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Curcumin inspired 2-chloro/phenoxy quinoline analogues: Synthesis and biological evaluation as potential anticancer agents

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ABSTRACT

Synthesis of twenty new curcumin inspired 2-chloro/phenoxy quinoline derivatives is outlined in this study. The obtained new chemical entities were screened *in vitro* for their cytotoxic activity towards various tumor cell lines. Of the compounds screened, **6c** and **9d** exhibited significant activity and the most active analogue **6c** displayed promising cytotoxicity against PC-3 (IC_{50} of 3.12 ± 0.11 μM), DU-145, NCI-H460 and 4 T1 cell lines. Further, **6c** and **9d** have 2.1 and 1.4 times more aqueous solubility, respectively, than curcumin. Additionally, the promising candidate **6c** could induce G2/M cell cycle arrest and apoptosis in PC-3 cells, as determined by AO-EB staining, DAPI staining, analysis of ROS levels as well as annexin binding assay.

Quinoline is one of the omnipresent structural motifs that occur in several natural compounds especially alkaloids (Cinchona and Camptotheca alkaloids) and pharmacologically active substances.[1] It constitutes an interesting and important class of compounds, with widespread biological activities including antimalarial,[2] anti-bacterial,[3] anthelmintic,[4] anticancer,[5] antifungal,[6] antihypertensive,[7] anti-inflammatory,[8] analgesic,[9] antiviral[10] and hypoglycemic[11] etc., ultimately making quinoline as "privileged substructure" for drug design. Quinoline or its derivatives have been incorporated extensively into a diverse set of therapeutically interesting drugs and drug candidates; for example (**i**, Fig. 1), antimalarials (Quinine and Chloroquine etc), anticancer (Topotecan and Bosutinib etc), antibacterial (fluoroquinolones like Ciprofloxacin), antiglaucoma (Carteolol), antiasthmatic, antiviral, antifungal-antiprotozoal, anthelmintic, cardiotonic and local anesthetic.[1d,12]

Additionally, 2-substituted quinoline moiety is ubiquitous among bioactive derivatives, like anticancer agents,[13] antileishmanial agents,[14] *CysLT* (LTD4) receptor antagonists,[15] HIV-1 replication inhibitors[16] and PDE4 inhibitors.[17] In particular, 2-alkoxy (aroxy)quinolines exist as substructures in numerous medicinally interesting compounds displaying a broad spectrum of biological activities, such as anticancer (SH80),[12a] anti-mycobacterial, antithrombin, antimalarial, immunosuppressive and many others.[18] Fig. 1 **(ii)** shows the structures of some of the bioactive 2-phenoxy/methoxy quinoline derivatives.

Curcumin (**a**, Fig. 2), is a phytochemical, gained from the dried rhizomes of Turmeric plant (*Curcuma longa*).[19] Despite the fact that curcumin possess versatile biological properties such as antioxidant, anti-inflammatory, anti-HIV as well as antitumor activities,[20] its utility is limited because of its poor water solubility and poor *in vivo* bioavailability.[21] The multiple therapeutic properties as well as the minimal bioavailability directed the route for the synthesis of a "super curcumin" without these problems. Preliminary structure activity relationship analysis of curcumin demonstrated that the lack of stability of curcumin under biological conditions is because of the β-diketone moiety and the active methylene group, hence the removal of β-diketone moiety may improve the stability of curcumin derivatives.[22] Based on this knowledge, significant efforts have been devoted for the synthesis of different biologically interesting heterocyclic curcumin analogues (**b–h**, Fig. 2).[23–29] As a part of our venture towards the development of potent curcumin congeners,[28,29] herein we have tried to probe the scope of curcumin based 2-chloro/phenoxy quinolines (Fig. 3) as anticancer and apoptosis inducing agents.

The desired compounds (1*E*,4*E*)-1-(2-chloroquinolin-3-yl)-5-phenylpenta-1,4-dien-3-ones (**6a–d**) and (1*E*,4*E*)-1-(2-phe-

