Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(1):106-110
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of some arylidene derivatives of thiazolopyrimidineas anticancer

Tawfeek Ahmed Ali Yahya[a]*, Jalal H. Abdullah[a], Mokhtar Abd Hafiz Al-Ghorafi[b] and Shada H. Yassin[a] and Hassan M. Almahbshi[c]

[a]*Medicinal Chemistry Department, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen*
[b]*Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen*
[c]*Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Sana'a University, Sana'a, Yemen*

ABSTRACT

*A series of arylidenesarylidenes**(D1-10)** were synthesized by reaction of the thiazolopyrimidinones**(C1&C2)** with the appropriate aldehyde. The arylidene derivatives **(D3)** and **(D8)** showed significant anticancer activity (IC_{50}= 4.32 and 4.72 µg/ml respectively) when compared to standard drug doxorubicin (IC_{50}= 3.76 µg/ml).*

Keywords: Chalcone,Pyrimidine, Thiazolopyrimidine, Anticancer.

INTRODUCTION

Cancer continues to represent the largest cause of mortality in the world and claims over 6 million lives each year [1]. Pyrimidines are among the pharmacologically most interesting chemical scaffolds that are widely spread in many natural products and in several interesting nucleoside and non-nucleoside compounds. Being a building unit of DNA and RNA, pyrimidine derivatives were found to be associated with a variety of chemotherapeutic effects including antimicrobial [2, 3], antitubercular [4], antifungal [5], antiviral [6], and antitumor activities [7, 8]. Furthermore, many pyrimidinethiones and their thioether derivatives were proved to exhibit potent anticancer as well as antimicrobialactivities [9, 10].

In view of the aforementioned facts, and as a continuation of an on-going research program devoted to the synthesis and characterization of different heterocyclic ring systems endowed with potential chemotherapeutic activities [11–23], it was sought of interest to design and synthesize certain chalcones and some derived pyrimidine, and thiazolopyrimidine cyclized ring structures substituted basically with methoxy and halogens based on the fact that incorporationof substituents would result in significant enhancement of several biological activities due to the effect of compounds' lipophilicity [24–26]. The newly synthesized compounds were designed so as to comprise substituted aryl rings attached to a pyrimidine counterpart with thione functionality. Moreover, it was considered of interest to annulate the pyrimidine ring in a thiazolopyrimidine structure in order to investigate the effect of such structure modification on the expected biological activities. The aim of the present study is the development of novel chemical entities that might serve as lead molecules in field of cancer management.

