NJC

PAPER

View Article Online
View Journal



Cite this: DOI: 10.1039/c5nj02444g

# $MoO_2Cl_2$ catalyzed efficient synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones/thiones and polyhydroquinolines: recyclability, fluorescence and biological studies†

Sravanthi Devi Guggilapu,[a] Santosh Kumar Prajapti,[a] Atulya Nagarsenkar,[a] Guntuku Lalita,[b] Ganga Modi Naidu Vegi[b] and Bathini Nagendra Babu*[a]

Received (in Montpellier, France) 11th September 2015,
Accepted 9th November 2015

DOI: 10.1039/c5nj02444g

www.rsc.org/njc

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 the diversity oriented synthesis of Biginelli and Hantzsch reactions. Biologically important and highly structured conjugates of dihydropyrimidinone and polyhydroquinoline derivatives containing coumarin, pyrazole, indole and triazole moieties were synthesized in good to excellent yields. Compound **4o** exhibited blue fluorescence at a maximum UV absorbance $\lambda_{max}$ of 326 nm. In the 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.

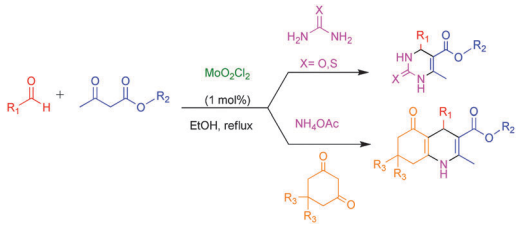
## Introduction

Molybdenum coordination chemistry is one of the intriguing research areas due to the inevitable occurrence of Mo in the active sites of molybdoenzymes.[1] Some of the potential applications of molybdenum compounds such as corrosion inhibitors,[2a] lubricants,[2a,b] pigments,[2c,d] smoke suppressants,[3a] and fertilizers[3b] have also been reported. Moreover, recently, molybdenum(VI) dichloride dioxide ($MoO_2Cl_2$) has been gaining importance on account of its ease of availability, less toxicity, thermal stability and water tolerant nature.[4a,b] 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] the hydrophosphonylation of aldehydes,[5b] the reduction of imines, esters, sulfoxides and pyridine *N*-oxides to the corresponding amines, alcohols, sulfides and pyridines respectively,[5c,d] the epoxidation of double bonds, the oxidation of alcohols to carbonyl compounds,[5e] the conversion of β-hydroxycarbonyls into α-bromo 1,3-dicarbonyls,[6a] the formation of carbamates from alcohols and isocyanates.[6b,c] Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in combinatorial chemistry with the 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 the 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 $\alpha_{1a}$-adrenergic antagonist.[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 fluorescent properties, which can be further utilized in the synthesis of new biological and chemical probes.[12]

In view of the biological, industrial and synthetic importance of polyhydroquinolines and dihydropyrimidinones, a plethora of protocols and catalytic systems have been developed for these

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Balanagar, Hyderabad, 500037, India. E-mail: bathini.niperhyd@gov.in; Fax: +91-40-23073751; Tel: +91-40-23073740
[b] Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Balanagar, Hyderabad 500037, India

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5nj02444g




Scheme 1 $MoO_2Cl_2$ catalyzed synthesis of dihydropyrimidinone/thiones and polyhydroquinolines.

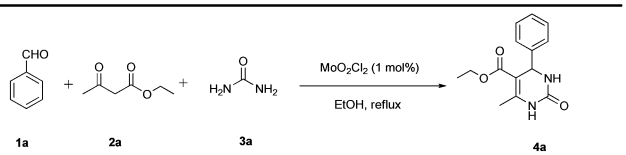
significant organic transformations. However, the application of non-noble metal complexes based on molybdenum ($MoO_2Cl_2$) as a Lewis acid catalyst in the diversity oriented synthesis of dihydropyrimidinones/thiones and polyhydroquinolines remains unexplored. To the best of our knowledge this is the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

## Results and discussion

### Synthesis of dihydropyrimidinones/thiones and polyhydroquinolines

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 the 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 an 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

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.

