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# Synthesis and Antioxidant Evaluation of Indole Quinoline Derived Chalcones

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A series of novel indole quinoline derived chalcones were synthesized using cost-effective synergetic catalytic system consisting of heterogeneous basic bleaching earth clay (pH 12.5) and PEG-400 as solvent at ambient temperature with the yields of 60-76%. All these chalcones were characterized by spectral data. Both the DPPH and SOR scavenging assays were performed to evaluate their antioxidant nature of these compounds.

**Keywords: Indole quinoline derivative, Bleaching earth clay, PEG-400, Antioxidant activity.**

## INTRODUCTION

Quinoline scaffold is one of the widely existing alkaloids [1-3] with varying pharmacological activities [4,5]. Hybrid quinoline analogues coupled with other heterocycles have also been exploited as key intermediates for the synthesis of meso/nano-structures with increased electronic and photonic applications [6-8] along with development of novel drug candidates [9-17]. Among them, chalcones are found to be one of the important biological active moieties [18]. Henceforth, synthesis of indole derived chalcones is of continued interest for synthetic chemists [19-21].

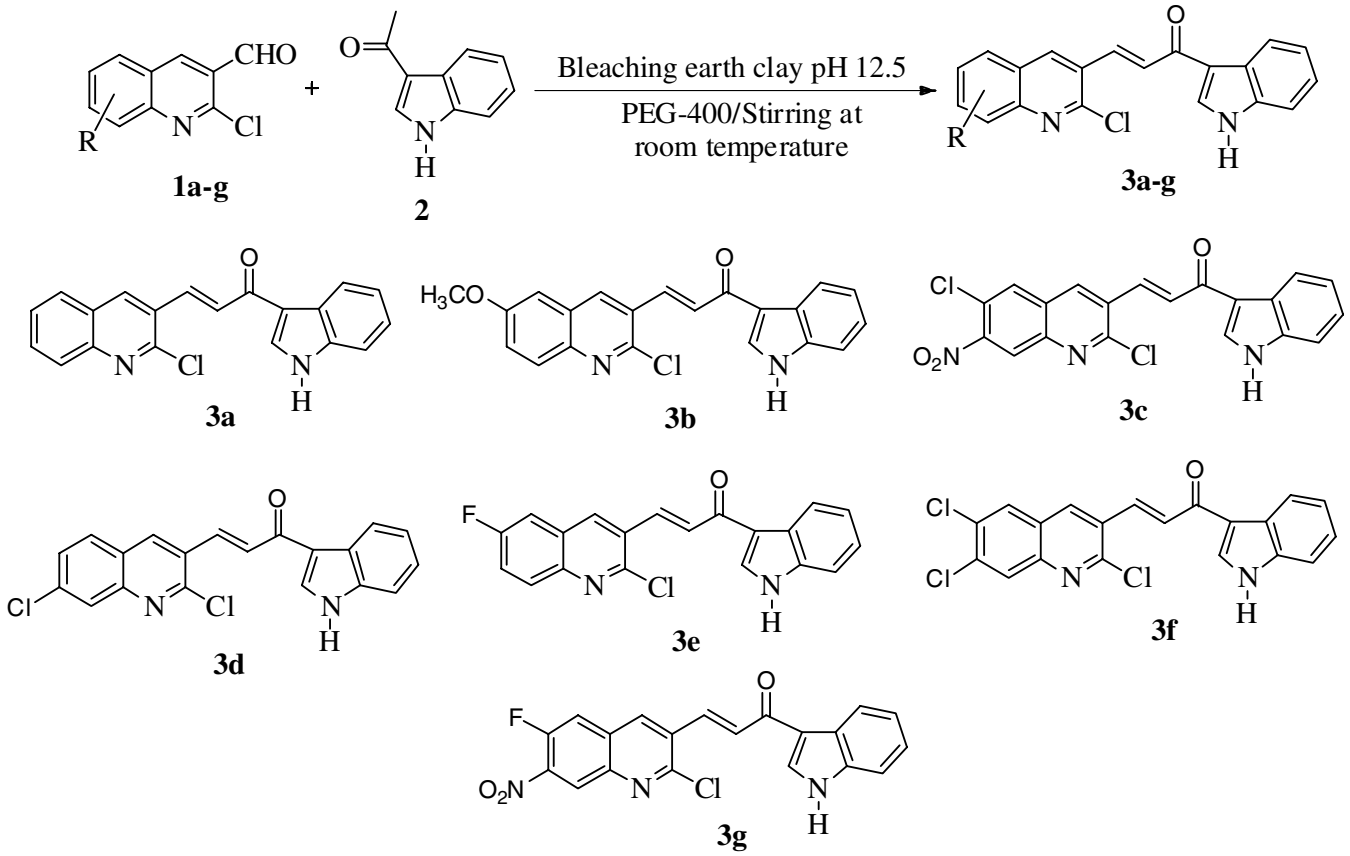
In large scale operations, due to the demand for increased eco-friendly synthetic approaches, several heterogeneous catalysts were replaced over conventional catalysts. One such is bleaching earth clay (pH 12.5), which has been exploited in several organic transformations due to possessing larger surface area [22-25].

