Synthesis and *In-Vitro* Antitumor Activity of Selected 7-Fluoro-6-(4-methyl-1-piperazinyl)-2-(thiosubstituted)-4(3*H*)-quinazolinones

Raid J. Abdel-Jalil*,[1], Ehab Al-Momani[2], Lubna Tahtamooni[3], H.-Juergen Machulla[4] and Wolfgang Voelter*,[5]

[1]*Chemistry Department, College of Science, Sultan Qaboos University, Muscat, Oman*

[2]*Chemistry Department, Faculty of Science, Hashemite University, Zarqa, Jordan*

[3]*Biology Department, Faculty of Science, Hashemite University, Zarqa, Jordan*

[4]*PET-Zentrum, UniversitätsKlinikum Tübingen, Röntgenweg 15, D-72076 Tübingen, Germany*

[5]*Interfakultüres Institut für Biochemie, Universität Tübingen, Hoppe-Seyler Straße 4, D-72076 Tübingen, Germany*

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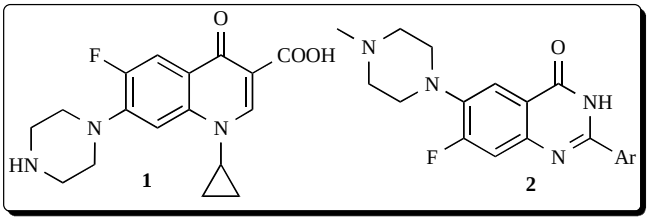
Abstract: A new series of 7-fluoro-6-(4-methyl-1-piperazinyl)-2-(thiosubstituted)-4(3*H*)-quinazolinones was synthesized as potential antitumor agents by multi-step synthesis starting with the commercially available 3-chloro-4-fluoroaniline. The most promising candidate, 7-fluoro-6-(4- methyl-1-thyl-1-piperazinyl)- 2-thioethyl-4(3*H*)-quinazolinone (**5a**), was screened in 60 human cancer cells by NCI.

Keywords: Quinazolinone derivatives, piperazine derivatives, anticancer activity.

INTRODUCTION

Structural modification of heterocyclic compounds comprises at least half of all organic chemistry research worldwide, in particular, heterocyclic structures from the basis of many pharmaceutical, agrochemical, veterinary and natural products. Quinazolinone is a class of fused heterocycles that are of considerable interest due to the diverse range of biological properties, e. g. anticancer [1-3], diuretic [4], anti-inflammatory [5], anticonvulsant [6] and antihypertensive activities [7]. Moreover, quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, animals or microorganisms [8-10].

It is known that 2-mercapto-4-quinazolinone (Hsqualone) derivatives are one of the most potent PARP(poly(ADP-ribose) polymerase) inhibitors evaluated recently to avoid the lack of ATP and NAD causing mitochondrial dysfunction and cell damage [11-13]. On the other hand, the presence of piperazine and fluorine substituents as appendages plays vital roles in enhancing the antimicrobial activities of the quinolone drugs [14], e. g. ciprofloxacine® (**1**). We have shown recently [15] that some derivatives of 2-aryl-7-fluoro-6-(4-methyl-1-piperazinyl)-4-(3*H*)quinazolinones (**2**) have significant antitumor activities when tested in a three cell line panels consisting of MCF (breast), NCI-H460 (lung) and SF-268 (CNS).



It is known that structural variations cause new physical and biological properties. Molecular modification of a promising lead compound is still a major line of approach for the discovery of new drugs. Molecular modification involves the efforts to introduce (a) new residue(s) which potentially may increase the desired activity. The broad band of microbial activities associated with quinazolinones and our previous findings of promising antitumor activities of some quinazolinones, prompted us for the synthesis of some quinazolinones modified with alkylthio at position 2, piperazinyl at position 6 and flouro residues at position 7 with an objective to obtain enhanced antitumor activities.

RESULTS AND DISCUSSION

Chemistry

The synthesis of target compounds was achieved by the route depicted in Scheme **1**.

