JOURNAL OF PURE & APPLIED MICROBIOLOGY, Nov. 2014. Vol. **8**(Spl. Edn. 2), p. 629-637

Synthesis and Antimicrobial Activity of Some Novel 8-Hydroxy-7-Iodoquinoline-5-Sulfonamide Derivatives

Nagy M. Khalifa[1,2]*, Ahmad Eweas[2,3],
Mohamed A. Al-Omar[1] and Wael Hozzein[4,5]

[1]Pharmaceutical Chemistry Department, Drug Exploration & Development Chair (DEDC),
College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia.
[2]Department of Therapeutical Chemistry, Pharmaceutical and Drug Industries Division,
National Research Centre, Dokki 12622, Cairo, Egypt.
[3]Pharmaceutical Chemistry Department, College of Pharmacy, Taif University, Taif, Saudi Arabia.
[4]Bioproducts Research Chair, College of Science, King Saud University, Riyadh 11451, Saudi Arabia.
[5]Botany Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt.

(Received: 06 August 2014; accepted: 22 October 2014)

Herein we report a series of novel 8-hydroxyquinoline-5-sufonamide derivatives, which were synthesized, characterized and tested as antimicrobial agents *in vitro*. The reaction of the key intermediate 8-hydroxy-7-iodoquinoline-5-sulfonyl chloride with different secondary amines, aromatic amines, glycine and hydrazine hydrate, followed by reaction of hydrazide derivative with various ketonic and mono acid anhydride compounds yielded the desired sufonamide derivatives. All the new compounds were characterized by spectral and elemental analyses. Some of the newly synthesized final compounds were evaluated for their *in vitro* antibacterial and antifungal activities against pathogenic strains. The preliminary screening results indicated that most of the compounds demonstrated moderate to good antibacterial and antifungal activities, comparable to the standard drugs.

Key words: 8-Hydroxy-7-iodoquinoline; Hydrazide-hydrazone derivatives; Schiff,s bases; Antimicrobial activities.

Resistance to antibiotics is one of the major challenges facing treatment of bacterial infections, highlighting the need for novel antibacterial compounds that are effective towards resistant strains. Consequently, the search for new antimicrobial agents will always remain an important and challenging task for medicinal chemists. Quinoline is an important heterocyclic contained in various classes of pharmacological agents that can play an important role in biochemical processes[1,2]. A number of compounds incorporating quinoline have been clinically used as antifungal, antibacterial and antiprotozoic drugs[3–9] as well as antituberculotic agents[10–13], antibiotic[14,15], antileishmanial[16], antimalarial[17-19], antihypertensive[20], anti-proliferative [21,22], anti-depressant[23], anticonvulsant[24], antiinflammatory[25], antioxidant[26], HIV integrase inhibitors (e.g., FZ41),[27,28] and anticancer activities [29-31]. Some quinoline analogs showed also antineoplastics activity[32]. This moiety forms the core structural unit of a number of biologically interesting compounds, such as gastric acid secretion

---

* To whom all correspondence should be addressed.
E-mail: nagykhalifa@hotmail.com

inhibitors[33]. Iodofunctionalized organic molecules have established themselves as versatile intermediates in synthetic organic chemistry based on the ability of iodo substituent's to facilitate carbon-carbon bond formation and metal exchange[34]. In view of this, we are of the opinion that, several 7-iodo-8-hydroxyquinoline derivatives linked to different Sulfonamides and hydrazones may possess remarkable pharmacological activity. Hence, we embarked on the synthesis of title compounds to improve specificity and efficiency of these scaffolds against microorganisms.

RESULTS AND DISCUSSION

The title compounds were synthesized by a series of reactions as shown in Schemes 1, 2. The required key intermediate 8-Hydroxy-7-iodoquinoline-5-sulfonyl chloride (**1**) was synthesized by stirring 8-hydroxy-7-iodoquinoline-5-sulfonic acid with chlorosulfonic acid at room temperature followed by treating the chloro derivative **1** with different secondary amines to afford the corresponding sulfone derivatives **2a-d** and **3a,b**. The key intermediate **1** was then converted to Sulfonamides **4a-c** and **5a,b** by heating it with arylamines and glycine respectively (Scheme 1).

The hydrazones **7** and **8** were prepared through reaction of acid hydrazide **6** with substituted aromatic aldehydes and aldohexose sugar in the presence of ethanol and catalytic amount of acetic acid. Condensing **6** with cyclohexanone and mono acid anhydrides in glacial acetic acid gave rise to the corresponding sulfonamides derivatives 9-12, respectively (scheme 2). The newly synthesized compounds were characterized by ^{1}H NMR,^{13}C NMR, IR, MS and elemental analysis.

Antimicrobial evaluation

The *in vitro* preliminary antimicrobial screening of newly synthesized compounds against antibacterial and antifungal strains was screened by considering zone of inhibition of growth with their different concentrations using tetracycline (30ug) and erythromycin (25ug) as standards. The antimicrobial screening revealed that, few of the tested compounds showed good inhibition against various tested microbial strains compared to the standard drug. Compound **6** is found to be more potent against *Pseudomonas aeruginosa*, *Salmonella typhi* and *Escherichia coli* than the reference drugs tetracycline and erythromycin. Compounds **2b** and **5b** exhibited excellent antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. respectively. Remaining compounds showed moderately or no activity against all the strains. It is interesting to note that compounds **2a, 2b** and **6** displayed good antibacterial as well as antifungal activities against most pathogenic strains. Results of antimicrobial studies have been presented in Table 1.

