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PHOSPHOMOLYBDIC ACID IMPREGNATED-SILICA (PMA-SILICA) CATALYZED MICRO WAVE ASSISTED SOLID PHASE SYNTHESIS OF 3,4-DIHYDRO-1H-CHROMENO[4,3-D]PYRIMIDINE-2,5-DIONE/THIONE DERIVATIVES

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Abstract : A green solid phase synthetic methodology has been developed for the synthesis of 3,4-Dihydro-1H-Chromeno[4,3-d]pyrimidine-2,5-Dione/Thione Derivatives under microwave using PMA-Silica as Solid Phase acid catalyst within a short reaction time. PMA-Slica has prepared and characterized by IR-Spectroscopy. The products has been isolated and identified by melting point and IR spectroscopy.

***IndexTerms* - Component,formatting,style,styling,insert.**

INTRODUCTION

The design of chemical goods and processes known as "green chemistry" aims to minimize the usage of potentially harmful ingredients and use as alternative perspective on the possible applications of chemical engineering and chemistry. [1] One of important goal of green chemistry is improve atom economy of a chemical synthesis. [2] To achieve strict green chemistry, it's best to minimize the use of volatile organic solvents and carry out reactions in clean conditions (no solvents).[3] 3,4-Dihydropyrimidines[3,4-DHCPMs] have attracted significant interest in both synthetic and medical research because of their pharmalogical and biological characteristics [4] as an anticancer, anti-tumour [5],anti-diabetes, anti-vasodilator, antioxidant [6], anti-inflammatory [7], anti-viral [8] activities. Dihydrochromenopyrimidines (DHCPMs) and coumarin based moiety having several biological properties.[9] The common methodology for the synthesis of DHCPM is the multi-component reaction of aldehyde, 4-hydroxycoumarin and urea/thiourea in distinct solvent medium and presence of catalyst. Previous methodology involves L-proline in water [10], Fe3O4@SiO2@(BuSO3H) as catalyst under MWI in water [11], Barbituric acid and L-proline as a organo catalyst under MWI condition [12], SLS-in water[13], etc. Solid acidic support/catalyst has drawn a lot of interest in organic synthesis these days because of a number of benefits, including simplicity in the separation process, compatibility with the environment, a low cost, great selectivity, lack of toxicity, etc.In this study we are focused on solid phase synthesis of the aforesaid moiety under solvent free condition. Heteropolyacids (HPAs) have gained attention due to their potential commercial worth and environmental advantages. [14] A thorough investigation, shows that HPAs with their Keggin structure, belonging to the polyoxometalate class, had inherent Br¨onsted acidity comparable with super acids, as well as relatively excellent thermal stability.[15] A higher number of accessible acid sites is required for improved catalytic activity because HPAs have a low specific surface area (1–10 m2 g-1).HPAs can be distributed on a solid support with a large surface area to achieve this.We have used silica, a cheap, environmentally friendly, biodegradable material having widespread synthetic availability, simple synthesis method, low toxicity, high thermal stability, and exceptional biocompatibility.[16].We herein used PMA-silica as solid acid support/catalyst for the synthesis of [3,4-DHCPMs] derivatives without solvents.To the best of our knowledge this is the first report of PMA-silica catalysed synthesis of Dihydrochromenopyrimidines derivatives.

RESULTS AND DISCUSSION

Preparation of PMA-Silica

1 g of PMA and 25 ml of methanol were taken in a round-bottom flask and stirred until the PMA was totally dissolved. 10 g of silica gel for column chromatography (60-120 mesh) was added into it. The mixture was stirred for 4 hours on magnetic stirrer. After completion of stirring methanol was eliminated using rotary-evaporator. The resulting solid was dried in air for 24 hrs.

Identification of Catalyst

The formation of PMA-Silica was confirmed by comparative IR spectra study as shown in Fig 1. It was evident from the spectral study that the relative peaks of PMA and Silica was found in the spectra of PMA-Silica