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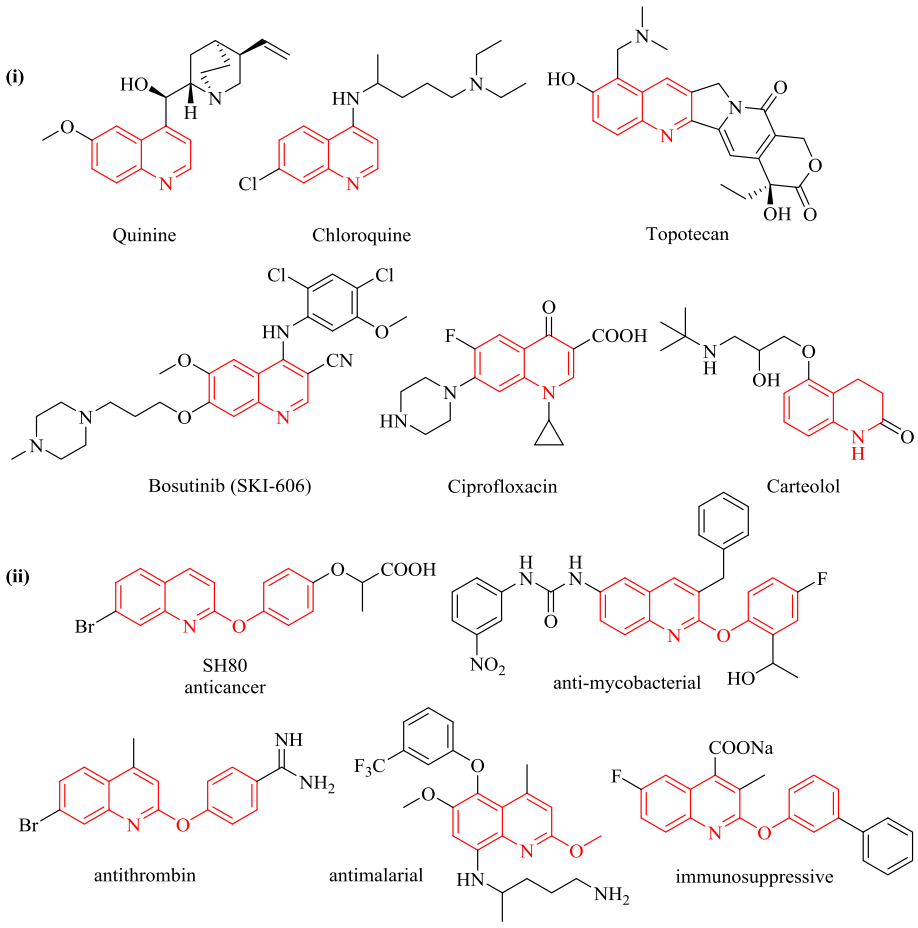

Fig. 1. **(i)** Some of the representative examples of quinoline drugs and drug candidates. **(ii)** Structures of 2-phenoxy/methoxy quinoline derivatives of biological interest.

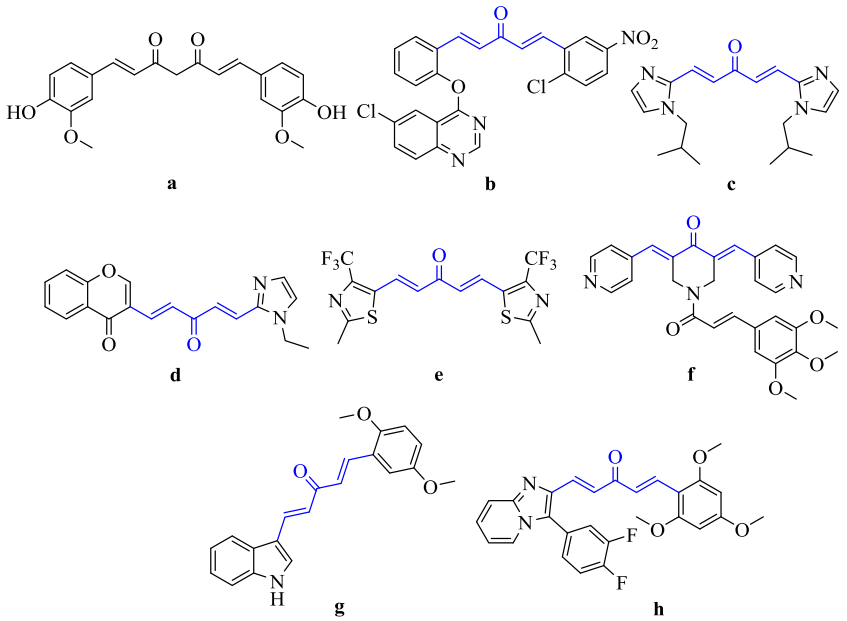

Fig. 2. Structures of curcumin and its congeners.

noxyquinolin-3-yl)-5-phenylpenta-1,4-dien-3-ones (**9a**–**p**) were synthesized from chalcones (**3a**–**f**) and 2-chloroquinoline-3-carbaldehyde (**5**) or 2-phenoxyquinoline-3-carbaldehyde derivatives (**8a**–**d**) as shown in Scheme 1. The aldehydes (**1a**–**f**) were converted into chalcones (**3a**–**f**) *via* Claisen-Schmidt condensation reaction with acetone using 15% NaOH.[30] Next, acetanilide was cyclized with $POCl_3$ by the versatile Vilsmeier-Haack reaction and the resulting 2-chloroquinoline-3-carbaldehyde (**5**)[31] was