INTRODUCTION

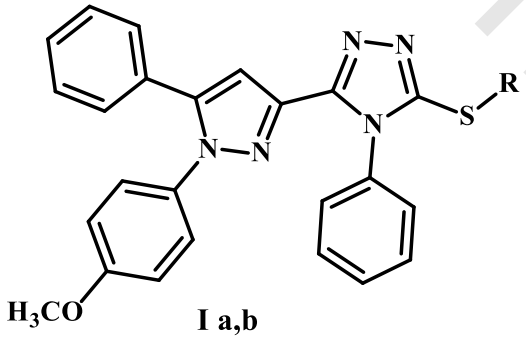
Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Azoles and its derivatives, a class of well-known nitrogen containing heterocyclic compounds, occupy an important position in medicinal chemistry having a wide range of bioactivities such as antimicrobial [(1-3)], anticancer [(4)], anti-inflammatory [(5)], antidepressant [(6,7)], anticonvulsant [(8)], antihyperglycemic [(9)], antipyretic [(10)] and selective enzyme inhibitory activities[(11)]. In the present thesis we focused mainly on pyrazoles, oxadiazoles, thiadiazoles and triazoles.

Pyrazoles

Literature survey revealed that pyrazole derivatives possess diverse pharmacological activities:

Anticancer activity:

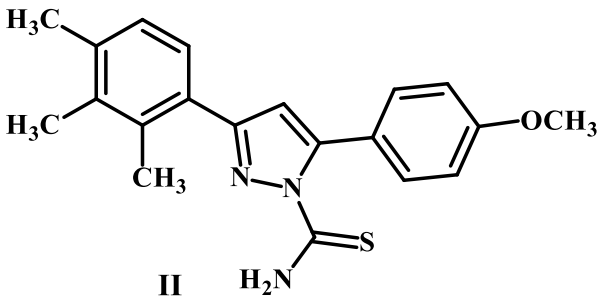
Good antitumor activity against breast carcinoma cell line (MCF-7) and cervix carcinoma cell line (HELA) was displayed by 3-(1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazol-3-yl)-5-(substituted thio)-4-phenyl-4*H*-[1,2,4]-triazole derivatives, **Ia** (lC_{50}: 2.72 and 2.98 µg/ml, respectively) and **Ib** (lC_{50}: 3.63 and 3.92 µg/ml, respectively) compared to doxorubicin as a reference drug (lC_{50}: 6.71 and 8.72 µg/ml, respectively)[(12)].



I a,b

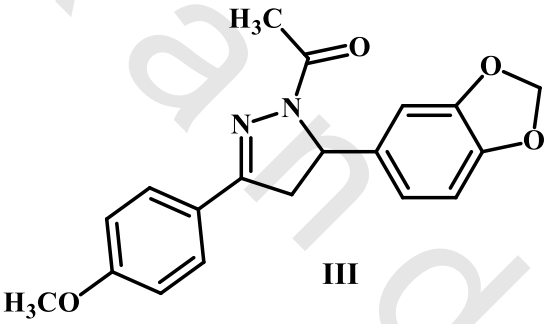
No.	R
a	Propanol-3-yl
b	oxiran-2-yl-methy

Furthermore, potent epidermal growth factor receptor (EGFR) inhibitory activity was displayed by 5-(4-methoxyphenyl)-3-(2,3,4-trimethylphenyl)-1*H*-pyrazole-1-carbothioamide **II** with IC_{50} of 0.07 µM, which was comparable to the positive control Erlotinib (IC_{50} = 0.03 µM). The role of EGFR has been most thoroughly studied in breast cancer, where it is over-expressed in 25–30% of cases and is correlated with a poor prognosis. In addition, compound **II** showed significant anti-proliferative activity against MCF-7 with IC_{50} of 0.08 µM [(13)].



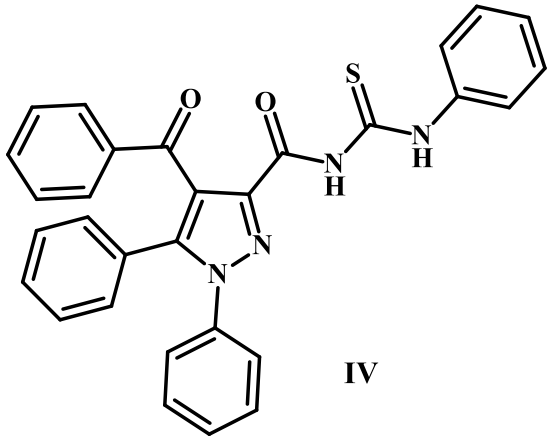
II

Moreover, potent telomerase inhibitory activity was displayed by 1-(5-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone **III** with IC_{50} value of 0.9 µM. Telomerase, a target for anticancer therapy , when activated it works to keep the short length of telomeres during dividing stage of cancer cells, which leads to their long life. Docking simulation showed that compound **III** could bind well with the telomerase active site and act as telomerase inhibitor. In addition, the anti-proliferative tests showed that compound **III** exhibited high activity against human gastric cancer cell SGC-7901 and human melanoma cell B16-F10 with IC_{50} values of 18.07 and 5.34 µM, respectively [(14)].



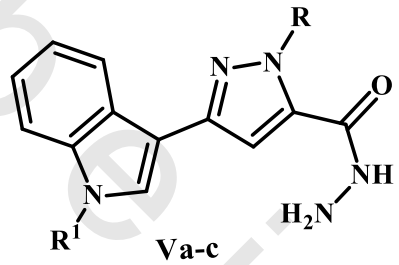
III

Also, a new series of acyl thiourea derivatives containing pyrazole ring demonstrated significant toxicity on human colon, liver and leukemia cancer cell lines. 4-Benzoyl-1,5-diphenyl-*N*-(phenylcarbamothioyl)-1*H*-pyrazole-3-carboxamide **IV** at 10 µM showed 30% inhibition on the Jurkat (human acute T-cell leukemia) cell lines after 24 h incubation [(15)].



IV

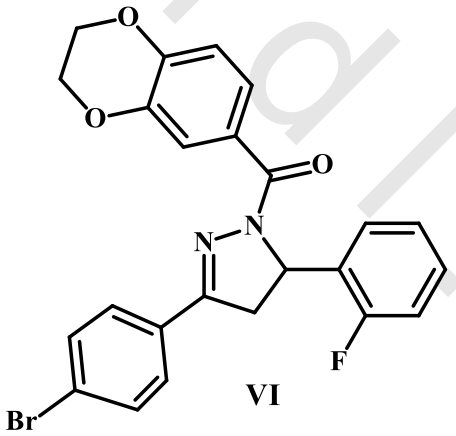
A novel series of 3-(1*H*-indole-3-yl)-1*H*-pyrazole-5-carbohydrazide derivatives **V a-c** were synthesized and evaluated for their cytotoxic activity by MTT method. Among the tested cell lines, human hepatocellular liver carcinoma (HepG-2), human gastric carcinoma (BGC823) and breast carcinoma (BT474) cell lines were more sensitive in response to the growth inhibition by compound **Va** (IC_{50} 1.65, 0.71 and 2.33μM, respectively), **Vb** (IC_{50} 1.32, 4.90 and 4.42 μM, respectively) and **Vc** (IC_{50} 3.14, 1.49 and 5.44 μM, respectively) as compared with the positive drug 5-fluoruracil (IC_{50} 2.7,6.15 and 72.9 μM, respectively) [16].