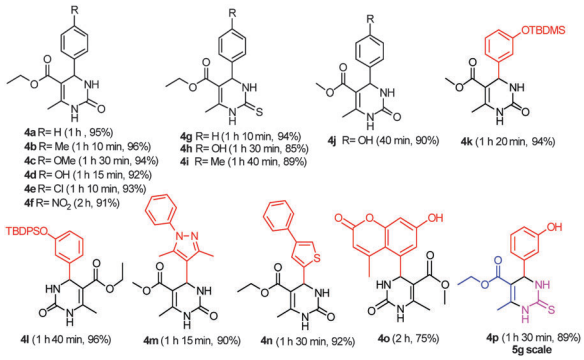
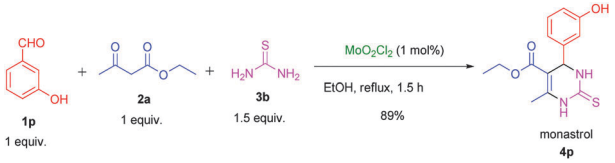



Fig. 1 Different dihydropyrimidinone/thiones synthesized *via* a one-pot three component Biginelli reaction.

95% yield in a short reaction time (Table 1, entry 4) and a 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 the 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). A control experiment in the absence of a catalyst resulted in nominal yield which proves the emphasis on the importance of a catalyst (Table 1, entry 10).

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 (Fig. 1). Interestingly, substrates involving acid sensitive protecting groups such as TBDMS and TBDPS afforded good yields with the absence of deprotected side products (Fig. 1, **4k** and **4l**). The present protocol was amenable to substituted heterocyclic aldehydes such as coumarin, pyrazole and thiophene where the reaction proceeded smoothly with excellent yields (Fig. 1, **4m** and **4n**) except in the case of coumarin derivatives; a moderate yield of 75% was obtained after 2 h (Fig. 1, **4o**). Similarly, thiopyrimidinones were also synthesized with high yields (Fig. 1, **4g–4i** and **4p**).

To test the feasibility of the reaction, a **5g** scale synthesis of monastrol (a specific inhibitor of mitotic kinesin Eg5) was attempted. 3-Hydroxy benzaldehyde, ethyl acetoacetate, thiourea were stirred under the optimized reaction conditions and achieved monastrol in 89% yield with 97.99% purity (ESI†) (Scheme 2).




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

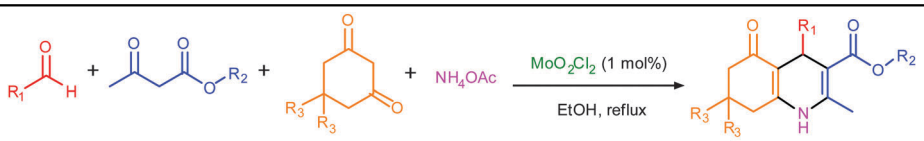
Encouraged with the successful synthesis of dihydropyrimidinones/thiones, our attention was shifted towards the synthesis of polyhydroquinolines. Polyhydroquinolines are generally synthesized *via* a Hantzsch reaction (a one-pot, four component reaction) using aldehyde, dimedone, β-ketoester and ammonium acetate. Several protocols have been reported for the synthesis of polyhydroquinolines[13–19] but still emphasis on the efficacy of the catalyst with high yields of products 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 products with 85% yield.

## Recyclability

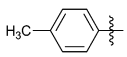
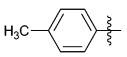
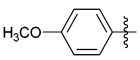
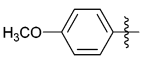
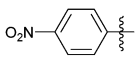
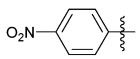
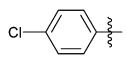
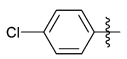
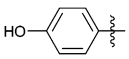
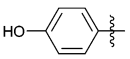
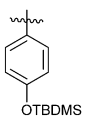
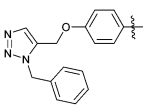
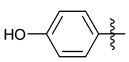
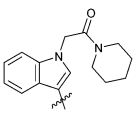
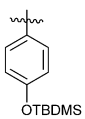
From the economical point of view as well as environmental concern, the recyclability of the $MoO_2Cl_2$ catalyst was tested upon the condensation of benzaldehyde, 1,3-cyclohexandione, ethyl acetoacetate and ammonium acetate using 1 mol% of $MoO_2Cl_2$ in EtOH (Table 2, entry 1).

