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Research Article

SYNTHESIS AND ANTI-CANCER PROPERTIES OF NOVEL QUINAZOLINE DERIVATIVES

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ABSTRACT

Quinazoline and their fused-ring systems are well known for their potential biological activity. In the present study a new quinazoline derivatives were synthesized. The newly synthesized compounds were characterized by IR, NMR analyses. All newly synthesized compounds were screened for their anticancer studies. The results revealed that some of the synthesized compounds have a significant biological activity as anticancer agents.

Keywords: Quinazolinederivatives, Anti-Cancer agents.

INTRODUCTION

During the ancient era the isolation of various compounds was done by the process of extraction. But this process was time consuming as well as laborious. Moreover the yield was very low and the process of isolation required large amount of the starting material. Today the process of isolation has been replaced by the synthetic routes. A large number of compounds can be synthesized by using small amount of chemicals. More over the Synthetic routes take less amounts of time and can easily be carried out. Quinazoline derivatives hold a place of significant in todays world for their important application in chemical, clinical and biological spheres. Medicinally quinazoline has been used in various areas especially as an analgesic[1,2], anti-oxidant[3-5], anti-cancer drugs[6-10], anti-inflammatory[11,12], anti-convulsant[13], anti-bacterial[14], anti-fungal[15] and anti-mycobacterial agents[16, 17]. It has also been found in the treatment of malaria[18, 19]. Considering the vast potential of quinazoline, it was thought appropriate to synthesized, characterized quinazoline analogues and investigates their biological activity. In this investigation, we have prepared quinazolinederivatives and characterized them using spectral data. Biological screenings of these compounds were also reported here.

MATERIALS AND METHODS

Experimental Instrumentation

All melting points are uncorrected and measured by use of an electrothermal capillary melting point apparatus. Infrared spectra were acquired with a Jasco FT/ IR-6100using **KBr**discs. **^{1}H NMR** spectra were acquired with Jeol 270 **MHz** andjeolsx 500 **MHz** spectrometers, using **TMS** as internal standard. Mass spectra were acquired with a Jeol**JMS-AX** 500. All reactions were followed and checked by **TLC** (aluminum-backed plates) with chloroform-methanol (9:1 V/V) as mobile phase. For detection the plates were sprayed with iodine.

Synthesis

5-Chloro-2-(isonicotinamido)benzoic acid (1)

A mixture of 5-chloroanthranilic acid (0.01 mol) and isonicotinyl chloride (0.27 g, 0.001 mol) in dry pyridine (30 mL) was stirred at room temperature for 12h. The reaction mixture was poured onto ice/water then, acidified with diluted HCl, the formed precipitated solid was then filtered off and recrystallized from acetic acid to give **1**.

Crystallized from acetic acid, yellow crystal, m.p. 205-209 ˚C**,** yield 82 %. Analysis: for $C_{13}H_9ClN_2O_3$,M.Wt. 276.5, calcd: C, 48.62; H, 2.82; N, 8.72. Found: C, 48.60; H, 2.83; N,

8.73. IR (KBr, cm^{-1}): 3310-3558 (OH), 3243 (NH), 1680 (C=O of COOH), 1652 (C=O of CONH), 1612 (C=N).
^{1}H NMR (DMSO- d_6,δ ppm): 6.57-7.96 (7H, m, $H_{aromatic}$), 8.63 (1H, s, NH exchangeable with D_2O) , 11.32 (1H, s, OH exchangeable with D_2O).$[M]^+$ m/z =276(58.16%) and $[M+2]^+$m/z =278(60%).

6-Chloro-2-(pyridin-4-yl)-4H-benzo[d][1,3]oxazin-4-one (2)
A mixture of compound **1** (0.27 g, 0.001 mol) and acetic anhydride (5 mL) was heated together upon fusion at 150 ^oC on sand bath for 2h. After cooling, the crude mass was recrystallized from ethanol to give dark brown crystals ofcompound **2**.
Crystallized from ethanol, dark brown, m.p. 195-197˚C, yield 82%. Analysis: forC_{13} H_7 ClN_2O_2 ,M.Wt. 258.5, calcd: C, 51.51; H, 2.33; N, 9.24. Found: C, 51.49; H, 2.31; N, 9.22. IR (KBr, cm^{-1}): 3035 (CH-aromatic), 1675 (C=O), 1626 (C=N).^{1}HNMR (DMSO- d_6, δ ppm): 7.72-8.53 (7H, m, $H_{aromatic}$).MS: **(***m/z*) 258(23.83%) and $[M+2]^+$*m/z* 260(29.99%).

