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APPLICATION INDOLE DERIVATIVE IN INFECTIOUS VIRAL DISEASES

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ABSTRACT:
The common nitrogen-containing heterocycles, such as indoles, that have been used in the development of antiviral drugs are the main topic of our review today. The main components of pharmacological medications that have biological activity against different types of viral infections are indoles heterocycles.

Keywords:
Indole, medication, antiviral design, pharmaceutical,

INTRODUCTION:

Infectious diseases are caused by many uncontrolled muted viruses
First of all, Millions of lives have been lost as a result of the sudden increase in infectious viral illness outbreaks in recent years. In spite of numerous established vaccinations and treatments for prevention and treatment, viruses continue to change and resurface as a threat to social cohesion, public health, and economic stability. One of the most prevalent and significant heterocycles in nature is the indole ring system One of the most prevalent and significant heterocycles in nature is the indole ring system. found in a remarkably wide range of physiologically relevant natural substances, ranging from complex alkaloids to simple derivatives like the neurotransmitter serotonin. Indoles are ubiquitous in biological chemistry and can be found in a wide range of physiologically significant natural compounds, from simple derivatives like the neurotransmitter serotonin to complex alkaloids like the antihypertensive alkaloid reserpine and the clinically used anticancer agents' vinblastine and mitomycin C. Moreover, an indole motif is present in some significant synthetic medications, such as sumatriptan, tadalafil, rizatriptan, and fluvastatin,

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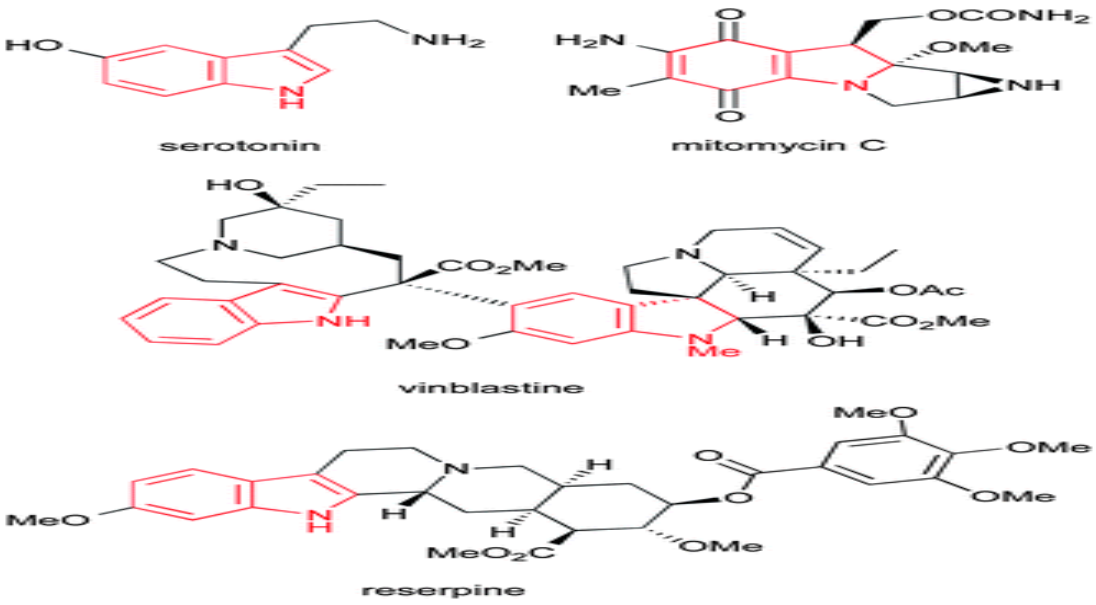

