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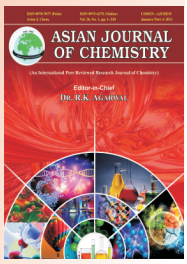

Design, Synthesis and Biological Evaluation of Some Novel Hexahydroquinoline-3-carbonitriles as Anticancer and Antimicrobial Agents

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The synthesis of ten novel 3-cyano-8-methyl-2-oxo-1,4-disubstituted-1,2,5,6,7,8-hexahydro-quinolines supported with benzensulfonyl and phenylthiocarbamoyl pharmacophores that are known to contribute to potential chemotherapeutic effects is described. They were evaluated *in vitro* for their antimicrobial activity against eight different microorganisms and for their cytotoxic effects against three different human tumor cell lines. The results revealed that nine compounds displayed variable inhibitory effects on the growth of the tested Gram-positive and Gram-negative bacteria with special pronounced activity against *S. aureus* and *E. coli* bacterial strains, in addition to a moderate antifungal activity against *C. albicans*. On the other hand, six compounds were able show remarkable cytotoxic efficiency against human colon carcinoma HT29, hepatocellular carcinoma Hep-G2 and Caucasian breast adenocarcinoma MCF7 cell lines. Collectively, the results would suggest that compounds **15** and **16** could be considered as possible dual antimicrobial-anticancer agents.

Keywords: Synthesis, N-benzensulfonyl, N-phenylthiocarbamoyl, cytotoxic agents, antimicrobial agents.

INTRODUCTION

Quinolines are well known and important nitrogen-containing heterocyclic compounds[1]. Quinoline derivatives have been established to possess considerable biological activities, which stimulated the research activity in this field[2]. They have several prominent effects, such as antimicrobial[3], antimycobacterial[4], antiinflammatory[5], analgesic[6] and anti-depressant[7] activities. Bi-functional quinoline derivatives dramatically increase the biological activity[8,9]. Various methods have been reported for their synthesis bi-fungsanal quinoline derivative[10,11]. It is used as intermediates for the formation of fused heterocyclic compounds such as pyrazolo quinoline pyrimidoquinolines[12,13]. The molecules having the quinolines framework have been largely investigated for optical-electrical applications for photophysical studies such as non-linear optical properties[14], photonic materials[15], devices, optical limiting[16], electrochemical sensing[17], light-emitting devices[18], Langmuir film[19] and solar cell materials[20]. However, the quinolines has been used extensively for the photo-alignment and photo-crosslinking unit in polymers[21]. Encouraged by these facts and in continuation with the wok related to the synthesis, spectral studies and biological properties of quinolines, herein is reported the synthesis of some novel hexahydro-quinoline-3-carbonitriles and their anticancer and antibacterial activities were investigated.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S infrared spectrophotometer using the KBr pellet technique. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 FT NMR spectrometer using tetramethylsilane as the internal standard and DMSO-d_6 as a solvent (Chemical shifts in δ, ppm). Elemental analyses were performed on a 2400 Perkin Elmer Series 2 analyzer and the found values were within ± 0.4 % of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum sheets (Type 60 F254, Merck) and the spots were detected by exposure to UV-lamp at λ 254.

3-Cyano-8-methyl-2-oxo-4-substituted 1,2,5,6,7,8-hexahydroquinolines (1, 2, 4, 6, 7 and 8) and 3-cyano-8-methyl-2-oxo-4-substituted 1,2,4,4a,5,6,7-octahydroquinolines (3 and 5): A mixture of the appropriate aldehyde (10 mmol), 2-methylcyclohexanone (1.46 g, 10 mmol), ethyl cyanoacetate (1.1 g, 10 mmol) and ammonium acetate (6.2 g, 80 mmol) in absolute ethanol (50 mL) was refluxed for 6 h. The reaction mixture was allowed to cool and the formed precipitate was filtered, washed with water, dried and recrystallized.

In case of bromo- and chloro benzaldehydes two products were obtained (**3** and **5**) which were separated by fractional

recrystallization. Physicochemical and analytical data are listed in Table-1. ^{1}H NMR spectral data are recorded in Table-2.

