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MoO2Cl2 catalyzed efficient synthesis of functionalized 3,4-dihydropyrimidin-2(1H)-ones/thiones and polyhydroquinolines: Recyclability, Fluoroscence and Biological studies

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PAPER

MoO_2Cl_2 catalyzed efficient synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones/thiones and polyhydroquinolines: Recyclability, Fluoroscence and Biological studies†

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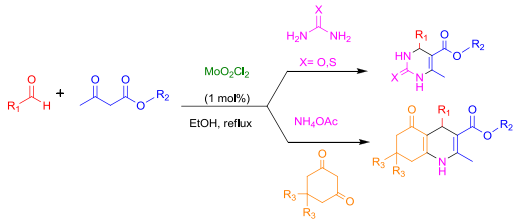
A simple, facile and efficient synthesis of functionalized dihydropyrimidinones and polyhydroquinolines using molybdenum (VI) dichloride dioxide (MoO_2Cl_2) has been developed. The present protocol demonstrates the exceptional tolerance towards acid labile protecting groups such as *tert*-butyl dimethyl silyl (TBDMS) and *tert*-butyl diphenyl silyl (TBDPS). This is the first report of exploring Lewis acid properties of MoO_2Cl_2 in diversity oriented synthesis of Biginelli and Hantzsch reactions. Biologically important and highly structured conjugates of dihydropyrimidinone, polyhydroquinoline derivatives containing coumarin, pyrazole, indole ande triazole moieties were synthesized in good to excellent yields. Compound 4o exhibited blue fluoroscence at maximum UV absorbance λ_{max} 326 nm. In preliminary MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide] assay, compound 4n displayed remarkable cytotoxic activity against A549 and PC3 cell lines while compound 7q was found to be cytotoxic against HGC-27 and PC3 cancer cell lines.

Introduction

Molybdenum coordination chemistry is one of the intriguing research areas due to inevitable occurrence of Mo in the active sites of molybdoenzymes.[1] Some of the potential applications of molybdenum compounds as corrosion inhibitors,[2a] lubricants,[2a,2b] pigments,[2c,2d] smoke suppressants,[3a] and fertilizers[3b] have also been reported. Moreover, recently, molybdenum(VI) dichloride dioxide (MoO_2Cl_2) is gaining importance on account of its ease in availability, less toxicity, thermal stability and water tolerant nature.[4a,4b] In addition, many research groups are exploiting the potential of MoO_2Cl_2 in modern organic synthesis.[4c] It has been widely used as an efficient catalyst for several organic transformations such as the hydrosilylation of aldehydes and ketones,[5a] hydrophosphonylation of aldehydes,[5b] reduction of imines, esters, sulfoxides and pyridine *N*-oxides to the corresponding amines, alcohols, sulfides and pyridines respectively,[5c,5d] epoxidation of double bonds, oxidation of alcohols to carbonyl compounds,[5e] conversion of β-hydroxycarbonyls into α-bromo 1,3-dicarbonyls,[6a] formation of carbamates from alcohols and isocyanates.[6b,6c] Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in combinatorial chemistry with facile and rapid creation of several multiple bonds in a one-pot reaction with minimal waste of time and energy.[7] Transition-metal catalyzed organic transformations comply with the principles of "Green Chemistry" such as minimization of waste, clean catalysts/reagents and minimum use of energy. In recent decades, dihydropyrimidinones and polyhydroquinolines derivatives (Biginelli and Hantzsch products) are the promising scaffolds that have gained importance in organic and medicinal chemistry owing to their pharmacological properties. Dihydropyrimidinones exhibit a broad range of biological activities such as anticancer, calcium channel modulator, anti-hypertensive, anti-viral, anti-oxidant, anti-bacterial, anti-inflammatory, neuropeptide Y (NPY) antagonist and α_{1a}-adrenergic antagonists.[8] Polyhydroquinolines are often used as antitumor, vasodilator, hepatoprotective, antiatherosclerotic, geroprotective, antidiabetic, antiasthmatic, antibacterial, anti-inflammatory and tyrosine kinase inhibitors.[9–11] Very recently, coumarin-dihydropyrimidinone hybrids have been reported to exhibit fluoroscent properties, which can be further utilized in the synthesis of new biological and chemical probes.[12]



Scheme 1: MoO_2Cl_2 catalyzed synthesis of dihydropyrimidinone\thiones and polyhydroquinolines.