Globally, cancer has emerged as a significant public health concern due to the rising annual diagnosis rate. Unfortunately, poor selectivity, harsh side effects, and drug resistance make chemotherapy less effective when used as the main cancer treatment. Thus, it has recently been suggested that immunotherapy and newly integrated, multi-targeted medicines be used. Drug resistance, invasiveness, and cancer cell survival have all been related to kinase activity in different cell signalling pathways. Because of this, anticancer medications that target serine/threonine kinases like BRAF and kinases like the epidermal growth factor receptor (EGFR) are becoming more and more well-liked. Consequently, kinase-targeting anticancer medications are becoming more and more common. Examples of these include the epidermal growth factor receptor (EGFR) and serine/threonine kinases like BRAF. Roughly 70% of melanoma, 100% of hairy cell leukemia, and 41% of hepatocellular carcinoma have RAF mutations. In the meantime, lung, breast, and epithelial malignancies have been shown to harbour EGFR mutations including T790M and C797S, which are significant therapeutic targets. Since many types of cancer have over-activated mutant RAF/EGFR pathways, these pathways are important targets for the development of anti-cancer drugs. Conversely, the indole skeleton, which may be found in a variety of natural products and active ingredients, is one of the most well-known structures with strong anticancer activity. Many indole compounds have been found to be potent anticancer drugs thus far, and some have even been put to use in clinical settings. Several indole-based compounds with tyrosine kinase inhibitory action have been discovered in the literature research. These compounds have been shown to exhibit potential EGFR inhibitory activity and potent anticancer activity against four cancer cell lines. Additionally showing encouraging EGFR inhibitory action. It has been determined that Compound II is a dual EGFRT790M/c-MET inhibitor that can be used to target NSCLC that is resistant. Compound II's IC50 values for EGFRT790M, EGFRL858R, and c-MET were 0.094, 0.099, and 0.597 µM, respectively. An EGFR TKI with a 200-fold selectivity index toward the EGFR T790M/L858R protein over wild-type EGFR is osimertinib, an indole-based medication. An EGFR TKI with a 200-fold selectivity index toward the EGFR T790M/L858R protein over wild-type EGFR is osimertinib, an indole-based medication. The FDA authorized osimertinib in 2015 for the treatment of NSCLC with EGFR T790M positivity. As EGFR-TK antiproliferative drugs, we recently reported on the

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discovery of a novel class of 5-chloro-3-hydroxymethyl-indole-2-carboxamides. With an IC50 value of 0.12µM, compound (R= 4-morpholin-4-yl) was the most effective EGFR inhibitor. with an IC_{50} value of 0.12µM.

A series of pyrazino[1,2-*a*] indol-1(2*H*)-ones has been reported as antiproliferative agents targeting EGFR and $BRAF^{V600E}$. Compound inhibits both EGFR and $BRAF^{V600E}$ with IC_{50} values of 1.7 µM and 0.1 µM, respectively. Following this, a series of structural modifications to our lead compound **V** to design and synthesize a new series of pyrazino[1,2-*a*] indol-1(2*H*)-ones. Compound was the most effective derivative, with a GI_{50} value of 1.107 µM against four cancer cell lines. inhibited EGFR with an IC_{50} of 0.08 µM but only moderately inhibited $BRAF^{V600E}$ with an IC_{50} of 0.15 µM. In another study, we describe our efforts to synthesize and optimize a novel class of potent antiproliferative agents . The antiproliferative activity of the target compounds is impressive. These compounds have a dual inhibitory effect on EGFR and $BRAF^{V600E}$, with IC_{50} values of 32 nM and 45 nM, respectively.

Motivated by the data presented above, and as part of our ongoing efforts to identify promising lead compounds for dual or multi-targeted anticancer agents, we present herein the design and synthesis of a novel class of indole-2-carboxylates, as well as 1,2-dihydropyrrolo[3,4-*b*] indol-3(4*H*)-ones, compounds, as dual EGFR/$BRAF^{V600E}$ inhibitors with antiproliferative activity. The new compounds will be evaluated for their safety profile by assessing their effect on the viability of human normal cell lines, while their antiproliferative activity will be evaluated against a panel of four cancer cell lines. The most potent compounds will be evaluated for their ability to inhibit wild-type EGFR ($EGFR^{WT}$) and $BRAF^{V600E}$ as a potential mechanistic target for their antiproliferative effects. Furthermore, the most potent EGFR inhibitors will be tested for their inhibitory effect against mutant-type EGFR ($EGFR^{T790M}$), and the most potent anti-BRAF agents will be tested for their anticancer effect against the LOX-IMVI melanoma cell line, which has $BRAF^{V600E}$ kinase overexpression. Finally, docking studies will be performed to investigate these compounds' binding interactions within the active sites of target enzymes.

