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ONE-POT SYNTHESIS OF TETRAHYDROPYRIMIDINES CHROMEN USING INDIUM CHLORIDE AS THE CATALYST AND ITS BIOLOGICAL ACTIVITY

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ABSTRACT
The extensive applications and synthetic studies of novel Heterocyclic Compounds in new drugs via the MCR strategy are now becoming incredibly valuable in both industry and academia. The significant classes of Heterocyclic Compounds found in most of the marketed drugs are the derivatives of pyrimidine, which are essential constituents of nucleic acids. The fused tetrazolo pyrimidines are novel nitrogen heterocycles. This is how both pyrimidines, tetrazole skeletons properties and are the core moiety of several API ingredients and exhibit a wide range of biological activity. Indium chloride has been an because of its effectiveness in a variety of organic transformations and non-hazardous nature, affordable and commercially available reagents have garnered a lot of attention. The substituted chromones are indicated to have great anti-bacterial activity against the ATCC 29313 and ATCC 11229 bacteria, after the screening of 5 newly synthesized compounds, **21a** and **21e** displayed high activity gram Gram-positive bacteria.
Keywords: MCRs, Tetrahydro Pyrimidine, Chromen, Indium Chloride, and Cyclic Transition.
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INTRODUCTION

Multi-component reactions [MCR][1-3], in which two or more reactants react via a cyclic transition state leading to the formation of an acyclic structure. In multicomponent reactions, many strategies exist. They are tmc-MCR, ac-MCR, Nc-MCR -MCR, and MCR involving cycloadditions. From different categories of multicomponent reactions, non-catalyzed multicomponent reactions mediated by PEG-400[9] efficient one in the synthesis of Heterocyclic Compounds. One-pot reactions are extremely chemoselective, versatile, and concurrent with high atom efficiency.[4-6]

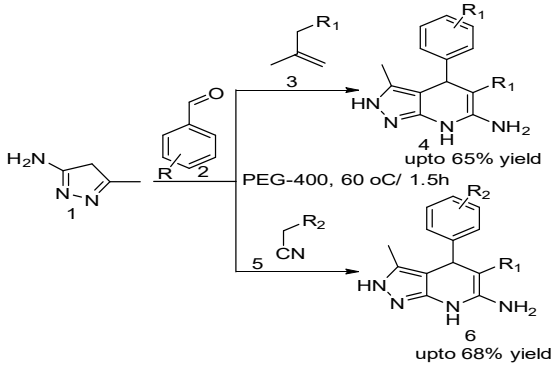

Fig.-1: PEG-400 Mediated Multi-Component Synthesis of *pyrazolo [3,4-b] pyridines)*
DABCO Catalyzed Five-Component Approach for Benzo[a]Pyrazolo [4,3:5,6] Pyran [2,3-C] phenazine Sinan Efficient Green Reaction Medium[16]

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The main aim of multi-component reactions is to follow the green chemistry principles with the replacement of hazardous chemical technologies by conducting their action in neat condition [7-11] (or) by performing reactions with the help of a phase transfer catalyst (or) conducting reactions in molecular ionic liquid (or) performing the reaction by using water as solvent. The formation of fused di-tetrazolo pyrimidines was characterized by Bulow from 5-aminotetrazole reacting with active methylene group-containing compounds in the presence of carboxaldehyde.[12-16] Literature Background Multicomponent synthesis PEG PEG-mediated organic synthesis. Poly ethylene glycol (PEG-400) mediated multicomponent, green approach towards fused pyrazol pyridines.[17-19]

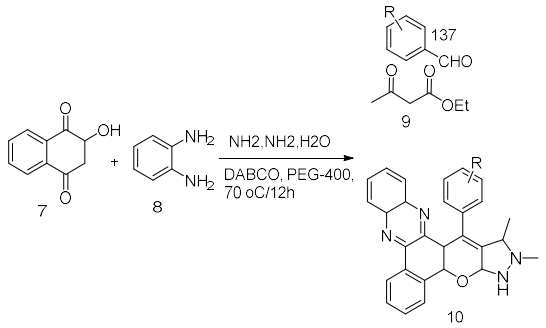


Fig.-2: Synthesis of Fused *Benzo [a] pyrazolo [4',3':5, 6] Pyran* Derivatives in PEG

The simple method for the synthesis of 3, 4, dihydropyridine was first reported by Biginelli[6] and involved a 3-component 1-pot cyclocondensation reaction of α-chain β-ketoester and urea or thiourea in the presence of acid catalysts such as hydrochloric acid in ethanol reflux at temperature 127-128ºC (Fig.-3).