Recently [15], we described the synthesis of 2-amino-4-fluoro-5-(4-methyl-1-piperazinyl)benzamide (**3**) as a valuable intermediate for the synthesis of potentially biologically active heterocycles by a multi-step synthesis starting with the commercially available 3-chloro-4-fluoroaniline, including acylation, nitration, deacylation, piperazinylation, cyanation,

*Address correspondence to these authors at the Chemistry Department, College of Science, Sultan Qaboos University, P B No. 36, PC 123, Muscat, Oman; Fax: +968 241 41469; E-mail: jalil@squ.edu.om

Interfakultäres Institut für Biochemie, Eberhard-Karls-Universität Tübingen, Hoppe-Seyler-Str. 4, D-72076, Tübingen, Germany; Fax: +49 7071 650016; E-mail: wolfgang.voelter@uni-tuebingen.de

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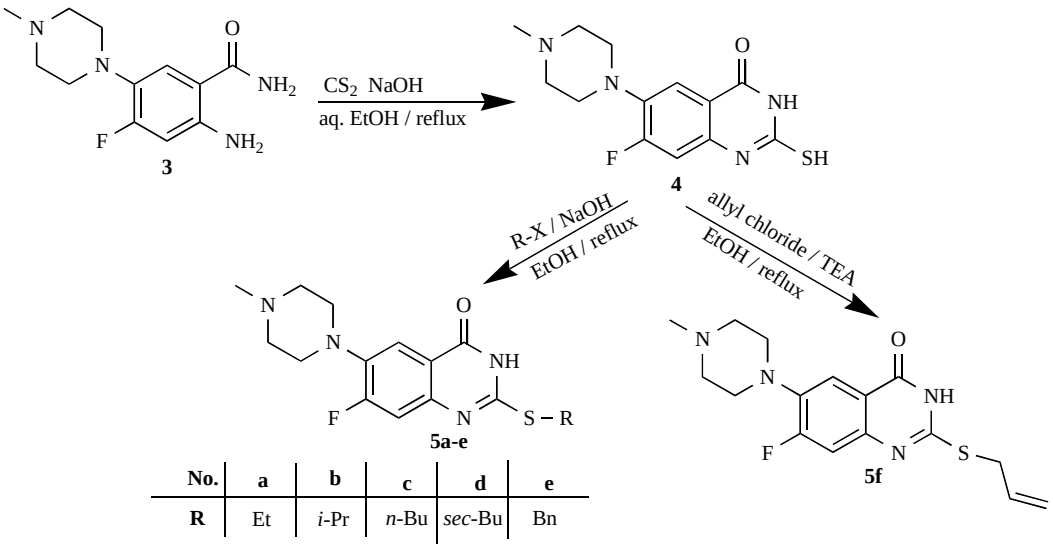

Scheme 1. Convenient strategy for the synthesis of -fluoro-6-(4-methyl-1-piperazinyl)-2-(thiosubstituted)-4(3*H*)-quinazolinones **5a-f**.

selective acidic hydrolysis to amide and reduction by tin(II) chloride in hydrochloric acid.

Condensation of **3** with carbon disulfide in the presence of sodium hydroxide in refluxing aqueous ethanol afforded 7-fluoro-6-(4-methyl-1-piperazinyl)-2-mercapto-4-(3*H*)-quinazolinone (**4**) in 73% yield. The latter was reacted with selected alkyl halides under similar reaction conditions to furnish the 7-fluoro-6-(4-methyl-1-piperazinyl)-2-(thiosubstituted)-4-(3*H*)-quinazolinones **5a-e** in 33-50% overall yield (Scheme **1**). Applying similar reaction conditions was unsuccessful to prepare 7-fluoro-6-(4-methyl-1-piperazinyl)-2-(thioallyl)-4-(3*H*)-quinazolinone (**5f**) despite numerous attempts. However, reaction of **4** with allyl chloride in the presence of triethyl amine (TEA), instead of sodium hydroxide, in refluxing ethanol gives **5f** in 30% yield. Structural confirmation of the synthesized intermediates and target products was attained by the aid of NMR, IR, mass spectrometry and elementary analyses (C, H, and N).