IR (KBr, ν_{max}, cm^{-1}): 3378-3264 (NH), 2239-2220 (CN), 1672-1668 (C=O). ^{13}C NMR (δ-ppm) for **1**: 15.1 (CH_3), 27.7, 27.9, 34.4, 34.9 (cyclohexyl C), 117.2 (CN), 95.7, 119.5, 132.7, 165.9 (CO), 169.4 (pyridine C), 126.2, 127.7, 128.4, 134.9 (Ar C). **2**: 15.4 (CH_3), 27.6, 28.1, 32.4, 34.5 (cyclohexyl C), 117.2 (CN), 96.7, 119.0, 133.0, 163.0 (CO), 169.4 (pyridone C), 122.2, 128.4, 131.7, 133.9 (Ar C). **3** : 18.2 (CH_3), 23.4, 23.6, 31.2 (C-5,6,7), 34.2 (C-4), 39.4 (C-3), 41.4 (C-4a), 116.8 (CN), 120.2, 126.8, 131.4,132.2, 132.6, 138.1 (Ar C) 171.2.0 (CO). **4**: 15.2 (CH_3), 27.8, 28.0, 34.6, 34.8 (cyclohexyl C), 117.6 (CN), 96.8, 119.4, 132.8, 162.9 (CO), 169.6 (pyridone C), 127.6, 128.8, 133.0, 133.2 (Ar C). **5**: 18.1 (CH_3), 23.2, 23.5, 31.0 (C-5,6,7), 34.1 (C-4), 39.6 (C-3), 41.2 (C-4a), 116.6 (CN), 126.9, 128.6, 129.4, 131.4, 132.2, 137.1 (Ar C), 171.3 (CO). **6**: 15.2 (CH_3), 27.8, 28.6, 34.4, 34,8 (cyclohexyl C), 56.0 (OCH_3), 117.3 (CN), 96.6, 120.2, 133.4, 164.7 (CO), 169 (pyridone C), 114.0, 127.2, 127.3, 161.2 (Ar C). **7**: 15.1 (CH_3), 20.5 (CH_3), 27.6, 27.8, 33.3, 34.2 (cyclohexyl C), 117.5 (CN), 96.0, 119.5, 133.0, 163.0 (CO), 169.2 (pyridone C), 125.9, 127.8, 128.6, 134.9 (Ar C). **8**: 15.3 (CH_3), 27.7, 28.0, 30.1, 34.2 (cyclohexyl C), 118.2 (CN), 101.6, 119.7, 132.7, 163.0 (CO), 169.3 (pyridone C), 126.4, 127.6, 130.6, 136.7 (thiophene C).

1-Benzensulfonyl-3-cyano-8-methyl-2-oxo-4-substituted 1,2,5,6,7,8-hexahydroquinolines (9-13): A mixture of the appropriate starting compound (**1**, **2**, **6-8**) (10 mmol) and benzenesulfonyl chloride (10 mmol, 1.77 g) in pyridine (10 mL) was heated under reflux for 4-6 h. After cooling the reaction mixture to room temperature, it was poured on crushed ice and the separated solid product was

TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS **1-18**

Compd.	R	R^1, R^2 or R^3	Yield (%)	m.p. (ºC)	m.f.	Calcd. (%)			Found (%)		
						C	H	N	C	H	N
1	C_6H_5	-	86	248-249	$C_{17}H_{16}N_2O$	77.25	6.10	10.60	77.36	6.22	10.72
2	4-BrC_6H_4	-	79	289-290	$C_{17}H_{15}N_2OBr$	59.49	4.41	8.16	59.50	4.42	8.24
3	4-BrC_6H_4	-	12	238-240	$C_{17}H_{17}N_2OBr$	59.14	4.96	8.11	59.25	5.02	8.30
4	4-ClC_6H_4	-	78	233-235	$C_{17}H_{15}N_2OCl$	68.34	5.06	9.38	68.44	5.13	9.41
5	4-ClC_6H_4	-	14	220-222	$C_{17}H_{17}N_2OCl$	67.88	5.70	9.31	67.98	5.62	9.39
6	4-$CH_3OC_6H_4$	-	85	250-252	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52	73.34	6.02	9.66
7	4-$CH_3C_6H_4$	-	82	246-248	$C_{18}H_{18}N_2O$	77.67	6.52	10.06	77.73	6.45	10.21
8	2-Thienyl	-	78	253-255	$C_{15}H_{14}N_2OS$	66.64	5.22	10.36	66.77	5.43	10.54
9	C_6H_5	-	72	233-234	$C_{23}H_{20}N_3O_3S$	68.30	4.98	6.93	68.10	5.11	7.10
10	4-BrC_6H_4	-	70	223-224	$C_{23}H_{19}N_3O_3SBr$	57.15	3.96	5.80	57.21	3.87	5.90
11	4-$CH_3OC_6H_4$	-	80	202-204	$C_{24}H_{22}N_3O_4S$	66.34	5.10	6.45	66.44	5.12	6.61
12	4-$CH_3C_6H_4$	-	82	186-188	$C_{24}H_{22}N_2O_3S$	68.88	5.30	6.69	69.24	3.98	8.87
13	2-Thienyl	-	82	224-226	$C_{21}H_{18}N_2O_3S_2$	61.44	4.42	6.82	61.32	4.62	6.90
14	C_6H_5	-	80	234-236	$C_{24}H_{21}N_3OS$	72.15	5.30	10.52	72.22	5.42	10.68
15	4-BrC_6H_4	-	84	138-140	$C_{24}H_{20}BrN_3OS$	60.25	4.21	8.78	60.33	4.39	8.62
16	4-$CH_3OC_6H_4$	-	83	210-212	$C_{25}H_{23}N_3O_2S$	69.91	5.40	9.78	70.02	5.34	9.84
17	4-$CH_3C_6H_4$	-	79	122-124	$C_{25}H_{23}N_3OS$	72.61	5.61	10.16	72.66	5.82	10.12
18	2-Thienyl	-	78	128-130	$C_{22}H_{19}N_3OS_2$	65.16	4.72	10.36	65.02	4.77	10.23

TABLE-2
^{1}H NMR SPECTRAL DATA (δ/ppm)[a] OF COMPOUNDS **1-18**

Compound	R	R'	CH_3 (d, 3H)	H-5, 6, 7, 8 (2m, 7H)	Ar-H	Others
1	C_6H_5	-	1.26	1.85, 2.29	6.92-7.68 (5H)	8.21 (s, 1H, NH)
2	4-BrC_6H_4	-	1.18	1.90, 2.23	7.19-7.38 (4H)	8.16 (s, 1H, NH)
3[b]	4-BrC_6H_4	-	1.71	1.74, 2.33	7.02-7.35 (4H)	8.05 (s, 1H, NH)
4[c]	4-ClC_6H_4	-	1.16	1.78, 2.13	7.22-7.34 (4H)	8.10(s, 1H, NH)
5	4-ClC_6H_4	-	1.74	1.80, 2.21	7.07-7.19 (4H)	8.25 (s, 1H, NH)
6	4-$CH_3OC_6H_4$	-	1.22	1.98, 2.28	6.99-7.26 (4H)	8.14 (s, H, NH), 3.73 (s, CH_3O)
7	4-$CH_3C_6H_4$	-	1.16	1.61, 2.19	7.01-7.55 (4H)	8.09 (s, 1H, NH), 2.34 (s, CH_3)
8	2-Thienyl	-	1.20	1.65, 2.27	7.31-7.64 (3H)	8.11 (s, 1H, NH)
9	C_6H_5	-	1.16	1.68, 2.21	7.14-7.85 (10H)	-
10	4-BrC_6H_4	-	1.18	1.66, 2.10	7.04-7.38 (4H)	-
11	4-$CH_3OC_6H_4$	-	1.21	1.65, 2.16	6.97-7.29(4H)	3.76 (s, CH_3O)
12	4-$CH_3C_6H_4$	-	1.19	1.68, 2.18	7.11-7.52 (4H)	2.34 (s, CH_3)
13	2-Thienyl	-	1.17	1.70, 2.16	7.33-7.62 (3H)	-
14	C_6H_5	-	1.15	1.69, 2.18	6.49-7.32 (10H)	6.23 (s, NH)
15	4-BrC_6H_4	-	1.16	1.65, 2.13	6.64-7.42 (9H)	6.31 (s, NH)
16	4-$CH_3OC_6H_4$	-	1.18	1.75, 2.14	6.47-7.19 (9H)	3.75 (s, CH_3O), 6.42 (s, NH)
17	4-$CH_3C_6H_4$	-	1.14	1.81, 2.22	6.52-6.18 (9H)	2.35(s, CH_3), 6.57 (s, NH)
18	2-Thienyl	-	1.16	1.76, 2.21	7.33-7.67 (8H)	6.24 (s, NH)

filtered, washed with water, dried and recrystallized from ethanol.