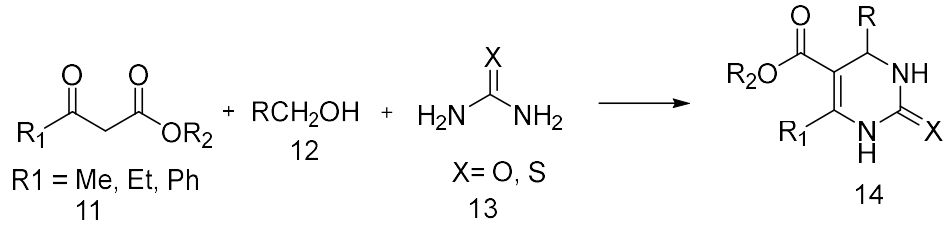


Fig.-3: Component *Biginelli* Reaction

In previous years, substitution of standard toxicant and Lewis acid catalyst and polluting Bronsted by eco-friendly reusable solid acid heterogeneous catalyst(s) has achieved substantial importance within the śyntheisis of the three,4-dihydropyrimidiniones. Thus, a good form of solid acid catalysts is supported by Lewis acids and Bronsted acids.

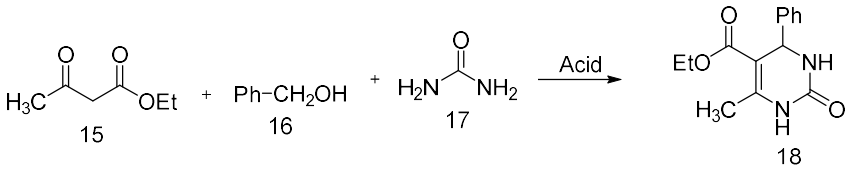


Fig.-4: Synthesis of Pyrimidines with the *Biginelli* Reaction

Table-1: Evaluation of Various Catalysts Utilized in the Bigineli Reaction to Produce 5-(éthoxycarbonlyl)-6 -methlyl-4 -phenyll-3,4 -dihydropyrimedin-2(*H*)-one

Catalyst	Temp (°C)	Yield of DHPM
I_2-Al_2O_3	MW	62 %
SiO_2-$NaHSO_4$	Reflux	78 %
Alum-SiO_2	80	72 %
Ferrihydrite in a silica aerogel	Reflux	62 %
Silica sulphuric acid	Reflux	72 %
$FeCl_3$-SiMCM-41	MW	81 %

Creation of Indole Derivatives. Biologically active substances called functionalized indoles can be produced in a number of ways. Recently, functionalized indoles have been produced by 3omponent coupling and cyclization of N-tosyl protected ethynyl aniline, paraformaldehyde, and piperidine in the presence of Au/ZrO2 101, following the Minnich method (Fig.-5).

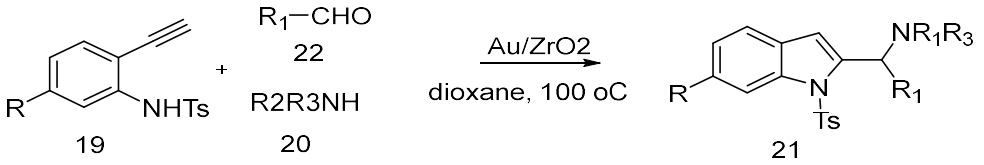


Fig.-5: Three Components Coupling and Cyclization of an *Aldehyde, Aminine*, And *N-Protected Ethynyl Aniline*

EXPERIMENTAL

Materials and Methods**:** The synthesis of tetra thiopyrimidines derivatives was outlined in Fig.-6. The intermediate 4H chromone, synthesized by freshly distilled phosphorous-oxychloride (487 mg4.4equiv), was added dropwise to DMF (348mg, 6.6equiv) at 5-10°C and stirred. The mixture was stirred for 15 minutes, and then the solution of 2-hydroxy acetophenone in DMF was added. The reaction mixtures was stirred at low temperatures for 30mins and then heated and stirred at 50-55 °C for 4 h. 3-carballdehyede (174 mg, 1 eq), Thio-urea (114mg, 1.5eq) and ethyl acetoacetate (130mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was added to 50ml round bottom flask and the reaction mixtures was refluxed 3 hours. Then the solid was filtered, dried, and purified by column chromatography. This composite was obtained as dark brown color solids in 90-94% yield. Melting point: 293-298°C.

