

Moisture compatible and recyclable indium (III) chloride catalyzed and microwave assisted efficient route to substituted 1*H*-quinolin-2-ones

I. R. Siddiqui,* Shayna Shamim, Archana Singh, Vishal Srivastava, and Sanjay Yadav

*Laboratory of Green Synthesis, Department of Chemistry
University of Allahabad, Allahabad-211002, India
Email: irsiddiquiau@rediffmail.com*

DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.b19>

Abstract

An efficient three component synthesis of highly functionalized 4-methyl-1*H*-quinolin-2-ones in one-pot from readily available coumarin, hydrazine and isatin catalyzed by a recyclable and moisture compatible InCl₃ under microwave irradiation has been developed. The synthesis involves a InCl₃ catalyzed dehydrative nucleophilic substitution on the lactone moiety of coumarin by the isatin hydrazone resulting in the formation of *N*-substituted lactams, 6-substituted-4-methyl-1-(2-oxo-1,2-dihydroindol-3-ylidenamino)-1*H*-quinolin-2-ones. The coumarin based transformation into substituted 1*H*-quinolin-2-ones proceeded smoothly with quantitative yields at ambient temperature.

Keywords: Quinolin-2-one, one-pot, microwave irradiation, indium (III) chloride

Introduction

The presence of a quinoline nucleus in the frame work of various pharmacologically active compounds with antiasthmatic,¹ antibacterial,² antifungal,³ antimalarial,⁴ antiviral,⁵ anti-inflammatory⁶ activities continue to promote their synthetic efforts. In addition, quinolines are valuable synthons used for the preparation of nano- and meso structures with enhanced electronic and photonic properties.⁷ A series of compounds derived from 8-hydroxyquinolines and styryl quinoline were recently synthesized as potential HIV-1 integrase inhibitors.^{8,9} Similarly, isatin β -thiosemicarbazone derivatives were found to demonstrate a range of antiviral activities against Maloney leukemia virus, vaccinia virus¹⁰⁻¹³ and inhibit HIV-1 replication.¹⁴ Furthermore, isatin derivatives were also found to show antiviral activity against HIV-2 and HIV-3 in MT-4 cells.¹⁵ Because of these biodynamic properties associated with quinolin-2-one and isatin, quinolin-2-ones incorporating an isatin moiety appear to be attractive scaffolds to provide

a chemical diverse drug like library. The classical synthetic protocols for quinolin-2-one derivatives which suffer from disadvantages such as low yields, lack of easy availability/preparation of reagents, prolonged reaction time, multistep procedures, harsh reaction conditions etc. has increased our interest in making an effort for the development of environmentally benign and more atom economical simple protocols for the synthesis of 1*H*-quinolin-2-one derivatives.

The development and applications of catalytic reactions is nowadays worldwide documented and discussed. In recent years there has been a phenomenal increase in the use of catalysts in synthesis of pharmacologically important organic compounds especially heterocycles. Recently, indium (III) chloride has emerged as a powerful Lewis acid catalyst imparting high chemo- and regioselectivity in various transformations.¹⁶ The versatility of indium (III) chloride because of its non-toxic nature, recyclability, readily availability, high selectivity¹⁷ and moisture compatibility¹⁸ encouraged us to carry out a coumarin based transformation into 1*H*-quinolin-2-ones in the presence of hydrazine under benign reaction conditions.

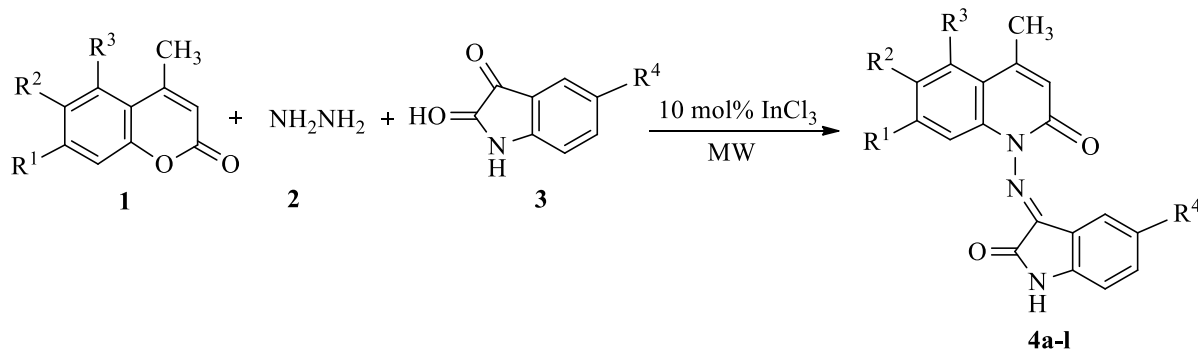
Multi component reactions (MCRs) are powerful synthetic tools which have changed the landscape of organic and medicinal chemistry due to their environment friendliness, atom economy and their ability to generate large library of compounds.¹⁹