In view of the biological, industrial and synthetic importance of polyhydroquinolines and dihydropyrimidinones, a plethora of

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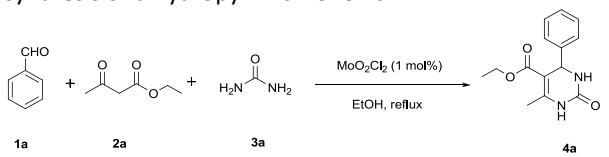
protocols and catalytic systems have been developed for these significant organic transformations. However, application of non-noble metal complexes based on molybdenum (MoO_2Cl_2) as a Lewis acid catalyst in diversity oriented synthesis of dihydropyrimidinones/thiones and polyhydroquinolines remains unexplored. To the best of our knowledge this is the first report of using MoO_2Cl_2, homogenous catalyst in the synthesis of dihydropyrimidinone/thione and polyhydroquinoline derivatives *via* Biginelli and Hantzsch reaction (Scheme 1).

Results and discussion

Synthesis of dihyropyrimidinones/thiones and polyhyroquinolines

A Biginelli test reaction was performed involving a mixture of benzaldehyde, ethyl acetoacetate, urea in the presence of MoO_2Cl_2 (0.5 mol%) in EtOH at room temperature for 24 h (Table 1, entry 1), and the dihydropyrimidinone product was obtained in less yield due to incomplete conversion of the reactants, thus it was assumed that thermal energy may be required to drive the reaction to completion. Furthermore, the effect of variation in temperatures from 50°C to reflux conditions, along with increase in catalyst concentrations were studied (Table 1, entries 2-5). To our delight, it was observed that 1 mol% of MoO_2Cl_2 in EtOH at reflux temperature afforded 95% yield in short reaction time (Table 1, entry 4) and further increment in catalyst concentration does not affect the reaction yield (Table 1, entry 5). Moreover, the catalytic efficiency of MoO_2Cl_2 was examined using different solvents (Table 1, entries 6-9). The yields and reaction time required depict that protic solvents (water, MeOH and EtOH) were more preferable than aprotic solvents (acetonitrile, THF). Among the protic solvents, EtOH gave the best results (Table 1, entry 4). Control experiment in absence of catalyst resulted in nominal yield which proves the emphasis on importance of catalyst (Table 1, entry 10).

Table 1: Optimization of reaction conditions for the synthesis of dihydropyrimidinone **4a**[a]



Entry	MoO_2Cl_2 (mol%)	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	0.5	EtOH	rt	24	35
2	0.5	EtOH	50	3	64
3	0.5	EtOH	reflux	2	80
4	1	EtOH	reflux	1	95
5	2	EtOH	reflux	1	96
6	1	Water	reflux	2	75
7	1	MeOH	reflux	2	72
8	1	CH_3CN	reflux	4	78
9	1	THF	reflux	6	67
10	-	EtOH	reflux	12	15

[a]Reaction conditions: Benzaldehyde (**1a**, 1 mmol), ethyl acetoacetate (**2a**, 1 mmol), urea (**3a**, 1.5 mmol) in EtOH (10 ml), [b]Isolated yield.

With the optimized reaction conditions in hand (Table 1, entry 4), the generality and scope of the present one-pot, three-component reaction was explored. The reaction with different aromatic aldehydes containing electron donating and withdrawing groups afforded excellent yields of 85-96% in 40 min to 2 h (Figure 1). Interestingly, substrates involving acid sensitive protecting groups such as TBDMS and TBDPS afforded good yields with the absence of deprotected side product (Figure 1, 4k and 4l). The present protocol was amenable to substituted heterocyclic aldehydes such as coumarin, pyrazole and thiophene where reaction proceeded smoothly with excellent yields (Figure 1, 4m and 4n) except in case of coumarin derivative; moderate yield of 75% was obtained after 2 h (Figure 1, 4o). Similarly, thiopyrimidinones were also synthesized with high yields ((Figure 1, 4g-4i and 4p).

