exhibit an important pharmacophore activities *viz*. antioxidant,11 antimicrobial12 and antidiabetic.13 Few of the literature reveals that, the presence of substituted phenyl *i.e.* 4-chlorophenyl or benzene sulfonamide at first position of pyrazole exhibit enhanced biological activities. Based on the above considerations, we hereby report the synthesis of 1-(4-chlorophenyl) pyrazole containing pyrazoline derivatives and its antitubercular activity against *Mycobacterial tuberculosis*.

Experimental:

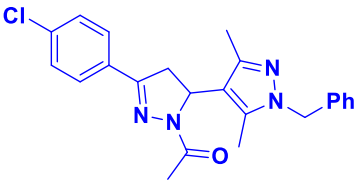


Entry	R	% yield
3a	Naphthalene	85
3b	Chlorobenzene	80
3c	Toluene	84
3d	o-phenol	86



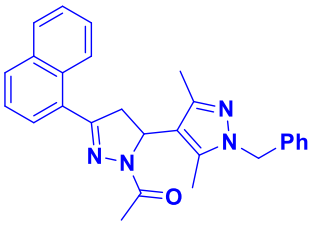
1-(1'-benzyl-5-(2-hydroxyphenyl)-3',5'-dimethyl-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)ethan-1-one

3a



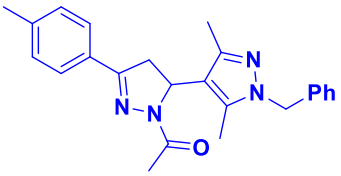
1-(1'-benzyl-5-(4-chlorophenyl)-3',5'-dimethyl-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)ethan-1-one

3b



1-(1'-benzyl-3',5'-dimethyl-5-(naphthalen-1-yl)-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)ethan-1-one

3c



1-(1'-benzyl-3',5'-dimethyl-5-(*p*-tolyl)-3,4-dihydro-1'*H*,2*H*-[3,4'-bipyrazol]-2-yl)ethan-1-one

3d

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Section C : Synthesis of Pyrazol- 4H-chromen-4-one derivatives

The word chromones are derived from the Greek word chroma, betokening “color”, which designates that many chromone derivatives exhibit a broad variety of colors. The rigid bicyclic chromone fragment has been relegated as a privileged structure in drug revelation, due to its use in a wide variety of pharmacologically active compounds such as anticancer, anti-HIV, antibacterial, and anti-inflammatory agents. Several chromone derivatives have adscititiously been reported to act as kinase inhibitors, to bind to benzodiazepine receptors, and as efficient agents in the treatment of cystic fibrosis. Chromones are utilized as scaffolds for the development of bioactive compounds

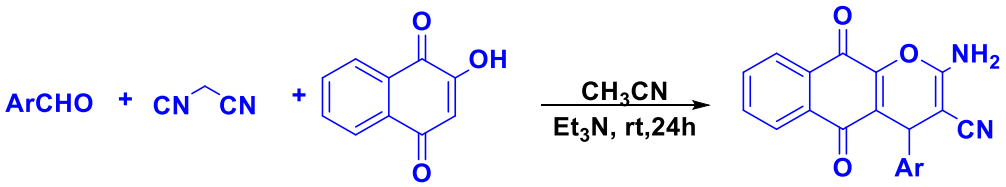
Chromones are oxygen-containing heterocyclic compounds acknowledged by their antioxidant properties. In an endeavor to develop novel agents with ameliorated activity, a series of compounds belonging to those chemical classes was yare. Chromones (4H-chromen-4-ones) constitute a paramount class of oxygenated heterocyclic compounds that commonly occur in nature [1]. Their immensely colossal variety of biological and pharmacological effects, dependent on structural features such as the type, number, and position of substituents affixed to the chromone nucleus, is well-documented and several derivatives are even currently utilized as therapeutic agents [2-4]. Despite the prosperous application of certain natural compounds as drugs, their structurally constrained accessibility imposed by biosynthetic pathways, the involute and time-consuming process of extraction and purification, or even their economically unfeasible synthesis on a gram-scale, often makes them not candidate drugs for the scientific and pharmaceutical industry in the quest for incipient therapeutic hits [5]. Being vigilant of this erudition, the development of incipient synthetic procedures applied for the synthesis of more efficient bioactive compounds constitutes a fascinating and sultry challenge for organic chemists.