Recent years have also witnessed a phenomenal growth in the application of microwave activation in organic synthesis.²⁰ The application of microwave activation in conjugation with metal halide catalysts in one-pot multi-component reactions provides an environmentally benign process associated with higher yield of products, mild reaction conditions, a significant reduction in reaction time, an enhanced reaction rate, all of which are additional eco-friendly attributes in the context of green chemistry.²¹

As part of our program to develop new, simple, efficient, clean, selective, environmentally benign methodologies for the synthesis of potential bioactive heterocycles we report here the catalytic activity of InCl₃ in a one-pot three-component efficient and clean synthesis of 1*H*-quinolin-2-one from coumarin in the presence of hydrazine²² (Scheme 1).

Result and Discussion

We have reported here a novel one-pot strategy for the synthesis of, hitherto, unknown highly substituted 1*H*-quinolin-2-one derivatives based on the MCR of isatin, hydrazine, and coumarins under microwave irradiation in the presence of 10 mol% of InCl₃ using ethanol as a solvent (Scheme 1). The usual work-up gave the corresponding 1*H*-quinolin-2-ones in excellent yields.



Scheme 1. InCl₃ catalyzed microwave assisted one-pot synthesis of quinolinones.

Compound	R ¹	R ²	R ³	R ⁴
4a	OH	H	H	H
4b	H	OH	H	H
4c	OH	H	OH	H
4d	OCH ₃	H	H	H
4e	OH	H	H	NO ₂
4f	H	OH	H	NO ₂
4g	OH	H	OH	NO ₂
4h	OCH ₃	H	H	NO ₂
4i	OH	H	H	CH ₃
4j	H	OH	H	CH ₃
4k	OH	H	OH	CH ₃
4l	OCH ₃	H	H	CH ₃

To generalize this reaction we have reacted various substituted isatin and coumarin derivatives and isolated the corresponding 1*H*-quinolin-2-ones in 80-90% yield (Table 1). In all cases the reaction proceeded smoothly in the presence of InCl₃. When InCl₃ was recycled and reused the yield of the products were almost same indicating that there is no drop in activity of the InCl₃. The results obtained from InCl₃ catalyzed microwave assisted synthesis of substituted 1*H*-quinolin-2-one derivatives in a one-pot process are summarized in Table 1. The reaction proceeded quantitatively in ethanol. When other solvents like THF, acetic acid were employed or when no solvent was used result obtained were disappointing and reactant itself was recovered. InCl₃ gave better yields as compared to other Lewis acid, such as SnCl₄, FeCl₃, and CuCl₂. This was studied by varying four Lewis acids and kept all the condition same as mentioned in experiment section. The yields obtained in four different experiments were shown in Table 2.

Table 1. InCl₃ catalyzed microwave assisted one-pot three component synthesis of quinolinones **4a-l**

