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Synthesis of Novel Quinoline Derivatives

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ABSTRACT

The thrust in the synthesis of various quinolone derivatives is increasing due to the potential biological profiles exhibited by these molecules. So synthesis of quinoline derivatives by reacting mesylated 2-(3-(hydroxymethyl)quinolin-2-yl)phenol with substituted aromatic amines and anilines is planned successfully with good yield. All the compounds synthesized were well characterized by spectral (NMR and MS) and analytical data.

Keywords: Quinoline, 2-(3-(hydroxymethyl) quinolin-2-yl) phenol, Aromatic amines.

INTRODUCTION

Quinoline derivatives are known to have wide applications as drugs and pharmaceuticals [1]. A combination of chromen or benzopyran with a quinoline moiety in a single molecule e.g. 6*H*-chromeno[4,3-*b*]quinoline[2] or 1-benzopyrano[3,4-*f*]quinoline[3] have also been explored for the identification of promising bioactive molecules. In view of known cytotoxicities of coumarins and chromeno [4,3-*b*]quinoline derivatives[4] we hypothesized that design of small molecules based on the literature the corresponding quinoline derivatives might show anticancer properties[5].

The synthesis of quinoline derivatives thus continues to be an attractive area of research [6] and the synthesis of various substituted quinolines has been largely described in the

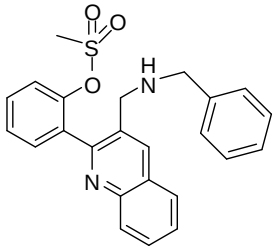
literature through different strategies [7,8]. The development of general methods for the synthesis and biological evaluation of new agents, retaining the 'core' quinoline moiety has been the subject of considerable synthetic effort. An essential component of the search for new leads in the drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functional scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules [9]. Herein we report synthesis of quinoline derivatives.

MATERIALS AND METHODS

Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H NMR was determined in $CDCl_3$ or DMSO-d_6 solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. MS spectra were obtained on a mass spectrometer. All chemicals and reagents were purchased from commercial sources and purified before use.

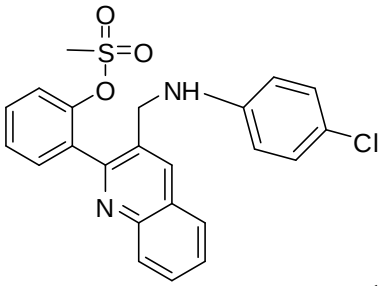
Procedure for the Synthesis of quinoline derivatives: To a suspension of 2-(3-(hydroxymethyl) quinolin-2-yl) phenol (**1**) (0.0512g, 0.203 mmol) in CH_2Cl_2 (10mL) triethyl amine (0.04mL, 0.3mmol) and methanesulfonyl chloride (0.04mL, 0.47mmol) were added at 0^{o}C. The reaction mixture was stirred for 4 hours at room temperature. Progress of reaction was monitored by TLC, on completion of reaction, quenched the reaction mixture with water and extracted with CH_2Cl_2 .The organic layer was washed with water, followed by saturated sodium carbonate solution and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum to yield the crude product. The above crude compound (**2**) was dissolved in CH_2Cl_2 (5 ml), cooled to 0^{o}C followed by addition of triethyl amine (0.09 ml, 0.7 mmol), corresponding aromatic amine or aniline (0.19 mmol) maintaining the temperature of reaction mixture at 0^{o}C during addition. The reaction mixture was stirred at room temperature for overnight followed by heating the reaction mixture at 60^{o}C for 1 h. The crude product was purified by column chromatography using 20% EtOAc in hexane as eluent, to yield the corresponding quinolone derivative.

2-(3-((benzyl amino) methyl) quinolin-2-yl) phenyl methanesulfonate (3a)



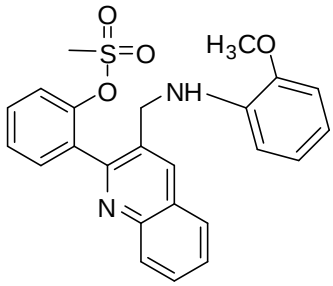
Yellow liquid; yield: 50%; R_f (30% ethyl acetate/ n-hexane) 0.61; ^{1}H NMR (400 MHz, $CDCl_3$): 2.6 (s, 3H), 3.65 (d, 2H), 3.83 (d, 2H), 7.22-7.42 (m, 5H), 7.55-7.62 (m, 5H),7.72 (t, 1H) , 7.90 (d, 1H), 8.15 (d, 1H), 8.50(s, 1H); EI-MS: m/z 419.1 $(M+H)^+$.

2-(3-((4-chlorophenylamino) methyl) quinolin-2-yl) phenyl methanesulfonate (3b)



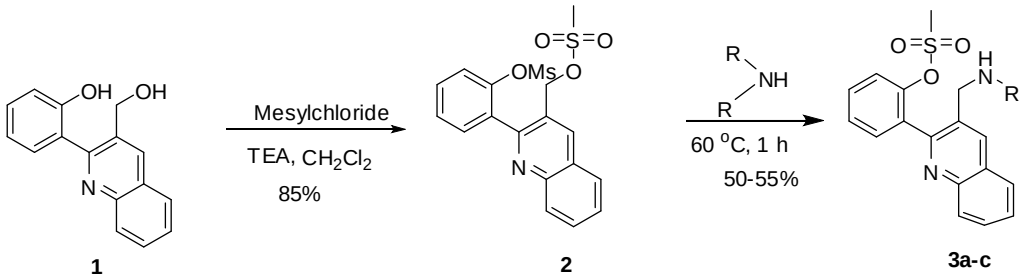
Red liquid; yield: 55%; R_f (30% ethylacetate/ n-hexane) 0.65; ^{1}H NMR (400 MHz, $CDCl_3$): 2.64 (s, 3H), 4.32-4.45 (m, 3H), 6.45 (d, 2H), 7.05 (d, 2H), 7.48-7.54 (m, 5H),7.70 (t, 1H), 7.80 (d, 1H), 8.10 (d, 1H), 8.20 (s, 1H); EI-MS: m/z 439 $(M+H)^+$.

2-(3-((2-methoxyphenylamino) methyl) quinolin-2-yl) phenyl methanesulfonate (3c)



Yellow liquid; yield: 52%; R_f (30% ethylacetate/ n-hexane) 0.63; ^{1}H NMR (400 MHz, $CDCl_3$): 2.1 (s, 2H), 2.64 (s, 3H), 3.84 (s, 3H), 6.2 (d, 1H), 6.50 (t, 1H), 6.62-6.68 (m, 2H), 7.50-7.54 (m, 1H), 7.60-7.65 (m, 4H), 7.70 (t, 1H), 7.90 (d, 1H), 8.10 (d, 1H), 8.20 (s, 1H); EI-MS: m/z 435.1 $(M+H)^+$.

RESULTS AND DISCUSSION



Scheme 1 Synthesis of 2-(3-(hydroxymethyl)quinolin-2-yl)phenol derivatives

The 2-(3-(hydroxymethyl) quinolin-2-yl) phenol compound (**1**) react with mesylchloride to form mesyl protected compound (**2**). In sue to this compound react with aromatic amines or anilines under heating conditions to form desired products (**3a-c**) in good yields. The obtained compounds (**3a-c**) were characterized by their NMR and mass spectral data.

APPLICATIONS

This work leads to the drug designing program in the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features

CONCLUSION

In conclusion synthesis of quinoline derivatives, which can diversity oriented for the creation of library of these molecules.

ACKNOWLEDGMENTS

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