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ANTICANCER EVALUATION OF AZETIDINONE AND THIAZOLIDINONE DERIVATIVES OF QUINOLONE

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ABSTRACT

Amino quinolone and their imines with five different benzaldehydes, azetidinone, and thiazolidinone derivatives were synthesised and compared for their anticancer activity. Two response parameters GI_{50} and TGI were calculated for each cell line. Among them, compounds **4b, 4e** and **5b** showed the highest activity for antitumor testing against panels of cell lines. The structures of these compounds have been established on the basis of elemental analysis and spectral data.

Key words: Anticancer, Azetidinone, Thiazolidinone, Quinolone

INTRODUCTION

The rise of drug resistance of potentially fatal diseases, such as tuberculosis, cancer and pneumonia, beside the re–emergence of other diseases present major challenges. The development of multidrug resistance is a major problem in the chemotherapy of human cancer[1]. One of these types was proved to involve a membrane–bound protein. P–glycoprotein (Pgp) acts as an efflux pump for anticancer drugs[2]. Recently, various compounds have been shown to inhibit Pgp–mediated drug efflux[3]. e.g. like verapamil[4], dihydropyridines (DHPS)[5], propafenone[6], antipsychotic drugs like phenothiazines[7], cyclosporins[8], thiainopipridine S9788[9], acridine carboxamido GF120918[10], quinoline MS209[11] and stipamide[12]. The first prototypic "Quinoline" and its modified analog ofloxacin showed remarkable in vitro cytotoxicity against panels of cell lines. With GI50 values in the low micromolar concentration range in most of human tumor cell lines tested by the "National Cancer Institute". Nowadays, the paucity of the reported synthetic methods and the biological evolution of quinolines invite a detailed investigation of chemistry of these interesting compounds and indicated that their synthesis is non trivial. Quinolones are known to possess important pharmacological activities[13] such as anti–HIV[14], antibacterial[15], antimicrobial[16], antitumor–anticancer[17], mammalian topoisomerase etc. The azetidinone[18] and thiazolidinone[19] derivatives also exhibit wide range of biological activities such as anticancer[20], antibacterial[21], antimicrobial etc.

In the present work, trias were adopted to synthesise three series of quinolines which bear Schiff base (imines), azetidinone and thiazolidinone moiety. This is meant to check, how much these structural visibilities would affect the antitumor activities of the products?