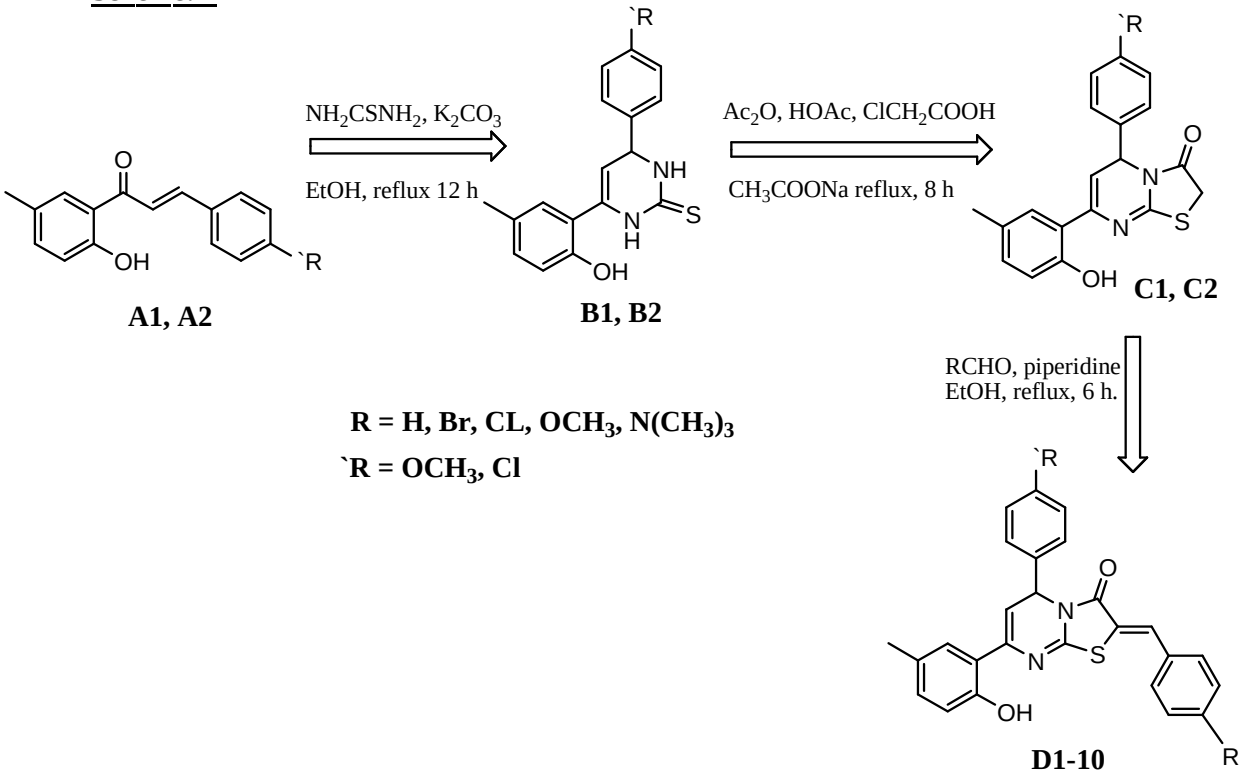
MATERIALS AND METHODS

Chemistry

Melting points were determined in open capillary tubes and are uncorrected.^{1}H NMR spectra were recorded on a Brucker AMX-400 (400 MHz) spectrometer using DMSO-d6 as solvent and TMS as an internal standard. All chemical shifts values are reported in δ scale downfield from TMS. Mass spectra were carried out using finnigan SSQ 7000 Gas Chromatograph –Mass. Infrared spectra were determined (KBr) using Shimadzu Infrared

spectrometer (IR-435) and FT-IR 1650 (Perkin Elmer). Homogenecity of the compounds was checked by TLC on silica gel plates. Characterization data of these compounds were tabulated in Table-1.

Scheme: 1



General procedure for the synthesis of3,4-dihydropyrimidine-2(1H)-thiones (B1& B2)
A mixture of the appropriate chalconesA1& A2 (1.0 mmol), thiourea (1.0 mmol), and anhydrous potassium carbonate (1.0 mmol) in ethanol (20 ml) was refluxed for 12 h, then allowed to cool to room temperature. The resulted precipitate was filtered and washed with ethanol. The precipitate was then suspended in water and neutralized with conc. hydrochloricacid, filtered, washed with water, dried, and recrystallized.Physicochemical and analytical data are recorded in Table 1.

Synthesis of 6-(2-Hydroxy-5-methylphenyl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione (B1)
IR (ν_{max}): 3415(OH), 3250–3164 (NH), 1665 (C–N), 1123(C=S). ^{1}HNMR (400 MHz, DMSO-d6), δ 2.51(s, 3H, CH_3), δ 3.78(s, 3H, OCH_3),δ 5.13(d, 1H, pyrimidine C4-H), δ 5.36 (d, 1H, pyrimidine C5-H), δ 6.69-7.71 (m, 7H, Ar-H), δ 9.0 (s, 1H, NH, D_2O exchangeable), δ 9.80 (s, 1H, 2 NH, D_2O exchangeable), δ 11.45 (s, 1H, OH, D_2O exchangeable). Mass: m/z 326 (M^+).

Synthesis of 6-(2-Hydroxy-5-methylphenyl)-4-(4-chlorophenyl)-3,4-dihydropyrimidine-2(1H)-thione (B2)
IR (ν_{max}): 3420(OH), 3219–3124 (NH), 1660 (C–N), 1125(C=S). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.53(s, 3H, CH_3), δ 5.16 (d, 1H, pyrimidine C4-H), δ 5.39 (d, 1H, pyrimidine C5-H), δ 7.11-7.92 (m, 7H, Ar-H), δ 8.9 (s, 1H, NH, D_2O exchangeable), δ 9.90 (s, 1H, 2 NH, D_2O exchangeable), δ 11.60 (s, 1H, OH, D_2O exchangeable). Mass: m/z 330 (M^+).

General procedure for the synthesis of thiazolo[3,2-a]pyrimidin-3(5H)-ones (C1& C2)
A mixture of compound **B**(1.0 mmol), chloroacetic acid (1.5 mmol), anhydrous sodium acetate (1.5 mmol), and acetic anhydride (5 mL) was heated under refluxin glacial acetic acid (20 mL) for 8 h. After being cooled to roomtemperature, the reaction mixture was poured onto ice coldwater and the precipitated solid was filtered, washedwith water, dried, and recrystallized from acetic acid.