Compound	Time MW (min).	Yield (%)			m.p. °C
		with InCl ₃		without catalyst	
		a	b		
4a	5	87	86	42	156-158
4b	5	83	83	46	157-159
4c	4	86	86	50	164-166
4d	4	83	83	45	145-147
4e	5	85	84	48	168-169
4f	6	81	81	43	167-169
4g	5	84	84	47	172-173
4h	6	81	81	41	165-166
4i	6	82	82	44	162-164
4j	5	84	84	43	163-164
4k	6	91	90	41	170-172
4l	5	89	89	49	152-153

a: Isolated yield with InCl₃ catalyst used 1st time

b: Isolated yield with InCl₃ catalyst used 2nd time

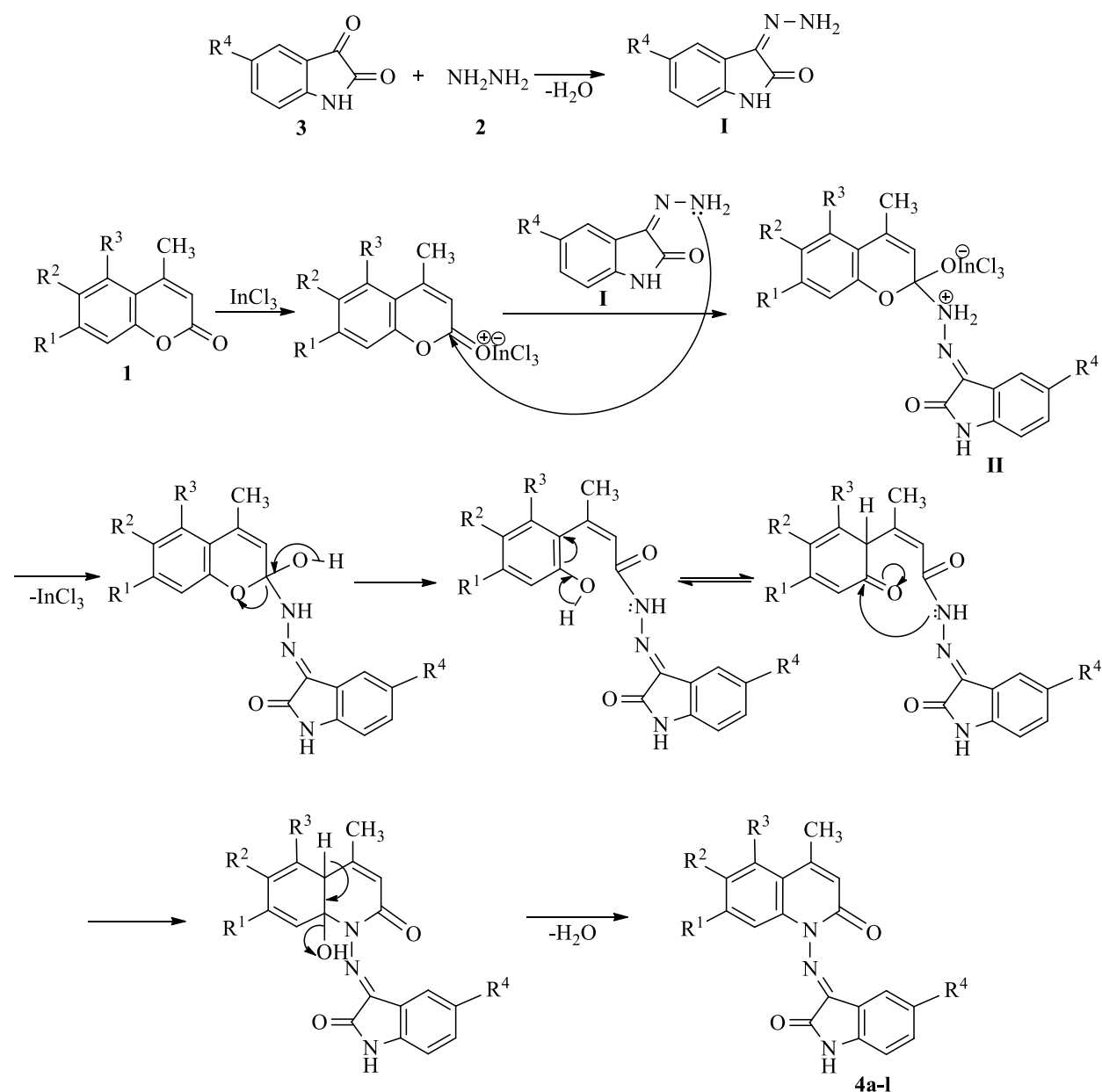
This supports that InCl₃ is much better Lewis acid for this reaction. The synthesis of highly functionalized 4-methyl-1*H*-quinolin-2-ones in a one-pot reaction has been developed and it was found that the envisaged three-component synthesis (Scheme 1) was successful. Experiments were completed within 4-6 min. as monitored by TLC showing the disappearance of the starting materials.