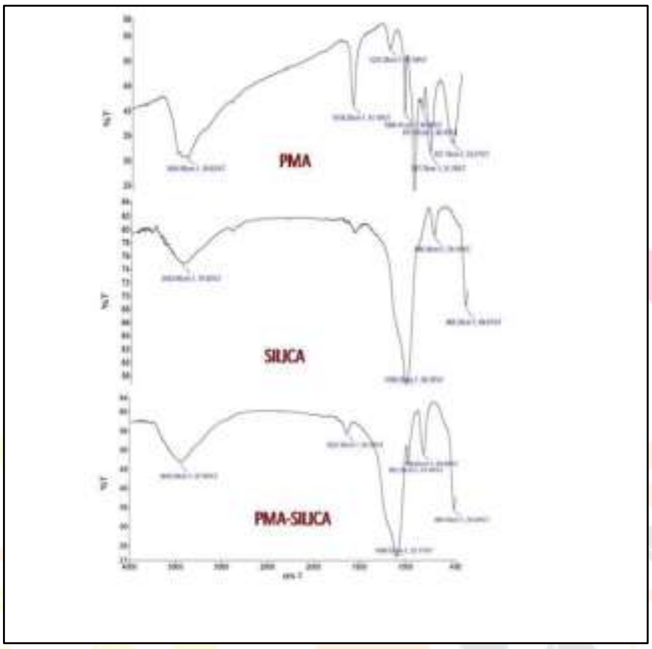
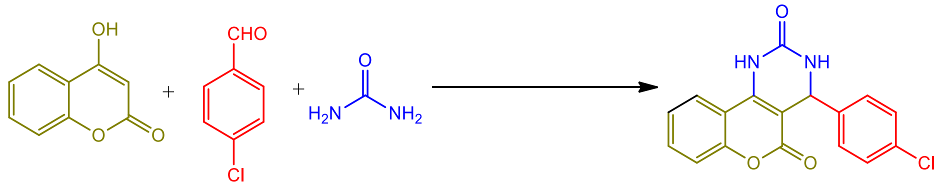


Fig 1: Comparative IR spectra of PMA, Silica and PMA-Silica

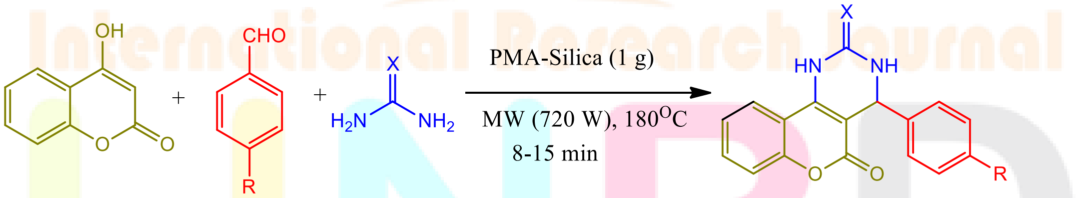
In order to find out the optimum reaction condition an extensive screening test was carried out by taking a representative reaction between 4-hydroxycoumarin (1) (1 mmol), p-chlorobenzaldehyde (2a) (1 mmol), and Urea (3a) (1 mmol) with different solid phase acid catalyst.

The reaction parameters such as temperature, amount of catalyst, reaction time etc. were also investigated and the outcomes have been summarized in Table 1. Initially the reaction was carried out by using silica by conventional heating method but no reaction was observed (Table1, entry 1) whereas using similar catalyst in microwave technique give a trace amount of product. (Table 1, Entry 2). Then we studied PTA-Silica (5 wt%) as solid support catalyst by both conventional and microwave technique (Table 1, Entry 3,4) but both cases a moderate yield was obtained. On increasing the amount of PTA to 10% showed very minor change in the yield of the product (Table 1, Entry 5,6). Subsequently we have used PMA-silica (5 wt %) as solid/acid catalyst) which provided a satisfactory yield of the expected compound within 1 hr 45 min in conventional method but in microwave method a good yield was obtained within 25 mins (Table 1, Entry 7,8). On increasing the weight % of PMA to 10 % showed excellent yield of the desired compound within 8 min in microwave technique whereas in conventional technique the reaction time was reduced than other catalyst (Table 1, Entry 9,10). Further increase of the concentration of PMA to 20% showed no effective increase of the product (Table 1, Entry 11,12). So with 10 wt % PMA- silica under microwave irradiation (180 °C, 720 w) was found to be the best technique for the synthesis of Dihydrochromenopyrimidines derivatives. Taking optimized condition in hand we further studied the scope of this reaction methodology by varying aldehyde and urea. In all the cases reaction progressed smoothly with good to excellent yield. The reactions were consistently carried out at the 1 mmol scale and no change of product yield was observed when scaled up to the 10 mmol scale. It is pertinent to mention here that aldehyde functionality with electron donating group yielded the desired product in short period of time with respect to the aldehyde having electron withdrawing group.