Antimicrobial screening

The antimicrobial activities for ten of the newly synthesized compounds were tested against representative pathogenic Gram positive, Gram negative and yeast strains by using the paper disc diffusion method [35]. In this method, two agar media; nutrient agar [36]) for bacteria and Sabouraud agar [37] for the yeast strains were prepared and sterilized by autoclaving at 120 ºC and 1.5 atm for 20 min. The agar plates were poured, left to cool down and after solidification they were inoculated with the bacterial and yeast strains by streaking. The synthesized compounds were dissolved in methanol at a final concentration of 10 mg/ml and 5 µl of each compound was loaded on a sterile filter paper disc (5 mm diameter; 50 µg per disc). The filter paper disc was then transferred aseptically into the inoculated agar plates along with commercially available tetracycline and erythromycin discs as positive controls and methanol as the negative control for comparison. The plates were then incubated at 37 ºC for 24 h for bacteria and at 30 ºC for 48-72 h for fungi. After incubation, diameters of the inhibition zones around the paper discs were measured in mm as an indication of the antimicrobial activities of the compounds.

EXPERIMENTAL

Chemistry

All melting points were uncorrected and were taken on a Boetius melting point microscope. The infrared (IR) spectra were recorded on a Bruker-Vector 22, Germany, using KBr discs at microanalytical center, Cairo university. ^{1}H and ^{13}C NMR spectra were performed on a Varian Gemini

300 MHz spectrometer or Jeol, JöEL 500 MHz instruments, using tetramethylsilane (TMS) as internal standard. All chemical shifts are quoted in ´ values using parts per million scale (ppm) downfield from TMS. Mass Spectra were recorded on a Hewlett-Packard 5988 A (1000 Hz) instrument, Shimadzu GCMS-QP-1000EX mass spectrometer at 70 ev, using the electron impact technique (EI). Elemental analysis were performed by the microanalytical unit at Cairo University and the results was found within the acceptable limits of the calculated values. All reactions were monitored by TLC using precoated Aluminum sheet silica gel Merck 60F_{254} plates and detection of the components was made by short and long UV light.

8-Hydroxy-7-iodoquinoline-5-sulfonyl chloride(1)

8-hydroxy-7-iodoquinoline-5-sulfonic acid (20 mmol) and chlorosulfonic acid (8 ml) was stirred at room temperature overnight. Then, the reaction mixture was poured into ice-water and the formed yellow precipitate was filtered off, dried and crystallized from methanol to obtain the desired sulfonyl chloride derivative **1** in 76% yield; m.p. 263-265 ^{o}C; IR (KBr, cm^{-1}) ν_{max}: 3468 (OH); ^{1}HNMR (DMSO-d_6) δ: 7.35 (t, 1H, 8-HQ), 8.12 (d, 1H, 8-HQ), 8.41 (s, 1H, 8-HQ), 9.02 (d, 1H, 8-HQ), 11.53 (br s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 79.35, 122.84, 127.98, 134.16, 136.31, 139.14, 143.10. 152.32, 161. 25; MS: m/z 369 $[M]^{+}$; Anal. calcd. For $C_9H_5ClINO_3S$: C, 29.25; H, 1.36; N, 3.79. Found: C, 29.17; H, 1.23; N, 3.67%.

7-Iodo-5-(substituted-4-ylsulfonyl)quinolin-8-ol (2a-d) and 8-Hydroxy-7-iodo-N-substitutedquinoline- 5- sulfonamide (3a,b)

7-Iodo-8-Hydroxyquinoline-5-sulfonyl chloride (**1**) (10 mmol) was dissolved in dry MeOH (30 mL) and heated to reflux. Then different secondary amines namely, morpholine, piperazine, piperidine, N-methyl piperazine, *N*,*N*-bis dimethylamine and *N*,*N*-2-hydroxyethylamine (20 mmol) was added dropwise. After 3-5 h of heating the resulted mixture was concentrated *in vacuo* and the resulting oil put into dichloromethane (50 mL). The precipitate formed was filtered off and recrystallized from MeOH to afford the title compounds **2a-d** and **3a,b**, respectively.

7-Iodo-5-(morpholin-4-ylsulfonyl)quinolin-8-ol (2a)

Yield 66%; m.p. 183-185 ^{o}C; IR (KBr, cm^{-1}) ν_{max}: 3481 (OH); ^{1}HNMR (DMSO-d_6) δ: 3.01 (t, 4H, $2CH_2$), 3.81 (t, 4H, $2CH_2$), 7.31 (t, 1H, 8-HQ), 8.09 (d, 1H, 8-HQ), 8.45 (s, 1H, 8-HQ), 9.05 (d, 1H, 8-HQ), 11.41 (br s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 43.79, 66.02, 79.10, 122.81,

Table 1. The antimicrobial activities of compounds2a, 2b,2c,3b,3c, 5b, 6, 7, 8 and 11expressed as inhibition zones of growth in mm against the used test organisms.

Test Organism[a] Compound	B.s.	S.a.	M.l.	P.a.	S.t.	E.c.	P.v.	M.p.	C.a.	C.g.
2a	12	-	10	-	-	±[b]	±	15	15	-
2b	18	22	-	±[b]	10	19	13	-	29	22
2c	±	-	-	-	-	-	-	-	-	-
3b	-	-	-	-	-	-	-	-	-	-
3c	9	-	9	-	-	-	±	13	-	-
5b	19	22	-	7	9	14	12	-	27	20
6	20	33	-	38	38	42	9	-	27	21
7	8	-	8	-	-	-	±	9	±	-
8	10	-	10	-	-	±	±	13	-	-
11	-	-	-	-	-	-	-	-	-	-
Tetracycline 30ug	25	22	20	±	22	23	18	15	-	-
Erythromycin 25ug	36	35	32	11	11	13	25	18	-	-

[a] B.s., *Bacillus subtilis*; S.a., *Staphylococcus aureus*; M.l., *Micrococcus luteus*; P.a., *Pseudomonas aerugenosa*; S.t., *Salmonella typhi*; E.c., *Escherichia coli*; P.v., *Proteus vulgaris*; M.p., *Mycobacteriumpheli*; C.a., *Candida albicans*; and C.g., *Candida glabrata*.