After the completion of the 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 Fig. 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) | Pdt | Yield[b] (%) | Entry | $R_1$ | $R_2$ | $R_3$ | Time (min) | Pdt | 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 | 18 |  | OEt | Me | 36 | **7r** | 82 |
| 9 |  | OMe | Me | 23 | **7i** | 89 | 19 |  | OEt | Me | 38 | **7s** | 80 |
| 10 |  | OMe | Me | 30 | **7j** | 90 | | | | | | | |

[a] Reaction conditions: aldehyde (1 mmol), β-ketoester (1 mmol), 1,3-cyclohexadione/dimedone (1 mmol), ammonium acetate (1.2 mmol), EtOH (10 mL), $MoO_2Cl_2$ (1 mol%), reflux. [b] Isolated yield. [c] Reaction performed on a 5 g scale.

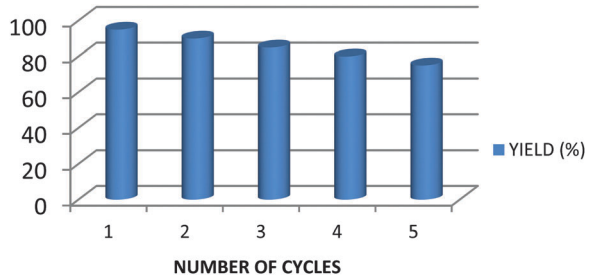
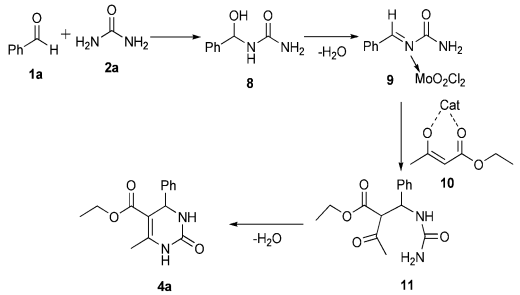



Fig. 2 Catalyst recyclability chart of compound **7a**.



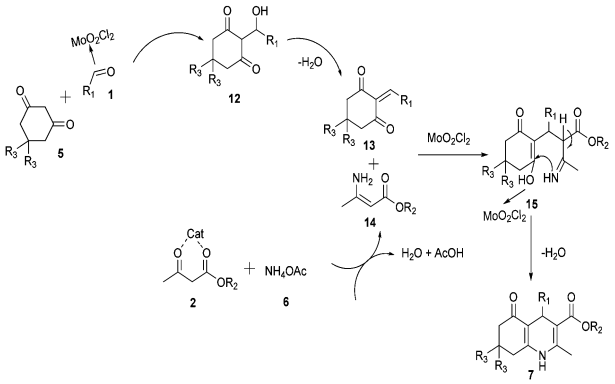

Scheme 3 Plausible mechanism for dihydropyrimidione formation using $MoO_2Cl_2$.

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 the co-ordination of $MoO_2Cl_2$ resulting in the 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**.

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

## 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). The fluorescent emission spectrum of compound **4o** was quite similar to umbelliferone with a Stokes shift of 71 nm. Blue fluorescence was observed when **4o** was irradiated at maximum UV absorbance $\lambda_{max}$ 326 nm (Fig. 3). This result could be an inception to utilize the properties of compound **4o** in further development of the chemical probes.




Scheme 4 Plausible mechanism for polyhydroquinoline formation using $MoO_2Cl_2$.

Table 3 Fluorescence properties of coumarin derivatives

| Compound | Absorbance $\lambda_{max}$ (nm) | Emission $\lambda_{max}$ (nm) | Stoke shift (nm) |
|---|---|---|---|
| Umbelliferone[a] | 324 | 392 | 68 |
| **4o** | 326 | 397 | 71 |

[a] Values were obtained from ref. 21.