The ^{1}H NMR spectrum of **4** shows two doublets at δ 7.40 and δ 7.04 which indicate the presence of two aromatic protons, H-5 and H-8, respectively. The H-8 proton is more shielded than H-5 and has a larger ortho coupling with the adjacent fluorine atom $J_{H8\text{-}F}$ = 13.2 Hz compared to the meta coupling $J_{H5\text{-}F}$ = 9.3 Hz. The methyl protons, N-CH_3, appear at δ 2.23 ppm and the methylene protons of the piperazine moiety appear as two broad singlets at δ 3.01 and δ 2.45 assigned to (C2′-H/C6′-H) and (C3′-H/C5′-H), respectively [15]. The amide protons resonate as a broad singlet at δ 13.09 ppm, while the S-H proton appears as a singlet at δ 1.88 ppm. In the ^{13}C NMR spectrum, the N-CH_3 carbon resonates at δ 46.15 ppm, and the methylene carbons of the piperazine moiety appear at δ 55 and 51 ppm assigned to (C2′-H/C6′-H) and (C3′-H/C5′-H), respectively. The aromatic carbons show the following signals, 113.80, 116.14, 137.5, 138.9, 158.1, and 159.9, while the C=O carbon signal appears at δ 173.9 ppm and C=N resonates at δ 161.4 ppm.

In the ^{1}H NMR spectra of the new quinazolinones, the aromatic protons (H-5 and H-8) appear as two doublets around δ 7.48-7.51 and δ 7.20-7.31 ppm, respectively. The H-5 protons are more deshielded and show a smaller coupling with the adjacent fluorine atom ($J_{H\text{-}F}$ = 9.3-9.6 Hz) than those of H-8 ($J_{H\text{-}F}$ = 13.5-13.8 Hz). The methyl protons, N-CH_3, appear as a singlet around δ 2.22 ppm (s, 3H), while the methylene protons of the piperazine moiety appear as two broad singlets in the range of δ 2.96-3.33 ppm and δ 2.50-3.23 ppm, assigned to (C2′-H/C6′-H) and (C3′-H/C5′-H), respectively. The N-H protons give rise to broad singlets in the range of δ 12.46-12.62 ppm.

In the ^{13}C NMR spectra of **5a-f**, the carbonyl resonate around δ 160.9-173.7 ppm and the imines (C=N) around δ 157.3-169.3 ppm. The aromatic carbons resonate around δ 112.2-155.8 ppm.

Antitumor Activity

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-ethylthio-4(3*H*)-quinazolinone (**5a**) was selected by the Developmental Therapeutic Program Division of Cancer Treatment, National Cancer Institute (NCI), Besthesda, United States, for antitumor screening [17].

This program is designed to screen compounds for potential antitumor activity. The operation of this screen utilizes 60 different human tumor cell lines [17] derived from nine cancer types including: leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. The aim is to prioritize for further evaluation, synthetic compounds or natural product samples showing selective growth inhibition (GI) or cell killing of particular tumor cell lines [18].

The screening is a two-stage process, beginning with the evaluation of the compound against the 60 cell lines at a single dose of 10 μM. The output from the single dose screen is reported as a mean graph and is available for analysis by a special statistical and analytical program. The percent of growth inhibition (GI) was shown as mean graph [19]. In this graph, the positive and negative values are plotted against a vertical line which represents the mean GI found in

the 60 cell lines at single drug dose of 10 μM. Projecting values = mean GI %– GI %.

The mean graph of **5a** values is shown in Fig. (**1**).

As depicted in Fig. (**1**), the 2-(ethylthio)-7-fluoro-6-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (**5a**) exerted cytotoxic and growth inhibition activity, but there is a large difference in tumor type specificity. The highest levels were