Table 2. Effect of different Lewis acids on yield (%)

Entry	Lewis acid	Yields %
1	InCl ₃	87
2	CuCl ₂	46
3	FeCl ₃	41
4	SnCl ₄	35

To ascertain whether the MW and InCl₃ combination truly improved the yield or simply increased conversion rates, we performed a comparative experiment in the absence of the catalyst InCl₃. It was found that the products were obtained only in 40-50% yield, confirming the functional role of InCl₃ as the catalyst. The rate enhancement can be rationalized on the basis of the formation of a dipolar activated complex **II** in these reactions (Scheme 2) and the greater stabilization of the dipolar activated complex by dipole-dipole interactions with the

electromagnetic field of the microwave may reduce the activation energy (G^*) resulting in the rate enhancement.



Scheme 2. Proposed mechanism for the synthesis of quinolin-2-ones in the presence of $InCl_3$ as catalyst.

Spectral analysis of **4a-l** supported the success of the MW-mediated one-pot triple condensation. The 1H NMR spectra of **4 a-l** exhibited multiplets in the region δ 6.42-7.70 which were indicative of 1*H*-quinolin-2-one derivatives. In the ^{13}C NMR spectra, signals in the region δ 107-156 for aromatic carbons, δ 161-163 for $C=O$, δ 155 for the $C=N$ and δ 112-151 for $C=C$ of

the heterocyclic ring as well as signals in the region δ 25 for the $-\text{CH}_3$ carbons supported the formation of **4a-l**.

The possible mechanism for the formation of products **4a-l** is illustrated in Scheme 2. The intermediate **I** resulting from the initial condensation of the isatin **3** with hydrazine hydrate **2**, followed by nucleophilic substitution on the lactone moiety of the coumarin resulted in the final product **4a-l**. This nucleophilic substitution was catalyzed by InCl_3 which enhances the electrophilicity of the carbonyl group of the lactone moiety of the coumarin. The nucleophilic substitution was followed by dehydration under the reaction conditions.

Conclusions

In conclusion, we have developed an unprecedented, original three-component, one-pot approach for the synthesis of highly substituted *1H*-quinolin-2-one derivatives under microwave irradiation using InCl_3 as a catalyst. The experimental simplicity, high yield of products, recyclability of the InCl_3 catalyst, and the short reaction times associated with the method presented here for the synthesis of the hitherto unknown *1H*-quinolin-2-one derivatives renders it to be of broad interest for synthetic and medicinal chemistry and can be applied for the synthesis of other related compounds.

Experimental Section

General. All chemicals used were of reagent grade and used as received without further purification. Melting points were determined in an open glass capillary method and are uncorrected. A laboratory microwave oven BP-310 was used for the syntheses. ^1H -NMR spectra were recorded at 400 MHz and ^{13}C -NMR Spectra at 100 MHz on a Bruker Avance DPX FT spectrometer in CDCl_3 using TMS as an internal reference. Mass spectra were determined on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analysis was carried out using a Coleman automatic C, H and N analyser. The progress of the reaction was monitored by TLC (Merk silica gel).

Typical procedure for the synthesis of *1H*-quinolin-2-ones

A mixture of 4-methyl-coumarin **1** (4 mmol), hydrazine hydrate **2** (6 mmol), isatin **3** (4 mmol) and 10 mol % of InCl_3 were added to ethanol (20 ml). The reaction mixture was stirred well for 5 min. After that the reaction mixture was subjected to microwave irradiation at 60 °C for the time given in the Table 1 and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture is cooled to room temperature and washed with cold ethanol. The product was dried and purified by column chromatography (ethyl acetate:*n*-hexane 2:8).