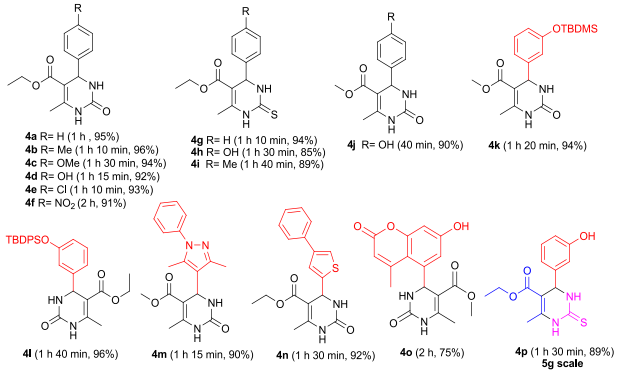
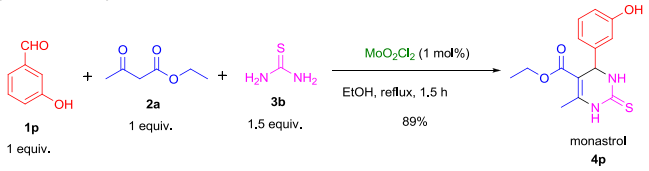


Figure 1: Different dihydropyrimidinone\thiones synthesized via one-pot three component Biginelli reaction

To test the feasibility of the reaction, a 5g scale synthesis of monastrol (specific inhibitor of mitotic kinesin Eg 5) was attempted. The 3- hydroxy benzaldehyde, ethyl acetoacetate, thiourea were stirred under the optimized reaction conditions and achieved monastrol in 89% yield with 97.99% purity† (Scheme 2).



Scheme 2: MoO_2Cl_2 catalyzed 5 g scale synthesis of monastrol.

Encouraged with the successful synthesis of dihydropyrimidinones/thiones, our attention was shifted towards the synthesis of polyhydroquinolines. Polyhydroquinolines are generally synthesized *via* Hantzsch reaction (one-pot, four component reaction) using aldehyde, dimedone, β-ketoester and ammonium acetate. Several protocols have been reported for the synthesis of polyhydroquinolines[13-19] but still emphasis on the efficacy of catalyst with high yields of product creates requisite to explore newer methodologies. Fascinatingly, we found the potential utility of MoO_2Cl_2 in one-pot, four component synthesis of polyhydroquinolines in admirable yields. Various substituted

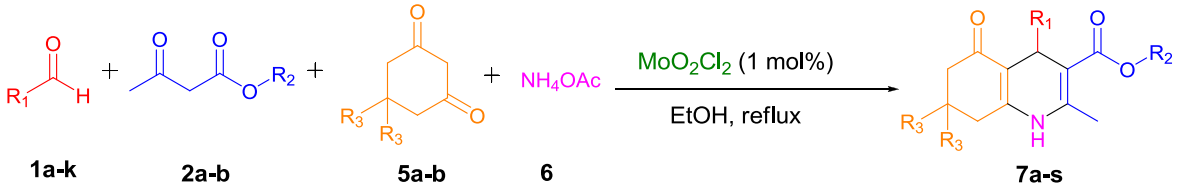
aromatic and heteroaromatic aldehydes (1 mmol) were treated with dimedone/1,3-cyclohexanedione (1 mmol), β-ketoesters (1 mmol), ammonium acetate (1.2 mmol) in the presence of MoO_2Cl_2 (1 mol%) in EtOH at reflux temperature. Gratifyingly, the desired products (**7a-s**) were formed in 20-40 min with 80-94% yields as shown in Table 2. Polyhydroquinolines with an acid labile protecting group (TBDMS) were synthesized in superior yields (Table 2, 7g, 7j). Triazole and indole containing substrates were also employed in the synthesis of polyhydroquinolines and the desired products were accomplished in excellent yields (Table 2, 7q, 7s). Large scale synthesis of 7k (Table 2) was performed using benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate to obtain desired product with 85% yield.

Recyclability

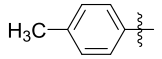
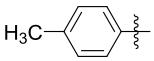
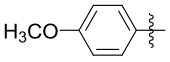
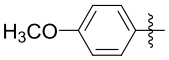
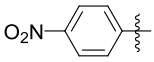
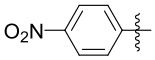
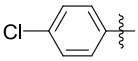
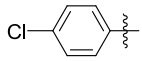
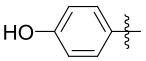
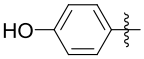
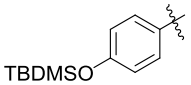
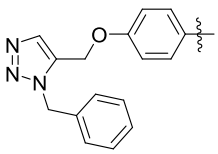
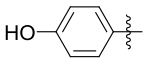
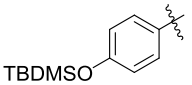
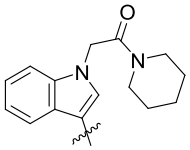
From the economical point of view as well as environmental concern, the recyclability of MoO_2Cl_2 catalyst was tested upon the condensation of benzaldehyde, 1,3-cyclohexandione, ethyl acetoacetate and ammonium acetate using 1 mol% of MoO_2Cl_2 in EtOH (Table 2, entry 1).