Table 1: Optimization study using 1a, aldehyde 2a and 3a



Entry	Catalyst	Temp	Method	Amount (g)	Time	Yield (%)
1	SiO_2	120	Conventional	1	1 hr 55 min	no reaction
2	SiO_2	180	MW (720 W)	1	30 min	trace
3	PTA-Silica(5 wt.%)	120	Conventional	1	48 min	32
4	PTA-Silica(5 wt.%)	180	MW (720 W)	1	25 min	46
5	PTA-Silica(10 wt.%)	120	Conventional	1	1 hr 45 min	35
6	PTA-Slica(10 wt.%)	180	MW (720 W)	1	25 min	48
7	PMA-Silica(5 wt.%)	120	Conventional	1	1 hr 45 min	62
8	PMA-Silica(5 wt.%)	180	MW (720 W)	1	20 min	86
9	PMA-Silica(10 wt.%)	120	Conventional	1	1 hr 45 min	88
10	PMA-Silica(10 wt.%)	180	MW (720 W)	1	8 min	96
11	PMA-Silica(10 wt.%)	180	MW (720 W)	1.5	8 min	96
11	PMA-Silca(20 wt.%)	120	Conventional	1	1 hr 40 min	88
12	PMA-Silica(20 wt.%)	140	MW (720 W)	1	8 min	96