7-Hydroxy-4-methyl-1-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4a). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0 (s, 1H, OH, exchangeable with D₂O), 6.35 (s, 1H, CH), 6.42-7.70 (m, 7H, Ar-H), 8 (s, 1H, NH). ¹³C-NMR: δ = 25.1, 107.5, 111.2, 112.4, 119.4, 120.5, 123.1, 124.0, 124.2, 127.8, 129.2, 131.0, 137.3, 138.7, 151.0, 155, 156.7, 161, 163. MS (EI): *m/z* 319 (M⁺). Anal. Calcd. For C₁₈H₁₃N₃O₃ (319): C, 67.71; H, 4.10; N, 13.16%. Found: C, 67.70; H, 4.10; N, 13.25%.

6-Hydroxy-4-methyl-1-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4b). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0(s, 1H, OH, exchangeable with D₂O), 6.35 (s, 1H, CH), 6.59-7.70 (m, 7H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.1, 112.4, 113.6, 115.1, 120.5, 121.7, 123.1, 124.2, 128.2, 128.5, 129.2, 131.0, 138.7, 151.0, 152.8, 155.0, 161.0, 163.0. MS (EI): *m/z* 319 (M⁺). Anal. Calcd. For C₁₈H₁₃N₃O₃: C, 67.71; H, 4.10; N, 13.16 %. Found: C, 67.78; H, 4.21; N, 13.11%.

5,7-Dihydroxy-4-methyl-1-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4c). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0(s, 2H, 2xOH, exchangeable with D₂O), 6.35 (s, 1H, CH), 5.89-7.70 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.4, 98.4, 100.1, 106.6, 112.4, 120.5, 123.1, 124.2, 129.2, 131.0, 138.7, 151.0, 155.0, 156.7, 158.1, 161.0, 163.0. MS (EI): *m/z* 335 (M⁺). Anal. Calcd. For C₁₈H₁₃N₃O₄: C, 64.47; H, 3.91; N, 12.53%. Found: C, 64.40; H, 3.98; N, 12.61%.

7-Methoxy-4-methyl-1-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4d). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 6.35 (s, 1H, CH), 6.46-7.70 (m, 7H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.1, 56.0, 105.9, 109.6, 112.4, 119.1, 120.5, 123.1, 124.2, 127.4, 129.2, 131.0, 136.9, 138.7, 151.0, 155.0, 161.0, 161.4, 163.0. MS (EI): *m/z* 333 (M⁺). Anal. Calcd. For C₁₉H₁₅N₃O₃: C, 68.46; H, 4.54; N, 12.61%. Found: C, 68.52; H, 4.51; N, 12.68%.

7-Hydroxy-4-methyl-1-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4e). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0 (s, 1H, OH, exchangeable with D₂O), 6.35 (s, 1H, CH), 6.42-8.5 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.1, 107.5, 111.2, 112.4, 119.4, 121.4, 124.0, 124.3, 126.1, 127.8, 137.3, 144.1, 144.8, 151.0, 155.0, 156.7, 161.0, 163.0. MS (EI): *m/z* 364 (M⁺). Anal. Calcd. For C₁₈H₁₂N₄O₅: C, 59.34; H, 3.32; N, 15.38%. Found: C, 59.26; H, 3.39; N, 15.41 %.

6-Hydroxy-4-methyl-1-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4f). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0 (s, 1H, OH, exchangeable with D₂O), 6.35 (s, 1H, CH), 6.59-8.5 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.1, 112.4, 113.6, 115.1, 121.4, 121.7, 124.0, 124.3, 126.1, 128.2, 144.1, 144.8, 151.0, 152.8, 155.0, 161.0, 163.0. MS (EI): *m/z* 364 (M⁺). Anal. Calcd. For C₁₈H₁₂N₄O₅: C, 59.34; H, 3.32; N, 15.38%. Found: C, 59.42; H, 3.37; N, 15.41%.

5,7-Dihydroxy-4-methyl-1-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one (4g). ¹H-NMR: δ = 1.71 (s, 3H, CH₃), 5.0 (s, 2H, 2xOH, exchangeable with D₂O), 6.35 (s, 1H, CH), 5.89-8.5 (m, 5H, Ar-H), 8.0 (s, 1H, NH). ¹³C-NMR: δ = 25.4, 98.4, 100.1, 106.6, 112.4, 121.4, 124.0, 124.3, 126.1, 138.7, 144.1, 144.8, 151.0, 155.0, 156.6, 161.0, 163.0. MS

(EI): m/z 380 (M^+). Anal. Calcd. For $C_{18}H_{12}N_4O_6$: C, 56.85; H, 3.18; N, 14.73 %. Found: C, 56.93; H, 3.20; N, 14.84%.