IR (KBr, ν_{max}, cm^{-1}): 2236-2224 (CN), 1676-1668 (C=O pyridone), 1378-1372 and 1198-1172 (SO_2). ^{13}C NMR (δ-ppm) **9**: 15.1 (CH_3), 27.6, 27.9, 31.3, 34.4 (cyclohexyl C), 95.9, 119.8, 133.0, 163.2 (CO), 169.5 (pyridone C), 117.6 (CN), 125.6, 126.2, 127.7, 128.4, 128,8, 131.7, 134.9, 139.3 (Ar C).**10**: 14.9 (CH_3), 27.5, 27.7, 34.1, 34.4 (cyclohexyl C), 95.9, 119.8, 133.0, 163.2 (CO), 169.5 (pyridone C), 117.6 (CN), 123.1, 128.2, 131.7, 128.4, 128,8, 131.7, 134.9, 139.8 (Ar C). **11**: 15.3 (CH_3), 27.3, 27.8, 31.0, 34.2 (cyclohexyl C), 56.1 (OCH_3), 95.7 119.4, 132.7, 163.4 (CO), 169.7 (pyridone C), 117.2(CN), 114.1, 125.6, 127.2, 127.3, 128.8, 131.7, 139.3, 161.5 (Ar C). **12**: 15.7 (CH_3), 20.8 (CH_3), 27.8, 28.2, 32.3, 34.6 (cyclohexyl C), 117.4 (CN), 95.5, 119.2, 133.1, 164.2 (CO), 169.4 (pyridone C), 125.4, 126.1, 128.7, 129.0, 131.7, 131.9, 136.9, 139.4 (Ar C). **13**: 15.2 (CH_3), 27.1, 27.5, 31.3, 34.5 (cyclohexyl C), 95.2 119.6, 132.5, 163.2 (CO), 169.6 (pyridone C), 117.1(CN), 125.5, 126.5, 127.8, 128.7, 130.3, 131.6, 136.4, 139.1 Ar C).

3-Cyano-8-methyl-2-oxo-1-(phenylthiocarbamoyl)-4-substituted 1,2,5,6,7,8-hexahydroquinolines (14-18): A mixture of the appropriate quinoline derivative (**1**, **2**, **6-8**) (10 mmol) and the phenyl isothiocyanate (1.35 g, 10 mmol) in pyridine (10 mL) was heated under reflux for 6-8 h. After being cooled to room temperature, the reaction mixture was poured on ice cold water and the separated solid product was filtered, washed with water, dried and recrystallized from ethanol as needles.

IR (KBr, ν_{max}, cm^{-1}): 2232-2220 (CN), 1670-1665 (C=O pyridone), 1242-1228 (C=S). ^{13}C NMR (δ-ppm) **14**: 15.7 (CH_3), 27.9, 28.3, 32.4, 35.0 (cyclohexyl C), 117.5 (CN), 98.6, 120.2, 132.9, 162.7 (CO), 168.3 (pyridone C), 124.5, 125.3, 126.2, 127.7, 128.4, 128.8, 134.9, 139.4 (Ar C), 175.4 (CS). **15**: 15.6 (CH_3), 28.0, 28.2, 32.6, 34.9 (cyclohexyl C), 117.4 (CN), 99.2, 119.8, 132.7, 163.0 (CO) 169.4 (pyridone C), 122.5, 125.6, 127.5, 128.3, 128.8, 133.0, 133.3, 140.1 (Ar C), 175.0 (CS). **16**: 15.5 (CH_3), 27.8, 28.2, 32.3, 34.6 (cyclohexyl C), 56.1 (CH_3O), 118.2 (CN), 95.8, 119.6, 133.3, 164.0 (CO), 169.4 (pyridone C), 114.4, 126.5, 127.6, 128.4, 129.5, 130.5, 141.9, 160.5 (Ar C). **17**: 15.5 (CH_3), 27.9, 28.3, 32.3, 35.0 (cyclohexyl C), 117.3 (CN), 95.8, 119.3, 132.7, 162.9 (CO), 169.1 (pyridone C), 124.5, 125.2, 126.2, 128.7, 129.1, 131.9, 136.8, 139.5 (Ar C). **18**: 15.7 (CH_3), 27.8, 28.2, 32.2, 35.1 (cyclohexyl C), 117.1 (CN), 95.5, 119.4, 132.6, 162.7(CO), 169.4 (pyridone C), 117.1(CN), 124.5, 125.3, 126.4, 127.5, 128.9, 130.2, 136.3, 139.4 (Ar C).