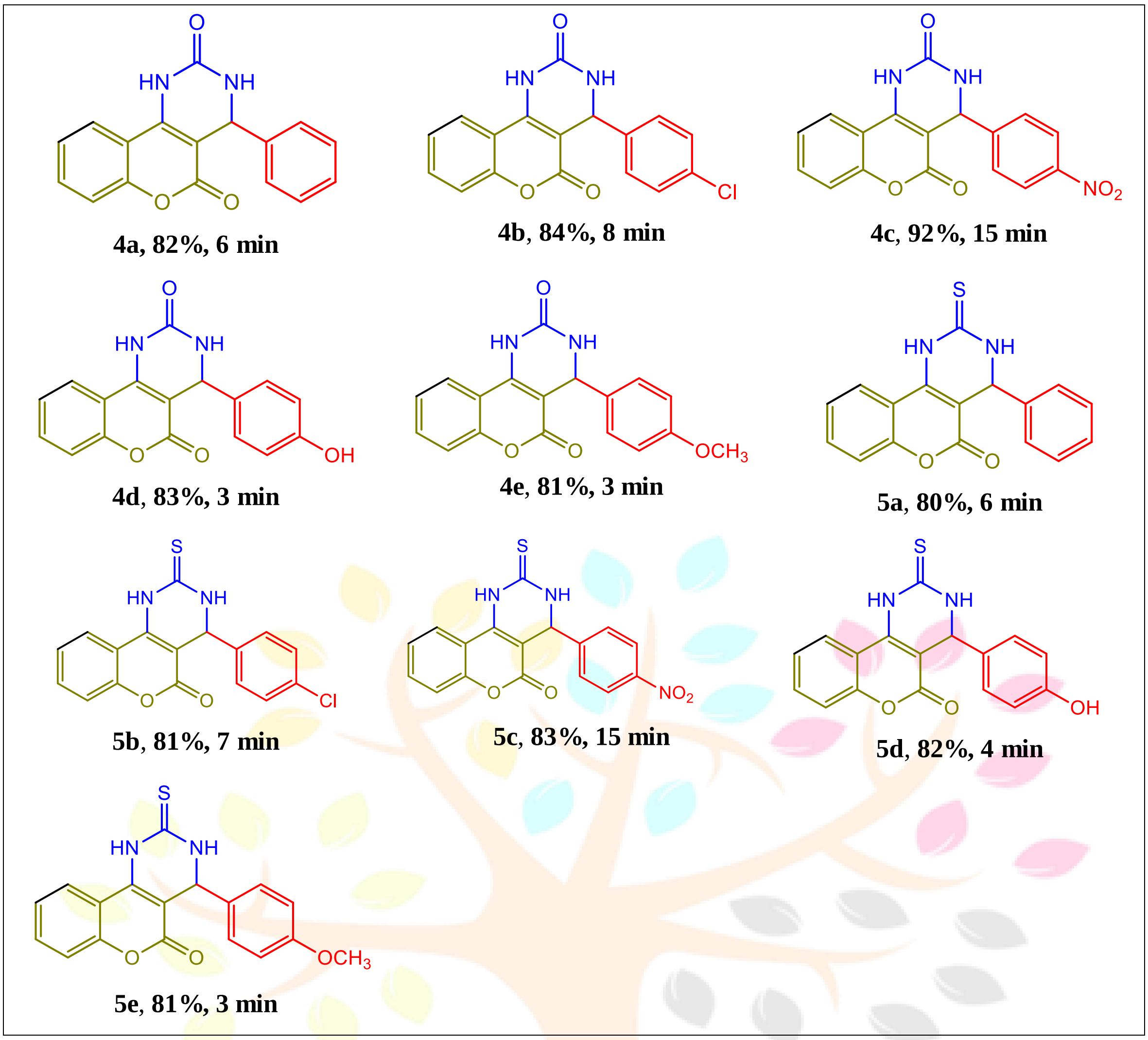
(1) **(2a-e)** **(3a-b)**

R= H, Cl, NO_2, OH, OMe X= O, S

Scheme 1: Synthesis of different Dihydrochromenopyrimidines derivatives using PMA-Silica as solid acid/Catalyst

A study regarding recovering and reprocessing of PMA -Silica was also performed. The isolated solid PMA -Silica from ethanol was dried under vacuum and dried overnight in air. The recovered material was directly used for new reaction. The catalyst was successfully reused five times without any pretreatment with admirable results (Fig. 2). Therefore, we preferred PMA-Silica as the solid phase reaction medium over environmentally unsafe organic