Va-c

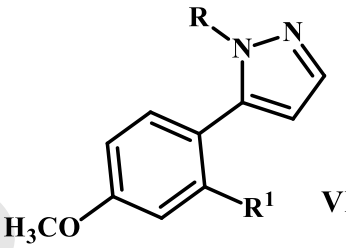
No.	R	R^1
a	4-Floro benzyl	n-propyl
b	n-propyl	2,4-dichloro benzyl
c	n-propyl	4-OCH_3 benzyl

Other series of 2,3-dihydrobenzo[b][1,4]dioxin-containing 4,5-dihydro-1*H*-pyrazole derivatives have been synthesized and evaluated for their B-Raf inhibitory and anti-proliferative activities, of which compound **VI** displayed the most potent activity with IC_{50} value of 0.11 μM and GI_{50} value of 0.58 μM, being comparable with the positive control Erlotinib (IC_{50} = 0.06 μM and GI_{50} = 8.12 μM) against B-Raf ^{V600E} and WM266-4 human melanoma cell line, respectively. Raf kinase (A- Raf, B-Raf and C-Raf) have been indicated to be critical for mediating cell proliferation and survival [17].



VI

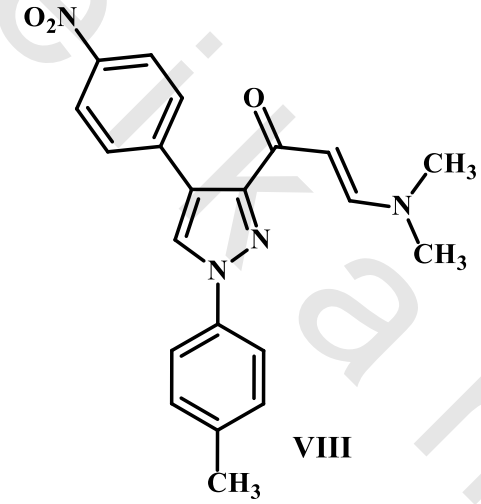
Furthermore, significant anti-proliferative activity was displayed by a series of 1,5 substituted aryl pyrazole derivatives **VII a-d** with IC_{50} values of 2.89, 5.62, 1.22 and 2.35 μM, respectively against ovarian carcinoma A2780 and with IC_{50} values of 5.38, 24.2, 1.56 and 7.51 μM, respectively against murine P388 (leukemia) cells compared to taxol, the classical antimicrotubular agent, as a reference with IC_{50} values of 2.3 and 4.9 μM against ovarian carcinoma A2780 and murine P388 (leukemia) cells, respectively. All compounds in particular **VIIb** showed a good level of apoptotic activity, similar or even better than that of taxol and vincristine [18].



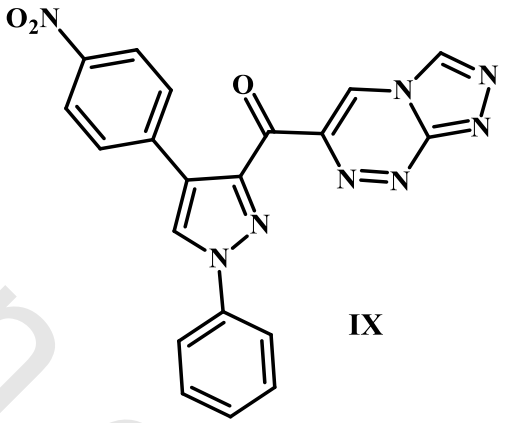
VII a-d

No.	Ar	R^1
a	2-pyridyl	H
b	4-chloro phenyl	H
c	2-pyridyl	OH
d	4-chloro phenyl	OH

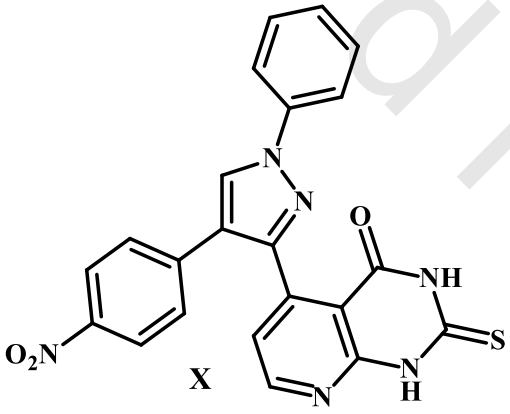
In addition, high cytotoxic activity was displayed by a series of novel *N*-aryl pyrazole derivatives **VIII, IX** and **X** against liver carcinoma cell line (HEPG2) with IC_{50} values of 0.884, 0.806 and 4.07 µg/well, respectively whereas IC_{50} of 5-fluorouracil as standard was 5 µg/well [19].



VIII



IX

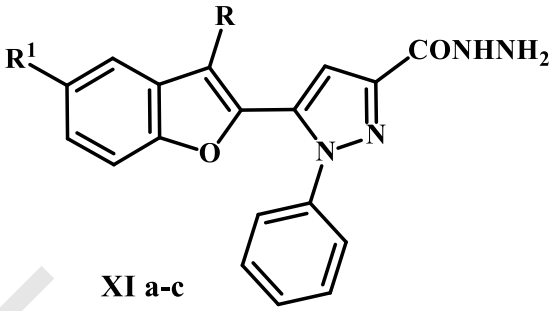


X

Antimicrobial activity:

Literature survey indicated that some pyrazole derivatives showed broad spectrum of biological activities.

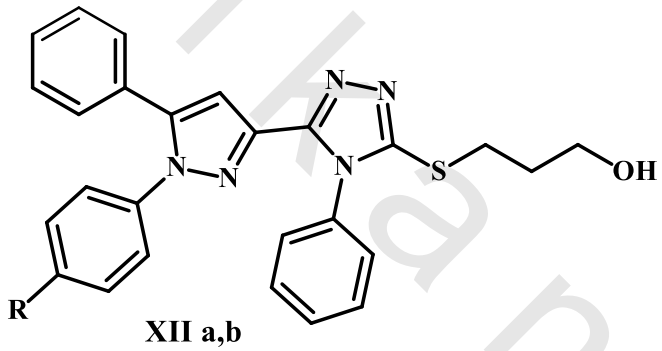
Incorporating pyrazole moiety with substituted/unsubstituted benzofuran in the same molecular frame work afforded a series of the trisubstituted pyrazole derivatives of which **XI a-c** proved to be highly active against *S. aureus* and *E. coli* [20].



XI a-c

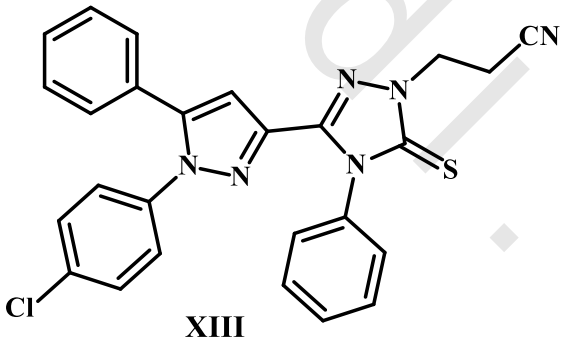
No.	R	R^1
a	H	H
b	H	Br
c	CH_3	Cl

Direct attachment of the substituted pyrazole ring with triazole-3-thiopropane-1-ol or triazole-3-thione afforded compounds **XII a,b** and **XIII** displaying good antibacterial activity against Gram-negative bacteria *E. coli* and *P. aeruginosa* and Gram-positive bacteria *B. subtilis* and *S. aureus.* In addition, compounds **XII a,b** and **XIII** exhibited good antifungal activity [12].