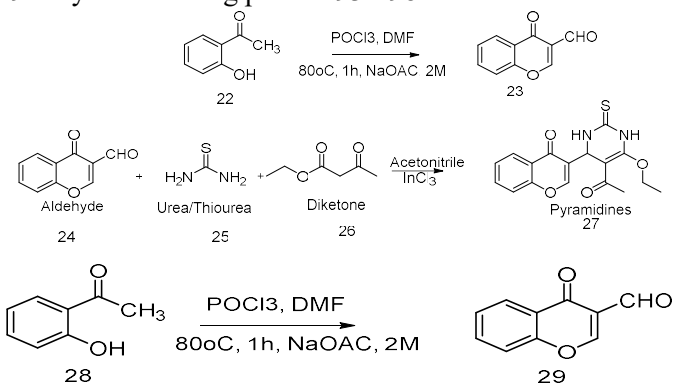


Fig.-6: General Preparation of *2:4-Oxo-4H-chromene-3-carbaldehyde*

Newly refined phosphorus oxychloride (487 mg4.4equiv) was added dropwise to DMF (348mg 6.6equiv) at 5-10 °C and blended. The combination was blended for 15 min, and afterward the arrangement of 2-hydroxyacetophenone(1equiv100mg) in DMF was added dropwise at 0-5°C. The combination was cooled to RT, filled with ice-water, and NaoAc. The consolidated natural stages were washed with water and afterwards a line solution and gathered under vacuum. MP 152-154°C.

General Preparation of (186a-E): Tetrahydro Pyrimidines

Synthisís of *3-(5-acetyll - 6- ethoxy - 2- thioxo -1, 2, 3, 4-tetra hydro pyrimidine- 4- yl) 4 Hchromen- 4-one (21a)*:

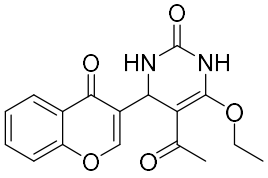
To a 50ml round bottom flask aldehyde (**21a**)4-oxo-4Ħ-chromine-3-carballdehyde (174 mg, 1 eq), thiourea (114mg, 1.5eq) and ethyl acetoacetate (130mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was added. The reaction mixtures were refluxed for 3 hours. Then the solid was filtered, dried, and purified by column chromatography. This compound was obtained as dark brown solids in 90 -94% yield. Melting point: 292-298^{0}C.

Analytical Discussion

^{1}H NMR (400 MHz, DMSO δ in ppm): 8.1(1*H*, s, aromatic *H*) 7.0-8.1 (4*H*, m, Aromatic *H*), 4.7 (1*H*, s, methyene), 2.20 (2*H*, q, -CH_2) 9.16and10.6 (2*H*, s, N-H), 2.380(3*H*, s, CH_3),1.25(3*H*, t, CH_3) Anal. Calcd

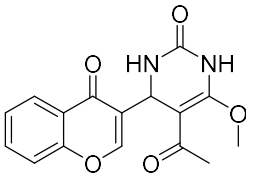
for $C_{17}H_{16}N_2O_4S$: C, 52.29; H, 4.68; N, 08.13; found C, 52.42; H, 4.30; N, 08.05%. MASS m/z foundfor $C_{17}H_{16}N_2O_4S$: 345.0 $[M-1]^+$.

Synthesis of *5-acetyll-6-ethoxy -4-(4 -oxo-4H-chromin-3-yl)-3,4 – dihydropyridine - 2(1H)-one (21b)*: To a 50ml round bottom flask aldehyde (**21a)**4 -oxo -4H -chromine-3-carbaldeheyde174 mg, 1eq, urea90mg, 1.5eq and ethyl acetoacetate (130mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was added. The response combination was refluxed 3 hours. Then the solid was filtered, dried, and purified by column chromatography. This composite was obtained as brown color solids in 89% yield. Melting point: 282-288^{O}C.



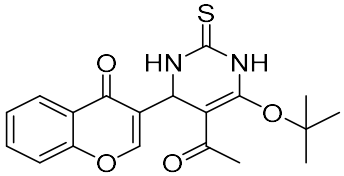
^{1}H NMR (400MHz DMSO 8 in ppm)1.19(3*H*, s, methyl),2.27(3*H*, s, methyl)4.10 (2*H*, q, methylene),5.25 (1*H*, s, methylene),7.24(1*H*, s, Aromatic *H*)7.52(1*H*, t, Aromatic *H*),7.67(1*H*, d, Aromatic *H*),7.80(1*H*, t, Aromatic *H*),8.09 (1*H*, d, Aromatic *H*),8.17(1*H*, s, NH),9.24(1*H*, s, N-H) Anal.
Calcd. For $C_{17}H_{16}N_2O_5$: C,62.19; H,4.91; N,08.53; found C,61.89; H,4.58; N,8.52
MASS m/z found for $C_{17}H_{16}N_2O_5$: 329$[M-1]^+$