Polyethylene glycol, an eco-friendly recyclable solvent, owing to its low vapour pressure, acts as a suitable phase transfer catalyst in several organic transformations [26-28]. In continuation of present studies on novel synthetic protocols for the construction of pharmacologically relevant heterocycles [29-32], we, herein, report the synthesis of a series of indole quinoline derived chalcones using PEG-400 as green reaction solvent and bleaching earth clay (pH 12.5) as heterogeneous catalyst medium and screening of their antioxidant properties.

## EXPERIMENTAL

**Experimental procedure:** 1-(*1H*-Indole-3-yl) ethanone (1 mmol) was dissolved in PEG-400 as a reaction solvent (3 mL). To this was added, bleaching earth clay (pH 12.5) (10 mol%) and the mixture was stirred for 10 min at room temperature. Substituted chloroquinoline-3-carbaldehyde (1 mmol) was then added to the reaction mixture and stirred at 25 ºC for 10 h and then poured onto crushed ice (25 g) and acidified with 10% aqueous HCl. The organic mass was extracted with dichloromethane and washed with water. The extract was dried with anhydrous $Na_2SO_4$ and concentrated to get the product (**Scheme-I**). The purification of compounds (**3a-g**) was carried out using a silica gel (E. Merck 100-200 mesh column in $CHCl_3$:$CH_3OH$, 9:1).

**Compound 3a:** Yellow crystal, yield: 65%, m.p.: 230-234 ºC, IR (KBr, $cm^{-1}$): 3301, 3002, 1702, 1629. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.21 (s, 1H, NH), 6.02 (s, 1H), 6.22 (d, 1H, *J*




**Scheme-I:** Synthesis of indole quinoline derivatives (**3a-g**)

= 16 Hz), 6.63 (d, 1H, *J* = 16 Hz), 7.21 (s, 4H), 7.32 (s, 4H), 7.42 (s, 1H), *m.f./m.w.*: $C_{20}H_{13}N_2OCl$/332, MS: *m/e* (M+1) 333.

**Compound 3b:** Yellow crystal, yield: 60%, m.p.: 250-253 ºC, IR (KBr, $cm^{-1}$): 3302, 3020, 1708, 1635, 1108. $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H, $OCH_3$), 4.23 (s, 1H, NH), 6.01 (s, 1H), 6.62 (d, 1H, *J* = 16 Hz), 7.18 (s, 1H), 7.19 (s, 1H), 7.21 (d, 1H, *J* = 16 Hz), 7.22 (s, 4H), 7.41 (s, 1H), *m.f./m.w.*: $C_{21}H_{15}N_2O_2Cl$/362, MS: *m/e* (M+1) 363.

**Compound 3c:** Cream yellow crystal, yield: 62%, m.p.: 285-287 °C, IR (KBr, $cm^{-1}$): 3310, 3017, 1720, 1628. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.21 (s, 1H, NH), 6.01 (s, 1H), 6.65 (d, 1H, *J* = 16 Hz), 7.23 (d, 1H, *J* = 16 Hz), 7.24 (s, 4H), 7.28 (s, 1H), 7.31 (s, 1H), 7.42 (s, 1H), *m.f./m.w.*: $C_{20}H_{11}N_2O_3Cl_2$/412, MS: *m/e* (M+1) 413.

**Compound 3d:** Yellow crystal, yield: 68%, m.p.: 249-251 ºC, IR (KBr, $cm^{-1}$): 3301, 3030, 1717, 1628, 757. $^1H$ NMR (300 MHz, $CDCl_3$): δ 6.62 (d, 1H, *J* = 16 Hz), 7.21 (d, 1H, *J* = 16 Hz), 7.22 (s, 4H), 7.23 (s, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.07 (s, 1H), 11.54 (s, 1H), *m.f./m.w.*: $C_{20}H_{11}N_2OClF$/350, MS: *m/e* (M+1) 351.