After completion of reaction, EtOH was evaporated and ethylacetate was added to the reaction mixture followed by usual aqueous workup. The aqueous layer was separated, decanted, and dried to recover MoO_2Cl_2. Later, the recovered MoO_2Cl_2 catalyst was reused for 5 consecutive cycles. The yields obtained after each run are depicted in Figure 2.

Table 2: MoO_2Cl_2 catalyzed synthesis of polyhydroquinolines[a]



1a-k **2a-b** **5a-b** **6** **7a-s**

Entry	R_1	R_2	R_3	Time (min)	Product	Yield[b] (%)	Entry	R_1	R_2	R_3	Time (min)	Product	Yield[b] (%)
1		OEt	H	20	**7a**	94	11[c]		OEt	Me	28	**7k**	85
2		OEt	H	25	**7b**	88	12		OEt	Me	20	**7l**	90
3		OEt	H	30	**7c**	86	13		OEt	Me	24	**7m**	89
4		OEt	H	32	**7d**	82	14		OEt	Me	24	**7n**	90
5		OEt	H	25	**7e**	90	15		OEt	Me	25	**7o**	93
6		OEt	H	30	**7f**	87	16		OEt	Me	22	**7p**	91
7		OEt	H	32	**7g**	92	17		OEt	Me	29	**7q**	85
8		OEt	H	40	**7h**	80							
9		OMe	Me	23	**7i**	89	18		OEt	Me	36	**7r**	82
10		OMe	Me	30	**7j**	90	19		OEt	Me	38	**7s**	80

[a]Reaction conditions: Aldehyde (1 mmol), ß-ketoester (1 mmol), 1,3-cyclohexanedione\dimedone (1 mmol), ammonium acetate (1.2 mmol), EtOH (10 mL), MoO_2Cl_2 (1 mol%), reflux. [b]Isolated yield. [c]Reaction performed in 5g scale.

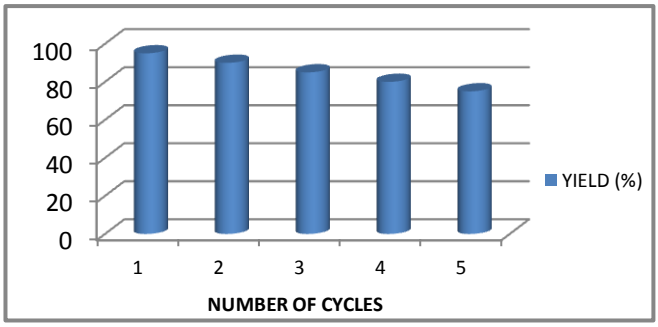
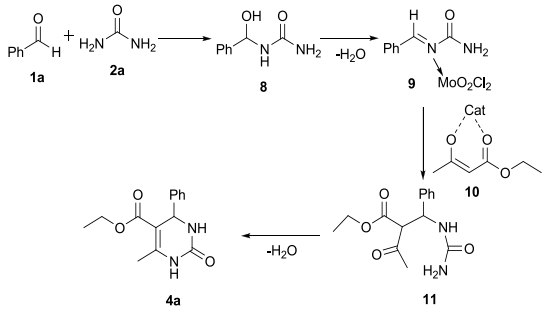


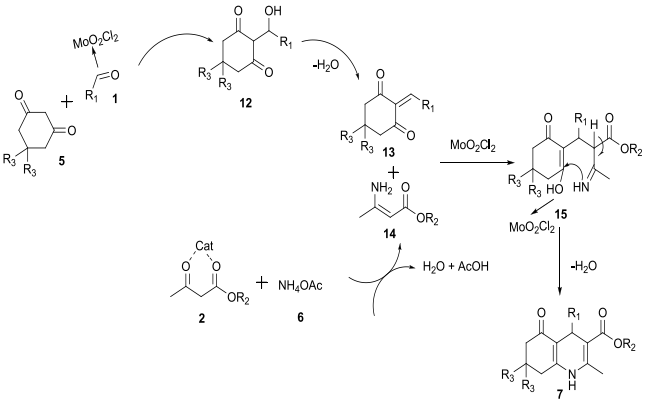
Figure 2: Catalyst recyclability chart of compound 7a

A plausible mechanistic pathway for the synthesis of dihydropyrimidinones/thiones is outlined in Scheme 3, which is in similarity with the established mechanism as reported in the literature.[20] The one-pot Biginelli reaction may be initiated with the reaction of aldehyde and urea followed by condensation activated by co-ordination of MoO_2Cl_2 resulting in formation of acyl imine intermediate **8**, a rate limiting step. Further, the iminium intermediate **9** undergoes nucleophilic attack by the β-dicarbonyl ester enolate to produce open chain intermediate ureide **11**, followed by cyclization and subsequent loss of water to afford dihydropyrimidinone **4a**.