Biological activity

***in vitro* MTT cytotoxicity assay:** All the newly synthesized compounds were investigated for their *in vitro* cytotoxic effect *via* the standard MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method against a panel of three human tumour cell lines namely; Caucasian breast adenocarcinoma MCF7, hepatocellular carcinoma Hep-G2 and colon carcinoma HT29. The results are presented in Table-3 as LC_{50} (μg/mL, μM) which is the lethal concentration of the compound which causes death of 50 % of the cells in 24 h.

in vitro Antibacterial and antifungal activities

Minimal inhibitory concentration (MIC) measurement: The MIC of the most active compounds were measured using the twofold serial broth dilution method[22]. The MIC values in μg/mL (μM) of the compounds are listed in Table-4.

RESULTS AND DISCUSSION

The synthetic strategies adopted for the preparation of the intermediate and target compounds are described in **Schemes-I**. The key intermediates 3-cyano-8-methyl-2-oxo-4-substituted hexahydro- and octahydroquinolines **1-8** were synthesized *via* one-pot multicomponent reaction (MCR) of the appropriate aromatic aldehyde and 2-methylcyclohexanone, an excess of ammonium acetate and ethyl cyanoacetate in boiling ethanol. Such type of reactions has received considerable interest since it is easier to perform, gives higher yields and less time consuming, when compared with the traditional procedure that involved the formation of the 2-arylidene-6-methylcyclohexanones (chalcones) *via* Claisen-Schmidt condensation followed by cyclocondensation with ethyl cyanoacetate and ammonium acetate[23]. It is worthy to mention here, that when the aromatic aldehyde is bromo- or chloro benzaldehyde two products were isolated one is the expected quinoline derivatives (**2** and **4**) which is the major product and a side product (**3** and **5**) represent the reduced formula of **2** and **4**, respectively. This may be attributed to the electron withdrawing character of the halogen atoms. The IR spectra of the cyanoquinolines **1-8** exhibited absorption bands

TABLE-3
CYTOTOXIC EFFECTS LC_{50}; μg/mL (μM)[a] OF THE ACTIVE COMPOUNDS ON SOME HUMAN TUMOR CELL LINES USING THE MTT ASSAY

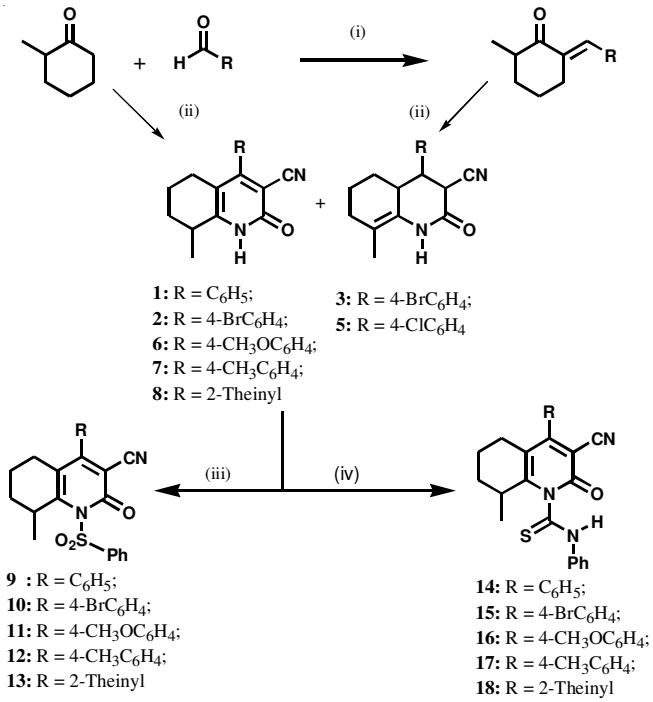
Compound	HT29[b]	Hep-G2[c]	MCF 7[d]
2	65.8 (220.2)	57.2 (191.5)	46.3 (155)
6	47.1 (160)	66.3 (226.8)	34.1 (116)
10	33.2 (68.6)	22.4 (46.3)	24.8 (51.3)
11	29.6 (68)	18.5 (64)	25.2 (58)
15	8.4 (19)	20.6 (47)	12.1 (28)
16	14.9 (32)	11.6 (25)	9.7 (21)
17	26.3 (70)	48.7 (131)	64.9 (175)
18	34.9 (77)	31.8 (70)	-
Doxorubicin[f]	21.1 (40)	1.69 (3)	2.14 (4)