Using Acid Catalyst:

Brønsted and Lewis acids are a useful catalyst for the synthesis of chromenes. There are several reports of using Brønsted acid *p*- toluenesulfonic acid (*P*-TSA) as a catalyst to prepare chromenes. For example, in 2009, synthesis of 8,9-dihydrospiro[chromeno[2,3- *d*]pyrimidine-5,3-indoline]-2,2,4,6(1*H*,3*H*,7*H*)-tetra one derivatives by a condensation reaction of barbituric acids, isatins and cyclohexane-1,3-diones in refluxing water in the presence of *p*-TSA for 10 h was reported[6] .

Using Base Catalyst:

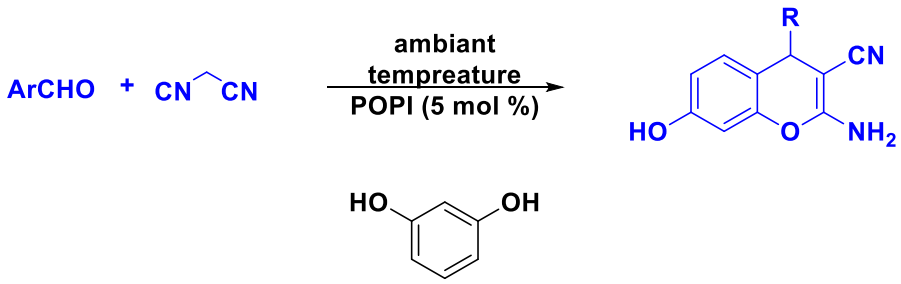
Synthesis of chromone derivatives in the presence of basic catalyst has also reported. Triethylamine (Et_3N) as inexpensive and available base catalyst was applied for preparation of chromenes. In 2009, a three- and pseudo-five-component synthetic protocol for the synthesis of benzo[*g*]- and dihydropyrano[2,3]chromone derivatives *via* addition and subsequently cyclization of 2- hydroxynaphthalene-1,4-dione or 2,5-dihydroxycyclohexa-2,5- diene-1,4-dione to the condensation product of an aldehyde with malononitrile in the presence of a catalytic amount of Et_3N in CH_3CN at ambient temperature was reported.[7]



Using Organocatalyst

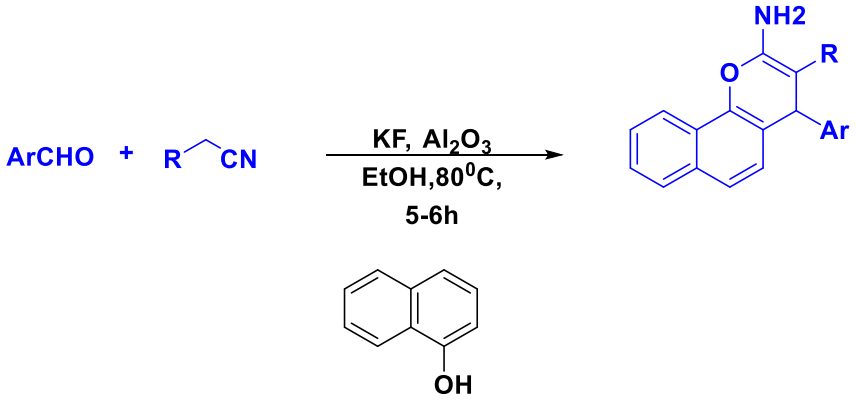
Organocatalysts as a green catalyst with low toxicity were applied to prepare chromene derivatives. In 2014, Dekamin and coworker [8] introduced potassium phthalimide (POPI) as a mild basic organocatalyst for the synthesis of 2-amino-3-cyano-4*H*chromens. This green approach carried out by the reaction of aryl aldehydes, malononitrile and diverse phenols or enolizable C-H

activated acidic compounds under mechanochemical ball milling conditions in the presence of potassium phthalimide (POPI), at ambient temperature. This protocol was also used to the production of 4*H*-benzo[*b*]pyrans.