Synthesis of *5-aceteyl-6-methoxy-4-(4-oxo-4H-chroman-3-yl)-3,4-dihydropyirimidin-2 (1H)-one(21c)*: To a 50ml round bottom flask aldehyde (**21a**) 4-oxo-4H-chromine-3-carbaldehyede 174 mg, 1 eq, urea 90mg, 1.5eq and methyl acetoacetate (124mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was mixed. The reaction has refluxed for 3 hours. Then, at that point, the strong was separated, dried, and cleansed by section chromatography. This compound was obtained as light brown color solids in 90 % yield. Melting point: 252-259^{O}C.



^{1}HNMR (400 MHz, DMSO δ in ppm) 1.19 (3*H*, s, methyl), 2.27 (3*H*, s, methyl)4.10,5.25 (1*H*, s, methylene),7.24(1*H*, s, Aromatic *H*)7.52(1*H*, t, Aromatic *H*),7.67(1*H*, d, Aromatic *H*), 7.80(1*H*, t, Aromatic *H*), 8.09(1*H*, d, Aromatic *H*), 8.17(1*H*, s, N-H), 9.24(1*H*, s, N-H)Anal Calcd for $C_{16}H_{14}N_2O_5$: C, 61.19; H, 4.91; N, 8.53; found C,60.89; H, 4.58; N,8.49; MASS m/z found for $C_{16}H_{14}N_2O_5$: 315$[M-1]^+$.

Synthesis of *3- (5-acetyll -6-(tert-butoxy)-2 –thioixo-1, 2, 3, 4-tetrahydro pyrimidine - 4-yl)- 4H-chroman -4-one (21d)*:
To a 50ml round bottom flask aldehyde (**21a**) 4-oxo-4H chromine-3-carbaldehlyde174mg, 1eq, thiourea114mg, 1.5eq and tert-butyl 3-oxobutanoaete (158mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was added. The response combination was refluxed for 4 hours. Then the solid was filtered, dried, and purified by column chromatography. This compound was obtained as dark brown solids in 92% yield. Melting point: 302-305 ^{O}C.

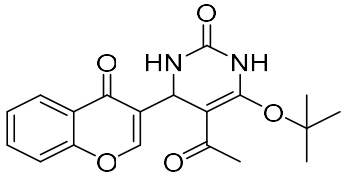


^{1}H NMR (400MHzDMSO δinppm): 8.1(1*H*, s, Aromatic *H*) 7.0-8.1(4*H*, m, Aromatic *H*),4.7 (1*H*, s, methylene), 2.20 (2*H*, q, CH_2) 9.16and10.6 (2*H*, s, N-H), 2.380(3*H*, s, CH_3),1.09(9*H*, s, (CH_3)3Anal. Calcd.

for $C_{19}H_{20}N_2O_4S$: C,62.29; H, 4.68; N,8.13; found C,62.42; H, 4.3; N, 8.05%. MASS m/z found for: $C_{19}H_{20}N_2O_4S$ 373.0 $[M-1]^+$.

Syntheisis of *5-acetyll-6-(tert-butoxy)–4-(4-oxo-4H–chroman–3–yl) - 3, 4 –dihydropyridine –2(1H)-(21e)*:

To a 50ml round bottom flask aldehyde (**21a**) 4–oxo 4 Hchromane-3–carbaldehyde 174mg, 1eq, urea 90mg, 1.5eq and tert-butyl 3-oxobutannoate (158mg 1eq) $Incl_3$ as the catalyst and acetyl nitrile was added. Their mixture was refluxed for 4 hours. Then the solid was filtered, dried, and purified by column chromatography. This composite was obtained as light brown color solids in 85%yield. Melltingpoint:299-305^{O}C.



^{1}H NMR (400MHz DMSO δ in ppm): 8.1(1*H*, s, Aromatic *H*) 7.0-8.1 (4*H*, m, Aromatic *H*), 4.7(1*H*, s, methylene), 2.20 (2H, -CH_2) 9.16 and10.6 (2*H*, s, N-H), 2.38(3*H*, s, CH_3),1.09(9*H*, s, (CH_3) 3Anal. Calcd. for $C_{19}H_{20}N_2O_5$:C, 62.29; H4.67; N, 08.13; found C, 62.42; H,4.30; N,08.05%
MASS; m/z found for: $C_{19}H_{20}N_2O_5$357.0 ([M-1]$^+$