Physicochemical and analyticaldata are recorded in Table 1.

7-(2-Hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (C1)
IR (ν_{max}): 3419(OH), 1723 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.52(s, 3H, CH_3), δ 3.91(s, 3H, OCH_3), δ 4.11 (d,1H, SCH_2), δ 4.24 (d,1H, SCH_2), δ 5.62 (d,1H, thiazolopyrimidine C5-H), δ 5.81 (d,1H, thiazolopyrimidine C6-H), δ 6.7-8.31 (m, 7H, Ar-H), δ 11.63 (s, 1H, OH, D_2O exchangeable). Mass: m/z 366 (M^+).

7-(2-Hydroxy-5-methylphenyl)-5-(4-chlorophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (C2)
IR (ν_{max}): 3419(OH), 1723 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.55 (s, 3H, CH_3), δ 4.15 (d,1H, SCH_2), δ 4.26 (d,1H, SCH_2), δ 5.65 (d,1H, thiazolopyrimidine C5-H), δ 5.86 (d,1H, thiazolopyrimidine C6-H), δ 6.9-8.42 (m, 7H, Ar-H), δ 11.67 (s, 1H, OH, D_2O exchangeable). Mass: m/z 370 (M^+).

General procedure for the synthesis of Substitutedbenzylidene-2H-thiazolo[3,2-a]pyrimidin-3(5H)-ones (D1-10)
To a solution of **C** (1.0 mmol) and piperidine (3 drops) in absolute ethanol (20 mL) was added the appropriate aldehyde (1.0 mmol). The mixture was heated under reflux for 6 h where a solid product partially crystallized. The reaction mixture was left to cool and the separated solid product was filtered, washed with cold ethanol, dried, and recrystallized.

2-Benzylidene-7-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D1)
IR (ν_{max}): 3422(OH), 1725 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.54 (s, 3H, CH_3), δ 3.93(s, 3H, OCH_3), δ 4.11 (d,1H, SCH_2), δ 4.24 (d,1H, SCH_2), δ 5.79 (d,1H, thiazolopyrimidine C5-H), δ 6.10 (d,1H, thiazolopyrimidine C6-H), δ 7.10-8.38 (m, 12H, Ar-H), δ 8.80(s, 1H, CH=C), δ 12.03 (s, 1H, OH, D_2O exchangeable). Mass: m/z 454 (M^+).

2-(4-Bromobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D2)
IR (ν_{max}): 3428(OH), 1721 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.53 (s, 3H, CH_3), δ 3.90(s, 3H, OCH_3), δ 4.13 (d,1H, SCH_2), δ 4.29 (d,1H, SCH_2), δ 5.80 (d,1H, thiazolopyrimidine C5-H), δ 6.15 (d,1H, thiazolopyrimidine C6-H), δ 7.12-8.43 (m, 11H, Ar-H), δ 8.76(s, 1H, CH=C), δ 12.06 (s, 1H, OH, D_2O exchangeable). Mass: m/z 534 (M^++2), 532 (M^+).

2-(4-Chlorobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D3)
IR (ν_{max}): 3430(OH), 1723 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.54 (s, 3H, CH_3), δ 3.92(s, 3H, OCH_3), δ 4.11 (d,1H, SCH_2), δ 4.27 (d,1H, SCH_2), δ 5.82 (d,1H, thiazolopyrimidine C5-H), δ 6.20 (d,1H, thiazolopyrimidine C6-H), δ 7.02-8.53 (m, 11H, Ar-H), δ 8.77(s, 1H, CH=C), δ 12.08 (s, 1H, OH, D_2O exchangeable). Mass: m/z 489 (M^+).

2-(4-Methoxybenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D4)
IR (ν_{max}): 3428(OH), 1719 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.46 (s, 3H, CH_3), δ 3.87 (s, 3H, OCH_3), δ 3.93 (s, 3H, OCH_3), δ 4.05 (d,1H, SCH_2), δ 4.20 (d,1H, SCH_2), δ 5.80 (d,1H, thiazolopyrimidine C5-H), δ 6.17 (d,1H, thiazolopyrimidine C6-H), δ 6.96-8.43 (m, 11H, Ar-H), δ 8.77(s, 1H, CH=C), δ 12.08 (s, 1H, OH, D_2O exchangeable). Mass: m/z 486 (M^+).