The synthesis of target compounds **3a–e**, **4a–c**, and **5a–c** is depicted in **Scheme 1**. 5-chloro-3-formyl indole-2-carboxylate **1** [] was reacted with amines **2a–e** [] through reflux in ethanol followed by reduction of the intermediate imine with $NaBH_4$ under reductive-amination conditions to yield secondary amines **3a–e** which subjected to saponification with Li OH to afford a carboxylic acids **4a–c**. The structures of compounds **3a–e** and **4a–c** were confirmed using ^1H NMR, ^{13}C NMR, and HRESI-MS spectroscopy (Varian Inova, University of Aberdeen, Meston Building, Aberdeen AB24 3UE, UK). ^1H NMR spectrum of compound **3c** revealed the presence of a singlet signal δ 9.12 ppm of indole NH, the characteristic signals of ethyl group in the form of quartet at δ 4.33 ppm (2H) and triplet at δ 1.35 ppm (3H), a singlet signal at δ 4.18 ppm (2H) of CH_2NH- group, and two triplets (each of 2H) at δ 2.88 and 2.74 ppm of $NHCH_2CH_2$ group. Moreover, the spectrum revealed the presence of the characteristic signals of both piperidine and aromatic protons. HRESI-MS *m/z* of **3c** clad for $[M + H]^+$ $C_{25}H_{31}ClN_3O_2$: 440.2099, found: 440.2100. The disappearance of the characteristic signals of the ethyl group in the form quartet at δ 4.33 ppm (2H) and triplet at δ 1.35 ppm (3H) and the appearance of a singlet signal at δ 3.43 ppm (2H) corresponding to COOH and $NHCH_2$ characterize the ^1H NMR spectrum of **4c**.

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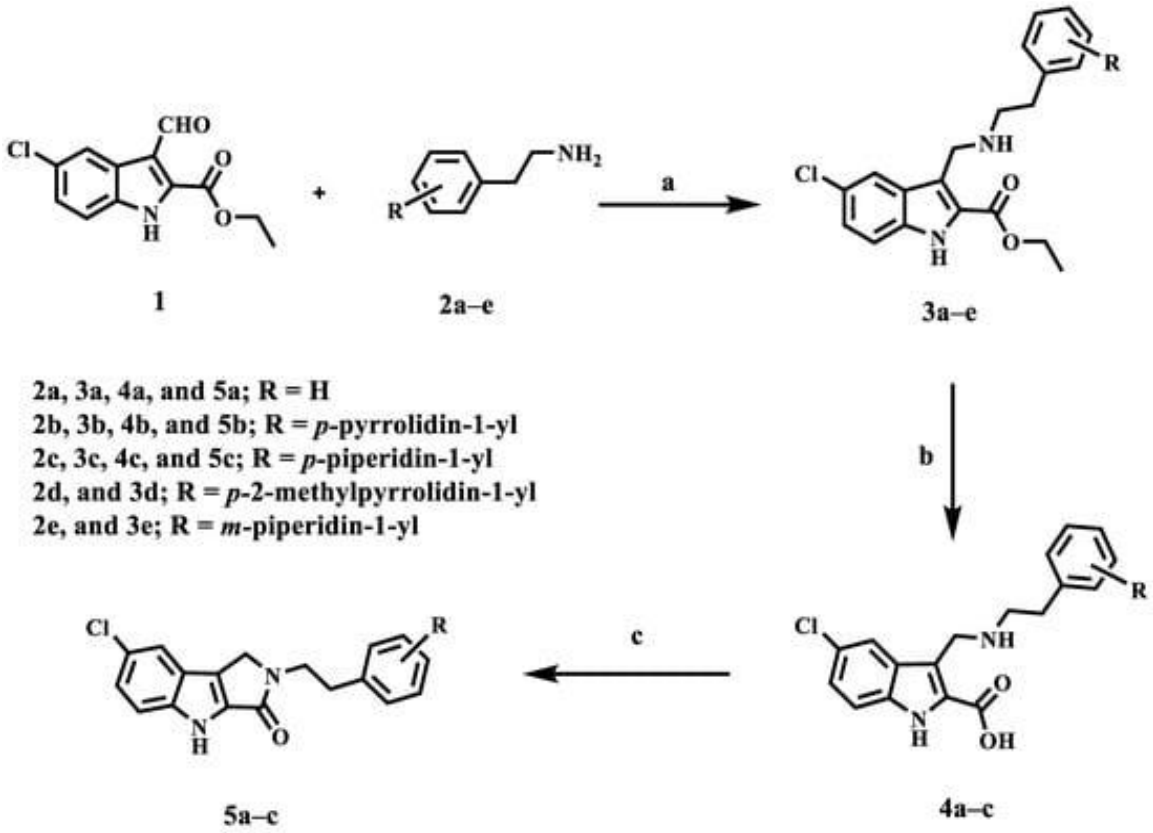