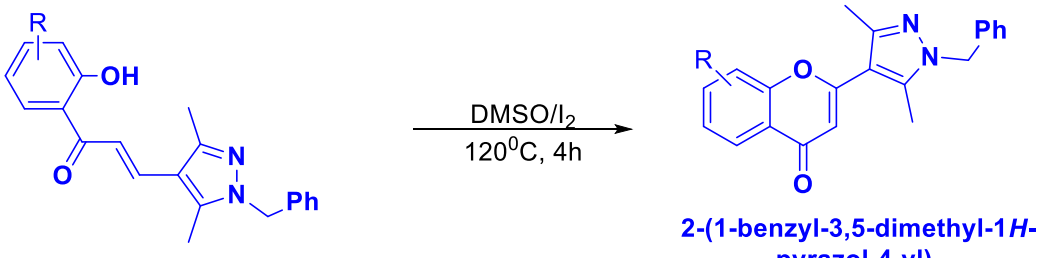


Using Inorganic Catalyst

In 2004, a series of 2-aminochromene derivatives such as 2-aminobenzo-[*h*]chromene and naphtho[1,2-b;6,5-*b*']dipyrans derivatives were synthesized from arylaldehyde, malononitrile or ethyl cyanoacetate with 1-naphthol or 1,5-naphthalenediol in refluxing ethyl alcohol catalyzed by KF-Al2O3 at 80°C.[9]



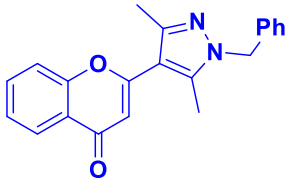
Present work:



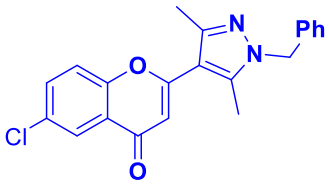
(*E*)-3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one

2-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one

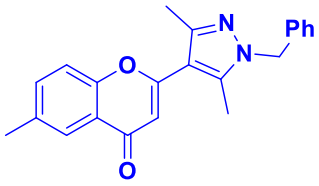
Entry	R	% yield
4a	H	81
4b	Cl	83
4c	Br	84
4d	Me	82



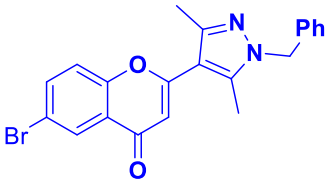
2-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one (4a)



2-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-4*H*-chromen-4-one (4b)



2-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-methyl-4*H*-chromen-4-one (4d)



2-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-bromo-4*H*-chromen-4-one (4c)

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Part-II: Biological Activities

In view of these observation and importance of these novel chalcones, Chromones and Pyrazoles compounds, we have successfully done the synthesis of a series of novel Chromones and Pyrazoles, biologically important pharmacophores. We submitted sample of chalcones, chromones and pyrazoles for biologically activity.

Conclusion: These unexpected results and success in deriving reaction mechanism encouraged us in getting involved with this work. Finding associated with these results are documented to Department of Biotechnology, SPPU. Mechanistic study of reaction mechanism, biological screening of synthesized products, possible applications of such highly functionalized molecules and the computational studies are under progress. These results would be the fruitful outcome of this project.

Outcome of Project:

- Young Scientist Award for the best poster presentation in Organic Chemistry section in 38th Annual National Conference, of Indian Council of Chemist's held at Jaipur National University on 26th -28th Dec. 2019.
- My self-Enrolled For Ph,D. Under The Guidance Of Prof. L. R. Patil research centre- SCS College, Shrigonda, Dist- Ahmednagar
- We found anticancer activity w.r.t. our design project molecules & biological activity evaluation is in progress.
- Research paper is in process