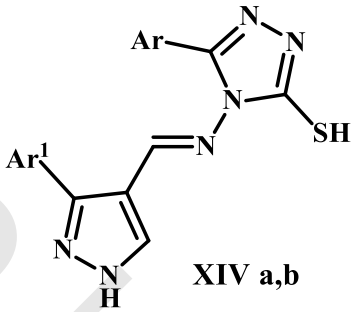
XII a,b

No.	R
a	H
b	Cl



XIII

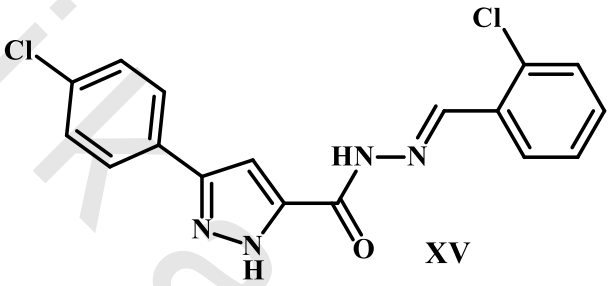
Moreover, 1,2,4-triazole derivatives containing substituted pyrazole moiety attached through azomethine linkage gave compounds **XIV a** and **b** exhibited potent antibacterial activity against *S. aureus*, *B. subtilis* and *P. aeruginosa* as compared to standard drug ceftriaxone [21].



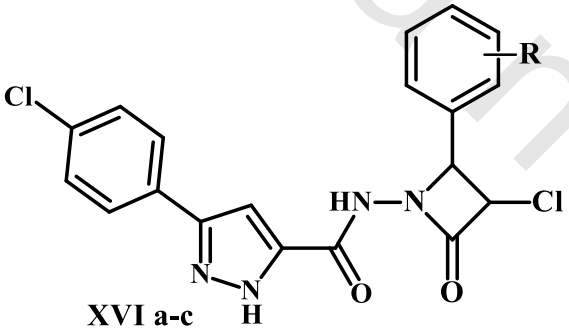
XIV a,b

No.	Ar	Ar^1
a	1-Naphthyloxymethyl	2,5-Dichlorothiophene
b	6-Methylnicotinyl	2,4-Dichlorophenyl

Additionally, new hydrazones **XV**, 2-azetidinones **XVI (a-c)** and 4-thiazolidines **XVII (a-c)** templates bearing substituted pyrazole moieties were found to possess potent activity against *E.coli* and *M. tuberculosis* [22].

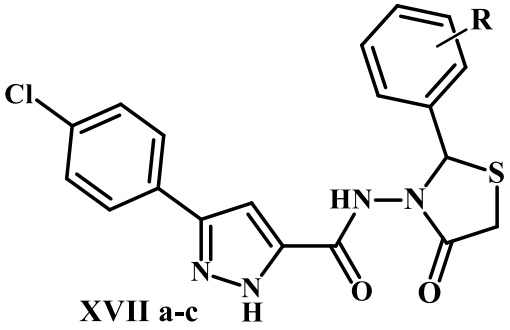


XV



XVI a-c

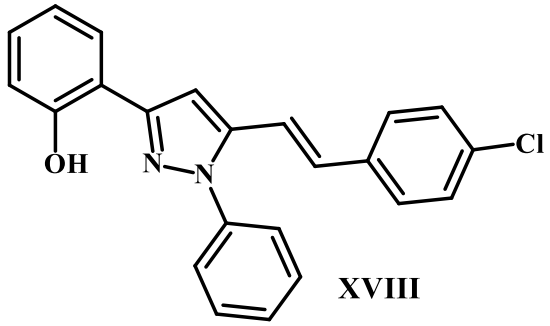
No.	R
a	2-OH
b	4-OH
c	2-Cl



XVII a-c

No.	R
a	2-OH
b	4-OH
c	2-Cl

On the other hand, inclusion of the substituted pyrazole moiety with styryl moiety having a chloro substitution in the same molecular frame work afforded compound **XVIII** with better antibacterial activity against *X. campestris* and *A. tumafeciens* as compared with the standard streptomycin [23].



XVIII

Moreover, good antimicrobial activity aganist *S. aureus* was displayed by pyrazoline-1-thiocarboxamide **XIX** and isonicotinoyl pyrazoline **XX** [24].

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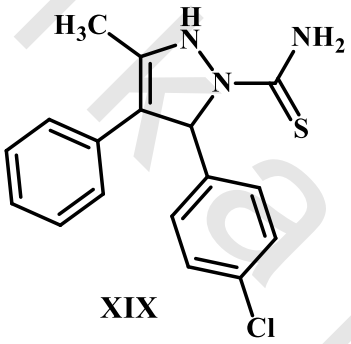
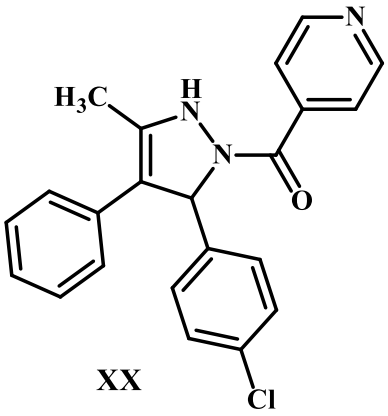
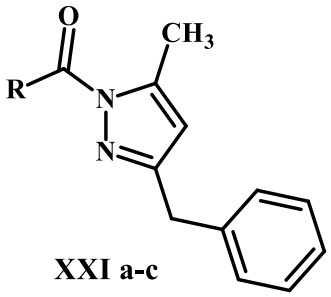


XIX



XX

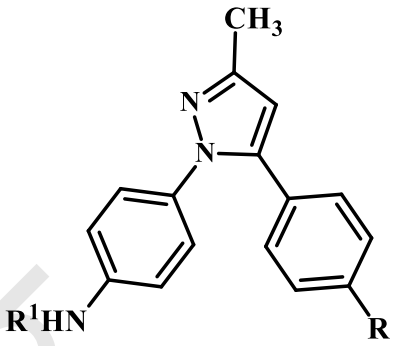
In addition, among a series of substituted aroyl pyrazole derivatives **XXI a-c,** significant activity against *B. aureus* and *B. subtilis* was displayed by compounds **XXIa** and **b** while **XXIc** showed significant activity against *M. luteus* and *E. coli* [25].



XXI a-c

No.	Ar
a	3-Br-C_6H_4-
b	2-NO_2-C_6H_4-
c	3-NO_2-C_6H_4-

Whereas, a moderate antimicrobial activity against *E.coli* was displayed by a series of 4-(pyrazol-1-yl)-*N*-substituted aniline derivatives **XXII a-f** [26].

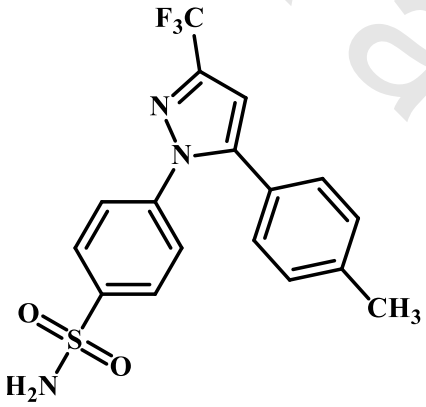


XXII a-f

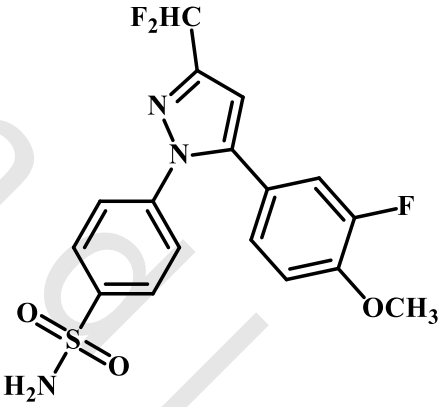
No.	R	R^1
a	CH_3	CH_3
b	C_2H_5	CH_3
c	Cl	CH_3
d	CH_3	C_2H_5
e	C_2H_5	C_2H_5
f	Cl	C_2H_5

Anti-inflammatory activity:

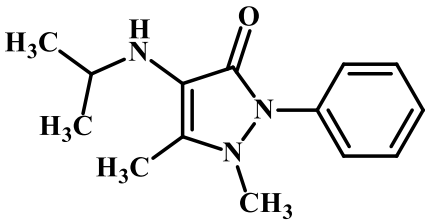
Among the highly marketed COX-2 inhibitors having pyrazole nucleus, celecoxib is a safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocyclic template that is known to selectively inhibit the COX-2 enzyme. Some other examples of pyrazole derivatives such as deracoxib, ramifenazone and famprofazone have been reported as potent NSAIDs [27].