6-Chloro-2-(pyridin-4-yl)quinazolin-4(3H)-one (3)
Procedure A
A mixture compound **1** (2.7 g, 0.01 mol), ammonium acetate (0.77 g, 0.01 mol), ammonium hydroxide (2 mL) and 10% sodium hydroxide (5 mL) in pyridine (15 mL), was heated under reflux for 2h. then left to cool. The reaction mixture was then titurated with cold water (50 mL) and neutralized with 1N HCl (5 mL) the resulting precipitated solid was collected by filtration, washed with water, dried and recrystallized from ethanol to givecompound **3**

Procedure B
A mixture of compound **2** (2.58 g, 0.01 mol) and ammonium acetate (0.01 mol) in ethanol (50 mL), was refluxed for 5h. the mixture then cooled and the separated solid was filtered off and recrystallized to give compound**3**, m.p. and mixed m.p. determined with authentic sample gave no depression.
Crystallized from ethanol , yellow crystal, m.p. 185-187˚C, yield 78%. Analysis: for C13H8ClN3O, M.Wt. 257.5, calcd: C, 51.68; H, 2.67; N, 13.91. Found: C, 51.66; H, 2.65; N, 13.89. IR (KBr, cm^{-1}): 3421 (NH), 3074 (CH aromatic), 1751 (C=O), 1595 (C=N).^{1}H NMR (DMSO- d6**,** δ ppm): 6.90-7.90 (7H, m, H-$_{aromatic}$), 9.0 (1H, s, NH, exchangeable with D2O).MS: [M]+m/z 257(38.86%) and[M+2]+m/z 259.

6-chloro-4-chloro-2-(pyridin-4-yl)quinazoline (4)
A mixture of compound **3** (2.5 g, 0.01 mol) and phosphorus pentachloride (0.015 mol) in phosphorus oxychloride (20 mL) was heated on a water bath for 8 h. and the reaction mixture poured gradually onto crashed ice. The separated solid was filtered off, dried then recrystallized from acetic acid to give compound**4**.
Crystallized from acetic acid, yellow crystal, m.p. 130-135˚C, yield 82 %. Analysis: for C_{13} H_7 Cl_2N_3 ,M.Wt. 276, calcd: C,48.71; H, 2.20; N, 13.11. Found: C, 48.69; H, 2.18; N, 13.09. IR (KBr, cm^{-1}): 3020 (CH aromatic), 1620 (C=N). ^{1}H NMR (DMSO- d_6, δ ppm): 6.70-8.20 (7H, m, $H_{aromatic}$).MS: **(***m/z*) $[M+1]^+$m/z276(12.14%).

1-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)ethanone (5)
A mixture of compound **4** (2.75 g, 0.01 mol) and *p*-aminoacetophenone (0.01 mol) in pyridine (30 mL) was refluxed for 6h. and the reaction mixture poured gradually on water and then neutralized till acidification. The precipitate was filtered off, dried and recrystallized.
Crystallized from methanol, yellow crystal, m.p. 120-123˚C, yield 65 %. Analysis for$C_{21}H_{15}ClN_4O$, M.Wt. 374.5, calcd: C, 60.16; H, 3.61; N, 13.36. Found: C, 60.10; H, 3.56; N, 13.40. IR (KBr, cm^{-1}): 3421 (NH), 3099 (CH aromatic), 2937 (CH aliphatic), 1772 (C=O), 1612 (C=N). ^{1}H NMR (DMSO- d_6, δ ppm): 2.10 (3H, s,CH_3), 6.20 (1H, s, NH exchangeable with D_2O) 7.51-8.90 (11H, m, $H_{aromatic}$),.
MS$[M]^+$m/z374(30.30%) and$[M+2]^+$m/z =376.