Panel/Cell Line	GI percent
Non-small-cell lung cancer	
A549/ATCC	105.51
EKVX	98.93
HOP-62	95.44
HOP-92	31.62
NCI-H226	95.60
NCI-H23	89.67
NCI-H322M	91.21
NCI-H460	108.06
NCI-522	90.72
Colon cancer	
COLO 205	96.95
HCC-2998	111.80
BCT-116	92.27
HCT-15	128.65
HT29	103.79
KM12	102.52
SW-620	98.56
Breast cancer	
MCF7	101.73
NCI/ADR-RES	109.94
MDA-MB-231/ATCC	95,59
S 578T	97.59
MDA-MB-435	110.74
BT-549	99.12
T-47D	110.91
Ovarian cancer	
IGROV1	83.05
OVCAR-4	108.99
OVCAR-5	99.62
OVCAR-8	94.42
SK-OV-3	108.60
Leukaemia	
CCRF-CEM	98.16
K-562	77.84
MOLT-4	107.19
RPMI-8226	137.98
SR	102.33
Renal cancer	
786-0	103.54
A498	85.26
ACHN	121.63
RXF 393	104.65
SN12C	105.61
TK-10	114.68
UO-31	78.03
Melanoma	
LOX IMVI	107.25
MALME-3M	93.38
M14	93.65
SK-MEL-2	97.69
SK-MEL-28	109.49
SK-MEL-5	89.18
UACC-257	97.95
UACC-62	101.64
Prostate cancer	
PC-3	113.26
DU-145	92.75
CNS cancer	
SF-268	102.66
SF-295	98.51
SF-539	101.36
SNB-19	104.52
SNB-75	95.42
U251	99.38

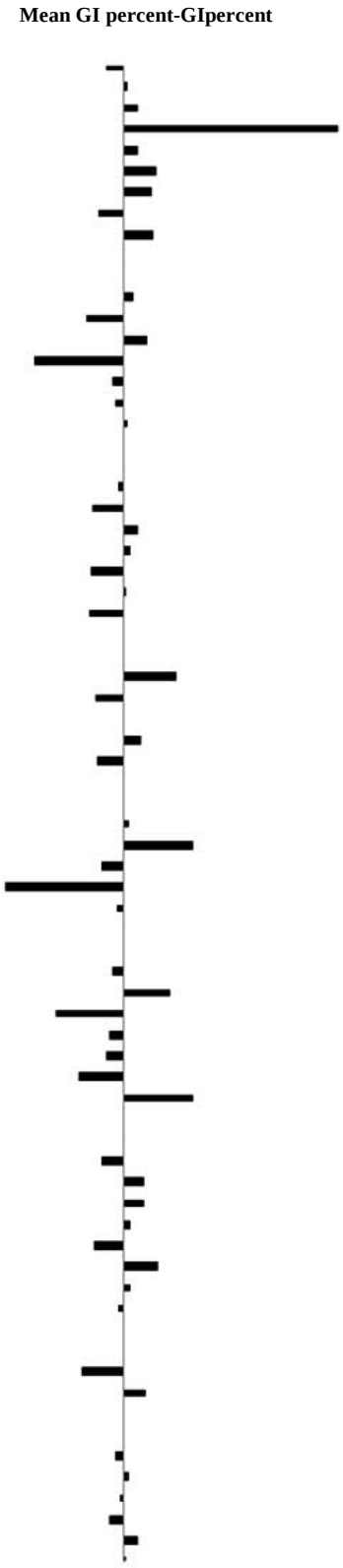

Fig. (1). Mean Graph illustrates the pattern of activity at the *GI50 (50% growth inhibition)* level of effect for **5a**. Mean = 99.96; Delta = 68.34; Range = 106.36.