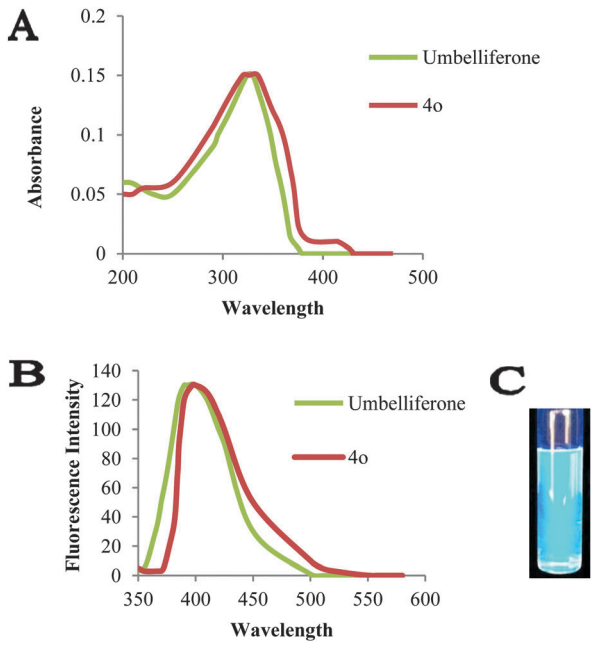



Fig. 3 (A) Normalized UV-vis spectra of MeOH. (B) Normalized fluorescence emission spectra of MeOH with excitation on $\lambda_{max}$ of the compound. All spectra were recorded at a concentration of 30 μm in MeOH. (C) Blue fluorescence of compound **4o** was observed at $\lambda_{max}$ 326 nm.

## 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. Similar scaffolds have been reported earlier for their potent biological activities.[22] This prompted us to further examine the *in vitro* cytotoxic potential of

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.

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 the 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 compound (**4n**) showed $IC_{50}$ of 10.4 μM against A549 and 19.3 μM for PC3 cancer cell lines. Compound **7q** showed $IC_{50}$ 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.

## Conclusion

An efficient and operationally simple protocol was developed for the synthesis of dihydropyrimidinones and polyhydroquinolines. The $MoO_2Cl_2$ catalyst offers striking advantages such as less-toxicity, water-tolerance, thermal-stability, and most importantly 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 in a 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 and *tert*-butyl diphenyl silyl were well tolerated. The coumarin-dihydropyrimidinone hybrid (**4o**) exhibited blue fluorescence at $\lambda_{max}$ 326 nm, which could be useful as a chemical probe. Compounds **4n** and **7q** displayed promising anticancer activity directing towards the development as the potential anticancer agents.

## Experimental section

### General

The $MoO_2Cl_2$ 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 an Agilent 1200 series LC instrument coupled with a QTOF mass spectrometer (Q-TOF LC/MS 6540 series equipped with an ESI source and operated in the 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 (Fig. 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 the completion of the reaction, as indicated by TLC analysis, the solvent was evaporated. The resulting mass was extracted with ethyl acetate (3 × 10 mL) followed by the 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), methyl/ethyl acetoacetate **2** (1 mmol), and 1,3-cyclohexanedione/dimedone **5** (1 mmol), $NH_4OAc$ **6** (1.2 mmol) in EtOH (10 mL) was refluxed in the presence of $MoO_2Cl_2$ (1 mol%). After the completion of the reaction, the contents were extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, water, dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by silica gel column chromatography (EtOAc : hexane) as an eluent to give desired product **7**.

## Acknowledgements

The authors thank Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers (Govt. of India) for providing funds.

## References

1 (*a*) J. M. Tunney, in *Comprehensive Coordination Chemistry II*, ed. J. McMaster and C. D. Garner, Elsevier, Amsterdam, 2003, vol. 8, p. 459; (*b*) J. H. Enemark, J. J. A. Cooney, J.-J. Wang and R. H. Holm, *Chem. Rev.*, 2004, **104**, 1175; (*c*) C. J. Whiteoak, G. J. P. Britovsek, V. C. Gibson and A. J. P. White, *Dalton Trans.*, 2009, 2337; (*d*) A. L. Bingham, J. E. Drake, M. B. Hursthouse, M. E. Light, R. Kumar and R. Ratnani, *Polyhedron*, 2006, **25**, 3238; (*e*) R. J. Butcher, B. R. Penfold and E. Sinn, *J. Chem. Soc., Dalton Trans.*, 1979, 668.

2 (*a*) E. R. Braithwaite, in *Molybdenum an outline of its chemistry and uses*, ed. J. Haber, Elsevier, Amsterdam, 1994; (*b*) E. R. Braithwaite and A. B. Greene, *Chem. Ind.*, 1978, **46**, 405; (*c*) W. W. Williams and J. W. Conley, *Ind. Eng. Chem.*, 1955, **47**, 1507; (*d*) W. G. Huckle and E. Lalor, *Ind. Eng. Chem.*, 1955, **47**, 1501.

3 (*a*) F. W. Moore, G. A. Tsigdinos and T. R. Weber, *Polym. Sci. Technol.*, 1984, **26**, 215; (*b*) U. C. Gupta, *Molybdenum in agriculture*, Cambridge University Press, Cambridge, 1997.