[b] ±; doubtful result.

127.61, 133.58, 135.82, 138.22, 143.75. 152.36, 160.04; MS: m/z 420 $[M]^+$; Anal. calcd. For $C_{13}H_{13}IN_2O_4S$: C, 37.16; H, 3.12; N, 6.67. Found: C, 37.09; H, 3.07; N, 6.51%.

7-Iodo-5-(piperazin-4-ylsulfonyl)quinolin-8-ol (2b)

Yield 61%; m.p. 164-166 °C; IR (KBr, cm^{-1}) ν_{max}: 3465 (OH); ^{1}HNMR (DMSO-d_6) δ: 2.98 (t, 4H, $2CH_2$), 3.35 (t, 4H, $2CH_2$), 7.34 (t, 1H, 8-HQ), 8.05 (d, 1H, 8-HQ), 8.52 (s, 1H, 8-HQ), 9.07 (d, 1H, 8-HQ), 11.48 (br s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 43.65, 47.31, 79.23, 122.76, 127.54, 133.49, 135.76, 138.29, 143.61. 152.19, 159.82; MS: m/z 419 $[M]^+$; Anal. calcd. For $C_{13}H_{14}IN_3O_3S$: C, 37.24; H, 3.37; N, 10.02. Found: C, 37.18; H, 3.28; N, 9.92%.

7-Iodo-5-(piperidin-4-ylsulfonyl)quinolin-8-ol (2c)

Yield 70%; m.p. 147-149 °C; IR (KBr, cm^{-1}) ν_{max}: 3509 (OH); ^{1}HNMR (DMSO-d_6) δ: 1.47 (m, 6H, $3CH_2$), 3.12 (t, 4H, $2CH_2$), 7.31 (t, 1H, 8-HQ), 8.05 (d, 1H, 8-HQ), 8.48 (s, 1H, 8-HQ), 9.03 (d, 1H, 8-HQ), 11.37 (br s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 25.07, 26.11, 45.17, 79.36, 123.85, 127.43, 132.89, 134.75, 137.59, 143.68. 152.24, 159.96; MS: m/z 418 $[M]^+$; Anal. calcd. For $C_{14}H_{15}IN_2O_3S$: C, 40.20; H, 3.61; N, 6.70. Found: C, 40.16; H, 3.55; N, 6.63%.

7-Iodo-5-(N-methylpiperazin-4-ylsulfonyl) quinolin-8-ol (2d)

Yield 53%; m.p. 196-198 °C; IR (KBr, cm^{-1}) ν_{max}: 3482 (OH); ^{1}HNMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 2.97 (t, 4H, $2CH_2$), 3.29 (t, 4H, $2CH_2$), 7.33 (t, 1H, 8-HQ), 8.01 (d, 1H, 8-HQ), 8.54 (s, 1H, 8-HQ), 9.04 (d, 1H, 8-HQ), 11.42 (br s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 41.76, 45.13, 47.66, 79.42, 123.78, 128.12, 132.79, 134.65, 137.52, 143.46. 152.31, 159.74; MS: m/z 433 $[M]^+$; Anal. calcd. For $C_{14}H_{16}IN_3O_3S$: C, 38.81; H, 3.72; N, 9.70. Found: C, 38.69; H, 3.61; N, 9.60%.

8-Hydroxy-7-iodo-N,N-diethylquinoline-5-sulfonamide (3a)

Yield 58%; m.p. 171-173 °C; IR (KBr, cm^{-1}) ν_{max}: 3495 (OH); ^{1}HNMR (DMSO-d_6) δ: 0.98 (t, 6H, $2CH_3$), 3.37 (q, 4H, $2CH_2$), 7.25 (t, 1H, 8-HQ), 8.06 (d, 1H, 8-HQ), 8.47 (s, 1H, 8-HQ), 9.03 (d, 1H, 8-HQ),