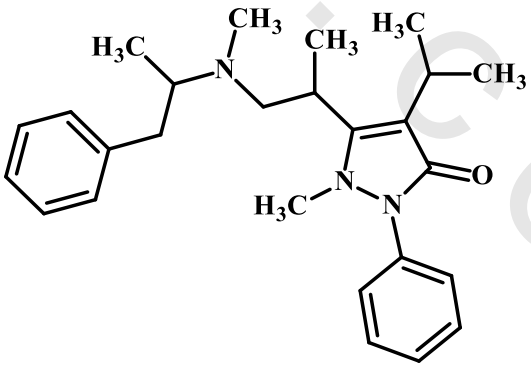
Celecoxib



Deracoxib



Ramifenazone



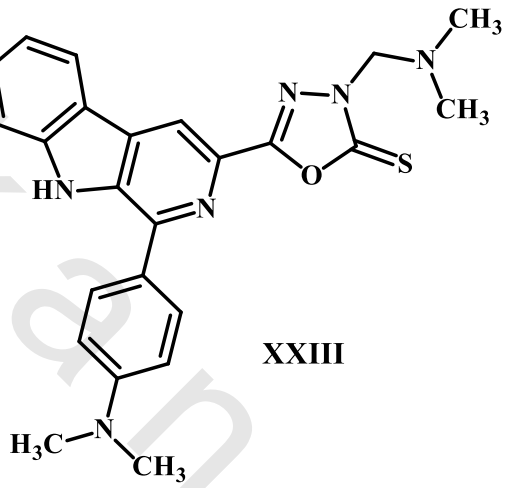
Famprofazone

1,3,4-Oxadiazole

1,3,4-Oxadiazoles represent an important class of heterocyclic compounds. Their derivatives possess a broad spectrum of biological activities such as:

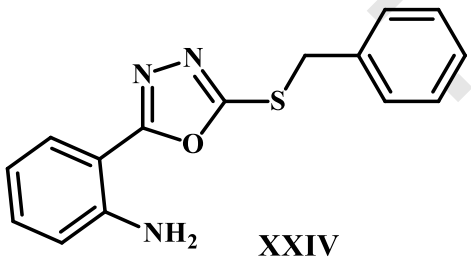
Anticancer activity

Potent antitumor activity was displayed by a series of β-carboline derivatives bearing a 3-alkyl amino (methyl)2-thioxo-1,3,4-oxadiazol-5-yl group at C-3. Compound **XXIII** was the most active derivative exhibiting potent activity against melanoma (UACC-62), and lung (NCI-460) cell lines with GI_{50} values of 0.88 and 1.01 mM, respectively [28].



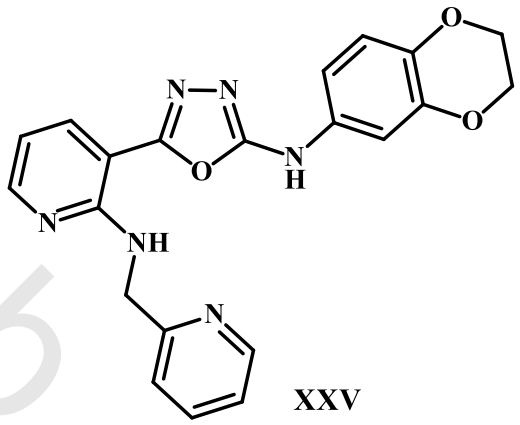
XXIII

Among a series of 2-(benzylthio)-5-aryloxadiazole derivatives, compound **XXIV** demonstrated the most potent anti-proliferative activity and EGFR inhibitory activity (IC_{50} = 1.09 μM for MCF-7, and IC_{50} = 1.51 μM for EGFR) [29].

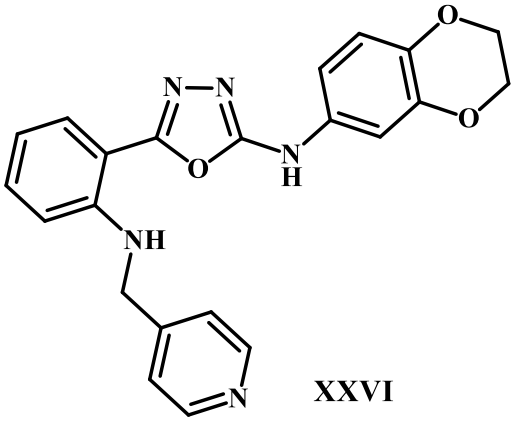


XXIV

Literature survey revealed that, [(2,3-dihydro-benzo[1,4]dioxin-6-yl)-[1,3,4]oxadiazol-2-yl]-amine derivatives **XXV (IMC-094332)** and **XXVI (IMC-038525)** have been identified as a novel scaffold of tubulin small molecule inhibitors. *In vitro*, compound **XXVI** caused mitotic arrest at nano-molar concentrations in epidermoid carcinoma and breast tumor cells, including multi-drug resistant cells [30].

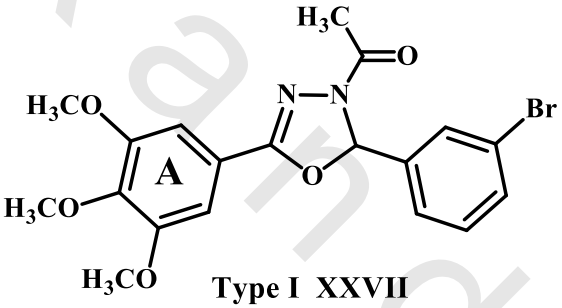


XXV

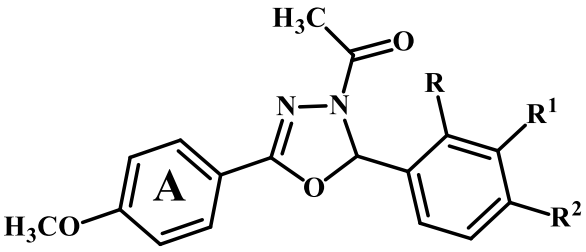


XXVI

Also, potent anti-proliferative activities against murine L1210 leukemia cells were displayed by two types of 2,5-diaryl-1,3,4-oxadiazoline derivatives. Among type I class, having three methoxy groups on the A ring, compound **XXVII** displayed an IC_{50} of 0.6 ± 0.7 μM, and among type II class, having a single methoxy group on the A ring, compounds **XXVIII a,b** displayed an IC_{50} of 0.5 ± 0.06 μM [31].