7-Methoxy-4-methyl-1-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one

(4h). 1H -NMR: δ = 1.71 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.35 (s, 1H, CH), 6.46-8.5 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ^{13}C -NMR: δ = 25.4, 56.0, 105.9, 109.6, 112.4, 119.1, 121.4, 124.0, 124.3, 126.1, 127.4, 136.9, 144.1, 144.8, 151.0, 155.0, 156.6, 161.0, 161.4, 163.0. MS (EI): m/z 378 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4O_5$: C, 60.32; H, 3.73; N, 14.81%. Found: C, 60.29; H, 3.65; N, 14.89%.

7-Hydroxy-4-methyl-1-(5-methyl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one

(4i). 1H -NMR: δ = 1.71 (s, 3H, CH_3), 2.35 (s, 3H, OCH_3), 5.0 (s, 1H, OH, exchangeable with D_2O), 6.35 (s, 1H, CH), 6.42-7.6 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ^{13}C -NMR: δ = 20.9, 25.1, 107.5, 111.2, 112.4, 119.1, 120.4, 123.0, 127.8, 129.9, 131.7, 133.4, 135.7, 147.3, 151.0, 155.0, 156.7, 161.0, 163.0. MS (EI): m/z 333 (M^+). Anal. Calcd. For $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61%. Found: C, 68.43; H, 4.61; N, 12.56%.

6-Hydroxy-4-methyl-1-(5-methyl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one

(4j). 1H -NMR: δ = 1.71 (s, 3H, CH_3), 2.35 (s, 3H, OCH_3), 5.0 (s, 1H, OH, exchangeable with D_2O), 6.35 (s, 1H, CH), 6.59-7.6 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ^{13}C -NMR: δ = 20.9, 25.1, 112.4, 113.6, 115.1, 120.4, 121.7, 123.0, 128.2, 128.5, 129.9, 131.7, 133.4, 135.7, 151.0, 152.8, 155.0, 161.0, 163.0. MS (EI): m/z 333 (M^+). Anal. Calcd. For $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61%. Found: C, 68.49; H, 4.61; N, 12.68%.

5,7-Dihydroxy-4-methyl-1-(5-methyl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one

(4k). 1H -NMR: δ = 1.71 (s, 3H, CH_3), 2.35 (s, 3H, OCH_3), 5.0 (s, 2H, 2 x OH, exchangeable with D_2O), 6.35 (s, 1H, CH), 5.89-7.6 (m, 5H, Ar-H), 8.0 (s, 1H, NH). ^{13}C -NMR: δ = 20.9, 25.4, 98.4, 100.1, 106.6, 112.4, 120.4, 123.0, 129.9, 131.7, 133.4, 135.7, 138.7, 151.0, 155.0, 156.6, 158.1, 161.0, 163.0. MS (EI): m/z 349 (M^+). Anal. Calcd. For $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03 %. Found: C, 65.40; H, 4.41; N, 12.08 %.

7-Methoxy-4-methyl-1-(5-methyl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-1H-quinolin-2-one

(4l). 1H -NMR: δ = 1.71 (s, 3H, CH_3), 2.35 (s, 3H, OCH_3), 3.73 (s, 3H, OH, exchangeable with D_2O), 6.35 (s, 1H, CH), 6.46-7.6 (m, 6H, Ar-H), 8.0 (s, 1H, NH). ^{13}C -NMR: δ = 20.9, 25.1, 56.0, 105.9, 109.6, 112.4, 119.1, 120.4, 123.0, 127.4, 129.9, 131.7, 133.4, 135.7, 136.9, 151.0, 155.0, 161.0, 161.4, 163.0. MS (EI): m/z 347 (M^+). Anal. Calcd. For $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10%. Found: C, 69.13; H, 4.89; N, 12.15%.

Acknowledgements

We gratefully acknowledge financial support from CSIR, New Delhi, India. Authors are also thankful to RSIC, CDRI, Lucknow and IISc Bangalore India, for providing elemental and spectral analysis.