solvents. Besides, the methodology involved minimization of chemical impurity, easy work-up procedure and nonexistence of large volumes of waste from the discarded chromatographic static phases. The structures of the final products were well characterized by using IR spectroscopy and melting point determination.

Table 2: PMA- Silica Catalyzed synthesis of different Dihydrochromenopyrimidines derivatives



4a, 82%, 6 min

4b, 84%, 8 min

4c, 92%, 15 min

4d, 83%, 3 min

4e, 81%, 3 min

5a, 80%, 6 min

5b, 81%, 7 min

5c, 83%, 15 min

5d, 82%, 4 min

5e, 81%, 3 min

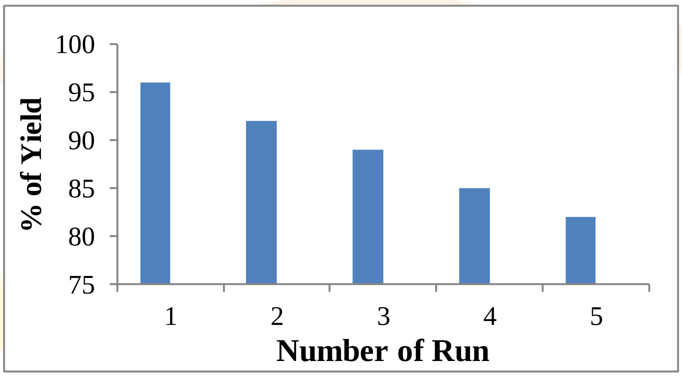
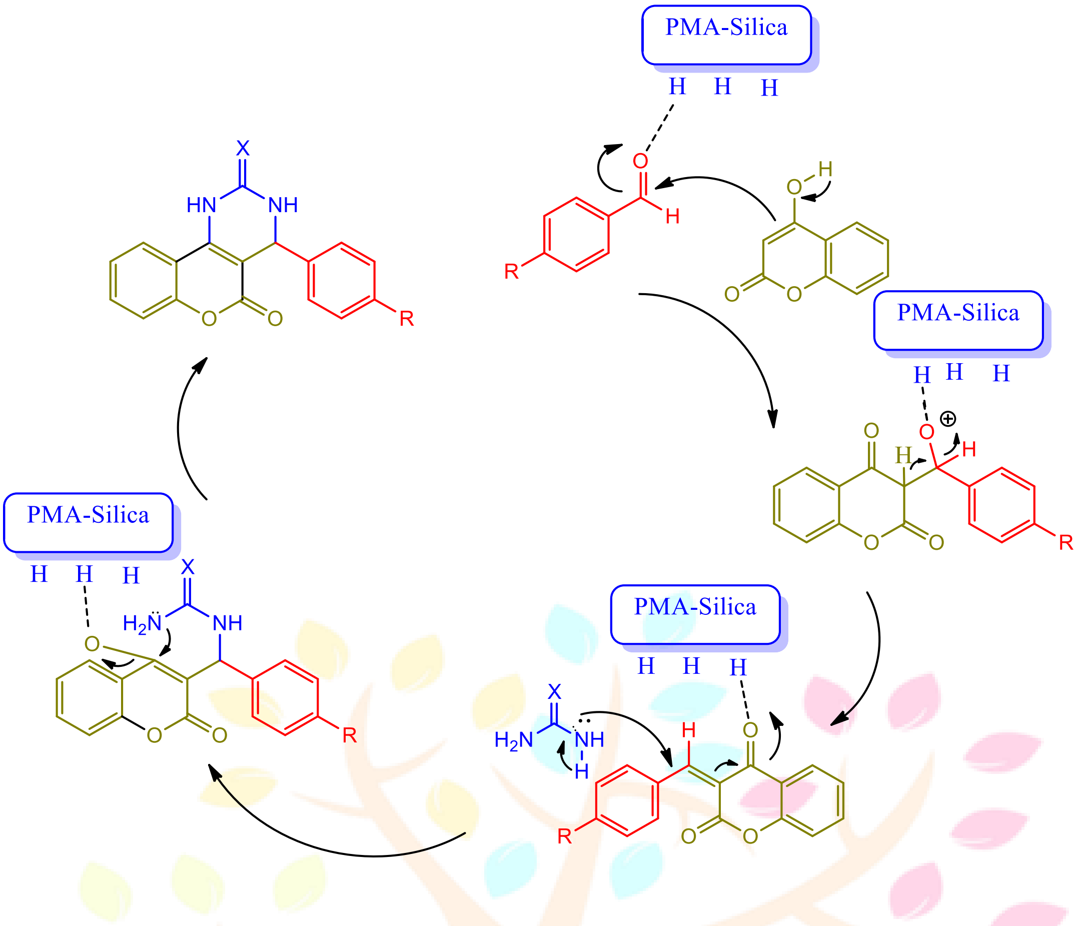


