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Quinolones derivatives as DNA-topoisomerase I- inhibitors: A new step for cancer treatment.

Introduction:

In order for cells to function, DNA topoisomerase enzymes must be present. For example, many antibiotic and cancer chemotherapeutic treatments are directed at the function of topoisomerase enzymes, which exhibit a significant role in maintaining the DNA topology during DNA replication and transcription. Camptothecin, a cancer-fighting natural medication, is generated from plants. irinotecan and topotecan are both derived from the alkaloid camptothecin, which specifically targets this malignancy (Pommier, 2006). Anticancer drugs targeting both tyrosine phosphodiesterase I and topoisomerase I (Nguyen et al., 2012); polyphenolics compound (Kuriyama et al., 2013); “2-[3-(1,3-dicarboxypropyl-ureido) pentanedioic acid (DUPA)” (Roy et al., 2015); anthracycline (Oki, 1984), were the potent TOP-inhibitors, which was developed and synthesized for effective cancer treatment. The yearly number of cancer patients is predictable to climb from 14.1 million in 2012 to 21.6 million by 2023, making it one of the most common health issue in the world (Peng et al., 2017; Kovvuri et al., 2018). The antimalarial, antibiotic, and anticancer properties of quinoline derivatives have been studied (Van de Walle et al., 2020; Singh et al., 2020). TOP1 is a ubiquitous nuclear enzyme required for several cellular functions, including DNA replication and transcription (Tang et al., 2019; Marzi et al., 2018). The enhanced susceptibility of cancer cells to TOP1 inhibitors is shown by the over-expression of TOP1 and impaired DNA repair in rapidly proliferating cancer cells. Because of this, TOP1 is a useful and well-validated anticancer strategy (Majumdar et al., 2015). In addition to hydrogen bonding between TOP1 residues, TOP1 inhibitors attach at the interface of “TOP1-DNA cleavage complexes (TOP1ccs)” through establishing hydrophobic contacts with the base pairs, results in irrevocable double strand breakage and cell death because to irrevocable TOP1ccs. That's why they're called

"TOP1 Poisons": inhibitors of TOP1 that keep TOP1 cells stable (Pommier et al., 2006; Lv et al., 2016).

Work Analysis:

Within this article, two classic sequences of "4-alkoxy-2-arylquinolines" **14 and 19** were developed and synthesized. The researcher intends to create possible anticancer agents targeting Topoisomerase-I (TOP1ccs). For this "1-(2,amino-4,5,dimethoxyphenyl)ethenone **(9)**" was first synthesised and characterised. The melting temperatures, IR spectra, and NMR spectra of all produced compounds were also evaluated. To get yellow crystals of compounds **11a and b**" compound **9** was dissolved in dry THF, Et3N, and benzoyl chloride according to the proper methods to prepare the "benzoyl derivatives **(11a, b)**". It was necessary to neutralized the biphasic mixture using 1 M HCl to achieve a pH of 7 in order to make the quinolones **(12a, b)**. Using a combination of **12a or b** with potassium hydroxide and potassium iodide and stirred, the critical intermediates (13a-d) were synthesised further to yield compounds **13a-d** that did not need any additional purification. To make the "4-alkoxy-2-arylquinolines **(14a-p)**", DMF solution (dry) was used to combine **13a-d** with KI and anhydrous K_2CO_3. The "2-aminoacetophenone" derivative **9** was reacted with the suitable "aroyl chloride" to produce **15a-c** and the same process as **11a, b** was utilized to produce the aroyl derivatives for compound **(16a-c)**. The identical method as 12a and b was followed for **17a-c** synthesis. As with **13a-d**, the critical intermediates **18a-c** were synthesised by the identical methods. Using a combination of **18a-c**, KI, and anhydrous K_2CO_3 was stirred in DMF solution to synthesized desired "4-alkoxy-2-arylquinolines **(19a-c)**". The combination was then supplemented with 4-hydroxymorpholine then cooled in ice water and treat with water and hexane to remove the precipitated solid. The organic layers were then recovered, washed with water, and dried over anhydrous Na2SO4 before being vacuum evaporated. Sulforhodamine B (SRB) was used in an *in vitro* cytotoxicity experiment on 59 cancer cell lines at NCI (USA) (Abo-Ashour et al., 2018; Eldehna et al., 2019). The "3'-[^{32}P]-labelled 117-bp DNA substrate oligonucleotide" was used for the topoisomerase I-mediated DNA cleavage test (Dexheimer and Pommier, 2008).