General procedure for preparation of compounds (6a-d, 7a-d)
A mixture of compound **5** (1.12 g, 0.003 mol) and the appropriate aromatic aldehydes, namely, benzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde and/or 4-nitrobenzaldehyde (0.003mol), malononitrile and / or ethylcyanoacetate (0.021 mol) and excess ammonium acetate in n-butanol (50 ml) was refluxed for 10 hrs. The reaction mixture was concentrated till its half volume, then cooled and left overnight. The precipitate was filtered off, dried under vacuum then recrystallized from DMF / water.

2-amino-6-(4-(6-chloro-2-(pyridine-4-yl)quinazoline-4-ylamino)phenyl)-4-phenyl nicotinonitrile (6a)
Crystallized from Di methyl formamide, white crystals, m.p. 162-164˚C, yield 57%. Analysis for $C_{31}H_{20}ClN_7$, M.Wt 525.5, calcd: C, 65.27;

H, 3.53; N, 17.19. Found: C, 65.25; H, 3.51; N, 17.17. IR (KBr, cm^{-1}): 3366, 3205 (NH_2,NH),3037 (CH-aromatic), 2191 (C≡N), 1615 (C=N). ^{1}H NMR (DMSO- d_6, δ ppm): 5.12,9.14 (3H,2s, NH, NH_2exchangeable with D_2O).7.27-8.08 (17H, m, $H_{aromatic}$).
MS: **(***m/z*) $[M]^+$m/z525(95.15%) and $[M+2]^+$m/z 527(68.93%).

6-[(4-(B-chloro-2-(pyridine-4-yl)quinazoline-4-ylamino)phenyl)-2-amino-4-(4-methoxy-phenyl)]-pyridine-3-carbonitrile (6b)
Crystallized from Di methyl formamide, yellow crystal, m.p. 99-102˚C, yield 55%.Analysis for $C_{32}H_{22}ClN_7O$, M.Wt. 555.5, calcd: C, 64.01; H, 3.69; N, 16.33.Found: C, 63.98; H, 3.66; N, 16.31. IR (KBr, cm^{-1}):3365,3204 (NH_2,NH), 3100 (CH aromatic), 2991 (CH aliphatic), 2191 (C≡N), 1660 (C=O), 1619 (C=N).
^{1}H NMR (DMSO- d_6, δ ppm): 3.79 (3H, s, OCH_3),6.90-8.20 (16H, m, $H_{aromatic}$) ,6.17,9.18 (3H,2s, NH, NH_2 exchangeable with D_2O).
MS: **(***m/z*) $[M]^+$m/z **=**555(88.24%) and $[M+2]^+$m/z =557(48%).

2-amino-6-(4-(6-chloro-2-(pyridine-4-yl)quinazoline-4-ylamino)phenyl)-4-(4-chlorophenyl)]-nicotinonitrile (6c)
Crystallized from Di methyl formamide, white crystal.m.p. 130-131˚C, yield 80%. Analysis for $C31H19Cl_2N7$,M.Wt. 560, calcd: C, 61.55; H, 3.17; N, 16.21. Found: C, 61.60; H, 3.05; N, 16.08. IR (KBr, cm^{-1}): 3364,3203 (NH2,NH), 3022 (CH aromatic) 2191 (C≡N) , 1612 (C=N).^{1}H NMR (DMSO- d6,δ ppm): 7.70- 8.50 (16H , m , $H_{aromatic}$)10.10-11.20 (3H,2s, NH, NH2 exchangeable with D2O), MS: [M]+ m/z560(23.50) and [M+2]+m/z 562(22%).

2-amino-6-(4-(6-chloro-2-(pyridine-4-yl)quinazoline-4-ylamino)phenyl)-4-(4-nitrophenyl)]-nicotinonitrile (6d)
Crystallized from Di methyl formamide, dark crystal, m.p. 200-203˚C, yield 67%. Analysis for $C_{31}H_{19}ClN_8O_2$, M.Wt. 570.5, calcd: C, 60.50; H, 3.11; N, 18.21. Found: C, 60.48; H, 3.09; N, 18.19. IR (KBr, cm^{-1}): 3364,3203 (NH_2,NH), 3022 (CH aromatic) 2191 (C≡N) , 1623 (C=N).
^{1}H NMR (DMSO- d_6,δ ppm): 7.67- 8.50 (16H , m , $H_{aromatic}$),6.12-9.14 (3H,2s, NH, NH_2 exchangeable with D_2O), .
MS: **(***m/z*) $[M]^+$m/z570(77.78%) and $[M+2]^+$m/z 572.