**Compound 3e:** White creamy solid, yield: 72%, m.p.: 250-255 ºC, IR (KBr, $cm^{-1}$): 3312, 3023, 1721, 1635, 755 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.23 (s, 1H, NH), 6.05 (s, 1H), 6.61 (d, 1H, *J* = 16 Hz), 7.18 (s, 4H), 7.19 (s, 1H), 7.22 (d, 1H, *J* = 16 Hz), 7.28 (d, 1H), 7.41 (s, 1H), 7.61 (d, 1H), *m.f./m.w.*: $C_{20}H_{13}N_2OClF$/351, MS: *m/e* (M+1) 352.

**Compound 3f:** White crystal, yield: 70%, m.p.: 290-295 ºC, IR (KBr, $cm^{-1}$): 3310, 3010, 1722, 1626, 727. $^1H$ NMR (300 MHz, $CDCl_3$): δ 6.61 (d, 1H, *J* = 16 Hz), 7.20 (s, 4H), 7.21 (d, 1H, *J* = 16 Hz), 7.22 (s, 1H), 7.32 (s, 1H), 7.40 (s, 1H), 8.03 (s, 1H), 11.51 (s, 1H), *m.f./m.w.*: $C_{20}H_{11}N_2OCl_3$/400, MS: *m/e* (M+1) 401.

**Compound 3g:** White crystal, yield: 76%, m.p. > 300 ºC, IR (KBr, $cm^{-1}$): 3301, 3007, 1718, 1628, 768. $^1H$ NMR (300 MHz, $CDCl_3$): δ 6.61 (d, 1H, *J* = 16 Hz), 7.11 (s, 1H), 7.21 (s, 4H), 7.23 (s, 1H), 7.25 (d, 1H, *J* = 16 Hz), 7.41 (s, 1H), 8.12 (s, 1H), 11.56 (s, 1H), *m.f./m.w.*: $C_{20}H_{11}N_3O_3ClF$/395, MS: *m/e* (M+1) 396.

## RESULTS AND DISCUSSION

In a preliminary experiment, a model reaction between 1-(*1H*-indole-3-yl) ethanone (**2**, 1 mmol) and chloroquinoline-3-carbaldehyde (**1a**, 1 mmol) to convert it into corresponding (*E*)-3-(2-chloroquinolin-3-yl)-1-(1*H*-indol-3-yl)prop-2-en-1-one (**3a**) was studied. The effect of various reaction parameters, such as effect of solvent/catalyst, temperature and reaction condition was evaluated to optimize the reaction (Table-1).

The product was not formed under neat condition at higher temperature (Table-1, entry 1). Then individual screening of some basic catalyst such as triethylamine (TEA), piperidine, morpholine and also PEG-200, 400, 600 as solvent was studied for the same model reaction but none of these catalysts and solvents gave satisfactory yield (Table-1, entries 2-4 and 6-8). We also tried the reaction by using Bleaching earth clay catalyst as a heterogeneous catalyst to achieve the good yield (Table-1, entries 5). The effect of bleaching earth clay catalyst along

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS[a]

| Entry | Solvent/catalyst | Temp. (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Neat | 90 | 24 | NR |
| 2 | $Et_3N$ | 90 | 24 | 10 |
| 3 | Piperidine | 90 | 24 | 15 |
| 4 | Morpholine | 90 | 24 | 15 |
| 5 | Bleaching earth clay | 90 | 24 | 40 |
| 6 | PEG-200 | 90 | 12 | 45 |
| 7 | PEG-400 | RT | 10 | 54 |
| 8 | PEG-600 | RT | 10 | 50 |
| 9 | PEG-200/bleaching earth clay | RT | 12 | 55 |
| 10 | PEG-400/bleaching earth clay | RT | 10 | 65 |
| 11 | PEG-600/bleaching earth clay | RT | 12 | 60 |
| 12 | Water/bleaching earth clay | 90 | 24 | 18 |
| 13 | DCM/bleaching earth clay | 90 | 24 | 27 |
| 14 | MeOH/bleaching earth clay | 90 | 24 | 35 |
| 15 | EtOH/bleaching earth clay | 90 | 24 | 37 |
| 16 | Acetonitrile/bleaching earth clay | 90 | 24 | 40 |

[a]1-(1*H*-indole-3-yl)ethanone (**2**, 1 mmol) , substituted chloroquinoline-3-carbaldehyde (**1a**, 1 mmol), bleaching earth clay and PEG-400; [b]Isolated yields; NR = no reaction.

with PEG-200, 400 and 600 solvent system at room temperature and higher temperature was also studied (Table-1, entries 9-11). The overall findings of this experiment was that the combination of PEG-400 with bleaching earth clay catalyst at ambient temperature gives the best results in terms of yield and time as shown in (Table-1, entry 10) but the replacement of PEG-400 by universal solvent water with bleaching earth clay did not furnish the desired product in high percentage yield (Table-1, entry 12). Next, we tested polar protic solvents such as methanol, ethanol also the reaction conducted in polar aprotic solvents, such as acetonitrile, dichloromethane with bleaching earth catalyst at 90 ºC, were found to be resulted in lower product yield under above condition (Table-1, entry 13-16).