Fig 2: Reusability of PMA-Silica

A plausible mechanism for the synthesis of dihydrochromenopyrimidine has been demonstrated in Fig 3. The acidic proton from PMA-Silica solid acid/catalyst first activated the C-O group of aldehyde. Then vianeucleophilic addition reaction with hydroxycoumarin we get compound (I). Again protonation takes place and via elimination of H3O+ we get compound (II). Now compound (II) and urea/thiourea undergoes Michael addition reaction and via elimination of water we get our desired product, compound (III).



Scheme 2: Plausible mechanism for the synthesis of dihydrochromenopyrimidine

EXPERIMENTAL

Progress of the reaction was monitored by TLC (Thin Layer Chromatography), by using silica gel plate. Melting points were determined by using an open capillary tube with a melting point apparatus and were uncorrected. IR Spectra were recorded on PerkinElmer Spectrum Two infrared spectrophotometer using Potassium Bromide (KBr) pellet of the pure product.

GENERAL PROCEDURE FOR THE SYNTHESIS OF 3,4-DIHYDRO-1H-CHROMENO[4,3-D]PYRIMIDINE-2,5-DIONE/THIONE AND ITS DIFFERENT DERIVATIVES

1.0 mmol of aldehyde, 1.0 mmol of urea/thiourea and 1.0 mmol of 4-hydroxycoumarin and 100 mg of PMA-Silica were taken together in a petri dish and mixed well. The mixture was exposedunder microwave irradiation (720 MHz,180^{0}C) with 2 min interval. The progress of the reaction was monitored by TLC using Pet Ether: Ethyl-Acetate (70:30& 60:40). After completion of the reaction mixture was stirred with 20 ml Ethanol and the catalyst was filtered. The filtrate was then concentrated over water bath and kept for recrystallisation. The crystal of the product was recovered and washed with cold ethanol.