6-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (7a)
Crystallized from methanol, white crystal, m.p. 290-293˚C, yield 68%. Analysis for $C_{31}H_{19}ClN_6O$,M.Wt. 526.5, calcd: C, 65.16; H, 3.35; N, 14.71. Found: C, 65.14; H, 3.33; N, 14.69. IR (KBr, cm^{-1}): 3421,3365 (2NH), 3026 (CH aromatic), 2221 (C≡N), 1654 (C=O), 1628 (C=N).
^{1}H NMR (DMSO- d_6,δ ppm): 5.03-9.77(2H, 2s, 2NHexchangeable with D_2O) , 6.82-8.05(17H, m, $H_{aromatic}$ and CH of pyridine ring).
MS: **(***m/z*) $[M]^+$m/z526(66.13%) and $[M+2]^+$m/z 528.

6-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7b)
Crystallized from ethanol.Yellow crystal, m.p. >300˚C, yield 68%. Analysis for $C_{32}H_{21}ClN_6O_2$, M.Wt. 556.5, calcd: C, 63.90; H, 3.52; N, 13.97. Found: C, 63.43; H, 3.50; N, 13.95. IR (KBr, cm^{-1}): 3212,3198 (2NH), 3010 (CH-aromatic), 2207 (C≡N), 1711 (C=O), 1623 (C=N).
^{1}H NMR (DMSO- d_6, δ ppm):3.76 (3H, s, OCH_3), 6.82-8.05(16H, m, $H_{aromatic}$ and CH of pyridine ring), 5.63-9.77(2H, 2s, 2NHexchangeable with D_2O).
MS: **(***m/z*) $[M]^+$m/z556(10.0%) and $[M+2]^+$m/z 558(0.48%).

6-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7c)
Crystallized from Dioxane, white crystal, m.p. > 300˚C, yield 76%. Analysis for $C_{31}H_{18}Cl_2N_6O$, M.Wt. 561, calcd: C, 61.45; H, 2.99; N, 13.87.Found : C, 61.43; H, 2.97; N, 13.85. IR (KBr, cm^{-1}): 3125,3110 (2NH), 3030 (CH-aromatic), 2216 (C≡N), 1666 (C=O), 1627 (C=N).
^{1}H NMR (DMSO- d_6, δppm): 6.82-8.05(16H, m, $H_{aromatic}$ and CH of pyridine ring), 5.63-9.77(2H, 2s, 2NHexchangeable with D_2O).
MS: (*m/z*) $[M]^+$ m/z561(51.16%) and $[M+2]^+$m/z 563(50.39%).

6-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7d)
Crystallized from Acetic acid, dark crystals, m.p. 285-286˚C, yield 80%.Analysis for$C_{31}H_{18}Cl\ N_7\ O_3$,M.Wt. 571.5, calcd: C, 60.40; H, 2.94; N, 15.91. Found : C, 60.30; H, 2.86; N, 15.73. IR (KBr, cm^{-1}): 3219,3125 (2NH), 3050 (CH aromatic), 2215 (C≡N), 1680 (C=O), 1629 (C=N).
^{1}H NMR (DMSO- d_6, δppm): 6.82-8.05(16H, m, $H_{aromatic}$ and CH of pyridine ring), 5.63-9.77(2H, 2s, 2NHexchangeable with D_2O).
MS: **(***m/z*) $[M]^+$m/z571(13.31%) and $[M+2]^+$m/z 573(13.60%).

General procedure for preparation of compounds (8a-d)

A mixture of 11 (1.12 g, 0.003 mol) and (0.003mol) of the appropriate aromatic aldehyde namely benzaldehyde, 4-methoxy benzaldehyde, 4-chloro benzaldehyde and 4-nitro benzaldehyde in 10 % ethanolic sodium hydroxide solution (50 ml) was shaken at room temperature for 48 hrs, then refluxed for 1 hrs and then poured onto ice-cold water. The precipitate that appeared after neutralization with dilute HCL was filtered off and recrystallized from acetic acid to give compounds 8a-d.