2-(4-Dimethylaminobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D5)
IR (ν_{max}): 3421(OH), 1716 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.47 (s, 3H, CH_3), δ 2.64 (s, 6H, $N(CH_3)_2$, δ 3.83 (s, 3H, OCH_3), δ 4.06 (d,1H, SCH_2), δ 4.22 (d,1H, SCH_2), δ 5.81 (d,1H, thiazolopyrimidine C5-H), δ 6.15 (d,1H, thiazolopyrimidine C6-H), δ 6.89-8.32 (m, 11H, Ar-H), δ 8.75(s, 1H, CH=C), δ 12.04 (s, 1H, OH, D_2O exchangeable). Mass: m/z 497 (M^+).

2-Benzylidene-7-(2-hydroxy-5-methylphenyl)-5-(4-chlorophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D6)
IR (ν_{max}): 3428(OH), 1720 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.55 (s, 3H, CH_3), δ 4.12 (d,1H, SCH_2), δ 4.27 (d,1H, SCH_2), δ 5.82 (d,1H, thiazolopyrimidine C5-H), δ 6.12 (d,1H, thiazolopyrimidine C6-H), δ 7.20-8.43 (m, 12H, Ar-H), δ 8.83 (s, 1H, CH=C), δ 12.07 (s, 1H, OH, D_2O exchangeable). Mass: m/z 458 (M^+).

2-(4-Bromobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-chlorophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D7)
IR (ν_{max}): 3423(OH), 1720 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.52 (s, 3H, CH_3), δ 4.12 (d,1H, SCH_2), δ 4.27 (d,1H, SCH_2), δ 5.81 (d,1H, thiazolopyrimidine C5-H), δ 6.13 (d,1H, thiazolopyrimidine C6-H), δ 7.19-8.48 (m, 11H, Ar-H), δ 8.79(s, 1H, CH=C), δ 12.09 (s, 1H, OH, D_2O exchangeable). Mass: m/z 539 (M^++2), 537 (M^+).

2-(4-Chlorobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-chlorophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D8)
IR (ν_{max}): 3428(OH), 1720 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.50 (s, 3H, CH_3), δ 4.10 (d,1H, SCH_2), δ 4.25 (d,1H, SCH_2), δ 5.85 (d,1H, thiazolopyrimidine C5-H), δ 6.22 (d,1H, thiazolopyrimidine C6-H), δ 7.10-8.70 (m, 11H, Ar-H), δ 8.90(s, 1H, CH=C), δ 12.11 (s, 1H, OH, D_2O exchangeable). Mass: m/z 493 (M^+).

2-(4-Methoxybenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-chlorophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D9)
IR (ν_{max}): 3425(OH), 1718 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.43 (s, 3H, CH_3), δ 3.96 (s, 3H, OCH_3), δ 4.09 (d,1H, SCH_2), δ 4.23 (d,1H, SCH_2), δ 5.81 (d,1H, thiazolopyrimidine C5-H), δ 6.19 (d,1H, thiazolopyrimidine C6-H), δ 6.71-8.45 (m, 11H, Ar-H), δ 8.80 (s, 1H, CH=C), δ 12.04 (s, 1H, OH, D_2O exchangeable). Mass: m/z 490 (M^+).

2-(4-Dimethylaminobenzylidene)-7-(2-hydroxy-5-methylphenyl)-5-(4-dimethylaminophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (D10)
IR (ν_{max}): 3423(OH), 1719 (C=O). ^{1}HNMR 400 MHz, DMSO-d6), δ 2.49 (s, 3H, CH_3), δ 2.67 (s, 6H, $N(CH_3)_2$, δ 4.09 (d,1H, SCH_2), δ 4.27 (d,1H, SCH_2), δ 5.86 (d,1H, thiazolopyrimidine C5-H), δ 6.19 (d,1H, thiazolopyrimidine C6-H), δ 6.84-8.12 (m, 11H, Ar-H), δ 8.71(s, 1H, CH=C), δ 12.01 (s, 1H, OH, D_2O exchangeable). Mass: m/z 501 (M^+).