Again in order to obtain the desired product in good yield, we have optimized the bleaching earth clay catalyst concentration in wt. % for the same reaction (Table-2). Use of 5 and 7 mol% of catalyst gave lower yield of the product (Table-2, entries 1-2) even after a prolonged reaction time. 10 mol% of catalyst concentration was sufficient to obtain good yield of product but use of 12 mol% of catalyst was not able to increase the yield of product.

TABLE-2
CATALYTIC STUDY OF BLEACHING EARTH CLAY IN PRESENCE OF PEG-400

| Entry | Catalyst (wt.%) | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | 5 | RT | 12 | 40 |
| 2 | 7 | RT | 12 | 54 |
| 3 | 10 | RT | 10 | 65 |
| 4 | 12 | RT | 10 | 65 |

Therefore, 10 mol% of basic bleaching earth clay catalyst in presence of PEG-400 at ambient temperature, is sufficient to push the reaction in forward direction as shown in Table-2. The disappearance of aldehyde proton in both IR and $^1$H NMR, formation of *trans*-olefinic bond at d 6.63 and 6.22 ppm in $^1$H NMR, confirmed the formation of **3a**. It was further strengthened with the ESI Mass spectrum of **3a** (M+1) at *m/z* 333. With the optimized reaction conditions set, as shown in experimental procedure, 7 compounds of indolo quinoline derived chalcones were synthesized as shown in **Scheme-I**. The catalyst can be recyclable and reused.

## Antioxidant evaluation

**DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay:** The DPPH radical scavenging assay was performed as described earlier by Bartolome *et al.* [33].

**Superoxide radical (SOR) scavenging assay:** The superoxide anion scavenging assay was performed by the previously published method [34].

All the synthesized compounds were evaluated for antioxidant activity. Moreover, it is observed that compounds **3a**, **3b** and **3g** are good scavenger of DPPH and superoxide free radicals. A maximum DPPH radical activity was recorded by **3g** (23.10 ± 0.55) while **3b** (30.65 ± 0.23) possess maximum superoxide radical scavenging ability. The results obtained are shown in Table-3.

TABLE-3
SUMMARY OF DPPH, SOR RADICAL SCAVENGING ACTIVITY OF INDOLOQUINOLINE DERIVATIVES

| Compound | DPPH | SOR |
|---|---|---|
| **3a** | 21.78 ± 0.24 | 13.75 ± 0.63 |
| **3b** | 22.96 ± 0.35 | 30.65 ± 0.23 |
| **3c** | 13.33 ± 0.63 | 28.03 ± 0.40 |
| **3d** | 13.67 ± 0.45 | NR |
| **3e** | 17.50 ± 0.34 | 21.63 ± 0.45 |
| **3f** | NR | 22.23 ± 0.65 |
| **3g** | 23.10 ± 0.55 | 21.70 ± 0.20 |
| Ascorbic acid | 63.81 ± 0.41 | 23.35 ± 0.29 |

The result summarized are the mean value of n = 2 ± S.D., NR = no reaction under experimental condition

A vast literature is available regarding the antioxidative properties of indole quinoline derivatives. Moreover, the antioxidant properties of indole quinoline shows that they can neutralize hydroxyl radical, which are the most aggressive in relation to membrane injury [35]. In addition, 2-chloro-3-carbaldehyde-7-methyl quinoline and 2-chloro 3-benzyl-7-methyl quinoline are reported as good scavenger of –OH radicals [36].

Present result was in agreement with the result of the earlier reported quinoline derivatives such as 7-chloro-4-aminoquinoline [37] and 1,3-oxazole[4,5-*c*]quinoline [38]. Considering the above results, it can be summarized that various substitution groups at 4′ and 5′-position strengthen the biological activity of quinoline derivatives. The substitution of -OMe, -$NO_2$, at 4′-position and F at 5′-positions in parent compound seems to be the most compatible structure configuration for the scavenging free radicals.

## Conclusion

A series of novel indole quinoline derived chalcones were synthesized by using effective synergetic catalytic system consisting of green basic bleaching earth clay (pH 12.5) and

PEG-400 as solvent system. Considering the results of the present studies, the tested indole quinoline derivative could be considered as potential antioxidant agent. Moreover, the compounds with various 5′-substituted groups can be used as a lead for further development of novel antioxidant agents.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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