2-amino-6-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-4-phenylnicotinonitrile (8a)

Crystallized from acetic acid, white crystal, m.p. 266-268˚C, yield 57%. Analysis for $C_{28}H_{19}ClN_4O$, M.Wt. 462.5, calcd: C, 66.28; H, 3.77; N, 11.04. Found: C, 66.26; H, 3.75; N, 11.02. IR (KBr, cm^{-1}): 3425 (NH), 3075 (CH aromatic), 2942(CH aliphatic), 1660(C=O) , 1595 (C=N). ^{1}H NMR (DMSO- d_6,δ ppm): 6.52-6.60 (2H, dd, HC=CH). 7.20-8.80 (16H, m,H $_{aromatic}$), 11.2 (1H, s,NH, exchangeable with D_2O).
MS: $[M]^+$m/z462(60.0%) and $[M+2]^+$m/z 464.

1-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (8b)

Crystallized from acetic acid, yellow crystal, m.p. >300˚C, yield 55 %. Analysis for $C_{29}H_{21}ClN_4O_2$, M.Wt.492.5, calcd: C, 64.81; H, 3.94; N, 10.43. Found: C, 64.72; H, 3.85; N, 10.49. IR (KBr, cm^{-1}): 3433 (NH), 3064 (CH-aromatic), 2912 (CH-aliphatic), 1673(C=O), 1613 (C=N). ^{1}H NMR (DMSO- d_6, δ ppm): 3.70 (3H, s, OCH_3), 6.52-6.60 (2H, dd, HC=CH),6.60-7.80 (15H, m, H $_{aromatic}$), 9.71 (1H, s, NH, exchangeable with D_2O). MS: $[M]^+$m/z492(50.32%) and $[M+2]^+$m/z 494.

1-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (8c)

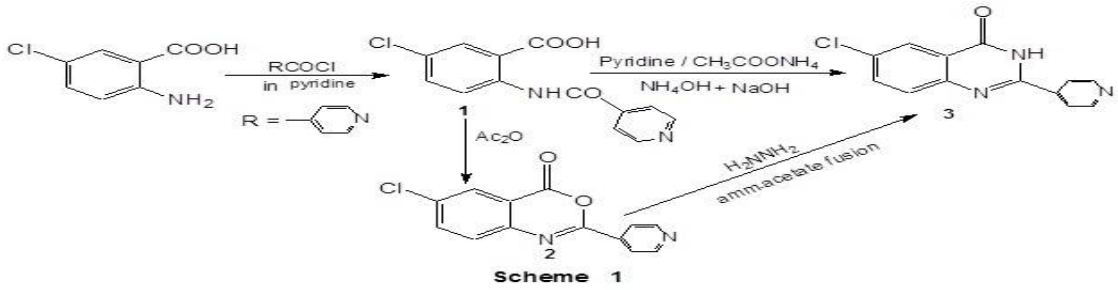
Crystallized from ethanol, white crystal, m.p.>300˚C, yield 80%. Analysis for $C_{28}H_{18}Cl_2N_4O$, M.Wt. 497, calcd: C, 62.07; H, 3.35; N, 10.34. Found: C, 62.05; H, 3.33; N, 10.32. IR (KBr, cm^{-1}): 3340 (NH), 3064 (CH aromatic), 2972 (CH aliphatic), 1675(C=O),1592 (C=N).^{1}H NMR (DMSO- d_6,δ ppm): 6.22-6.60 (2H, dd, HC=CH),7.20-8.80 (15H, m, H $_{aromatic}$),11.51 (1H, s, NH, exchangeable with D_2O). MS: $[M]^+$m/z497(70.23%) and $[M+2]^+$m/z 499.

1-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (8d)