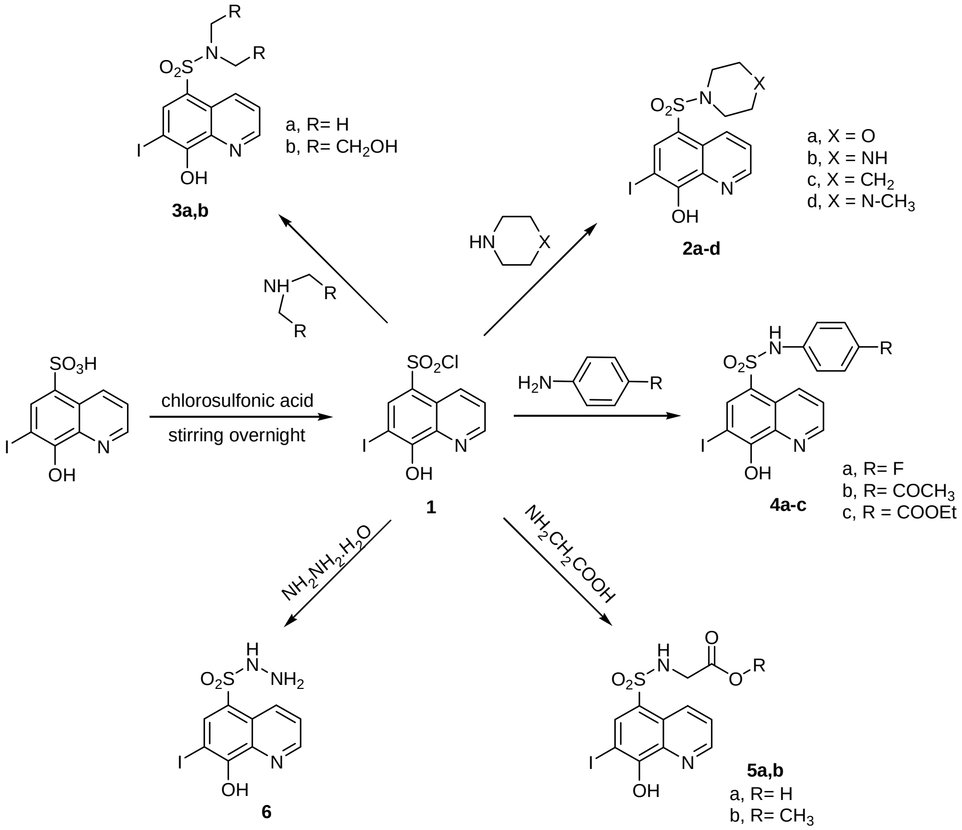

Fig. 1. Synthetic route to compounds 2-6

11.35 (s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 14.26, 39.18, 79.33, 123.65, 127.42, 132.58, 134.61, 135.87 143.11, 152.24, 159.20; MS: m/z 406 $[M]^+$; Anal. calcd. For $C_{13}H_{15}IN_2O_3S$: C, 38.44; H, 3.72; N, 6.90. Found: C, 38.39; H, 3.67; N, 6.83%.

8-Hydroxy-7-iodo-N,N-bis(2-hydroxyethyl) quinoline- 5-sulfonamide (3b)

Yield 65%; m.p. 229-231 °C; IR (KBr, cm^{-1}) ν_{max}: 3479 (OH); ^{1}HNMR (DMSO-d_6) δ: 3.41 (t, 4H, $2CH_2$), 4.19 (t, 4H, $2CH_2$), 7.28 (t, 1H, 8-HQ), 8.05 (d, 1H, 8-HQ), 8.49 (s, 1H, 8-HQ), 9.01 (d, 1H, 8-HQ), 11.46, 12.38 (2s, 3H, 3OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 52.34, 61,82, 79.21, 123.68, 127.39, 132.43, 134.56, 135.80, 143.15, 152.32, 159.26; MS: m/z 438 $[M]^+$; Anal. calcd. For $C_{13}H_{15}IN_2O_5S$: C, 35.63; H, 3.45; N, 6.39. Found: C, 35.59; H, 3.38; N, 6.31%.

N-(4-Substitutedphenyl)-8-hydroxy-7-iodoquinoline -5-sulfonamide (4a-c)

Obtained in similar way to compounds **2** from 7-iodo-8-hydroxyquinoline-5-sulfonyl chloride and different substituted arylamines namely, p-fluoroaniline, p-amino acetophenone and p-aminoethylbenzoate.

N-(4-Fluorophenyl)-8-hydroxy-7-iodoquinoline-5-sulfone (4a)

Yield 64%; m.p. 209-211°C; IR (KBr, cm^{-1}) ν_{max}: 3480 (OH); ^{1}HNMR (DMSO-d_6) δ: 6.85 (d, 2H, phenyl), 7.01 (d, 2H, phenyl), 7.33 (t, 1H, 8-HQ), 8.12 (d, 1H, 8-HQ), 8.50 (s, 1H, 8-HQ), 9.09 (d, 1H, 8-HQ), 9.64, 11.45 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 79.23, 115.32, 117.94, 123.17, 127.88, 132.72, 134.71, 135.20, 137.67, 143.22. 150.89, 153.14, 159.79; MS: m/z 444 $[M]^+$; Anal. calcd. For $C_{15}H_{10}FIN_2O_3S$: C, 40.56; H, 2.27; N, 6.31. Found: C, 40.46; H, 2.19; N, 6.19%.