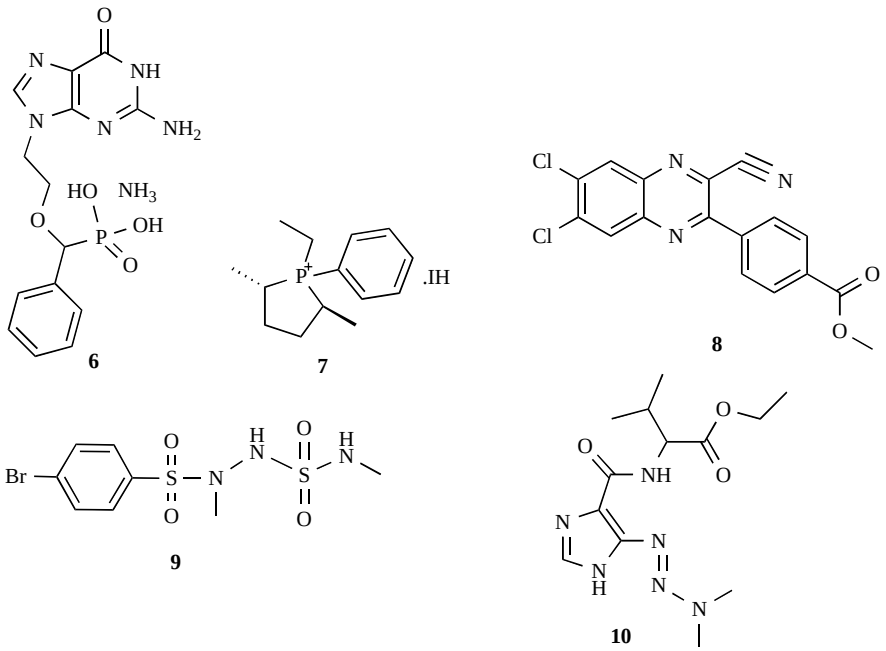

Fig. (2). The structure of compounds having the most similar GI50 pattern of activity to **5a**, identified using COMPARE analysis of the synthetic compound screening database [27-30].

observed in colon cancer and leukemia-derived cell lines, while the lowest level was observed in non-small cell lung cancer. In addition, this compound showed tumor cell specificity, evident in RPMI-8226 and HCT-15.

Analysis of the data depicted in Fig. (**1**), revealed that compound **5a** showed antiproliferative activity against almost half (27/59) of the human tumor cell lines used by NCI/DTP. It was particularly effective against most types of renal cancer cell lines (5/7), specifically ACHN and leukemia (3/5), in particular RPMI-8226. Others have found that 3-(3-phenyl-isoxazol-5-yl) or 3-[(3-phenyl-isoxazol-5-yl)-amino]-substituted 4(3H)-quinazolinone derivatives have antineoplastic activities against 2 limphoma cell lines (U937 and human burkitt limphoma) and one leukemia cell line (K-562) [20]. The same group also reported that 6-chloro-2-styryl-3-(pyrimidin-2yl)-4(3H)-quinazolinone has an anti-growth activity against MCF7 breast cancer cell line, and it exerted its action *via* inhibition of tubulin assembly [21]. Moreover, studying the mechanism of action of **5a** through investigating its effect on cell cycle progression, tubulin polymerization, cell viability, and induction of apoptosis [22], is still under intensive investigation and the results will be published in a due course.

Having measured the anticancer activity of **5a** in the 60 cell lines, we sought to determine the Pearson Correction Coefficient (PCCs) [23] between **5a** values and the anticancer activity profiles of the synthetic compounds, previously analyzed and stored in the National Cancer Institute Drug Screen database. To determine this correlation, the mean graph values were used as a "seed" in a COMPARE Analysis [24-26]. The COMPARE analysis [27] indicated high correlations (> 0.6) with a number of compounds. The most similar GI50 pattern of activity of **5a** was found with compounds **6-10** (Fig. **2**) using COMPARE analysis.

These results, together with the low value of the PCC in the COMPARE analysis, may suggest that this nucleus may have a mechanism of action that could be related to that of pure intercalating drugs. We suppose that both, the planar chromophore and the side chain are fundamental for the interaction with DNA.

EXPERIMENTAL

Chemistry

Melting points (°C) were measured on a SMP2 Stuart apparatus and uncorrected. All new compounds were analyzed for C, H, and N, and agreed with the calculated percentages (± 0.4 %). Infrared (IR) spectra were recorded as KBr discs on a Nicolet-MAGNA-IR-560 spectrometer.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer and the chemical shifts are reported in δ ppm relative to TMS as internal standard. Electron impact mass spectra were measured on a Shimadzu 2010A LC-MS mass spectrometer. 3-Chloro-4-fluoroaniline was obtained from Acros, *N*-methylpiperazine was purchased from Aldrich, and the selected alkyl halides were acquired from Aldrich, Fluka, Riedel-de Haën, and Panreac.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-mercapto-4(3H)-quinazolinone 4