Measurement of potential cytotoxicity by SRB assay in NCI (Cairo, Egypt)
The cytotoxic activity of the synthesized compounds was measured in vitro using the Sulfo-Rhodamine-Bstain (SRB) assay method as descirbed by Skehan et al.[27]

Cells were plated in 96-multiwell microtiter plate (10^4 cells/well) for 24h before treatment with the test compound to allow attachment of cells to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compound under test (0, 5, 12.5, 25, and 50 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the tested compounds for 48 h at 37 ºC and in atmosphere of 5% CO2. After 48 h, cells were fixed, washed, and stained for 30 min with0.4% (wt/vol) SRB dissolved in 1% acetic acid. Excess unbound dye was removed byfour washes with 1% acetic acid and attached stain was recovered with Tris–EDTA buffer. Color intensity was measured in an ELISA reader at a wavelength of 570 nm. The relation between surviving fraction and drug concentration is plotted to get the survival curve for breast tumor cell line after the specified time. The molar concentration required for 50% inhibition of cell viability (IC50) was calculated. Doxorubicin was used as reference drug. The results are listed in table (II).

RESULTS AND DISCUSSION

Synthesis
The synthetic pathways utilized to prepare the target compounds are illustrated in Scheme 1. The 3,4-dihydro-1H-pyrimidine-2-thiones **(B1&B2)** were obtained by refluxing chalcones**(A1&A2)** with thiourea in the presence of potassium carbonate as a basic catalyst.

Table-I: Characterization data of the synthesized compounds

Compound No.	`R	R	Melting point(º)	Yield (%)	Molecular Formula
B1	Cl	-	210-12	65	$C_{17}H_{15}ClN_2O_2$
B2	OCH_3	-	214-6	67	$C_{18}H_{18}N_2O_2S$
C1	Cl	-	140-42	63	$C_{19}H_{15}ClN_2O_2$
C2	OCH_3	-	148-50	62	$C_{20}H_{18}N_2O_3S$
D1	OCH_3	H	121-3	68	$C_{26}H_{22}N_2O_3S$
D2	OCH_3	Br	125-7	67	$C_{27}H_{21}BrN_2O_3S$
D3	OCH_3	Cl	140-42	64	$C_{27}H_{21}ClN_2O_3S$
D4	OCH_3	OCH_3	124-6	65	$C_{28}H_{24}N_2O_4S$
D5	OCH_3	$N(CH_3)_2$	119-21	58	$C_{29}H_{27}N_3O_3S$
D6	Cl	H	234-36	70	$C_{26}H_{19}ClN_2O_2S$
D7	Cl	Br	155-157	60	$C_{26}H_{18}BrClN_2O_2S$
D8	Cl	Cl	159-61	71	$C_{26}H_{18}ClClN_2O_2S$
D9	Cl	OCH_3	113-5	67	$C_{27}H_{21}ClN_2O_3S$
D10	Cl	$N(CH_3)_2$	132-4	59	$C_{28}H_{24}ClN_3O_2S$

The thiazolopyrimidinones**(C1&C2)** could be prepared by reaction of pyrimidinethiones**(B1&B2)**with chloroaceticacid in the presence of anhydrous sodium acetate, aceticacid, and acetic anhydride. Finally, condensing thiazolopyrimidinones**(C1&C2)**with the appropriate aldehyde inthe presence of piperidine afforded the corresponding arylidenes**(D1-10)**(**Scheme 1)**.

Anticancer activity

In our study, the thiazolopyrimidinone**(C1&C2)**and arylidene derivatives **(D1, D2, D5, D6 & D7)**showed moderate to significant anticancer activity when compared with standard drugs. However it is less than standard drugs like Doxorubicin but compound **(D3)**and **(D8)**showed significant anticancer activity when compared to standard drug because of the presence of methoxy group at para position of phenyl ring. Data were presented in TABLE II revealed the IC_{50} of the synthesized compounds.

TABLE –II: Anticancer Activity of the Synthesized Compounds (IC_{50}) (Against MCF7 Cell Line)

Compound No.	IC_{50} (µg/ml)	Compound No.	IC_{50} (µg/ml)
B1	11.20	D5	8.21
B2	12.45	D6	8.21
C1	7.85	D7	7.99
C2	8.61	D8	4.72
D1	6.52	D9	9.10
D2	7.84	D10	10.9
D3	4.32	Doxorubicin	3.76
D4	6.76		

CONCLUSION

On the basis of biological screening against the MCF7 Cell Line, arylidene derivatives **(D3)** and **(D8)** showed significant anticancer activity when compared to standard drug doxorubicin.