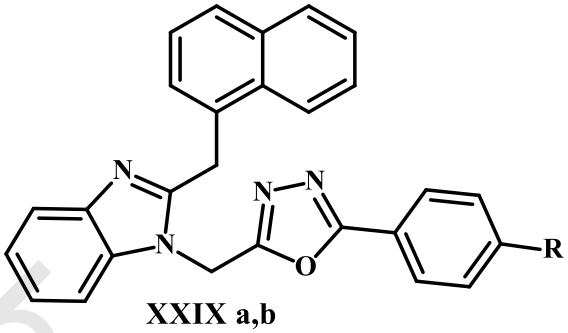
Type I XXVII



Type II XXVIII a,b

No.	R	R^1	R^2
a	OCH_3	H	H
b	H	OCH_3	OCH_3

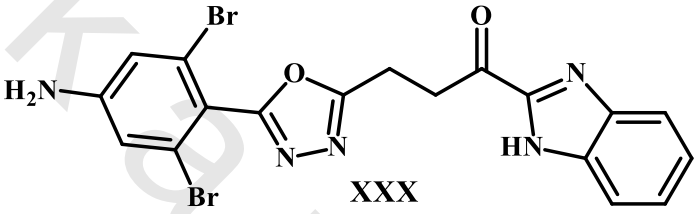
Furthermore, potent anticancer activity was displayed by a novel series of 2-(naphthalen-1-ylmethyl)-1*H*-benzimidazole derivatives **XXIX a,b** bearing substituted 1,3,4-oxadiazole moiety. Compound **XXIXa** was found to be the most active of the series that showed high activity against breast cancer MDA-MB-468 and melanoma SK-MEL-28 cell lines with growth percent of 36.23 and 47.56, respectively. Compound **XXIXb** showed moderate activity against non-small cell lung cancer NCI-H522 and renal cancer UO-31 with growth percent of 32.73 and 40.53, respectively [32].



XXIX a,b

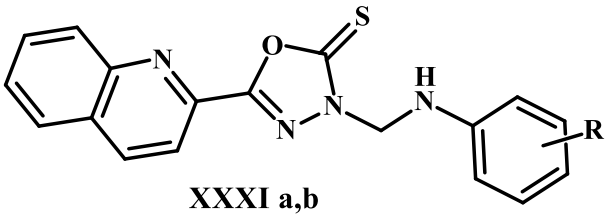
No.	R
a	4-NO_2
b	4-OCH_3

Among another series of benzimidazole derivatives bearing 1,3,4-oxadiazole moiety, compound **XXX** exhibited significant growth inhibition at a single dose and was further screened at 10-fold dilutions of five different concentrations against full NCI-60 cell panel with GI_{50} values ranging from 0.49 to 48.0 µM and found superior for the non-small cell lung cancer cell line HOP-92 (GI_{50} 0.49, TGI 19.9, LC_{50}>100) [33].



XXX

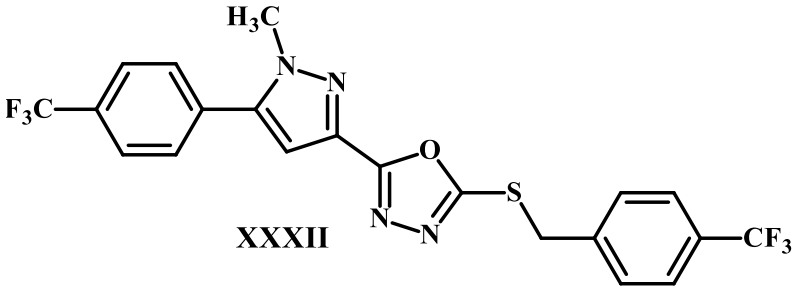
Furthermore, substantial broad spectrum antitumor activity against the three cancer cell lines (HepG2, SGC-7901 and MCF-7) was exhibited by a series of novel quinoline analogues **XXXI** possessing 1,3,4-oxadiazole moiety. Compounds **XXXI a** and **b** displayed the most potent anticancer activities which were comparable to the positive control 5-fluorouracil. In addition, compounds **XXXI a** and **b** showed the most potent telomerase inhibitory activity with IC_{50} 0.8 and 0.9 µM, respectively [34].



XXXI a,b

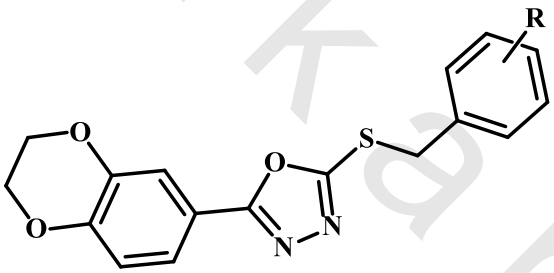
No.	R
a	2-F
b	4-Cl

A novel combinatorial library of a series of 1,3,4-oxadiazole linked to biologically active N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety at C-5 position, was synthesized and evaluated for *in vitro* cytotoxic activity by MTT assay. Amongst the tested compounds, compound **XXXII** was the most promising anticancer agent with IC_{50} value of 15.54 µM against MCF-7 cells, compared to doxorubicin as standard [35].



XXXII

Moreover, a series of 1,4-benzodioxan containing 1,3,4-oxadiazole moiety **XXXIII a-e** showed broad-spectrum antitumor activity with IC_{50} concentration range of 7.21-25.87 µM against four different cancer cell lines (human liver cancer cell HEPG2, human cervical cancer cell HELA, human colorectal carcinoma SW1116 and gastric carcinoma BGC823) compared with the 5-fluorouracil. In addition, compound **XXXIIIa** possessed the most potent telomerase inhibitory activity (IC_{50} 1.27 ± 0.05µM) [(36)].



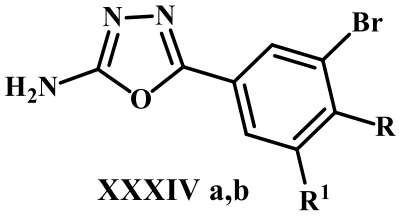
XXXIII a-e

No.	R
a	2-CH_3
b	2-Br
c	3-Br
d	4-Br
e	2-I

Antimicrobial activity:

The widespread of drug resistance upon treating infectious diseases has underlined the need for new, safer, and more efficient antimicrobial agents. Many researchers have reported excellent antimicrobial activity for compounds containing the 1,3,4-oxadiazole core.

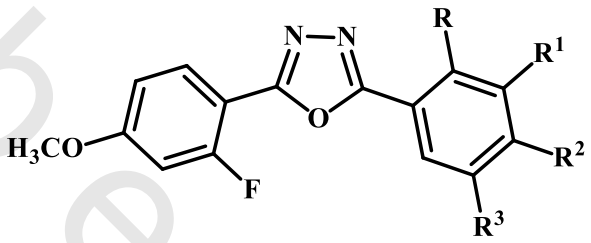
Novel 2-amino-5-substitutedphenyl-1,3,4-oxadiazole derivatives **XXXIV (a,b)** exhibited approximately similar activity to the standard Streptomycin against *K. pneumoniae*, *E. coli*, *B. subtilis* and *S. aureus* [(37)].



XXXIV a,b

No.	R	R^1
a	OH	H
b	H	Br

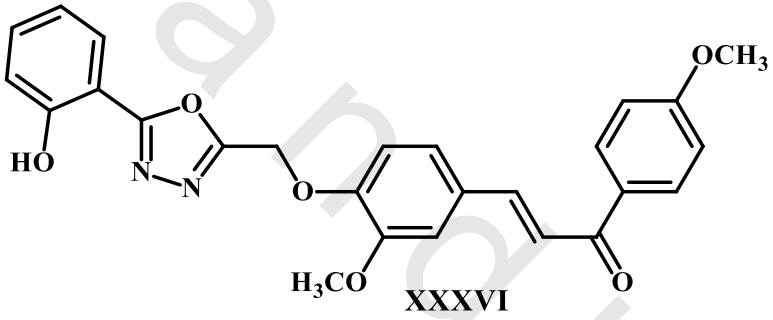
Also, 2,5-diphenyl-1,3,4-oxadiazole derivatives had antibacterial activity where compounds **XXXV a** and **b** showed excellent antibacterial activity against *E. coli* and *P. aeruginosa* at low concentration of of 3 µg/ml compared with the standard drug furacin (MIC 6, 12.5 µg/ml) against *E. coli* and *P. aeruginosa*, respectively. Compound **XXXVc** exhibited significant antifungal activity against *C.albicans* and showed highest inhibition at 3 µg/ml concentration compared with the standard drug fluconazole (MIC 6 µg/ml) [38].