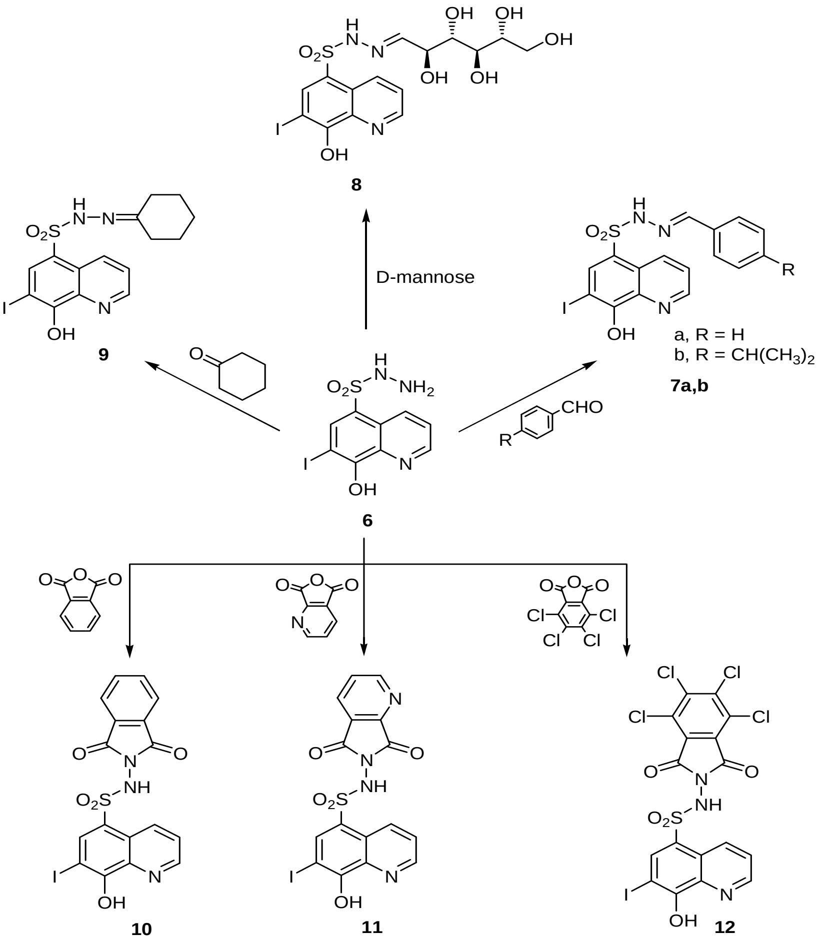

Fig. 2. Synthetic route to compounds 7-12

N-(4-Acetylphenyl)-8-hydroxy-7-iodoquinoline-5-sulfonamide (4b)

Yield 57%; m.p. 226-228°C; IR (KBr, cm^{-1}) ν_{max}: 3466 (OH); ^{1}HNMR (DMSO-d_6) δ: 2.54 (s, 3H, CH_3), 6.78 (d, 2H, phenyl), 7.28 (t, 1H, 8-HQ), 7.50 (d, 2H, phenyl), 8.10 (d, 1H, 8-HQ), 8.46 (s, 1H, 8-HQ), 9.05 (d, 1H, 8-HQ), 9.82, 11.02 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 27.80, 79.14, 115.47, 123.31, 125.73, 127.56, 129.44, 132.64, 134.75, 135.19, 139.86, 143.27, 152.25, 159.61, 197.99; MS: m/z 468 $[M]^+$; Anal. calcd. For $C_{17}H_{13}IN_2O_4S$: C, 43.60; H, 2.80; N, 5.98. Found: C, 43.51; H, 2.69; N, 5.87%.

Ethyl-4-{[(8-hydroxy-7-iodoquinolin-5-yl)sulfonyl]amino}benzoate (4c)

Yield 62%; m.p. 157-159°C; IR (KBr, cm^{-1}) ν_{max}: 3501 (OH); ^{1}HNMR (DMSO-d_6) δ: 1.19 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 6.79 (d, 2H, phenyl), 7.24 (t, 1H, 8-HQ), 7.56 (d, 2H, phenyl), 8.05 (d, 1H, 8-HQ), 8.51 (s, 1H, 8-HQ), 9.02 (d, 1H, 8-HQ), 9.78, 11.37 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 14.35, 63.02, 79.25, 115.41, 121.45, 123.59, 127.39, 129.87, 132.55, 134.67, 135.24, 139.72, 143.18, 152.37, 159.22, 169.01; MS: m/z 498 $[M]^+$; Anal. calcd. For $C_{18}H_{15}IN_2O_5S$: C, 43.39; H, 3.03; N, 5.62. Found: C, 43.29; H, 2.93; N, 5.55%.

[(8-Hydroxy-7-iodoquinolin-5-yl)sulfonyl]amino}acetic acid (5a)

8-hydroxy- quinoline-5-sulfonyl chloride (**1**)(10 mmol) was suspended in dry dichloromethane (50 mL) and then, Glycine (10 mmol) and triethylamine (10 mmol) was added to it and the mixture was refluxed for 3 h. cooled, filtered and washed with dichloromethane and ethanol several times. The precipitate formed was crystallized from MeOH to afford compound **5a** in 87% yield, m.p. 203-205 °C; IR (KBr, cm^{-1}) ν_{max}: 3512, 3463 (2OH); ^{1}HNMR (DMSO-d_6) δ: 4.19 (s, 2H, CH_2), 7.22 (t, 1H, 8-HQ), 8.12 (d, 1H, 8-HQ), 8.53 (s, 1H, 8-HQ), 9.07 (d, 1H, 8-HQ), 10.35, 11.56 (2s, 2H, 2OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 49.01, 79.38, 123.60, 127.48, 132.52, 134.57, 135.78 143.01, 151.93, 159.11, 173.55; MS: m/z 408 $[M]^+$; Anal. calcd. For $C_{11}H_9IN_2O_5S$: C, 32.37; H, 2.22; N, 6.86. Found: C, 32.29; H, 2.10; N, 6.78%.

Methyl{[(8-hydroxy-7-iodoquinolin-5-yl)sulfonyl]amino}acetate (5b)

To a solution of **5a** (1 g) in methanol (50 mL). Conc. sulphuric acid was added slowly at 0-5 °C over a period of 30 min and refluxed for 2 h. After quenching into cold water, precipitated solid was filtered, washed with water, dried and crystallized from MeOH to afford compound **5b** in 93% yield, m.p. 112-114 °C; IR (KBr, cm^{-1}) ν_{max}: 3439 (OH); ^{1}HNMR (DMSO-d_6) δ: 3.81 (s, 3H, CH_3), 7.25 (t, 1H, 8-HQ), 8.05 (d, 1H, 8-HQ), 8.51 (s, 1H, 8-HQ), 9.03 (d, 1H, 8-HQ), 11.48 (s, 1H, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 46.23, 53.29, 79.45, 123.58, 127.32, 132.46, 134.50, 135.73 142.98, 151.87, 159.10, 171.02; MS: m/z 422 $[M]^+$; Anal. calcd. For $C_{12}H_{11}IN_2O_5S$: C, 34.14; H, 2.63; N, 6.64. Found: C, 34.09; H, 2.56; N, 6.58%.