RESULTS AND DISCUSSION

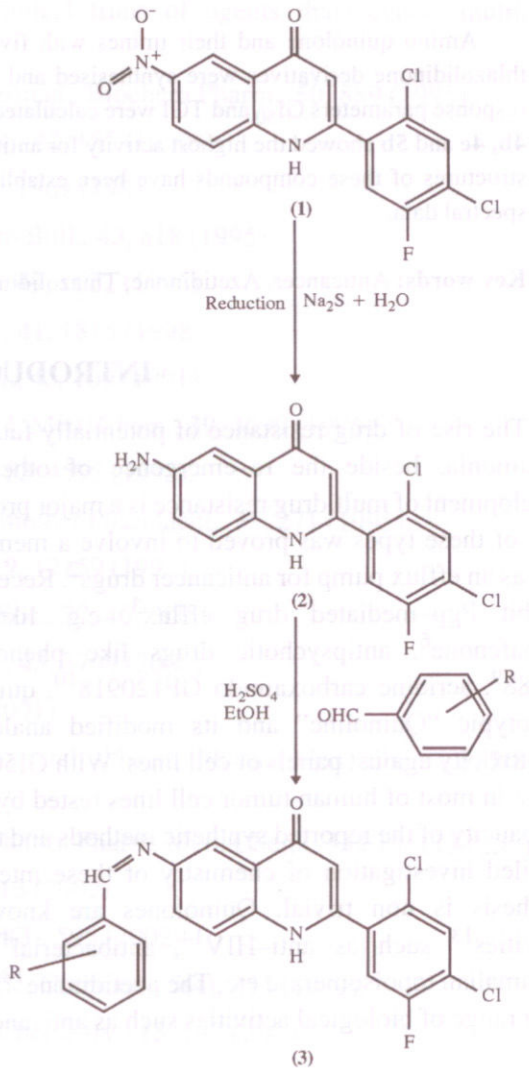
Antitumor testing

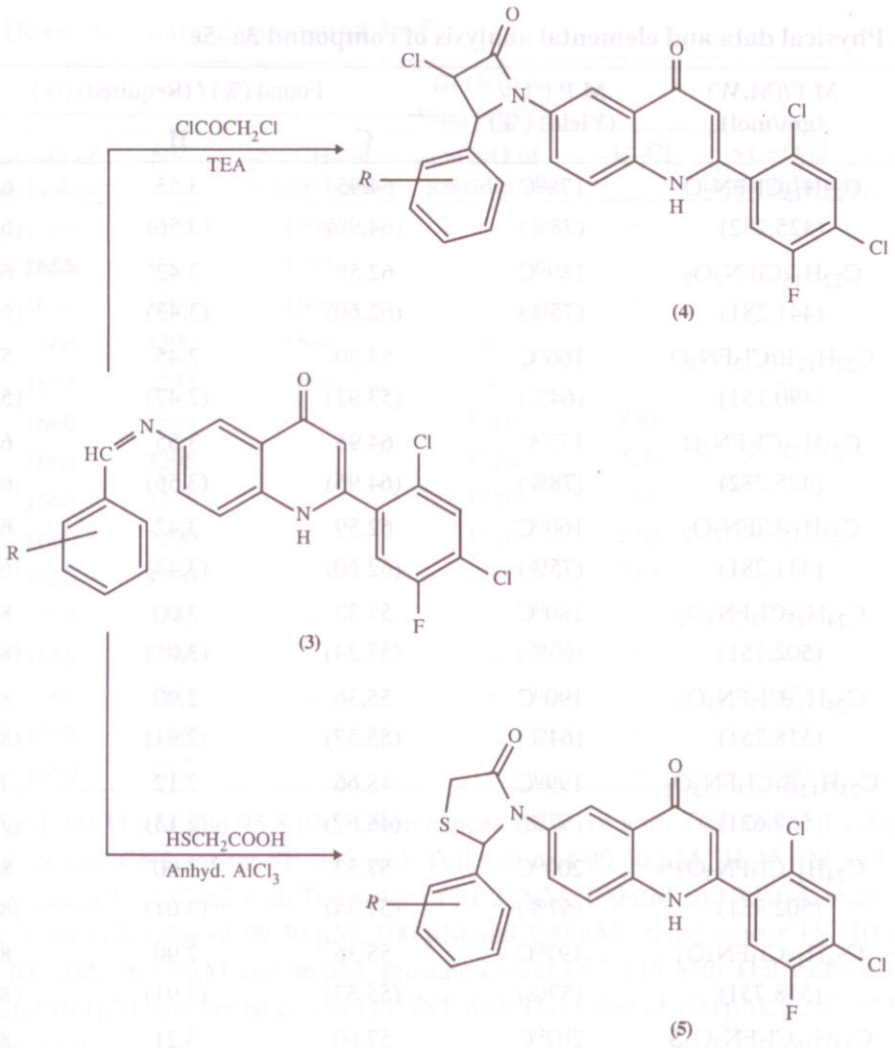
All compounds were at first tested by incubation with five different concentrations (0.01–100 μM) for their cytotoxic activity against nine tumor subpanels and create log concentration –% growth inhibition curves. The GI_{50} value corresponds to the compounds concentration causing 50% decrease in net growth. The TGI value is the compounds concentration in total growth inhibition. Subpanel and full panel mean–graph midpoint values (MG–MID) for certain agents are the average of individual real and default GI_{50}. TGI values of all cell lines in the subpanel or the full panel, respectively.

i).Cytotoxic activity for 50% of total net growth inhibition (GI_{50}):

The cytotoxic activity of compound **4b, 4e** and **5b** against leukemia MOLT–4 with GI_{50} value of 31.17 μM, 46.20 μM and 34.30 μM, non–small cell lung cancer HOP–92 with GI_{50} value of 61.28 μM, 64.52 μM and 49.90 μM, colon cancer HCT–15 with GI_{50} value of 62.67 μM, 50.98 μM and 50.0 μM, CNS cancer SF–295 with GI_{50} value of 63.48 μM, 76.67 μM and 51.20 μM, melanoma cancer UACC–62 with GI_{50} value of 67.52 μM, 73.35 μM and 67.0 μM, ovarian cancer IGROV1 with GI_{50} value of 72.65 μM, 69.78 μM and 64.7 μM, renal cancer TK–10 with GI_{50} value of 99.27 μM, 54.90 μM and 78.9 μM, prostate cancer DU–145 with GI50

REACTION SCHEME





Compound No.			R
3a	4a	5a	o-CH_3
3b	4b	5b	o-OCH_3
3c	4c	5c	p-Br
3d	4d	5d	p-CH_3
3e	4e	5e	o-OCH_3

value of 52.37 µM, 67.40 µM and 65 µM and breast cancer HS578T with GI_{50} value of 43.60 µM, 43.45 µM and 71 µM, respectively.