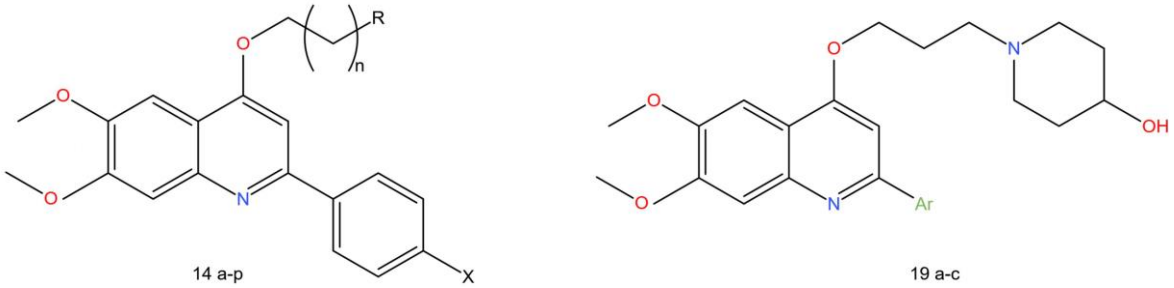
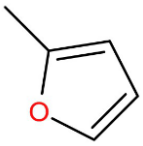
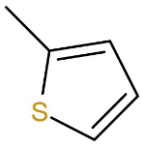
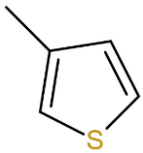


Fig. 1. Structure of target 4-alkoxy-2-arylquinolines (14a-p) and 4-alkoxy-2-arylquinolines (19a-c).

Table 1. Various functional moiety related to structure 14a-p (X, n and R) and 19a-c (Ar).

14	X	n	R	14	X	n	R
a	cl	1	Pyrroliidone	**i**	CF_3	1	Pyrroliidone
b	cl	1	4-Hydroxypiperidine	**j**	CF_3	1	4-Hydroxypiperidine
c	cl	1	Piperidine	**k**	CF_3	1	Piperidine
d	cl	1	Morpholine	**l**	CF_3	1	Morpholine
e	cl	2	Pyrroliidone	**m**	CF_3	2	Pyrroliidone
f	cl	2	4-Hydroxypiperidine	**n**	CF_3	2	4-Hydroxypiperidine
g	cl	2	Piperidine	**o**	CF_3	2	Piperidine
h	cl	2	Morpholine	**p**	CF_3	2	Morpholine
19a Ar=				**19b Ar=**			**19c Ar=** 

Findings:

The synthesis techniques used for the two derivative "4-alkoxy-2-arylquinolines" **14a-p and 19a-c**. The compound **11a, b** (benzoyl derivatives) were obtained in 81-85% yield by reacting the "2-aminoacetophenone derivative" **(9)** with derivative **10a, b (**benzoyl chloride) in THF solution at 0°C (Xia et al., 2001; Li et al., 2016). Quinolones derivative **12 a and b**, was obtained in excellent yield 91% and 90% respectively after the aldol condensation of benzoyl derivatives **11a, b** in nitrogen, yielding the quinolones 12a, b in 91 % and 90% yields, respectively. Quinolones (**12a,b)** were stirred in dry DMF for two hours with excess KOH and KI, then the nucleophile

generated in this reaction has been responded with “1-bromo-2-chloroethane” or “1-bromo-3-chloropropane” at room temperature to produce the O-alkylated regioisomers **13a-d** with 78% to 89% yield. (Elsayed et al., 2017). The O regioisomers of key intermediates **13a-d** have been verified. The target derivative "4-alkoxy-2-arylquinolines” (**14a-p**) produce in a excellent yield (63-92%) (Elsayed et al., 2017). The second series, "4-alkoxy-2-arylquinolines **19a–c**," was synthesized using the same procedures as the first series explained din methodology. The anticancer properties of all substances **(14 a-p; 19a-c)** were tested using different human cancer cells. New "4-alkoxy-2-arylquinolines” (**14a-p** and **19a-c**) anticancer medicines targeting the TOP1 enzyme have been designed and manufactured. All compounds were tested for their anticancer potential using the NCI method. Derivative **14m** was found more potent and affecting colon, leukaemia, and melanoma at submicromolar doses, according to GI50 MG-MID 1.26 mM. At submicromolar doses, **14e-h** and **14m-p** also exhibit potent activity against nine different cancer cell lines (leukaemia, NSCLC; colon, CNS; Melanoma; Ovarian; Renal; Prostate). TOP1-mediated DNA cleavage assay was used to investigate the TOP1 inhibitory potential of derivative "4-alkoxy-2 aryl quinolines **14e-h** and **14m-p**," As a result, derivative **14h** and **14p,** shown potent TOP-1 inhibitory effect among all the derivatives.

Future aspects

Without a doubt, quinoline compounds should be further investigated for their efficacy and selectivity as potential anti-cancer treatments. The creation of chemotherapeutic medicines for patients suffering from various types of cancer based on these chemicals, has tremendous promise in the future.

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