To a stirred mixture of 2-amino-4-fluoro-5-(4-methyl-1-piperazinyl)-benzamide (**3**) (4 g, 15.9 mmol) in ethanol (175 ml) and sodium hydroxide (3.5 g) in water (35 ml) was added carbon disulfide (9.6 ml, 158.5 mmol). The mixture was heated under reflux for 24 hr, then it was cooled to room temperature and neutralized with acetic acid to pH 7-8. The solid precipitate was then collected by filtration and recrystalized from ethanol to give compound (**4**) (3.4 g, 73 %); mp 246-248 ºC; ^{1}H NMR (DMSO-d_6): δ 13.09 (1H, s,

N-H), 7.40 (1H, d, *J* = 9.3 Hz, H-5), 7.04 (1H, d, *J* = 13.2 Hz, H-8), 3.01, 2.45 (each 4H, each bs, piperazine), 2.23 (3H, s, N-CH_3), 1.88 (1H, s, S-H); ^{13}C (DMSO-d_6): δ 173.89 (C=O), 161.39 (C=N), 113.80, 116.14, 137.53, 138.86, 158.05 and 159.85 (Ar), 54.97, 50.57 (piperazine), 46.15 (N-CH_3); IR (KBr) υ 3347 (NH), 1673 (C=O), 1626 (C=N) cm^{-1}; MS *m/z*: 294 (M^+). Anal. Calcd. for $C_{13}H_{15}FN_4OS$: C, 53.05; H, 5.14; N, 19.03; S, 10.89. Found: C, 53.12; H, 5.09; N, 19.17; S, 10.81 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-thiosubstituted-4(3H)-quinazolinones 5a-e

General Procedure

To a stirred solution of 7-fluoro-6-(4-methyl-1-piperazinyl)-2-mercapto-4(3*H*)-quinazolinone (**4**) (0.5 g, 1.7 mmol) in ethanol (10 ml) and sodium hydroxide (0.2 g, 5 mmol) in 2 ml water alkyl halide (8.5 mmol) was added. The solution was stirred at room temperature for 30 min, then heated under reflux over night, cooled to room temperature and 50 ml cold water added. The solid precipitate was then collected by filtration, washed with water, purified on a silica gel column with dichloromethane and methanol (9/1) as eluent.

The following compounds were prepared following the previous procedure.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-ethylthio-4(3H)-quinazolinone 5a

(Alkylating agent: *n*-iodoethane); Yield 0.25 g (45%); mp. 228-230 ºC. ^{1}H NMR (DMSO-d_6): δ 12.46 (s, 1H, N-H), 7.48 (d, *J* = 9.6 Hz, 1H, H-5), 7.20 (d, *J* = 13.8 Hz, 1H, H-8), 3.03, 2.50 (each bs, each 4H, piperazine), 2.23 (s, 3H, N-CH_3), 3.12 (q, *J* = 6.00 Hz, 2H, CH_3CH_2-), 1.30 (t, *J* = 6.00 Hz, 3H, CH_3CH_2-). ^{13}C (DMSO-d_6): δ 161.09 (C=O), 157.27 (C=N), 112.67, 115.00, 117.32, 139.13, 145.40, 155.65 (Ar), 55.04, 50.66 (piperazine), 46.18 (N-CH_3), 24.46 (CH_3CH_2-), 15.13 (CH_3CH_2-). IR (KBr): 3420, 1678, 1537 cm^{-1}; MS *m/z*: 322 (M^+). Anal. Calcd. for $C_{15}H_{19}FN_4OS$: C, 55.88; H, 5.94; N, 17.38;; S, 9.95. Found: C, 55.95; H, 5.87; N, 17.31;; S, 9.86 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-iso-propylthio-4(3H)-quinazolinone 5b