4 (*a*) C.-T. Chen, J.-H. Kuo, V. D. Pawar, S. M. Yogesh, S.-S. Weng, C.-H. Ku and C.-Y. Liu, *J. Org. Chem.*, 2005, **70**, 1188; (*b*) H. K. Kadam, *Synlett*, 2014, 1793; (*c*) K. Jeyakumar and D. K. Chand, *J. Chem. Sci.*, 2009, **121**, 111.

5 (*a*) A. C. Fernandes, R. Fernandes, C. C. Romao and B. Royo, *Chem. Commun.*, 2005, 213; (*b*) R. G. De Noronha, P. J. Costa,

C. C. Romao, M. J. Calhorda and A. C. Fernandes, *Organometallics*, 2009, **28**, 6206; (*c*) A. C. Fernandes and C. C. Romao, *Tetrahedron Lett.*, 2005, **46**, 8881; (*d*) A. C. Fernandes and C. C. Romao, *Tetrahedron*, 2006, **62**, 9650; (*e*) S. Maignien, S. Ait-Mohand and J. Muzart, *Synlett*, 1996, 439.

6 (*a*) K. Jeyakumar and D. K. Chand, *Synthesis*, 2009, 306; (*b*) C. Stock and R. Brückner, *Adv. Synth. Catal.*, 2012, **354**, 2309; (*c*) C. Stock and R. Brückner, *Synlett*, 2010, 2429.

7 (*a*) M. F. Moghaddam, H. Saeidian, Z. Mirjafary and A. Sadeghi, *J. Iran. Chem. Soc.*, 2009, **6**, 317; (*b*) P. J. Edwards, B. Allart, M. J. I. Andrews, J. A. Clase and C. Menet, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 425; (*c*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168.

8 (*a*) S. Goldman and J. Stoltefuses, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1559; (*b*) C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937; (*c*) J. P. Wan and Y. Liu, *Synthesis*, 2010, 3943; (*d*) C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879; (*e*) Suresh and J. S. Sandhu, *ARKIVOC*, 2012, **1**, 66.

9 (*a*) V. Klusa, *Drugs Future*, 1995, **20**, 135; (*b*) R. G. Bretzel, C. C. Bollen, E. Maeser and K. F. Federlin, *Am. J. Kidney Dis.*, 1993, **21**, 53; (*c*) R. Boer and V. Gekeler, *Drugs Future*, 1995, **20**, 499; (*d*) H. L. Davis and T. E. Davis, *Cancer Treat. Rep.*, 1979, **63**, 809.

10 (*a*) R. Simsek, U. B. Ismailoglu, C. Safak and I. Sahin-Erdemli, *Farmaco*, 2000, **55**, 665; (*b*) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. Zamboni, *J. Org. Chem.*, 1996, **61**, 3398; (*c*) Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu and C. C. Tzeng, *J. Med. Chem.*, 2001, **44**, 2374.

11 (*a*) G. Roma, M. D. Braccio, G. Grossi and M. Chia, *Eur. J. Med. Chem.*, 2000, **35**, 1021; (*b*) D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J. P. Falgueyeret, R. W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari and R. N. Yong, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1225; (*c*) M. P. Maguire, K. R. Sheets, K. Mcvety, A. P. Spada and A. Ziberstein, *J. Med. Chem.*, 1994, **37**, 2129.

12 F. Vitorio, T. M. Pereira, R. N. Castro, G. P. Guedes, C. S. Graebinab and A. E. Kümmerle, *New J. Chem.*, 2015, **39**, 2323.

13 (*a*) A. Kumar, S. Sharma, V. D. Tripathi, R. A. Maurya, S. P. Srivastava, G. Bhatia, A. K. Tamrakar and A. K. Srivastava, *Bioorg. Med. Chem.*, 2010, **18**, 4138; (*b*) L. E. Hinkel, *J. Chem. Soc. Trans.*, 1920, **117**, 137; (*c*) L. Saikia, D. Dutta and D. K. Dutta, *Catal. Commun.*, 2012, **19**, 1; (*d*) L.-M. Wang, J. Sheng, L. Zang, J.-W. Han, Z.-Y. Fan, H. Tian and C.-T. Qian, *Tetrahedron*, 2005, **61**, 1539.