IR spectra of the representative Compounds

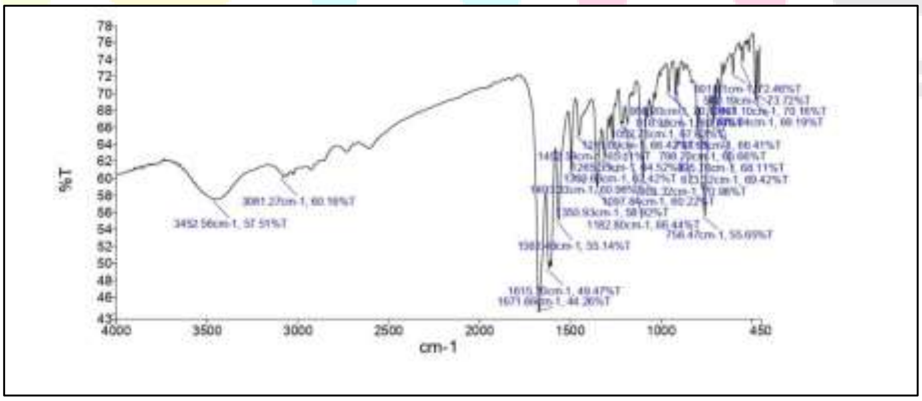


Fig 3: IR Spectra of Compound **4a**

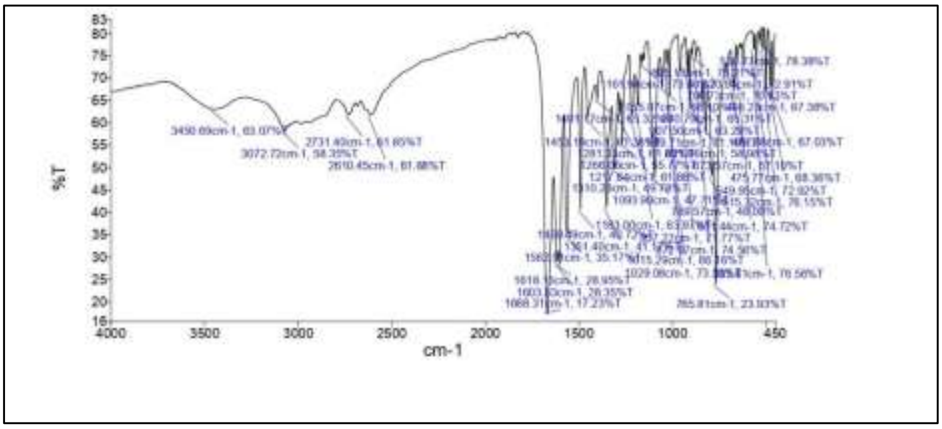


Fig 4: IR Spectra of Compound **4b**

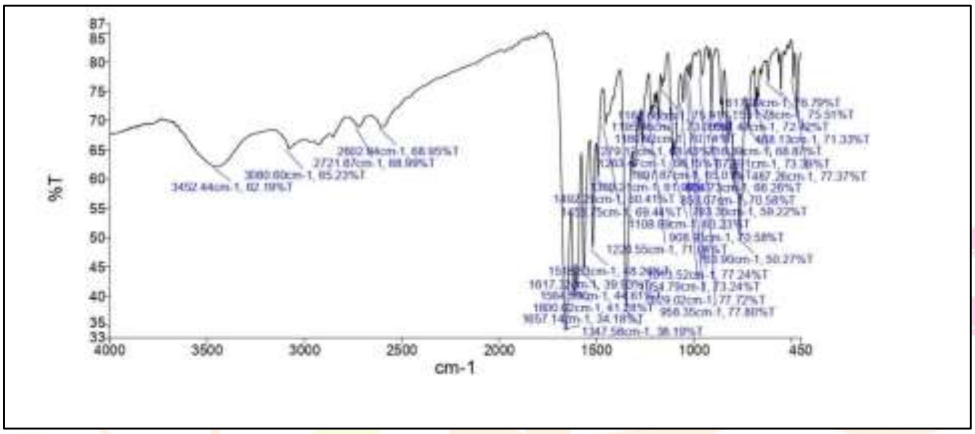


Fig 5: IR Spectra of Compound **4c**

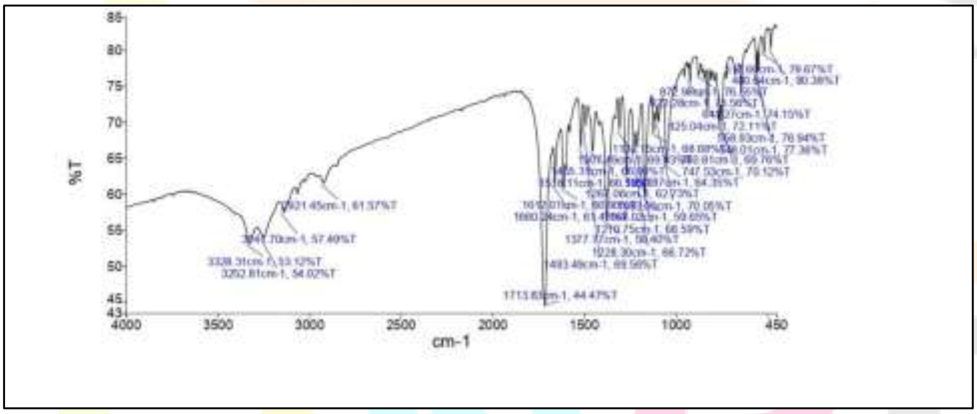


Fig 6: IR Spectra of Compound **4d**

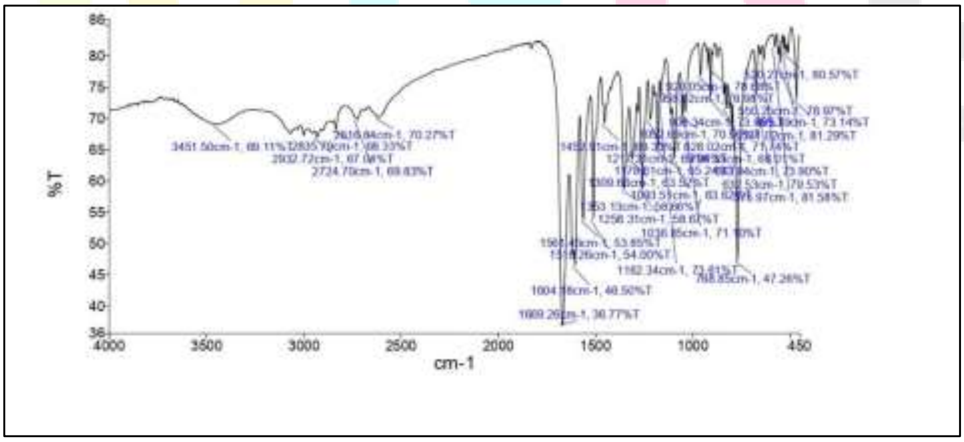


Fig 7: IR Spectra of Compound **4e**

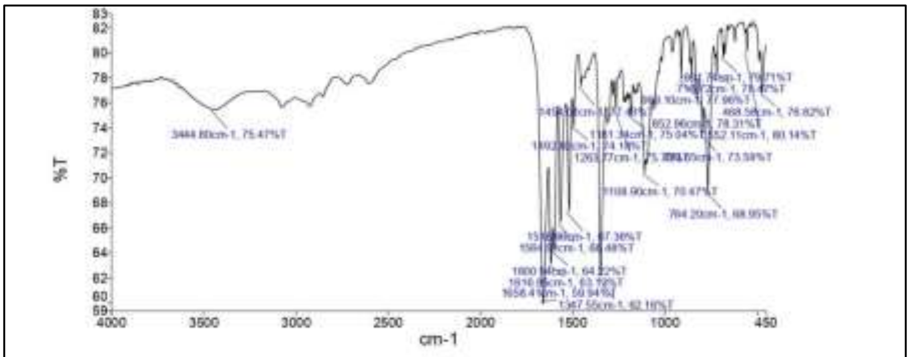


Fig 9: IR Spectra of Compound **5c**

Identification of the compounds

Representative IR peaks and Melting Point of different 3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione/thione derivatives

CONCLUSION

Compound	IR(υ cm^{-1})	Melting Point (^{0}C)	Literature Value
4a	3452, 3081, 1672,1615,1350	164	160-162
4b	3450, 3072, 1668,1603,1351,765	199	195-197
4c	3452, 3080, 1657,1600,1564,1347	227	220-222
4d	3328, 3252,2921,1713,1612,1377	228	225-227
4e	3451, 2932, 1669,1604,1353	204	206-208
5c	3444, 1658, 1600, 1564,1347,764	230	233-236

In conclusion, a green, chromatography free and product-selective reaction procedure has been developed with PMA-Silica as a recyclable solid phase catalyst for dihydrochromenopyrimidine derivatives affording good to excellent yield of the products under microwave irradiation. Successful exploration of environmentally benign solid phase synthesis has produced a green platform for the future.

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