(Alkylating agent: *iso*-iodopropane), Yield 0.23 g (40%); mp. 238-240 ºC. ^{1}H NMR (DMSO-d_6): δ 12.50 (s, 1H, N-H), 7.51 (d, *J* = 9.3 Hz, 1H, H-5), 7.29 (d, *J* = 13.5 Hz, 1H, H-8), 3.08, 2.60 (each bs, each 4H, piperazine), 2.31 (s, 3H, N-CH_3), 3.94-4.03 (m, 1H, $(CH_3)_2CH$-), 1.38 (d, *J* = 6.00 Hz, 6H, $(CH_3)_2$CH-). ^{13}C (DMSO-d_6): δ 160.94 (C=O), 155.10 (C=N), 112.85, 115.06, 117.33, 139.64, 157.91, 144.77 (Ar), 54.72, 50.21 (piperazine), 45.78 (N-CH_3), 36.07 ($(CH_3)_2CH$-), 23.17 ($(CH_3)_2$CH-). IR (KBr): 3418, 1648, 1582 cm^{-1}; MS *m/z*: 336 (M^+). Anal. Calcd. for $C_{16}H_{21}FN_4OS$: C, 57.12; H, 6.29; N, 16.65; S, 9.53. Found: C, 57.22; H, 6.33; N, 16.74; S, 9.48 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-butylthio-4(3H)-quinazolinone 5c

(Alkylating agent: *n*-bromobutane), Yield 0.28 g (47%); mp. 162-164ºC. ^{1}H NMR (DMSO-d_6): δ 12.50 (s, 1H, N-H), 7.49 (d, *J* = 9.3 Hz, 1H, H-5), 7.25 (d, *J* = 13.5Hz, 1H, H-8), 3.05, 2.50 (each bs, each 4H, piperazine), 2.22 (s, 3H, N-CH_3), 3.17 (t, *J* = 7.2 Hz, 2H, $CH_3CH_2CH_2CH_2$), 1.59-1.69 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.34-1.46 (m, 2H, $CH_3CH_2CH_2$ CH_2), 0.82 (t, *J* = 15.4 Hz, 3H, $CH_3CH_2CH_2CH_2$). ^{13}C (DMSO-d_6): δ 161.33 (C=O), 157.96 (C=N), 112.64, 115.02, 117.30, 139.10, 145.36, 155.83 (Ar), 54.98, 50.53 (piperazine), 46.16 (N-CH_3), 31.26 ($CH_3CH_2CH_2CH_2$-), 29.69 ($CH_3CH_2CH_2CH_2$-), 21.80 ($CH_3CH_2CH_2CH_2$-), 13.95 ($CH_3CH_2CH_2CH_2$-). IR (KBr): 34057, 1687, 1574 cm^{-1}; MS *m/z*: 350 (M^+). Anal. Calcd. for $C_{17}H_{23}FN_4OS$: C, 58.26; H, 6.62; N, 15.99; S, 9.15. Found: C, 58.33; H, 6.65; N, 16.07; S, 9.09 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-sec-butylthio-4(3H)-quinazolinone 5d

(Alkylating agent: *sec*-bromobutane), 0.30 g Yield (50 %); mp. 212-214 ºC. ^{1}H NMR (DMSO-d_6): δ 12.51 (s, 1H, N-H), 7.49 (d, *J* = 9.6 Hz, 1H, H-5), 7.30 (d, *J* = 13.5 Hz, 1H, H-8), 3.03, 2.50 (each bs, each 4H, piperazine), 2.16 (s, 3H, N-CH_3), 3.84-3.95 (m, 1H, $CH_3CH_2CH(CH_3)$-), 1.66-1.71 (m, 2H, $CH_3CH_2CH(CH_3)$-), 1.37 (d, *J* = 9.0 Hz, 3H, $CH_3CH_2CH(CH_3)$-), 0.97 (t, *J* = 7.7 Hz, 3H, CH_3CH_2CH (CH_3)-). ^{13}C (DMSO-d_6): δ 161.30 (C=O), 157.97 (C=N), 112.67, 115.00, 117.32, 139.13, 145.40, 155.65 (Ar), 54.97, 50.53 (piperazine), 46.16 (N-CH_3), 42.15 (CH_3CH_2CH (CH_3)-), 29.23 ($CH_3CH_2CH(CH_3)$-), 20.92 (CH_3CH_2CH (CH_3)-), 11.69 ($CH_3CH_2CH(CH_3)$-). IR (KBr): 3400, 1672, 1580 cm^{-1}; MS *m/z*: 350 (M^+). Anal. Calcd. for $C_{17}H_{23}FN_4OS$: C, 58.26; H, 6.62; N, 15.99; S, 9.15. Found: C, 58.28; H, 6.60; N, 16.05; S, 9.00 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-benzylthio-4(3H)-quinazolinone 5e