ii). Cytotoxic activity for 100% of total net growth inhibition (TGI):

The cytotoxic activity of compound **4b, 4e** and **5b** against leukemia MOLT–4 with TGI value of 100 µM, 93.56 µM and 86.3 µM, non–small cell lung cancer HOP–92 with TGI value

Table 1. Physical data and elemental analysis of compound 3a–5e

No	M.F/(M.W) (gm/mol)	M.P (°C)/ (Yield) (%)	Found (%) / (Required) (%)		
			C	H	N
3a	$C_{23}H_{15}Cl_2FN_2O$	178°C	64.95	3.55	6.58
	(425.282)	(78%)	(64.96)	(3.56)	(6.59)
3b	$C_{22}H_{15}ClFN_2O_2$	189°C	62.59	3.42	6.34
	(441.281)	(75%)	(62.60)	(3.43)	(6.35)
3c	$C_{22}H_{12}BrCl_2FN_2O$	166°C	53.90	2.45	5.71
	(490.151)	(64%)	(53.91)	(2.47)	(5.72)
3d	$C_{23}H_{15}Cl_2FN_2O$	177°C	64.95	3.55	6.58
	(425.282)	(78%)	(64.96)	(3.56)	(6.59)
3e	$C_{22}H_{15}ClFN_2O_2$	160°C	62.59	3.42	6.34
	(441.281)	(75%)	(62.60)	(3.43)	(6.35)
4a	$C_{24}H_{15}Cl_3FN_3O_2$	180°C	57.32	3.00	8.34
	(502.751)	(66%)	(57.34)	(3.01)	(8.36)
4b	$C_{24}H_{15}Cl_3FN_3O_3$	190°C	55.36	2.90	8.05
	(518.751)	(64%)	(55.57)	(2.91)	(8.10)
4c	$C_{23}H_{12}BrCl_3FN_3O_2$	199°C	48.66	2.12	7.39
	(567.621)	(57%)	(48.67)	(2.13)	(7.40)
4d	$C_{24}H_{15}Cl_3FN_3O_2$	200°C	57.32	3.00	8.34
	(502.751)	(57%)	(57.34)	(3.01)	(8.36)
4e	$C_{24}H_{15}Cl_3FN_3O_3$	197°C	55.36	2.90	8.05
	(518.751)	(57%)	(55.57)	(2.91)	(8.10)
5a	$C_{24}H_{16}Cl_2FN_3O_2S$	207°C	57.60	3.21	8.39
	(500.373)	(67%)	(57.61)	(3.22)	(8.40)
5b	$C_{24}H_{16}Cl_2FN_3O_3S$	211°C	55.81	3.11	8.13
	(516.372)	(58%)	(55.82)	(3.12)	(8.14)
5c	$C_{23}H_{13}BrCl_2FN_3O_2S$	196°C	48.86	2.31	7.42
	(565.242)	(60%)	(48.87)	(2.32)	(7.43)
5d	$C_{24}H_{16}Cl_2FN_3O_2S$	237°C	57.60	3.21	8.39
	(500.373)	(59%)	(57.61)	(3.22)	(8.40)
5e	$C_{24}H_{16}Cl_2FN_3O_3S$	222°C	55.81	3.11	8.13
	(516.372)	(68%)	(55.82)	(3.12)	(8.14)

Table 2. IR spectral data of compound 3a–5e

No.	IR (KBr) ν_{max} (cm^{-1})						
	>C=O of quinoline	–NH–	–N=CH– of Schiff–base	>C=O of azetidinone	–C–Cl	>C=O of thiazolidinone	–C–S–C
3a	1660	3295	1590	–	–	–	–
3b	1655	3299	1595	–	–	–	–
3c	1660	3290	1600	–	–	–	–
3d	1660	3290	1590	–	–	–	–
3e	1655	3295	1600	–	–	–	–
4a	1660	3299	–	1710	730	–	–
4b	1660	3295	–	1720	726	–	–
4c	1660	3295	–	1710	730	–	–
4d	1660	3290	–	1710	730	–	–
4e	1660	3290	–	1710	730	–	–
5a	1660	3295	–	–	–	1690	710
5b	1655	3290	–	–	–	1688	705
5c	1660	3295	–	–	–	1690	710
5d	1660	3290	–	–	–	1685	710
5e	1650	3290	–	–	–	1690	705

of 94.60 μM, 90.34 μM and 95.8 μM, colon cancer HCT–15 with TGI value of 100 μM, 100 μM and 97.5 μM, CNS cancer SF–295 with TGI value of 90.26 μM, 91.45 μM and 100 μM, melanoma cancer UACC–62 with TGI value of 91.22 μM, 100 μM and 90 μM, ovarian cancer IGROV1 with TGI value of 99.30 μM, 100 μM and 100 μM, renal cancer TK–10 with TGI value of 100 μM, 76.57 μM and 96 μM, prostate cancer DU–145 with TGI value of 100 μM, 100 μM and 100 μM and breast cancer HS578T with TGI value of 100 μM, 80.67 μM and 100 μM, respectively.