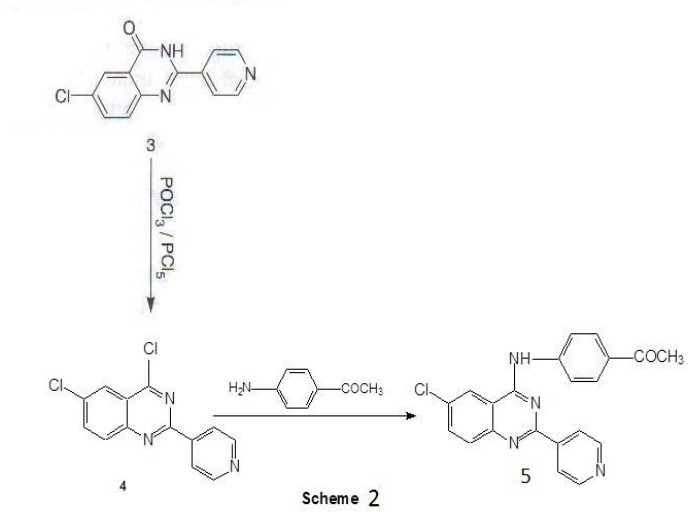
Crystallized from acetic acid, dark brown crystal, m.p.>300˚C, yield 67%.Analysis for $C_{28}H_{18}ClN_5O_3$M.Wt. 507.5, calcd: C, 60.88; H, 3.28; N, 12.68. Found: C, 60.86; H,3.26; N, 12.66. IR (KBr, cm^{-1}): 3240 (NH), 3064 (CH aromatic), 2972 (CH aliphatic), 1685(C=O),1592 (C=N).
^{1}H NMR (DMSO- d_6, δ ppm): 6.32-6.90 (2H, dd, HC=CH),7.20-8.20(15H, m, H $_{aromatic}$),10.10(1H, s, NH, exchangeable with D_2O). MS: $[M]^+$m/z507(40.65%) and $[M+2]^+$m/z 509.

RESULTS AND DISCUSSION

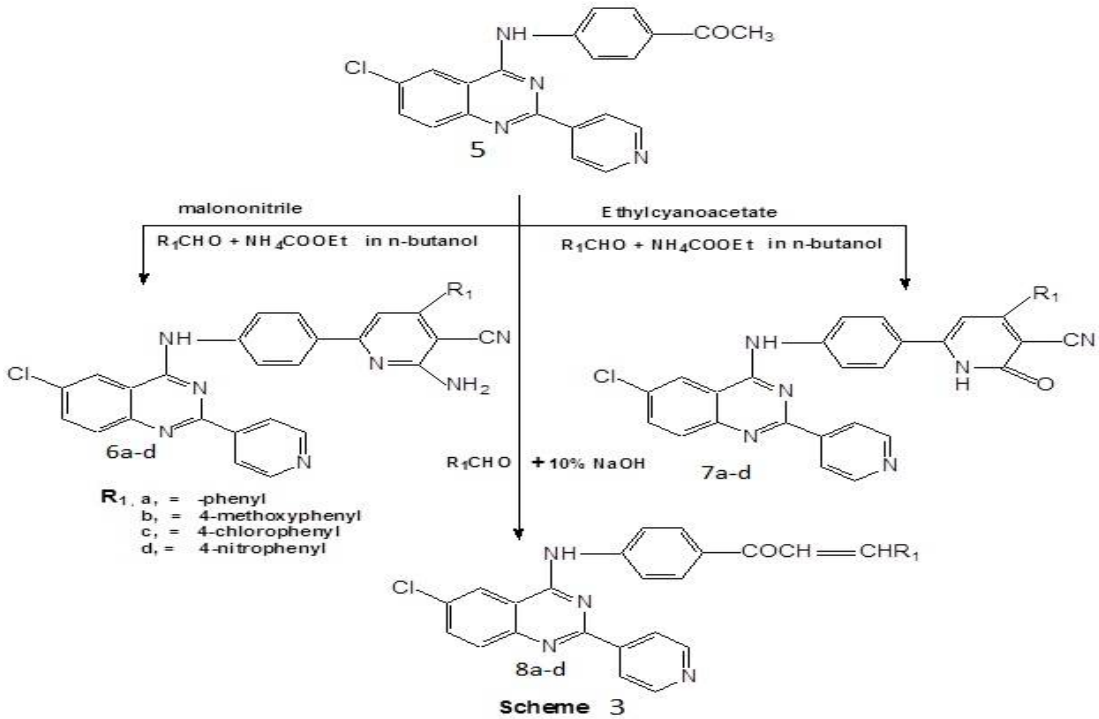
The starting material 5-chloro-2-(isonicotinamido)benzoic acid **(1)**was prepared by reaction of 5-chloroanthranilic acid with isonicotinyl chloride in dry pyridine. Cyclocondensation of compound **1** with acetic anhydride afforded6-chloro-2-(pyridin-4-yl)-4*H*-benzo[d][1,3]oxazin-4-one **2.**Interaction of 5-chloro-2-(isonicotinamido)benzoic acid **1** with ammonium acetate in the presence of ammonium hydroxide in sand bath afforded easily separated and highly yield product 6-chloro-2-(pyridin-4-yl)quinazolin-4(3*H*)-one **3.**Further confirmation of the compound**3** was obtained through its synthesis *via* another reaction route. Thus, the reaction of compound **2** with ammonium acetate afforded a product which was found to be identical in all respects (m.p., mixed m.p., and IR spectrum) with compound**3.** The stepwise synthesis of **4** was prepared *via* the chlorination of compound **3**with phosphorusoxy chloride in the presence of phosphoruspenta chloride to give 6-chloro-4-chloro-2-(pyridin-4-yl)quinazoline (4). Interaction of compound **4** with *p*-aminoacetophenone gave 1-(4-(6-chloro-2-(pyridin-4-yl)quinazolin-4-ylamino)phenyl)ethanone**5**.Compound **5** was reacted with appropriate aldehydes, namely benzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde, malononitrile and/ or ethyl cyano acetate , excess ammonium acetate in n-butanol to give compounds **6a-d** and **7a-d** respectively.Compound **5** was reacted with appropriate aldehydes, namely benzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde, in the presence of ethanolic sodium hydroxide solution afforded the derivatives **8a-d**, respectively.