(Alkylating agent: benzylchloride):, Yield 0.22 g (33%); mp. 240-246 ºC (dec.). ^{1}H NMR (DMSO-d_6): δ 12.60 (s, 1H, N-H), 6.91-7.46 (m, 7H, Ar), 2.96, 2.50 (each bs, each 4H, piperazine), 2.22 (s, 3H, N-CH_3), 4.29 (s, 2H, $C_6H_5CH_2$-). ^{13}C (DMSO-d_6): δ 173.75 (C=O), 169.26 (C=N), 110.13, 115.48, 118.24, 126.88, 128.83, 129.34, 133.72, 136.18, 140.42, 148.68, 156.82, 160.11 (Ar), 55.24, 51.15 (piperazine), 46.23 (N-CH_3), 23.75 ($C_6H_5CH_2$-). IR (KBr): 3423, 1661, 1579 cm^{-1}; MS *m/z*: 384 (M^+). Anal. Calcd. for $C_{20}H_{21}FN_4OS$: C, 62.48; H, 5.51; N, 14.57; S, 8.34. Found: C, 62.44; H, 5.43; N, 14.63; S, 8.40 %.

7-Fluoro-6-(4-methyl-1-piperazinyl)-2-allylthio-4(3H)-quinazolinone 5f

To a mixture of 7-fluoro-2-mercapto-6-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone (**4**) (0.5 g, 1.7 mmol) and triethylamine (0.5 mL, 3.6 mmol) in ethanol (10 mL), allyl chloride (0.65 g, 8.5 mmol) was added. The reaction mixture was heated under reflux for 4-6 hr and then concentrated under reduced pressure. The solid obtained was filtered and then purified on a silica gel column with dichloromethane and methanol (9/1) as eluent to give compound **5f**, Yield 0.18 g (31%); mp. 222-224 ºC. ^{1}H NMR (DMSO-d_6): δ 12.56 (s, 1H, N-H), 7.50 (d, *J* = 9.6 Hz, 1H, H-5), 7.31 (d, *J* = 13.5 Hz, 1H, H-8), 3.23, 2.53 (each bs, each 4H, piperazine), 2.23 (s, 3H, N-CH_3), 5.88-6.02 (m, 1H, CH_2=C*H*CH_2-), 5.35 (dd, *J* = 1.3, 16.9 Hz, 1H, CH_2=CHCH_2-), 5.14 (dd, *J* = 1.0, 9.9 Hz, 1H, CH_2=CHCH_2-), 3.87 (d, *J* = 6.9 Hz, 2H, CH_2=CHCH_2-). ^{13}C (DMSO-d_6): δ 161.11 (C=O), 157.78

(C=N), 112.22, 114.44, 116.67, 138.89, 145.56 and 154.44 (Ar), 53.33, 50.00 (piperazine), 45.56 (N-CH_3), 134.44 (CH_2=*C*HCH_2-), 118.89 (*C*H_2=CHCH_2-), 32.22 (CH_2=CH*C*H_2-). IR (KBr): 3436, 1660, 1581 cm^{-1}; MS *m/z*: 334 (M^+). Anal. Calcd. for $C_{16}H_{19}FN_4OS$: C, 57.47; H, 5.73; N, 16.75; S, 9.59. Found: C, 57.40; H, 5.77; N, 16.66; S, 9.54 %.

Screening of Antitumor Activity

The antitumor activity testing was performed by National Institute of Cancer (NCI), Besthesda, United States, following their standard protocols [16].

CONCLUSION

The synthesis of new substituted quinazolinones has been described. Out of 6 quinazolinone derivatives, one (**5a**) exerted significant cytotoxic and growth inhibition activity. High tumor type specificity levels were observed for colon cancer and leukemia-derived cell lines.

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