Scheme 3: Plausible mechanism for dihydropyrimidinones formation using MoO_2Cl_2

Plausible mechanism for MoO_2Cl_2 mediated Hantzsch reaction towards the synthesis of polyhydroquinoline is also proposed. First, aldehyde is activated by MoO_2Cl_2 and dimedone in enol form react in Knoevenagel fashion to give intermediate **13**. On other hand, the MoO_2Cl_2 activated β-ketoester and ammonium acetate affords enamine **14**. Then, the intermediate **13** and enamine **14** undergoes Michael reaction followed by intramolecular condensation to produce **7** (Scheme 4).



Scheme 4: Plausible mechanism for polyhydroquinolines formation using MoO_2Cl_2

Spectroscopic properties of Compound (4o)

Further, we measured the absorbance and emission maxima of umbelliferone and coumarin-dihydropyrimidinone derivatives (**4o**) in methanol at 30 µm concentration (Table 3). Fluoroscent emission spectrum of Compound **4o** was quite similar to umbelliferone with Stoke shift of 71 nm. Blue fluorescence was observed when **4o** was irradiated at maximum UV absorbance λ_{max} 326 nm (Figure 3). This result could be an inception to utilize the properties of compound **4o** in further development of the chemical probes.

Table 3: Fluoroscence properties of coumarin derivatives

Compound	Absorbance λ_{max} (nm)	Emission λ_{max} (nm)	Stoke shift (nm)
Umbelliferone[a]	324	392	68
4o	326	397	71

[a] Values were obtained from ref. 21.

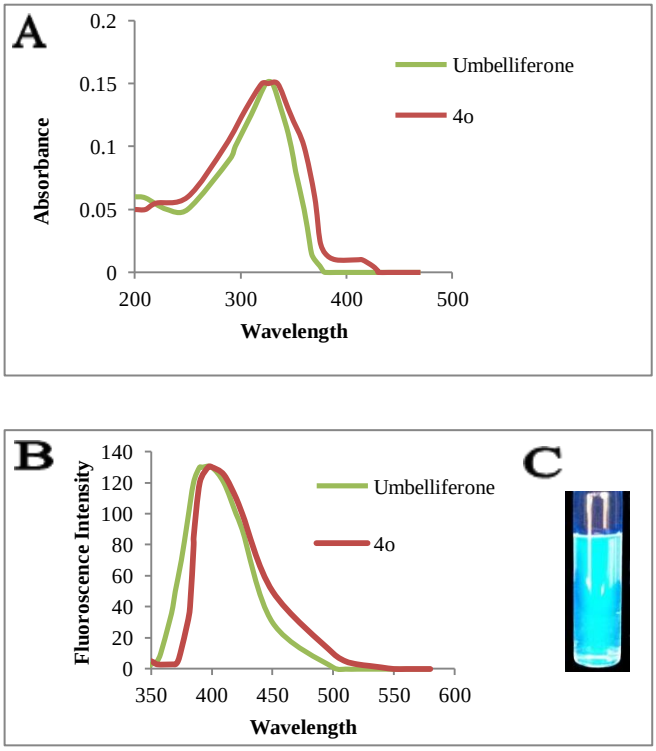


Figure 3: (A) Normalized UV-vis spectra in MeOH. (B) Normalized fluoroscence emission spectra in MeOH with excitation on λ_{max} of compound. All spectra were recorded at a concenctration of 30 µm in MeOH. (C) Blue fluoroscence of compound **4o** was observed at λ_{max} 326 nm.