XXXV a-c

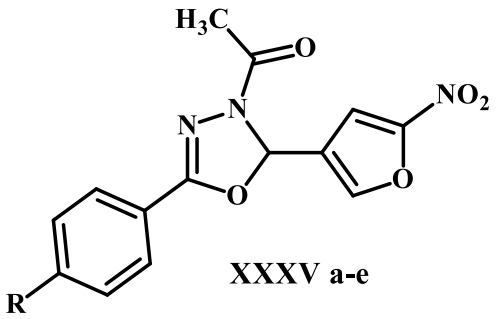
No.	R	R^1	R^2	R^3
a	CH_3	Br	H	H
b	F	F	F	H
c	Br	H	H	Cl

Moreover, several 2,5-disubstituted-1,3,4-oxadiazole derivatives exhibited good antibacterial activity. Among this series, compound **XXXVI** showed almost equivalent antibacterial activity to standard ciprofloxacin against *E. coli*, *S. aureus*, *P. aeruginosa* and *B. subtilis* [39].



XXXVI

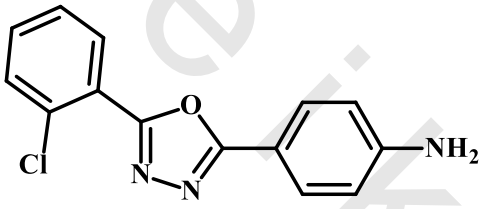
In studies of antistaphylococcal activity of a novel series of 1,3,4-oxadiazole derivatives **XXXV** linked to 5-nitrofuran moiety against strains of *S. aureus* resistant to methicillin and amino glycosides (MARSA), compounds **XXXV a-e** showed efficient antistaphylococcal activity with MICs between 4 to 32 µg/mL, being more potent than the standard drug chloramphenicol [40].



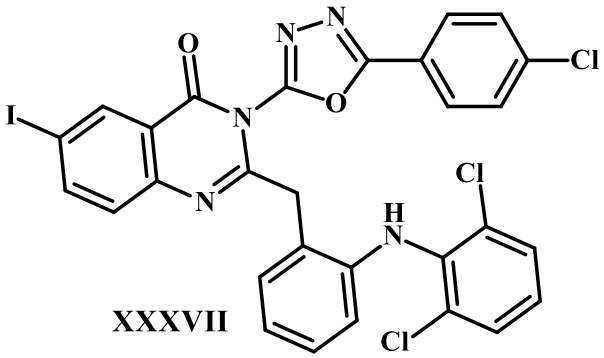
XXXV a-e

No.	R
a	H
b	CH_3
c	NO_2
d	Cl
e	OCH_3

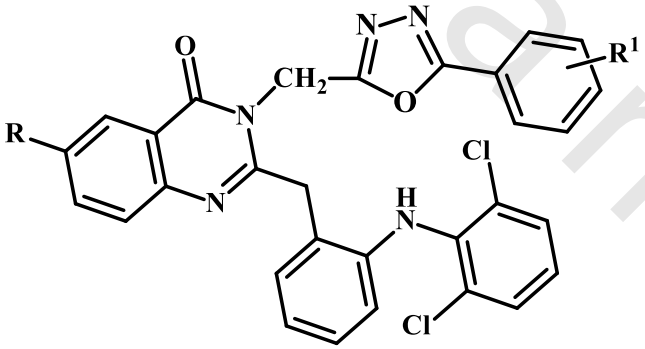
Very good antimicrobial activity was exhibited by amino substituted 1,3,4-oxadiazole derivative **XXXVI** and 1,3,4-oxadiazolyl-quinazolin4(3*H*)-one derivative **XXXVII** against *S. aureus* and *S. pyogenes* with MBC value of 100 µg/ml while the standard drug ampicillin had MBC value of 250 and 100 µg/ml , respectively. Introduction of CH_2 link between 3rd position of quinazolinone and 2nd position of oxadiazole afforded compounds **XXXVIII a,b** which were found more active than other two series against *E .coli* and *P. aeruginosa* with MBC value of 50 µg/ml, while standard drug ampicillin had MBC value of 100 µg/ml against the tested microorganisms [41].



XXXVI



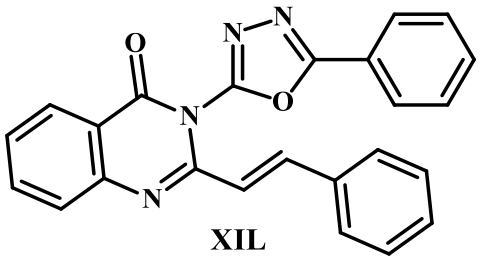
XXXVII



XXXVIII a,b

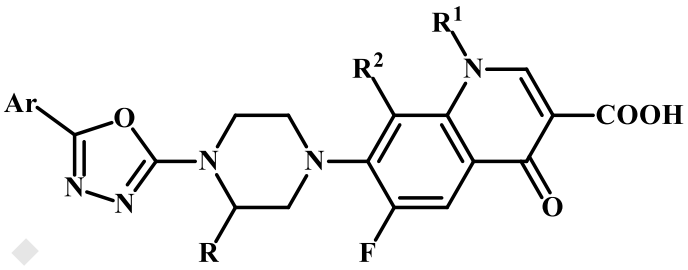
No.	R	R^1
a	Br	2-Cl
b	I	4-Cl

Moreover, inclusion of unsubstituted styryl moiety at position-2 of 1,3,4-oxadiazolyl-quinazolin-4(3*H*)-one **XIL** was effective in inducing a broad spectrum antibacterial activity where compound **XIL** showed good antibacterial activity against *B. subtilis, E. coli, S. aureus* and *P. vulgaris* [42].



XIL

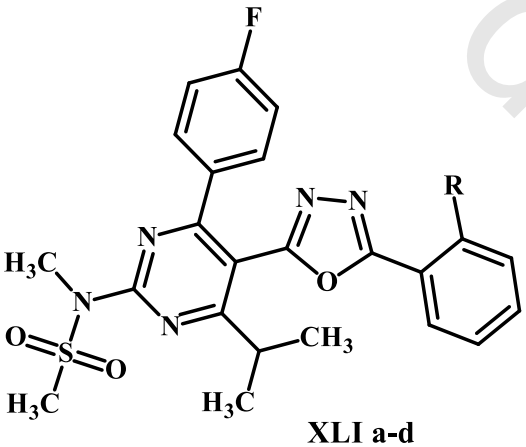
A series of 7-piperazinyl quinolone derivatives **XL** containing substituted 1,3,4-oxadiazole moiety exhibited good antimicrobial activity. Among this series, compounds **XL a,b** were found to be the most effective derivatives against *S. aureus* with pMIC value of 3.61 and 3.63, respectively compared with the standard drug ciprofloaxacin (pMIC 3.16). Compounds **XL c,d** were active against *B. subtilis* and *E. coli* [43].



XL a-d

No.	Ar	R	R^1	R^2
a	4-nitrophenyl	CH_3	Cyclopropyl	OCH_3
b	4-nitrophenyl	H	Ethyl	H
c	3,4-dinitrophenyl	H	Ethyl	H
d	3-nitrophenyl	CH_3	Cyclopropyl	OCH_3

In addition, novel pyrimidine substituted 1,3,4-oxadiazole derivative **XLI a-d** showed good antimicrobial activity against different Gram negative bacteria compared with the standard drug ciprofloaxacin [44].