Scheme 1



Scheme 2



Scheme 3

Biological activity

This study comprises the biological evaluation of some novel selected compounds of quinazoline derivatives which may possessing abroader spectrum of antitumor activity and fewer toxic side effects than Doxorubicin (DOX). Certain new quinazoline derivatives **(3,4,5,6b,6d,8b,8d)** weresynthesized ,charachterized, and subjected to ascreening system for evaluation of antitumor activity against Liver Cancer (HEPG2) tumor cell line.

The antitumor activity results indicated that the selected quinazoline derivatives showed antitumor activity against liver cancer (HEPG2) tumor cell line tested but with varying intensities in comparison to the known anticancer drug :Doxorubicin.

Results revelated that compounds **(6b,8d)** exhibited astrong growth inhibition activity against liver cancer (HEPG2) on the tested tumor panel cell line in comparison to the known anticancer drug Doxorubicin.

Table 1: Anticancer activity of selected Compounds (3,4,11,12b,14b and 14d)

compound	Cytotoxocity(IC50 in µg)
	HepG2c
3	32.41+/- 6.37
4	52.01 +/- 8.62
5	16.32 +/- 2.27
6b	2.04 +/- 0.63
8b	18.36 +/- 2.38
8d	8.23 +/- 1.51
Doxorubicin	0.009 µM

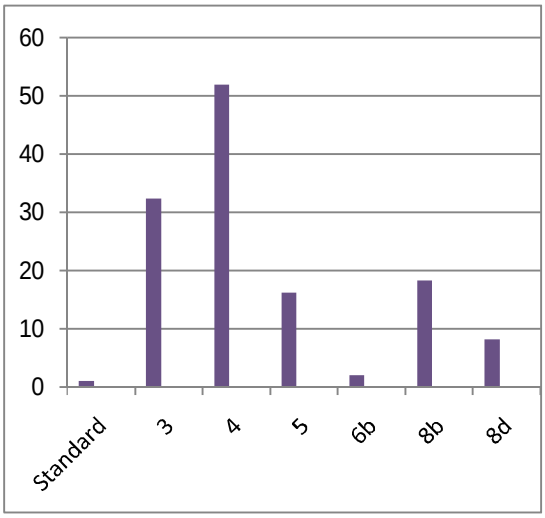


Fig. 1: Graphical representation of anticancer activity of compounds (3,4,5,6b,8b and 8d)

CONCLUSION

The varied biological activities of the newly synthesized compounds promoted to synthesis some new derivatives of these ring systems and study their anticancer activities their biological activities depended mainly on the nature and the position the substituents. The anticancer activity studies revealed that compounds **6b,8d** show strong effects against human hepatocellular liver carcinoma (HepG2). So we can say that synthesis of new derivatives of these compounds is still an active area of research. Where synthesis and study of the anticancer activities of new analogous of these compounds will be helpful for medicinal chemist to focus design of novel chemical entities containing quinazoline derivatives as a part of anticancer drugs.

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