14 (*a*) S. K. Kumar and K. N. Singh, *J. Heterocycl. Chem.*, 2010, **47**, 194; (*b*) M. Maheswara, V. Siddaiah, G. L. V. Damu and C. V. Rao, *ARKIVOC*, 2006, **2**, 201; (*c*) M. Kidwai, R. Chauhan, D. Bhatnagar, A. K. Singh, B. Mishra and S. Dey, *Monatsh. Chem.*, 2012, **143**, 1675; (*d*) D. S. Raghuvanshi and K. N. Singh, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52**, 1218.

15 (*a*) K. A. Undale, T. S. Shaikh, D. S. Gaikwad and D. M. Pore, *C. R. Chim.*, 2011, **14**, 511; (*b*) J. P. Nirmal, P. V. Dadhaniya, M. P. Patel and R. G. Patel, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49**, 587; (*c*) A. Rajendran, C. Karthikeyan and K. Rajathi, *Int. J. ChemTech Res.*, 2011, **3**, 810; (*d*) E. Rajanarendar, M. N. Reddy and S. Raju, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2011, **50**, 751.

16 (*a*) W. H. Correa and J. L. Scott, *Green Chem.*, 2001, **3**, 296; (*b*) J. L. Donelson, R. A. Gibas and S. K. De, *J. Mol. Catal. A: Chem.*, 2006, **256**, 309; (*c*) A. Kumar and R. A. Maurya, *Tetrahedron Lett.*, 2007, **48**, 3887; (*d*) S. Ko and C.-F. Yao, *Tetrahedron*, 2006, **62**, 7293.

17 (*a*) M. M. Heravi, K. Bakhtiari, N. M. Javadi, F. F. Bamoharram, M. Saeedi and H. A. Oskooie, *J. Mol. Catal. A: Chem.*, 2007, **264**, 50; (*b*) J. C. Legeay, J. Y. Goujon, J. J. V. Eynde, L. Toupet and J. P. Bazureau, *J. Comb. Chem.*, 2006, **8**, 829; (*c*) S. Ko, M. N. V. Sastry, C. Lin and C.-F. Yao, *Tetrahedron Lett.*, 2005, **46**, 5771.

18 (*a*) M. Tajbakhsh, H. Alinezhsd, M. Norouzi, S. Baghery and M. Akbari, *J. Mol. Liq.*, 2013, **177**, 44; (*b*) A. Kumar and R. A. Maurya, *Tetrahedron*, 2007, **63**, 1946; (*c*) N. N. Karade, V. H. Budhewar, S. V. Shinde and W. N. Jadhav, *Lett. Org. Chem.*, 2007, **4**, 16; (*d*) G. Song and B. Wang, *Synth. Commun.*, 2005, **35**, 2875; (*e*) S. R. Cherkupally and R. Mekala, *Chem. Pharm. Bull.*, 2008, **56**, 1002.

19 (*a*) X.-L. Zhang, S.-R. Sheng, X.-L. Lu and X.-L. Liu, *ARKIVOC*, 2007, **13**, 79; (*b*) U. C. Rajesh, S. Manohar and D. S. Rawat, *Adv. Synth. Catal.*, 2013, **355**, 3170; (*c*) M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshtiha and A. Davoodnia, *Synth. Commun.*, 2010, **40**, 523.

20 (*a*) C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937; (*b*) E. H. Hu, D. R. Sidler and U.-H. Dolling, *J. Org. Chem.*, 1998, **63**, 3454; (*c*) K. Folkers, H. J. Harwood and T. B. Johnson, *J. Am. Chem. Soc.*, 1932, **54**, 3751.

21 K. Azuma, S. Suzuki, S. Uchiyama, T. Kajiro, T. Santa and K. Imai, *Photochem. Photobiol. Sci.*, 2003, **2**, 443.

22 (*a*) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491; (*b*) R. Romagnoli, P. G. Baraldi, V. Remusat, M. D. Carrion, C. L. Cara, D. Preti, F. Fruttarolo, M. G. Pavani, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, J. Balzarini, M. A. Jordan and E. Hamel, *J. Med. Chem.*, 2006, **49**, 6425; (*c*) S. Mallena, M. P. H. Lee, C. Bailly, S. Neidle, A. Kumar, D. W. Boykin and W. D. Wilson, *J. Am. Chem. Soc.*, 2004, **126**, 13659; (*d*) V. Kumar, K. Kaur, G. K. Gupta and A. K. Sharma, *Eur. J. Med. Chem.*, 2013, **69**, 735.