Subpanel and full panel mean–graph midpoint values (MG–MID) for certain agents are the average of individual real and default GI_{50} and TGI values of all cell lines in the subpanel or the full panel, respectively. All the activity data are shown in the Tables 4 and 5, respectively.

EXPERIMENTAL

All melting points were determined in PMP–DM scientific melting point apparatus and are uncorrected. The IR spectra were recorded in KBr on a Perkin–Elmer RX 1 FT–IR Spectrophotometer (Serial No. 51448) and ^1H NMR spectra were determined with Perkin Elmer Model–32 NMR Spectrometer at 300 MHz using TMS as internal standard and $CDCl_3$ as solvent.

Table 3. ^{1}H NMR spectral data of compound 3a–5e

No.	^{1}H NMR δ ppm		
3a	6.58–8.2 (m, 8H, aromatic), 1.90 (s, 3H, Me)	9.0 (s, 1H, NH)	8.1 (s, 1H, N=CH),
3b	6.60–8.3(m,, 9H,, aromatic), 3.20 (s, 3H, OMe)	8.9 (s, 1H, NH)	8.1 (s, 1H, N=CH),
3c	6.70–8.3 (m, 9H, aromatic),	8.9 (s, 1H, NH),	8.1 (s, 1H, N=CH),
3d	6.65–8.2 (m, 9H, aromatic), 1.90 (s, 3H, Me)	8.9 (s, 1H, NH)	8.0 (s, 1H, N=CH),
3e	6.58–8.2 (m, 9H, aromatic), 3.20 (s, 3H, OMe)	8.9 (s, 1H, NH)	8.1 (s, 1H, N=CH),
4a	6.58–8.2 (m, 8H, aromatic), 3.7 (d, 1H, –C–CH–Cl)	9.0 (s, 1H, NH), 1.89 (s, 3H, Me)	2.6 (d, 1H, –N–CH–C),
4b	6.58–8.2(m, 9H, aromatic), 3.8 (d, 1H, –C–CH–Cl)	8.9 (s, 1H, NH), 1.89 (s, 3H, OMe)	2.7 (d, 1H, –N–CH–C),
4c	6.58–8.2(m, 9H, aromatic), 3.7 (d, 1H, –C–CH–Cl)	8.8 (s, 1H, NH)	2.6 (d, 1H, –N–CH–C)
4d	6.58–8.2(m, 9H, aromatic), 3.8 (d, 1H, –C–CH–Cl)	8.9 (s, 1H, NH), 1.89 (s, 3H, Me)	2.7 (d, 1H, –N–CH–C),
4e	6.58–8.2(m, 9H, aromatic), 3.7 (d, 1H, –C–CH–Cl)	8.9 (s, 1H, NH), 1.9 (s, 3H, OMe)	2.6 (d, 1H, –N–CH–C),
5a	6.58–8.2(m, 8H, aromatic), 4.2 (s, 1H, –CO–CH_2–S)	8.9 (s, 1H, NH), 1.90 (s,, 3H,, Me)	4.8 (s, 1H, –N–C–S),
5b	6.58–8.2(m, 9H, aromatic), 4.3 (s, 1H, –CO–CH_2–S)	8.9 (s, 1H, NH), 3.20 (s, 3H, OMe)	4.8 (s, 1H, –N–C–S),
5c	6.58–8.2(m, 9H, aromatic), 4.2 (s, 1H, –CO–CH_2–S)	9.0 (s, 1H, NH)	4.8 (s, 1H, –N–C–S),
5d	6.58–8.2(m, 9H, aromatic), 4.3 (s, 1H, –CO–CH_2–S)	8.9 (s, 1H, NH), 1.90 (s, 3H, Me)	4.8 (s, 1H, –N–C–S),
5e	6.58–8.2(m, 9H, aromatic), 4.3 (s, 1H, –CO–CH_2–S)	8.9 (s, 1H, NH), 3.20 (s, 3H, OMe)	4.8 (s, 1H, –N–C–S)

