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ORIGINAL ARTICLE

Synthesis and characterization of novel imidazoquinoline based 2-azetidinones as potent antimicrobial and anticancer agents

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Abstract A new series of *N*-substituted azetidinones **(9a–h)** synthesized by condensation of 4-arylidene hydrazino 1-isobutyl-1*H*-imidazo[4,5-*c*]quinolines **(8a–h)** with chloroacetyl chloride afforded 4-arylazetidin-2-ones **(9a–h)**. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses. All synthesized compounds were screened for their *in vitro* antimicrobial and anticancer activities. The hydrazone derivatives **(8a–h)** showed good antibacterial activity. Compounds **9a** and **9b** exhibited good anticancer activity. In a molecular docking study compounds **9a** and **9b** showed minimum binding energy and good affinity towards the active pocket. Thus, are believed to be good inhibitors of β-tubulin.

1. Introduction

The recent literature is enriched with findings about pharmacological activities of imidazoquinolines [1]. The synthesis of imidazoquinoline had been of increasing interest, since many of their derivatives exhibited useful applications such as antimalarial [2], anticonvulsant and antitumor agents [3]. Drugs with an imidazoquinoline motif include Imiquimod and Resiquimod (Fig. 1).

2-Azetidinones are an important class of heterocyclic compounds with potent antibacterial activity. Modification of the

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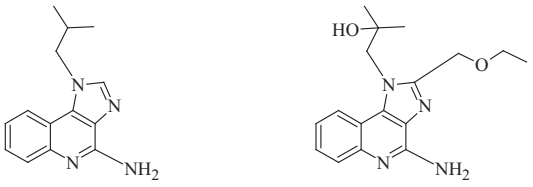

Figure 1 Structure of Imiquimod and Resiquimod.

β-lactam ring leads to compounds with diverse pharmacological activities, inducing cholesterol absorption inhibition, human tryptase, thrombin and chymase inhibition, vasopressin V1a antagonist activity, and antimicrobial, anticonvulsant and anti-inflammatory activities [4–8]. The drugs with 2-azetidinone scaffold are penicillins, cephalosporins, carbapenems, nocardicins, monobactams, clavulanic acid, sulbactams and tazobactams. These drugs had been used widely as chemotherapeutic agents to treat various microbial diseases [9–16].

Most studies outlaying are focused on the synthesis and pharmacological evaluations of imidazoquinoline and tetraimidazoquinoline compounds containing urea, thiourea, acylurea, sulphonylurea, amide, sulphonamide, oxime or *N*-oxide moieties at the 1-position [17–21].

Keeping in view of this and in continuation of our search for biologically potent molecules [22] we have synthesized a series of 3-chloro-4-arylsubstituted-1-[(1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-yl)amino]azetidin-2-ones **(9a–h)** by derivatization of imidazoquinoline at the 4-position and assessed their antimicrobial and anticancer activities.

Some of the anticancer drugs showed activity by binding selectively to β-tubulin, a protein subunit of microtubule and thereby disrupting the microtubule structure and function. Microtubules are highly dynamic, ubiquitous cellular organelles serving a variety of vital functions including mitosis, motility and transport in all eukaryotes. Many of these structures exist in a dynamic equilibrium in which assembly and disassembly of the soluble subunits are balanced. In such systems, the drug–βtubulin interaction results in a net loss of microtubules and accumulation of free tubulin. In view of the crucial roles, that microtubules play in many cellular processes, their drug-induced destruction eventually leads to the death of the organism [23]. Molecular docking technique plays an important role in discovering new drug molecules and predicting the conformations of drug molecule at the active site, hence in the present study, molecular docking studies of newly synthesized compounds were carried out to predict the β-tubulin inhibitory activity and results are reported.

2. Results and discussion

The synthesis of target compounds **9a–h** is outlined in (Scheme 1). Compound (4-chloro-1-isobutyl-1*H*-imidazo[4,5-c] quinoline **(6)** was synthesized from 2,4 dihydroxyquinoline **(1)** according to a previously reported procedure [24]. The compound 4-hydrazino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline **(7)** was prepared by the reaction of hydrazine hydrate with 4-chloro-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline **(6)**. The structure of 4-hydrazino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline **(7)** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses. The ^{1}H NMR spectrum of **7** showed singlet for NH at δ 7.14 ppm and a broad peak for NH_2 at δ 4.76 ppm. The IR spectrum of **7** showed absorption due to NH_2 at 3388, 3394 cm^{-1} and absence of the peak due to C–Cl at 877.7 cm^{-1} confirming the structure of **7**. The structure of compound **7** was also confirmed by a single crystal X-ray study [25].

The treatment of **7** with various substituted aromatic aldehydes in ethanol afforded hydrazones namely; 4-(substituted arylidenyliminoamino)1-isobutyl-1*H*-imidazo[4,5-*c*]quinolines **(8a–h)**. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data confirmed the structures of **8a–h**. The ^{1}H NMR spectrum of **8a** was characterized by the presence of CH═N protons, which appeared as a singlet at δ 9.67 ppm. The IR spectrum of **8a** showed common characteristic absorption peaks at 3371 cm^{-1} (NH) and 1590 cm^{-1} (C═N). The ^{13}C spectrum of **8a** was characterized by the presence of CH═N carbon at δ 152.40 ppm.

Compounds **(8a–h)** in DMF containing triethylamine were reacted with chloroacetyl chloride to afford corresponding 3-chloro-4-arylsubstituted-1-[(1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-yl)amino]azetidin-2-ones **(9a–h)**. The ^{1}H NMR spectrum of **9a** was characterized by the absence of CH═N protons at δ 9.67 ppm. The IR spectrum of **9a** showed common characteristic absorption peaks at 1765 cm^{-1} (C═O) and 762 (C–Cl). The absence of peaks due to (C═N) confirmed the cyclization of **8a** and formation of **9a**. The reaction of hydrazones with chloroacetyl chloride as per many earlier literature reports was carried out in dioxane [26]. In contrast to this, we have carried out the reaction in DMF [27]. A comparison of the effect of solvent and reaction time on yield of **9a–h** was satisfactory Table 1. The reaction proceeded in a faster rate compared with the earlier reported procedure, yield was satisfactory, and isolation was easier. Thus, makes the modified synthetic procedure of great synthetic utility.

The spectral values for all the compounds and elemental analyses are given in Section 5. The spectral studies and elemental analyses of hydrazone and azetidinone derivatives were in accordance with the proposed structure.

3. Biological screening

3.1. Antibacterial activity

The *in vitro* antibacterial activity of newly synthesized compounds **7**, **8a–h** and **9a–h** was determined by the cup plate method (diffusion technique) [28]. In this work, *Staphylococcus aureus* (Gram +ve), *Escherichia coli* (Gram −ve), *Streptococcus faecalis,* (Gram +ve) and *Klebsiella pneumoniae* (Gram −ve) were used to investigate the activity. The Procaine penicillin was used against *S. aureus, S. faecalis* and the Streptomycin was used against *E. coli*, *K. pneumoniae* as the standard drugs. The standard drugs and synthesized compounds were dissolved in a minimum quantity of DMF at concentrations of 1 and 0.5 mg/ml.

The antibacterial screening of compounds **8a–h** revealed that substituents have a significant role in the activity. Among the synthesized compounds **7**, **8a**, **8b**, **8c**, **8f**, **8g** and **8h** showed excellent activity against gram positive and gram negative strains. The activity of these compounds may be due to the mono, di-substituted electron-donating and withdrawing groups attached to a phenyl ring linked to azomethine. The derivatives containing a tri-substituted group attached to the