8-Hydroxy-7-iodoquinoline-5-sulfonohydrazide (6)

A mixture of compound **1** (10 mmol) and hydrazine hydrate (20 mmol) in methanol (30 mL) was stirred at room temperature for 12 h. The excess of solvent was distilled off and poured into ice. The solid thus obtained was filtered, washed with water and recrystallized from methanol to give compound **6** in 65% yield, m.p. 127-129 °C; IR (KBr, cm^{-1}) ν_{max}: 3521-3190 (NH_2, OH, NH); ^{1}HNMR (DMSO-d_6) δ: 4.91 (s, 2H, NH_2 exchangeable with D_2O), 7.26 (t, 1H, 8-HQ), 8.05 (d, 1H, 8-HQ), 8.47 (s, 1H, 8-HQ), 9.03 (d, 1H, 8-HQ), 9.67, 11.28 (2s, 2H, NH, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) δ: 79.30, 123.55, 127.53, 132.49, 134.62, 135.83 142.90, 151.88, 160.02; MS: m/z 365 $[M]^+$; Anal. calcd. For $C_9H_8IN_3O_3S$: C, 29.60; H, 2.21; N, 11.51. Found: C, 29.52; H, 2.14; N, 11.45%.

8-Hydroxy-7-iodo-N'-(substituted benzylidene) quinoline-5-sulfonohydrazide (7a,b)

To a suspension of the hydrazide **6** (1 mmol) in dry methanol (30 mL), was added the appropriate aromatic aldehydes namely, benzaldehyde and p-isopropylbenzaldehyde (1 mmol) and catalytic amount of acetic acid. The reaction mixture was allowed to reflux for 3-5 h. After completion of reaction, the solution was cooled to room temperature and concentrated under reduced pressure. The solid separated was filtered, dried and recrystallized from AcOH/H_2O to provide the corresponding hydrazone **7a,b.**

8-hydroxy-7-iodo-N'-[(Z)-benzylidene]quinoline-5-sulfonohydrazide (7a)

Yield 61% yield, m.p. 219-221 °C; IR (KBr, cm^{-1}) ν_{max}: 3475 OH), 3219 (NH); ^{1}HNMR (DMSO-d_6) δ: 7.23-7.78 (m, 7H, Ar-H + =CH), 8.03 (d, 1H, 8-HQ), 8.52 (s, 1H, 8-HQ), 9.01 (d, 1H, 8-HQ), 9.85, 11.64 (2s, 2H, NH, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 79.28, 123.47, 126.20, 128.79, 129.42, 131.25, 132.39, 133.96, 134.27, 136.12, 141.36, 143.17, 151.67, 157.31; MS: m/z 453 $[M]^+$; Anal. calcd. For $C_{16}H_{12}IN_3O_3S$: C, 42.40; H, 2.67; N, 9.27. Found: C, 42.28; H, 2.59; N, 9.18%.

8-Hydroxy-7-iodo-N’-[4-(propan-2-yl) benzylidene] quinoline-5-sulfonohydrazide (7b)

Yield 54% yield, m.p. 236-238 °C; IR (KBr, cm^{-1}) ν_{max}: 3510 OH), 3210 (NH); ^{1}HNMR (DMSO-d_6) δ: 1.36 (d, 6H, $2CH_3$),3.31 (m, 1H, CH),7.11 (t, 2H, phenyl), 7.24 (t, 1H, 8-HQ), 7.61 (d, 2H, phenyl), 8.05 (d, 1H, 8-HQ), 8.48 (s, 1H, 8-HQ), 9.02 (d, 1H, 8-HQ), 9.85, 12.06 (2s, 2H, NH, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 23.10, 37.21, 79.33, 123.50, 126.26, 127.42, 129.38, 131.14, 132.41, 134.46, 135.89 141.32, 143.16, 151.29, 152.04, 159.22; MS: m/z 495 $[M]^+$; Anal. calcd. For $C_{19}H_{18}IN_3O_3S$: C, 46.07; H, 3.66; N, 8.48. Found: C, 45.97; H, 3.59; N, 8.43%.

8-Hydroxy-7-iodo-N’-(2,3,4,5,6-pentahydroxy hexylidene) quinoline-5-sulfonohydrazide (8)

A mixture of the hydrazide **6** (1 mmol), D-mannose (1 mmol), in ethanol (30 mL), and a catalytic amount of glacial acetic acid (3 drops) was heated at reflux for 2 h. the reaction mixture was allowed to cool to room temperature, and the formed precipitate was filtered off, washed with ethanol, dried and crystallized from dioxane to give compound **8** in 57% yield, m.p. 141-143 °C; IR (KBr, cm^{-1}) ν_{max}: 3520-3217 (OH, NH); ^{1}HNMR (DMSO-d_6) δ: 3.19–3.6 (m, 2H, 6^2-H, $6^{''}$-H), 3.40-3.51 (m, 3H, 5^2-H, 4^2-H, 6^1-OH, D_2O exchangeable), 4.11 (d, 1H, 5^1-OH, D_2O exchangeable), 4.31 (d, 1H, 4^1-OH, D_2O exchangeable), 4.47 (m, 3H, 2^2-H, 3^2-H, 3^1-OH, D_2O exchangeable), 4.75 (d, 1H, 2^1-OH, D_2O exchangeable), 7.24 (t, 1H, 8-HQ), 7.60 (d, 1H, 1^2-H), 7.53 (d, 2H, phenyl), 8.10 (d, 1H, 8-HQ), 8.45 (s, 1H, 8-HQ), 9.04 (d, 1H, 8-HQ), 9.12, 11.86 (2s, 2H, NH, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 63.87, 67.23, 71.22, 72.30, 73.26, 79.34, 123.50, 127.03, 132.43, 133.82, 136.17, 142.61, 151.29, 153.75, 158.76; MS: m/z 527 $[M]^+$; Anal. calcd. For $C_{15}H_{18}IN_3O_8S$: C, 34.17; H, 3.44; N, 7.97. Found: C, 34.09; H, 3.38; N, 7.89%.