RESULTS AND DISCUSSION

Chemistry

Freshly distilled phosphorus oxychloride (487 mg4.4equiv) was added dropwise to DMF (348mg 6.6equiv) at 5-10 °C and stirring. The combination was stirred for 15 min, and the solution of 2-hydroxy aceto phenone(1equiv100mg) in DMF was added. The combined organic phases were washed with water and then brine and concentrated under vacuum. 4 -oxo-4-chromene-3-carbaldehyde(174mg,1eq), Thio-urea (114mg,1.5eq) and ethyl acetoacetate (130mg1eq) $Incl_3$ as the catalyst and acetyl nitrile was added. For three hours, the reaction mixture was refluxed. The solid was subsequently dried, filtered, and purified using column chromatography. The response combination was refluxed 3 hours. This compound was obtained as dark brown solids.

Biology

Anti-bacterial Activity: Compounds, **21a-e**Were selected for the research of in vitro antibacterial activity. aureus (ATCC 29313) and bacteria such as Escherichia coli (ATCC 11229), respectively. For the sake of reference, streptomycin has been a drug reference point in the antibacterial study. Compounds 21a and 21b have shown superior antibacterial activity with MIC 28at30µg/ml against a bacterial strain. Compound **21c** showsMIC29µg/mland5eshowsMIC30 µg / ml against E. coli (33µg/ml), shows more may be the cause of the observed strong antibacterial inhibitory.

The substituted chromones are indicated to have great anti-bacterial activity against the ATCC 29313 and ATCC 11229 bacteria, after the screening of 5 newly synthesized compounds, **21a** and **21e** display high activity gram Gram-positive bacteria.

Antibacterial Activity of Tetrahydroharmines

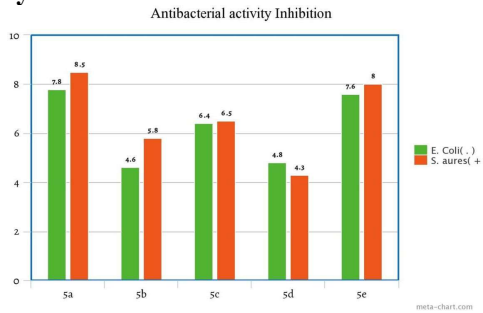
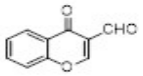
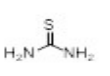
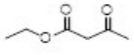
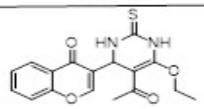
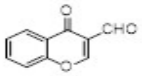
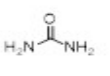
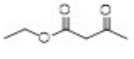
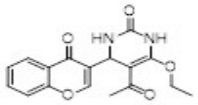
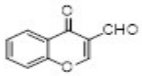
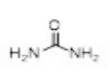
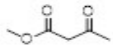
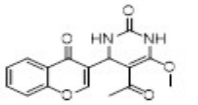
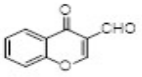
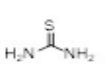
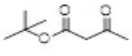
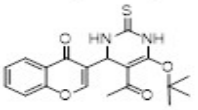
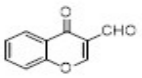
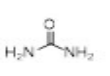
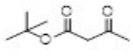
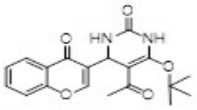


Fig.-7: Antibacterial Activity of *Tetrahydropyramidines*

Table-2: Tetrahydropyridine Derivatives (products **21a-e** respectively against S. No. 1,2,3,4 and 5)

S.no	Aldehyde	Urea/Thiourea	Diketone	Product	% yield
1					94%
2					89%
3					90%
4					92%
5					86%

CONCLUSION

Synthesized a new series of Tetrahydropyridine derivatives by using 4H-chromene, Diketoneand urea/thiourea **21a-e** in the presence of indium chloride as the catalyst**.** All the compounds were screened for Antibacterial activity.

Anti-bacterial Activity

All the titled compounds **21a-e** were examined for the anti-microbial investigation against 2(Gram-positive and negative) bacteria by utilizing the paper disc method. In the wake of solidifying the media, Petri plates were inoculated with the currently developing culture of the Escherichia coli and Staphylococcus aureus autonomously in the following way. Paper discs (5 mm diameter) were plunged into the different concentrations of the test solutions. In order to dry the paper disc, it was kept on Anti-biotic MED-3 agar in the Petri plates seeded with 1 ml of bacterial culture and incubated at 37 °C for 24 hrs. Among the test samples of the various concentrations, **21a-e,** the results revealed that the majority of synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-Negative bacteria **21a** and**21e** was best, and that of the Gram-Positive bacteria **21a and 21b** was best.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-7: Affordable and Clean Energy*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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