[a]LC_{50}: Lethal concentration of the compound which causes death of 50 % of cells in 24 h μg/mL(μM); [b]HT29 (Human colon carcinoma cell line); [c]Hep-G2 (Human hepatocellular carcinoma cell line); [d]MCF7 (Human breast cancer cell line); [e]Totally inactive against this cell line; [f]Positive control cytotoxic agent

TABLE-4
MINIMAL INHIBITORY CONCENTRATIONS [MIC, µg/mL (µM)] OF THE TESTED COMPOUNDS

Compound no.	*S. aureus*	*B. subtilis*	*M. luteus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*C. albicans*
2	50 (135.2)	100 (257.8)	-	50 (-)	100 (-)	-	-
6	50 (169.8)	100 (339.7)	-	25 (84.9)	100 (339.7)	-	-
9	50 (123.6)	100 (247.2)	-	100 (247.2)	100 (247.2)	-	-
10	12.5 (28.5)	25 (57)	100 (228)	6.25 (14.2)	25 (57)	100 (228)	25 (57)
11	12.5 (28.8)	50 (115.2)	100 (230.4)	12.5 (28.8)	25 (57.6)	-	25 (57.6)
14	25 (57.5)	100 (230)	200 (460)	25 (57.5)	50 (115)	-	100 (230.4)
15	6.25 (13.3)	25 (53.4)	25 (53.4)	6.25 (13.3)	12.5 (26.7)	50 (106.8)	12.5 (26.7)
16	25 (60)	50 (120)	50 (120)	12.5 (60)	100 (240)	-	50 (120)
18	12.5 (27.6)	50 110.6)	-	12.5 (27.6)	50 (110.6)	100 (221.2)	12.5 (27.6)
Ampicillin	6.25 (18)	12.5 (36)	12.5 (36)	6.25 (18)	12.5 (36)	12.5 (36)	-
Clotrimazole	-	-		-	-	-	6.25 (18)

[a]MIC > 200 (600) µg/mL (µM)



Scheme-I: Reagent and reaction conditions: (i) NaOH; (ii) $CNCH_2COOEt$/NH_4OAc, absolute EtOH, reflux, 6 h. (iii) $PhSO_2Cl$ in Pyridine, reflux 4-6 h; (iv) PhNCS in Pyridine, reflux 6-8 h

at 2239-2220 and 1672-1668 cm^{-1} for the CN and CO groups, respectively. Their ^1H NMR showed beside the aromatic protons two multiplets at δ 2.26-2.88 and 2.54-2.90 ppm corresponding to the protons of the cyclohexyl moiety in the quinoline derivatives **2**, **6**, **7** and **8** while in case of compounds **3** and **5**, the ^1H NMR exhibited beside the aromatic protons, two multiplets at δ 1.61-1.94 (6*H*), δ 2.30-2.38 (1*H*), a triplt at 3.12-3.24 (1*H*) and a doublet at δ 3.54-3.85 (1H, *J* = 9Hz) for the H-5,6,7, H-4a, H-4 and H-3, respectively (Table-2). The structures were further supported by ^{13}C NMR data. The hexahydroquinolines **1**, **2**, **6**, **7** and **8** obtained from **Scheme-I** were utilized as key intermediates for the synthesis of the target compounds **9-18**. In this respect, reacting compounds **1**, **2**, **6**, **7** and **8** with benzenesulfonyl chloride in a pyridine medium resulted in the introduction of a benzenesulfonyl moiety at position-1 to yield compounds **9-13**. Moreover, condensation of the same compounds with phenyl isothiocyanate in alkaline medium afforded the corresponding N-phenyl-thiocarbamoyl analogs **22-26**. The IR spectra of these compounds showed C=S absorption at 1242-1228 cm^{-1} as well as a C=O and CN absorptions in the regions 1670-1665 and 2232-2220 cm^{-1}. The structures were further supported from their ^1H NMR (Table-2) and ^{13}C NMR spectral data which exhibited beside the expected number of aliphatic and aromatic carbons, two signals at δ 162.7-163.0 and δ 175.0-175.4 for the CO and CS, respectively .