N-Cyclohexylidene-8-hydroxy-7-iodoquinoline-5-sulfonohydrazide (9)

A stirred glacial acetic acid suspension (20 mL) of hydrazide **6** (10 mmol) and cyclohexanone (10 mmol), was refluxed for 3 h and then allowed to cool to room temperature. The separated solid was collected by filtration, dried, and crystallized from AcOH/H_2O to yield the title derivative **9**, in 68% yield, m.p. 153-155 °C; IR (KBr, cm^{-1}) ν_{max}: 3489 (OH), 3201 (NH); ^{1}HNMR (DMSO-d_6) δ: 1.23-1.35 (m, 10H, CH_2),7.28 (t, 1H, 8-HQ), 7.59 (d, 2H, phenyl), 8.09 (d, 1H, 8-HQ), 8.42 (s, 1H, 8-HQ), 9.02 (d, 1H, 8-HQ), 9.46, 11.24 (2s, 2H, NH, OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 24.77, 27.12, 28.36, 79.41, 123.53, 127.11, 132.45, 134.26, 135.85, 143.01, 151.34, 159.20, 162.13; MS: m/z 445 $[M]^+$; Anal. calcd. For $C_{15}H_{16}IN_3O_3S$: C, 40.46; H, 3.62; N, 9.44. Found: C, 40.35; H, 3.49; N, 9.32%.

Synthesis of compounds 10-12

A stirred glacial acetic acid suspension (30 mL) of hydrazide **6** (1 mmol) and mono acid anhydride derivatives, namely phthalic anhydride, quinolinic anhydride and 1,2,4,5-tetrachlorophthalic anhydride (1 mmol), was heated at reflux for 1-3 h. The reaction mixture was concentrated under reduced pressure, cooled, and the separated solid was collected by filtration, dried, and crystallized from AcOH/ether to yield the corresponding imide derivatives **10**-**12**, respectively.

N-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-8-hydroxy-7-iodoquinoline-5-sulfon- amide (10)

Yield 76%; m.p. 161-163 °C; IR (KBr, cm^{-1}) ν_{max}: 3491, 3227 (OH, NH), 1715 (C=O); ^{1}HNMR (DMSO-d_6) δ: 7.18-8.23 (m, 6H, Ar-H), 8.54 (s, 1H, 8-HQ), 9.05 (d, 1H, 8-HQ), 9.86, 11.60 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 81.14, 123.62, 127.43, 128.01, 131.67, 132.58, 133.10, 134.66, 135.29, 143.15, 152.32, 158.73, 165.28; MS: m/z 495 $[M]^+$; Anal. calcd. For $C_{17}H_{10}IN_3O_5S$: C, 41.23; H, 2.04; N, 8.48. Found: C, 41.11; H, 2.01; N, 8.33%.

N-(5,7-Dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-8-hydroxy-7-iodo quinoline-5-sulfonamide (11)

Yield 68%; m.p. 185-187 °C; IR (KBr, cm^{-1}) ν_{max}: 3465, 3198 (OH, NH), 1719 (C=O); ^{1}HNMR (DMSO-d_6) δ: 7.22-9.14 (m, 7H, Ar-H), 9.75, 11.89 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6) ´: 79.43, 123.57, 127.39, 128.53, 129.16, 132.56, 134.51, 137.11, 139.26, 143.08, 147.15, 152.34, 153.245, 159.47, 165.32, 167.01; MS: m/z 496 $[M]^+$; Anal. calcd. For $C_{16}H_9IN_4O_5S$: C, 38.73; H, 1.83; N, 11.29. Found: C, 38.62; H, 1.72; N, 11.19%.

N-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-8-hydroxy-7-iodoquinoline-5-sulfonamide (12)

Yield 73%; m.p. 210-212 °C; IR (KBr, cm^{-1})

ν_{max}: 3520, 3217 (OH, NH), 17123 (C=O); ^{1}HNMR (DMSO-d_6) δ: 7.31 (t, 1H, 8-HQ), 8.10 (d, 1H, 8-HQ), 8.49 (s, 1H, 8-HQ), 9.03 (d, 1H, 8-HQ), 9.68, 11.79 (2s, 2H, NH and OH, exchangeable with D_2O); ^{13}CNMR (DMSO-d_6)´: 79.48, 123.59, 127.40, 129.32, 132.85, 134.61, 134.26, 135.67, 137.94, 143.19, 152.35, 159.20, 165.37; MS: m/z 633 $[M]^+$; Anal. calcd. For $C_{17}H_6Cl_4IN_3O_5S$: C, 32.25; H, 0.96; N, 6.64. Found: C, 32.12; H, 0.85; N, 6.49%.

ACKNOWLEDGMENTS

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group project no. RGP-VPP-320.