References

1. Doube, D.; Blouin, M.; Brideau, C.; Chan, C.; Desmarais, C.; Ethier, D.; Falguyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255.
2. Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. *Bioorg. Med. Chem.* **2000**, *8*, 69.
3. Moissev, I. K.; Zemtsova, M. N.; Trakhtenberg, P. L.; Kulikowa, D. A.; Pskobkina, I.; Neshchadim, G. N.; Ostapchuk, N. V. *Khim. Farm. Zh.* **1998**, *22*, 1448.
4. Craig, J. C.; Person, P. E. *J. Med. Chem.* **1971**, *14*, 1221.
5. Narsinh, D.; Anamik, S. *Ind. J. Pharm. Sci.* **2001**, *63*, 211.
6. Dillard, R. D.; Pavey, D. E.; Benslay, D. N. *J. Med. Chem.* **1973**, *16*, 251.
7. (a) Aggarwal A.K. and Jenekhe S. A., *Macromolecules* **1991**, *24*, 6806. (b) Zhang X., Shetty A. S. and Jenekhe S. A. *Macromolecules* **1999**, *32*, 7422. (c) Jenekhe S. A., Lu L. and Alam M. M., *Macromolecules* **2001**, *34*, 7315.
8. Polanski, J.; Niedbala, H.; Musiol, R.; Podeszwa, B.; Tabak, D.; Palka, A.; Mencil, A.; Finster, J.; Mouscadet, J. F.; Le Bret, M. *Lett. Drugs Des. Disc.* **2006**, *3*, 175.
9. Polanski, J.; Niedbala, H.; Musiol, R.; Podeszwa, B.; Tabak, D.; Palka, A.; Mencil, A.; Mouscadet, J. F.; Le Bret, M. *Lett. Drugs Des. Disc.* **2007**, *4*, 99.
10. Teitz, Y.; Barko, N.; Abramoff, M.; Ronen, D. *Chemotherapy* **1994**, *40*, 195.
11. Ronen, D.; Teitz, Y. *Antimicrob. Agents Chemother.* **1984**, *26*, 913.
12. Teitz, Y.; Ronen, D.; Vansover, A.; Stematsky, T.; Riggs, J. L. *Antiviral Res.* **1994**, *24*, 305.
13. Sherman, L.; Edelstein, F.; Shtacher, G.; Avramoff, M.; Teitz, Y. *J. Gen. Virol.* **1980**, *46*, 195.
14. Teitz Y.; Ronen D.; Vnsver A.; Stematsky T.; Rigg J. L. *Antiviral. Res.* **1994**; *24*; 305.
15. Pauwels R.; Balzarini J.; Baba M.; Snoeck R.; Schols D. J.; Herdewijin P. ; Desmyter J.; Clercq E. D. *J. Virol. Methods* **1988**; *20*; 309.
16. (a) Loh, T.-P.; Pei, J. *J. Chem. Soc., Chem. Commun.* **1996**, 2315. (b) Babu, G.; Perumal, P. T. *Aidrichim. Acta* **2000**, *33*, 16. (c) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (d) Li, J.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 793.
17. Ranu, B. C. *Eur J. Org. Chem.* **2000**, 2347
18. Paquette, L. A.; Mitzal, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 1937
19. (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
20. (a) McGee, D. P. C.; Martin, J. C.; Smee, D. F.; Verheyden, J. P. H. *Nucleosides and Nucleotides* **1990**, *9*, 815. (b) Ugi, I.; Domling, A. *Endeavour* **1994**, *18*, 115. (c) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537.

21. (a) Zeigler, T.; Kaisers, H. J.; Schlomer, R.; Koch, C. *Tetrahedron* **1999**, *55*, 8397. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (c) Meshram, H. M.; Sekhar, K. C.; Ganesh, Y. S. S.; Yadav, J. S. *Synlett* **2000**, 1273.
22. (a) Al-Bayati, R. I.; Al-Amiery, A. A. H.; Al-Majedy, Y. K. *Afr. J. Pure Appl. Chem.* **2010**, *4*(6), 74. (b) Bishnoi, A.; Saxena, R. *Indian J. Heterocyclic Chem.* **2001**, *11*, 4750.