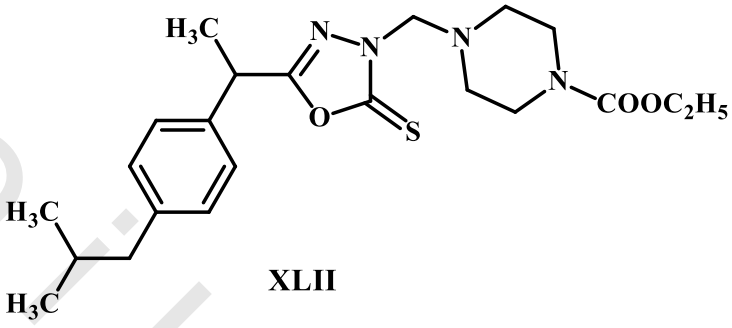


XLI a-d

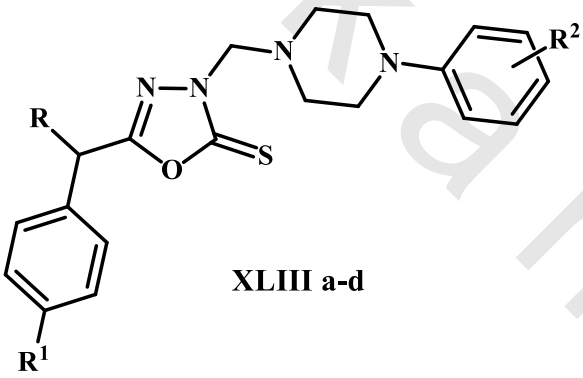
No.	R
a	Br
b	Cl
c	F
d	NO_2

Anti-inflammatory activity:

Literature survey revealed that 1,3,4-oxadiazol-2-thiones derivatives bearing substituted amino methyl moiety **XLII** and **XLIII a-d** were found to have anti-inflammatory activity greater than diclofenac sodium. In addition compounds **XLII** and **XLIIIc** showed increased analgesic activity against acetic acid induced writhring test in rats than the reference drug [(45)].



XLII



XLIII a-d

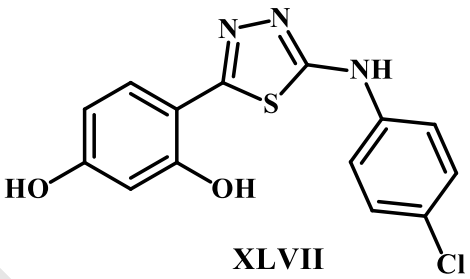
No	R	R^1	R^2
a	CH_3	$CHCH(CH_3)_2$	4-Cl
b	CH_3	$CHCH(CH_3)_2$	4-NO_2
c	CH_3	$CHCH(CH_3)_2$	4-F
d	H	SCH_3	3-Cl

1, 3, 4-Thiadiazole

Various 1,3,4-thiadiazole derivatives exhibit broad spectrum of pharmacological properties such as:

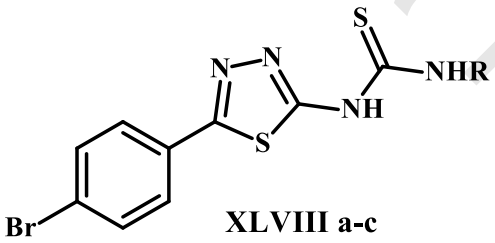
Anticancer activity

Prominent anti-proliferative activity against thyroid carcinoma FTC238 cells was displayed by 2-amino-1,3,4-thiadiazole derivative **XLVII** with IC_{50} of 6.4 µM without toxicity to normal cells [46].



XLVII

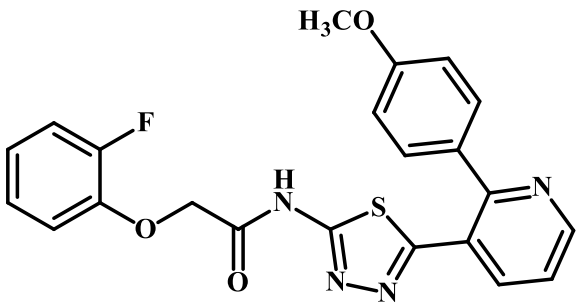
Also, good antitumor activity against non-small cell lung cancer cell line A549 was exhibited by 1,3-disubstituted thiourea derivatives **XLVIII a-c** containing a substituted 1,3,4-thiadiazole moiety with IC_{50} values of 4.83, 5.44 and 4.34 µM, respectively [47].



XLVIII a-c

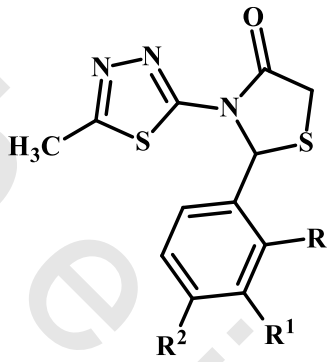
No.	R
a	$CH_2CH{=}CH_2$
b	C_4H_9
c	C_6H_{11}

Furthermore, high cytotoxic effect on human carcinoma cell line Caco-2 was displayed by phenoxy acetamide derivatives **XLIX** containing a substituted 1,3,4-thiadiazole moiety with IC_{50} value of 1.8 µM as compared with the standard 5-fluorouracil with IC_{50} value of 8.2 µM [48].



XLIX

Moreover, considerable anticancer activity was displayed by thiazolidin-4-one derivatives **L a-c** containing 1,3,4-thiadiazole moiety against human breast adenocarcinoma cells (MCF-7 cells) with IC_{50} values of 66.84, 60.71 and 46.34 µM, respectively compared with the clinically used anticancer drug cisplatin with IC_{50} value of 10.56 µM [49].

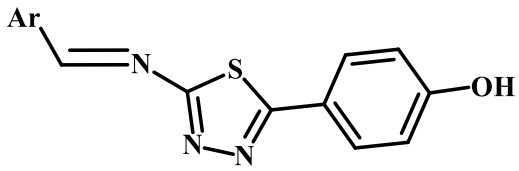


L a-c

No.	R	R^1	R^2
a	H	F	H
b	H	H	Cl
c	NO_2	H	H

Antimicrobial activity:

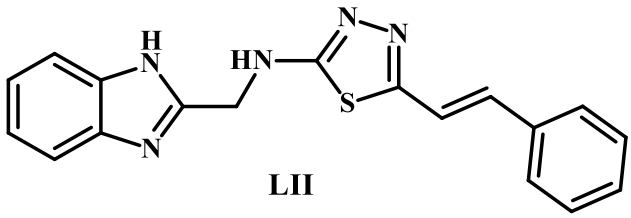
Potent antimicrobial activity against *B. subtilis, E.coli and C. albicans* was displayed by 4-[5-(arylidene amino)-1,3,4-thiadiazol-2-yl]phenol derivatives **LI a,b** [50].



LI a,b

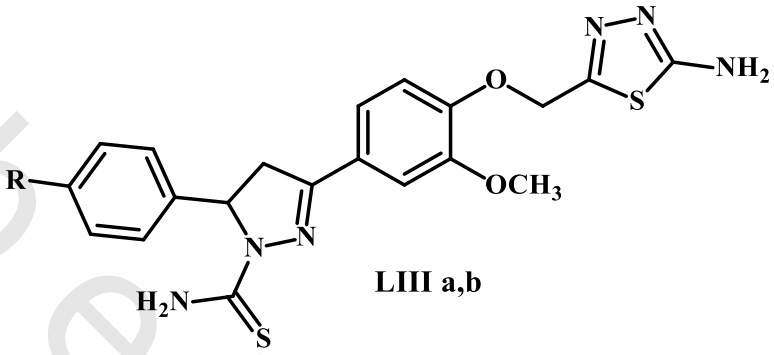
No.	Ar
a	4-Cl-C_6H_4
b	3-Cl-C_6H_4

In addition, good antibacterial activity towards Gram-positive and Gram-negative bacteria was displayed by substituted benzimidazole derivatives containing substituted 1,3,4-thiadiazole moiety **LII** [51].