REFERENCES

1. Musiol R., Serda M., Hensel-BielowkaS., J.Polanski, *Curr. Med. Chem.*, 2010; **17**:1960-1973.
2. Musiol R., Podeszwa B., Finster J., Niedbala H., Polanski J., *Monatsh. Chem.*, 2006; **137**:1211-1217.
3. Jampilek J., Musiol R., Pesko M., Kralova K., Vejsova M., Carroll J., Coffey A., Finster J., Tabak D., Niedbala H., Kozik V., Polanski J., Csollei J., Dohnal J., *Molecules*,2009; **14**:1145-1159.
4. Musiol R., Jampilek J., Buchta V., Silva L., Niedbala H., Podeszwa B., Palka A., Majerz-Maniecka K., Oleksyn B., Polanski J., *Bioorg. Med. Chem.*, 2006; **14**: 3592-3598.
5. Harris C., and Thorarensen A., *Curr. Med. Chem.*, 2004; **11**: 2213-2243.
6. Musiol R., Tabak D., Niedbala H., Podeszwa B., Jampilek J., Kralova K., Dohnal J., Finster J., Mencela A.,Polanski J., *Bioorg. Med. Chem.*, 2008; **16**: 4490-4499.
7. Palit P., Paira P., Hazra A., Banerjee S., Das Gupta A., Dastidar S.,MondalN., *Eur. J. Med. Chem.*, 2009; **44**: 845-853.
8. Musiol R., Jampilek J.,Kralova K., RichardsonD., Kalinowski D., Podeszwa B., Finster J., Niedbala H., Palka A., Polanski J., *Bioorg. Med. Chem.*, 2007; **15**: 1280-1288.
9. Rajanarendar E., Nagi M., Krishna S., Murthy K., Reddy N., V. Rajam., *Eur. J. Med. Chem.*, 2012; **55**: 273-283.
10. Vangapandu S., Jain M., R.ain J., Kaur S., SinghP., *Bioorg. Med. Chem.*,2004; **12**: 2501-2508.
11. Andries K., Verhasselt P., Guillemont J., H Gohlmann., NeefsJ.,Winkler H., Van Gestel J., Zhu M., Lee E., Williams P., de Chaffoy D., Huitric E., Hoffner S., Cambau E., Truffot-Pernot C., Lounis N.,Jarlier V., *Science*,2005; **307**: 223-227.
12. Vinsova J., Imramovsky A., Jampilek J., Monreal-Ferriz,J.Dolezal M., *Antiinfective Agents Med. Chem.*, 2008; **7**: 12-31.
13. Lilienkampf A., Mao J.,Wan B., Wang Y., Franzblau S.,Kozikowski A., *J. Med. Chem.*, 2009; **52**: 2109-2118.
14. Mahamoud A., Chevalier J., Davin-Regli A., Barbe J.,Pages J., *Curr. Drug Targ.*, 2006; **7**: 843-847.
15. Eswaran S., AdhikariA.,ShettyN., *Eur. J. Med. Chem.*, 2009; **44**: 4637.
16. Jain M., Khan S., Tekwani B., Jacob M., Singh S., SinghB.,Jain R., *Bioorg. Med. Chem.*, 2005; **13**: 4458-4466.
17. Charris J., Dominguez J., Gamboa N., RodriguesJ.,Angel J., *Eur. J. Med. Chem.*, 2005; **40**: 875-881.
18. Cunico W., Cechinel C., Bonacorso H., Martins M.,Zannata N., de Souza N.,Freitas I., SoaresR., Krettli A., *Bioorg. Med. Chem. Lett.*, 2006; **16**: 649-653.
19. N’DaD., J Breytenbach., SmithP., Lategan C., *Arzneimittelforschung*, 2010; **60**: 627-635.
20. Muruganantham N., Sivakumar R., Anbalagan N., Gunasekaran V.,Leonard J.,*Biol. Pharm.Bull.*,2004; **27**:1683-1687.
21. Kolokythas G., Pouli N., Marakos P., Pratsinis H.,Kletsas D., *Eur. J. Med. Chem.*,2006; **41**: 71-79.
22. Sedic M.,Poznic M., Gehrig P., Scott M., Schlapbach R., *Cancer Ther.*, 2008; **7**: 2121-2132.
23. Sun X.-Y., He X.-J., Pan C.-Y., Liu Y.-P.,Zou Y.-P., *Med. Chem. Res.*,.2012; **21**:3692-3698.
24. Guan L.-P., Jin Q.-H., Wang S.-F., Li F.-N.,Quan Z.-S., *Arch. Pharm. (Weinheim)*, 2008; **341**: 774-779.
25. El-GazzarA., Youssef M., YoussefA., Abu-HashemA., BadriaF., *Eur. J. Med. Chem.*, 2009; **44**: 609-624.
26. Ha Sook Chung,Won Sick Woo, *J. Nat. Prod.*, 2001; **64**: 1579-1580.
27. Polanski J., Niedbala H., Musiol R., Podeszwa B., Tabak D., Palka A., Mencel A., J.inster F., J Mouscadet., Le Bret M., *Lett.Drug Des. Discov.*, 2006; **3**: 175-178.
28. Polanski J., Niedbala H., Musiol R., Bodeszwa P., Tabak D., Palka A., Mencel A., Mouscadet J., Le Bret M., *Lett.Drug Des. Discov.*, 2007; **4**:

99-105.

29. Chan S., Chui C., Chan S., Kok S., Chan D., Tsoi M., Leung P., Lam A., Chan A., Lam K., Tang J., *ACS Med. Chem. Lett.*,2013; **4**: 170-174.
30. Lam K., Gambari R., Yuen M., Kan C., Chan P.,Xu L., Tang W., Chui C., Cheng Y., Wong S., Lau F., Tong S., Chan K., Lai B., Kok S., Cheng C., Chan A., Tang J.,*Bioorg. Med. Chem. Lett.*,2009; **19**: 2266-2269.
31. Gakhar G., Ohira T., Shi, A., HuaH., Nguyen T., *Drug Dev. Res.*, 2009; **69**: 526-534.
32. Sissi C., Palumbo M., *Curr. Med. Chem. Anti-Cancer Agents*, 2003; **3**: 439-450.
33. Abass M., *Heterocycles*, 2005, **65**: 901-965.
34. Kirsch G., Hesse S., Comel A., *Curr. Org. Synth.*, 2004; **1**: 47-63.
35. De beer E., Sherwood M.,Bacteriol J.,1945; **50**: 459-467.