Biological evaluation

***in vitro* MTT cytotoxicity assay:** The data obtained (Table-3) revealed that eight compounds namely **2**, **6**, **10**, **11**, **15**, **16**, **17** and **18** were able to affect cell viability of the tested tumour cell lines particularly the human colon carcinoma HT29 cell line whereas the rest of the compounds were totally inactive. In addition, the three tested human tumour cell lines exhibited variable degree of sensitivity profiles towards the active compounds. In terms of µg/mL concentration, the human colon carcinoma HT29 cell line showed pronounced sensitivity against compounds **15** and **16** (LC_{50} 8.4 and 14.9 µg/mL, respectively) even higher than that of doxorubicin (LC_{50} 21.1 µg/mL). Moreover, a remarkable cytotoxic potential was displayed by compounds **11** and **17** against the same cell line (LC_{50} 29.6 and 26.3 µg/ mL respectively) comparable to that of doxorubicin. The rest of the active compounds showed moderate to weak activity profiles against the same cell line with LC_{50} range of 33.2-34.9 µg/mL. On the other hand, the growth of the human hepatocellular carcinoma Hep-G2 cell line was found to be moderately inhibited by six of the active compounds with LC_{50} values range of 11.6-48.7 µg/ mL, among which compounds **11** and **15** (LC_{50} values 18.5 and 11.6 µg/mL, respectively) revealed the highest cytotoxic activity as compared to doxorubicin (LC_{50} 1.69 µg/mL). Regarding the human breast cancer MCF7, it was proved to be the least sensitive among the tested cell lines, as its growth was inhibited by only seven of the tested compounds. However, a remarkable growth inhibitory potential was shown by compounds **15** and **16** as evidenced from their LC_{50} values (12.1 and 9.7 µg/mL, respectively) when compared to doxorubicin (LC_{50} 2.14 µg/mL). A close examination of the structure of the active compounds showed that the 4-bromo and 4-methoxy groups at the C-4 aryl ring are the most favourable substituents. Although the key precursors **2** and **6** possessed moderate cytotoxic profiles,

yet sulfonylation as in (**10**, **11**), led to a noticeable enhancement in both the cytotoxic spectrum and potential. On the other hand, great improvement of the cytotoxic potential was linked to the introduction of a thiocarbamoyl substituent at position-1 (**15**-**18**). It could be clearly recognized that the bromo and methoxy derivatives (**15** and **16**) showed distinctive cytotoxic activities, whereas **17** and **18** were moderately active. Among these, the analogs **15** and **16** proved to be the most active members in this study with a broad spectrum of activity against the tested cell lines.

***in vitro* Antibacterial and antifungal activities:** All of the newly synthesized target compounds were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6633) and *Micrococcus luteus* (ATCC 21881) as examples of Gram-positive bacteria and *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Klebsiella pneumonia* (clinical isolate) as examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal potential against *Candida albicans* (ATCC 10231) and *Aspergillus niger* (recultured) fungal strains. Agar-diffusion method was used for the determination of the preliminary antibacterial and antifungal activities. Ampicillin trihydrate and clotrimazole were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm. The minimum inhibitory concentration (MIC) measurement was determined for compounds that showed significant growth inhibition zones (= 13 mm) using the two-fold serial dilution method[18]. As revealed from MIC data recorded in Table-4, [MIC expressed in both concentration units µg/mL (µM)], nine out of the twelve synthesized compounds **1**, **2**, **6**, **8** and **9-18** displayed variable inhibitory effects on the growth of the tested Gram-positive and Gram-negative microorganisms with pronounced activity against *S. aureus* and *E. coli* bacterial strains. In addition, some members exhibited moderate antifungal activity against *C. albicans*, whereas, all the tested compounds lacked antifungal potential against *Aspergillus niger*.