REFERENCES

[1] R. Sarkar, N.Mandal, *IJOP*., **2011**, 3, 370-380.
[2] N. S. Habib, R. Soliman, A. A. El-Tombary, S. A. El-Hawash,O. G. Shaaban, *Arch. Pharm. Res*., **2007**, 30, 1511–1520.
[3] A. Bazgira, M. M. Khanaposhtani, A. A. Soorki, *Bioorg. Med.Chem. Lett.*, **2008**, 18, 5800–5803.
[4] M. Johar, T. Manning, D. Y. Kunimoto, R. Kumara, *Bioorg. Med. Chem.*, **2005**, 13, 6663–6671.
[5] O. A. Fathalla, S. M. Awad, M. S. Mohamed, *Arch. Pharm. Res*., **2005**, 28, 1205–1212.
[6] B. Cosimelli, G. Greco, M. Ehlardo, E. Novellino, et al., *J. Med.Chem*., **2008**, 51, 1764–1770.
[7] J. Li, Y. F. Zhao, X. L. Zhao, X. Y. Yuan, P. Gong, *Arch. Pharm.Chem. Life Sci*., **2006**, 339, 593–597.
[8] H. M. Shallal, W. A. Russu, *Eur. J. Med. Chem.*, **2011**, 46, 2043–2057.
[9] N. N. Gulerman, H. N. Dogan, S. Rollas, C. Johansson,C. Celik, *Il Farmaco*., **2001**, 56, 953–958.
[10] A. A. Khalil, S. G. Abdel Hamide, A. M. Al-Obaid, H. I. El-Subbagh, *Arch. Pharm. Pharm. Med. Chem*., **2003**, 336, 95–103.
[11] H. T. Y. Fahmy, S. A. F. Rostom, A. A. Bekhit, *Arch. Pharm.Pharm. Med. Chem*., **2002**, 335, 213–222.
[12] H. T. Y. Fahmy, S. A. F. Rostom, M. N. S. Saudi, J. K. Zjawiony,D. J. Robins, *Arch. Pharm. Pharm. Med*. Chem., **2003**, 336, 216–225.
[13] S. A. F. Rostom, H. T. Y. Fahmy, M. N. S. Saudi, *Sci. Pharm*.,**2003**, 71, 57–74.
[14] S. A. F. Rostom, M. A. Shalaby, M. A. El-Demellawy, *Eur. J. Med.Chem*., **2003**, 38, 959–974.
[15] M. S. M. Al-Saadi, S. A. F. Rostom, H. M. Faid Allah, *SaudiPharm. J.*, **2005**, 13, 88–96.
[16] S. A. F. Rostom, *Bioorg. Med. Chem*. **2006**, 14, 6475–6485.
[17] H. M. Faid-Allah, M. S. Al-Saadi, S. A. F. Rostom, H. T. Fahmy,*Med. Chem. Res.*, **2007**, 16, 300–318.
[18] M. S. M. Al-Saadi, S. A. F. Rostom, H. M. Faid Allah, *Arch.Pharm. Chem. Life Sci*., **2008**, 341, 181–190.
[19] H. M. Faid-Allah, M. S. Al-Saadi, S. A. F. Rostom, *Saudi Pharm. J.*,**2008**, 16, 33–42.
[20] M. S. M. Al-Saadi, H. M. Faid Allah, S. A. F. Rostom, *Arch.Pharm. Chem. Life Sci*., **2008**, 341, 424–434.
[21] S. A. F. Rostom, H. M. A. Ashour, H. A. Abd El Razik, *Arch.Pharm. Chem. Life Sci*., **2009**, 342, 299–310.
[22] S. A. F. Rostom, G. S. Hassan, H. I. El-Subbagh, *Arch. Pharm.Chem. Life Sci.*, **2009**, 342, 584–590.
[23] S. A. F. Rostom, *Bioorg. Med. Chem.*, **2010**, 18, 2767–2776.
[24] C. Lin, J. Yang, C. Chang, S. Kuo, M. Leeb, L. Huanga, *Bioorg.Med. Chem.*, **2005**, 13, 1537–1544.
[25] L. Barboni, G. Giarlo, R. Ballini, G. Fontana, *Bioorg. Med. Chem.Lett*., **2006**, 16, 5389–5391.
[26]T. Walle, Semin. *Cancer Biol*., **2007**, 17, 354–362.
[27]P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney,M.R. Boyd, *J. Natl. Cancer Inst*.,**1990**,82(13),1107–1112.