Synthesis of 6–amino–2–(2',4'–dichloro,5'–fluorophenyl)–quinolin–4–(1H)–one (2) : Compound 1 (0.02 mole) suspended in a solution of sodium sulphide (14.4 g, 0.06 mole) in water (75.0 mL), was refluxed for 2.5 hr yielding a deep reddish brown solution. After cooling and diluting with water (75.0 mL) and strongly acidifying with HCl, the solution was boiled for 20 min and filtered. Addition of sodium carbonate precipitated free amine as orange–yellow compound, which was crystallized from ethanol to give 2, (60%), m.p (296^{0}C), C, H, N, I.R: >C=O(1660 cm^{-1}), –NH–(3299 cm^{-1}), –NH_2(3400 $cm^{-1}$and 3370 cm^{-1})^{1}H NMR– 6.95–7.90 (m, 6H, aromatic), –NH– (s, 1H, 8.4), –NH_2 (s, 2H, 4.9).

Table 4. (GI_{50}, μM) of in–vitro sub panel tumor cell lines and full panel mid–points

Comp. No.	Sub panel tumor cell lines									Full panel GI_{50} MG–MID
	I	II	III	IV	V	VI	VII	VIII	IX	
1	31.17	61.28	62.67	63.48	67.52	72.65	99.27	52.37	43.60	61.50
6	46.20	64.52	50.98	76.67	73.75	69.78	54.90	67.40	43.45	60.80
13	34.30	49.90	50.00	51.20	67.00	64.70	78.90	65.00	71.00	59.11

Table 5. (TGI, μM) of in–vitro sub panel tumor cell lines and full panel mid–points

Comp. No.	Sub panel tumor cell lines									Full panel TGI_{50} MG–MID
	I	II	III	IV	V	VI	VII	VIII	IX	
1	100	94.60	100	90.26	91.22	99.30	100	100	100	96.83
6	93.56	90.34	100	91.45	100	100	76.57	100	80.67	92.51
13	86.3	95.8	97.5	100	90	100	96	100	100	96.17

I : Leukemia; II : Non small cell lung cancer; III : Colon cancer; IV : CNS cancer; V : Melanoma; VI: Ovarian cancer; VII : Renal cancer; VIII : Prostate cancer; IX : Breast cancer; GI_{50} : full panel mid–points for 50% growth inhibitor; TGI : full panel mid–points for total growth inhibitor.

Synthesis of 6–(imino substituted phenyl)–2–(2',4'–dichloro–5'– fluorophenyl)–quinolin–4(1H)–one. [3a–3e] : To a mixture of 6–amino–2–(2',4'–dichloro,5'–fluorphenyl)–5–quinolin–4–(1)– one (0.01 mole) and various aldehyde (0.01 mole) in ethanol (30.0 mL) and one drop of H_2SO_4 was added. The reaction mixture was refluxed for 4 hr. The content was poured in ice cooled water; separated solid was dried and crystallized from ethanol.

Synthesis of 1–[2'–(2'',4''–dichloro–5''–fluorophenyl)–quinolin–4'(1H)–one]–3–chloro–4–(substituted phenyl)–2–azetidionone. [4a–4e] : A mixture of 6–(imino substituted phenyl)–2–(2',4'–dichloro–5'–fluorophenyl) –quinolin–4(1H)–one (0.01 mole) and triethylamine (0.02 mole) was dissolved in 1,4–dioxane (50.0 mL). To this well stirred cooled solution chloroacetylchloride (0.02 mole) was added drop wise during 20 min. The reaction mixture was then stirred for further 1 hr and refluxed for 8 hr.and filtered to separate the salt formed. The filtrate was concentrated to half its initial volume and then poured onto crushed ice. The product obtained was filtered, washed with water and recrystallized from ethanol

Synthesis of 3–[2'–(2'',4''–dichloro–5''–fluorophenyl)–quinolin–4'(1H)–one]–2– (substituted phenyl)–4–thiazolidinone. [5a–5e] : The 6–(imino substituted phenyl)–2–(2',4'–dichloro–5'–fluorophenyl)– quinolin–4(1H)–one (0.01 mole) with thioglycolic acid (0.02 mole) in presence of aluminium chloride (0.05 g) at 120^0C for 10–12 hr. The reaction mixture was then cooled and triturated with an excess of 10 percent sodium bicarbonate solution. The product obtained was filtered, washed several times with water and recrystallized from ethanol.

All the physical and analytical data are shown in the Table 1 and all the spectral data in the Tables 2 and 3, respectively.

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