Biological evaluation

In vitro evaluation

Among all the synthesized compounds **4m, 4n, 4o, 7q** and **7s** were found to be diverse and highly functionalized molecules. The similar scaffolds have been reported earlier for their potent biological activities.[22]This prompted us to further examine the *in vitro* cytotoxic potential of aforementioned

compounds. These compounds were evaluated against four cancer cell lines namely, A549 (lung cancer), HGC-27 (gastric cancer) and PC3 (prostate cancer), BT-549 (breast cancer) by employing MTT assay. Concentration response course analysis was performed to determine drug concentrations required to inhibit the growth of cancer cells by 50% (IC_{50}) after incubation for 48 h. The results of *in vitro* anticancer activity revealed that the compound (**4n)** showed IC_{50} of 10.4 µM against A549 and 19.3 µM for PC3 cancer cell lines. Compound **7q s**howed IC_{50} of 15.6 µM against HGC-27 and 19.4 µM for PC3 cancer cell lines (Table 4). These preliminary results indicate that compounds **4n** and **7q** could be the potential leads for the development of novel anticancer agents.

Table 4: *In vitro* anticancer activity (IC_{50} µM)

S.No.	Compound	A549	HGC-27	PC3	BT 549
1	**4m**	NA	NA	NA	NA
2	**4n**	10.4±1.7	22.1±2.2	19.3±1.3	26.8±2.7
3	**4o**	31.3±0.9	36.4±1.3	36.3±1.2	20.5±0.7
4	**7q**	28.6±2.6	15.6±2.4	19.4±1.6	NA
5	**7s**	NA	NA	NA	NA

NA: Not Active

Conclusion

An efficient and operationally simple protocol was developed for the synthesis of dihydropyrimidinones and polyhydroquinolines. The MoO_2Cl_2 catalyst offer striking advantages such as less-toxicity, water-tolerance, thermal-stability, and most important its reusability. MoO_2Cl_2 was reused for 5 consecutive cycles and desired products were obtained in good to moderate yields. Large scale syntheses were also established with good yields and short reaction time. Heterocyclic aldehydes were amenable in the present protocol. In the present method, acid sensitive protecting groups such as *tert*-butyl dimethyl silyl, *tert*-butyl diphenyl silyl were well tolerated. Coumarin-dihydropyrimidinone hybrid (**4o**) exhibited blue fluorescence at λ_{max} 326 nm, which could be useful as the chemical probe. Compounds **4n** and **7q** displayed promising anticancer activity directing towards the development as the potential anticancer agents.

Experimental section

General

MoO_2Cl_2 catalyst (Product no: 373710) was procured from Sigma Aldrich. Compounds were characterized by nuclear magnetic resonance using 300 and 500 spectrometers. ^{1}H NMR spectra were measured at 300 and 500 MHz. ^{13}C NMR spectra were measured at 75 and 125 MHz. Mass spectrometric studies were carried out on the Agilent 1200 series LC instrument coupled with QTOF mass spectrometer (Q-TOF LC/MS 6540 series equipped with ESI source and operated in positive ionization mode. UV absorption spectra and Fluorescence spectra were recorded on a Spectramax M4 spectrophotometer with a quartz cell of 10 mm optical path.

General procedure for the synthesis of dihydropyrimidinones/thiones from substituted benzaldehydes (Figure 1, 4a–p)

A mixture of aldehyde 1 (1 mmol), methyl/ethyl acetoacetate 2 (1 mmol), and urea/thiourea 3 (1.5 mmol) in EtOH (10 mL) was refluxed in the presence of MoO_2Cl_2 (1 mol%). After completion of reaction, as indicated by TLC analysis, the solvent was evaporated. The resulting mass was extracted with ethyl acetate (3X10 mL) followed by treatment of brine. The combined organic layers were evaporated and dried over anhydrous Na_2SO_4. Recrystallization using ethanol was performed to give pure product 4.

General procedure for the synthesis of polyhydroquinolines from substituted benzaldehydes (Table 2, 7a–t)

To a mixture of aldehyde 1 (1 mmol), and methyl/ethyl acetoacetate 2 (1 mmol), 1,3-cyclohexanedione/dimedone 5 (1 mmol), NH_4OAc 6 (1.2 mmol) in EtOH (10 mL) was refluxed in presence of MoO_2Cl_2 (1 mol%). After completion of the reaction, the contents were extracted with EtOAc (3X10 mL). The combined organic layers were washed with brine, water, dried over anhydrous Na_2SO_4. The solvent evaporated and crude product was purified by silica gel column chromatography (EtOAc: hexane) as eluent to give desired product 7.

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TABLE OF CONTENTS

TEXT	MoO_2Cl_2 catalyzed Biginelli, Hantzsch reactions and exploring spectroscopic, biological properties of novel compounds.
GRAPHIC