In terms of µg/mL concentration, among the tested Gram-positive bacterial strains, two organisms namely; *S. aureus* and *B. subtilis* showed relatively high sensitivity towards the active compounds. In this view, compound **15** was equipotent to ampicillin (MIC 6.25 µg/mL) against *S. aureus*, whereas the analogs **10**,**11** and **18** (MIC 12.5 µg/mL) were 50 % less active than ampicillin. With regard to the activity against *B. subtilis*, compounds **10** and **15** (MIC 25 µg/mL) showed half the activity of ampicillin. Concerning the antibacterial activity against the three tested Gram-negative strains, three analogs namely **10** and **15** were able to produce a distinctive growth inhibitory profile against *E. coli* (MIC 6.25 µg/mL) which was equipotent to ampicillin, whereas, compounds **11** and **18** (MIC 12.5 µg/mL), were 50 % less active than ampicillin against the same organism. Meanwhile, the tested *P. aeruginosa* strain showed moderate sensitivity towards most of the active compounds, particularly compound **15** (MIC 12.5 µg/mL) which was equipotent to ampicillin. On the other hand, only six compounds **10**, **11**, **14**, **15**, **16** and **18** were able to display a noticeable growth inhibitory potential against *C. albicans*, among which compounds **15** and **18** (MIC 12.5 µg/mL) were the most active members when compared with clotrimazole (MIC 6.25 µg/mL). A close examination of the structures of the active compounds revealed that, their antimicrobial activity is strongly bound to the nature of the substituent of the aryl ring at C-4, together with the substituent linked to position-1 of the ring structure. In general, it could be clearly recognized that potential antibacterial activity was connected with the brominated derivatives (R = 4-Br C_6H_4), whereas moderate activities were displayed by the methoxylated analogs (R = 4-CH_3O C_6H_4). In this context, the key hexahydro quinoline precursors **2** and **6** showed moderate antimicrobial potential, with particular effectiveness against *S. aureus* and *E. coli*. Introducing a benzenesulfonyl moiety at position-1 gave rise to three active compounds **9-11**, among which the bromo derivative **10** showed equipotent activity to ampicillin against *E. coli* and 50 % of its activity against *S. aureus*, *B. subtilis* and *P. aeruginosa*, together with an appreciable antifungal activity against *C. albicans*. Moreover, incorporating a substituted thiocarbamoyl counterpart as in compounds **14**,**15**,**16** and **18**, resulted in an obvious enhancement in both the antimicrobial potential and spectrum. It could be clearly recognized that the activity of these analogs is connected with the aryl substituent in position-4. Within this series, compound **15** (R = 4-Br-C_6H_4) was the most active member as it displayed a fourfold increase in the antimicrobial activity against *S. aureus*, *E. coli* and *P. aeruginosa* (MIC 6.25, 6.25 and 12.5 µg/mL, respectively), together with a remarkable antifungal activity (12.5 µg/mL), when compared with the parent **2**.

Conclusion

Six compounds were able show remarkable cytotoxic efficiency against human colon carcinoma HT29, hepatocellular carcinoma Hep-G2 and Caucasian breast adenocarcinoma MCF7 cell lines. The results revealed that compounds **11**, **15**, **16** and **17** showed considerable broad spectrum cytotoxic activity against the three tested cell lines, among which the analogs **15** and **16** proved to be the most active members in this study with special effectiveness against the human colon carcinoma HT29 and human breast cancer MCF7 cell lines even higher than that of doxorubicin, the reference standard cytotoxic agent utilized in this test. On the other hand, seven 1,2,5,6,7,8-hexahydro-quinoline derivatives displayed very good activity against *S. aureus* and *E. coli* bacterial strains, in addition to moderate antifungal activity against *C. albicans*. Compounds **10**, **11** and **15** could be considered as the most active broad spectrum antimicrobial members identified in this study. Among these, compound **15** proved to be the most active candidate as it showed equipotency to ampicillin against *S. aureus*, *E. coli* and *P. aeruginosa*, in addition to an obvious antifungal activity comparable with clotrimazole. The best antifungal activity was demonstrated by compounds **15** and **18** which possessed almost half the activity of clotrimazole against *C. albicans*.

Finally, the obtained antimicrobial and anticancer data makes such type of compounds a fruitful matrix for further development of more potent and selective cytotoxic and/or

antimicrobial agents. Compounds **15** and **16** could be considered as possible dual antimicrobial-anticancer candidates that deserve further investigation and derivatization in order to explore the scope and limitation of its biological activities.

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