Scheme 1. Synthesis of compounds **3a–e**, **4a–c**, and **5a–c**. *Reagents and conditions:* (**a**) $NaBH_4$, EtOH, reflux, 12 h to rt, 1 h, 78%; (**b**) LiOH, THF/ H_2O, 40 °C, 90%; (**c**) BOP, DIPEA, DMF, rt, overnight, 70%.

Conclusion: Using a variety of spectroscopic techniques, a new series of 5-chloro-indole-2-carboxylate and pyrrole [3,4-b] indol-3-one was produced and structurally described. The novel compounds exhibited strong antiproliferative properties against four human cancer cell lines, however they showed no cytotoxic effects on human normal cell lines. It was discovered that a few of the substances examined were dual inhibitors of BRAFV600E and EGFR, both of the wild type and mutant types. Using vemurafenib as a reference, molecular docking was used to look into the binding manner of the most potent antiproliferative drugs (3a–e) within the BRAFV600E binding site. The results showed that compound 3e fit more snugly within the active site than the other derivatives with para-amine substituents because it had an m-piperidinyl substitution at the phenethyl amine moiety.

Using vemurafenib as a reference, molecular docking was used to look into the binding manner of the most potent antiproliferative drugs (3a–e) within the BRAFV600E binding site. The findings demonstrated that compound 3e, which substitutes m-piperidinyl at the phenethyl amine moiety, suited the data more closely. Additionally, compounds 3b and 3e's docking experiments against EGFRT790M indicate that the ligand indole-2-carboxylate scaffold binds well, generating a combination of hydrophobic and H-bond interactions at the active site's hydrophobic pocket. Compounds 3a–e show strong pharmacokinetic and ADME properties, according to in silico ADME and pharmacokinetic prediction. After structural alterations, compounds 3b and 3e may function as anticancer drugs targeting

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the EGFRT790M and BRAFV600E pathways; however, additional in vitro and in vivo testing is required. Using vemurafenib as a reference, molecular docking was used to look into the binding manner of the most potent antiproliferative drugs (3a–e) within the BRAFV600E binding site. The findings demonstrated that compound 3e, which substitutes m-piperidinyl at the phenethyl amine moiety, suited the data more closely. Additionally, compounds 3b and 3e's docking experiments against EGFRT790M indicate that the ligand indole-2-carboxylate scaffold binds well, generating a combination of hydrophobic and H-bond interactions at the active site's hydrophobic pocket. Compounds 3a–e show strong pharmacokinetic and ADME properties, according to in silico ADME and pharmacokinetic prediction. After structural alterations, compounds 3b and 3e may function as anticancer drugs targeting the EGFRT790M and BRAFV600E pathways; however, additional in vitro and in vivo testing is required.

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