LII

Also, significant antibacterial and antifungal activities were displayed by 4,5-dihydropyrazole-1-carbothioamide derivatives **LIII a,b** containing 1,3,4-thiadiazole moiety [52].

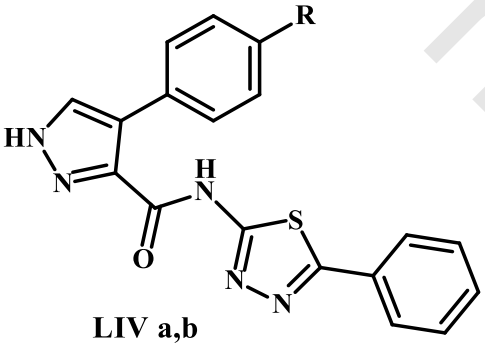


LIII a,b

No.	R
a	NO_2
b	F

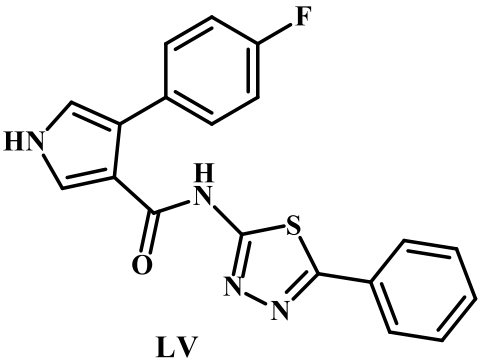
Anti-inflammatory activity:

Potent anti-inflammatory activity was exhibited by 1,3,4-thiadiazole systems containing pyrazole **LIV a,b** and pyrrole **LV** moieties with 77.27, 75.89, 76.24 % and 81.00, 80.55, 78.62 % inhibition in paw edema at 3 h and 5 h, respectively, compared to the standard drug indomethacin (74.82 and 80.32 % at 3 h and 5 h, respectively) [53].



LIV a,b

No.	R
a	4-NO_2
b	4-F



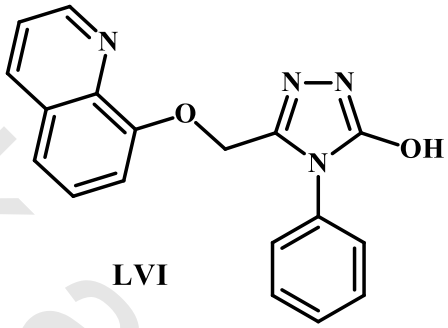
LV

1,2,4-Triazole

It is well-known that the derivatives of 1,2,4-triazole always possess a wide range of biological activities such as:

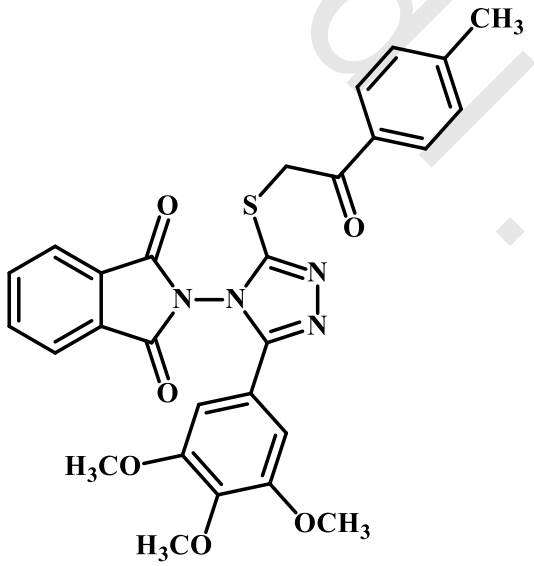
Anticancer activity:

Good *in-vitro* anti-proliferative activity against colon cancer cell line HT29 as well as breast cancer cell line MDA-MB231 was displayed by quinoline derivative **LVI** bearing a substituted 1,2,4-triazole moiety with IC_{50} values of 9.2 and 9.9 µM, respectively [54].



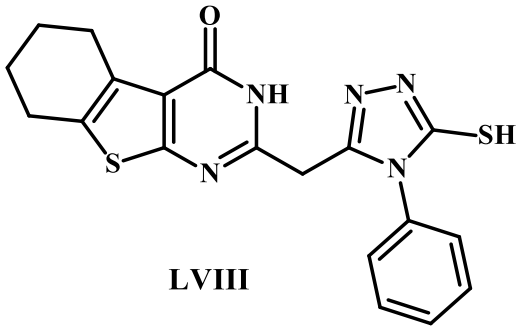
LVI

Moreover, four-fold improvement of the anticancer activity compared to 5-fluorouracil in inhibiting A549 and HepG2 cell proliferation was displayed by a novel isoindoline-1,3-dione containing 1,2,4-triazole moiety **LVII** with IC_{50} values of 6.76 and 4.44 µM, respectively [55].



LVII

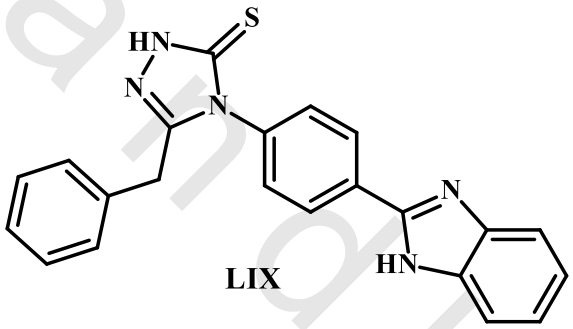
In addition, relative high cytotoxicity against HeLa cells was demonstrated by the new thieno[2,3-*d*]pyrimidin-4(3*H*)-one containing substituted 1,2,4-triazole **LVIII** with IC_{50} value of 9.5×10^{-4} µM but towards the other cells it exhibited proliferative effects [56].



LVIII

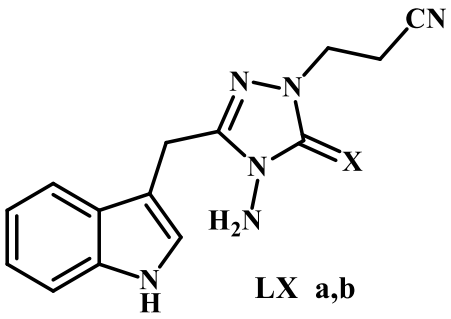
Antimicrobial activity:

Good antibacterial activity against Gram positive and Gram negative bacteria was displayed by the benzimidazole derivative **LIX** containing substituted 1,2,4-triazole-5-thione [51].



LIX

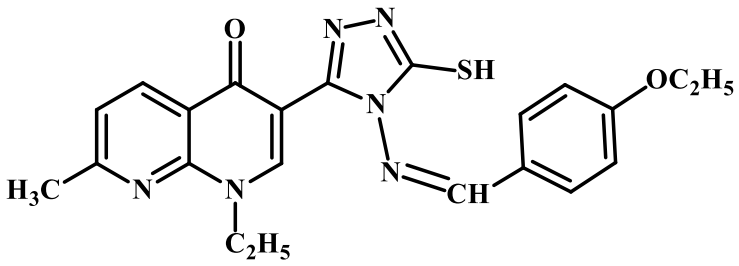
Furthermore, among a novel series of indole derivatives **LX** containing substituted 1,2,4-triazole moiety, Compounds **LX a**,**b** showed good antibacterial activity against *P.vulgaris*, *S. aureus* and *M. luteus* [57].



LX a,b

No.	X
a	O
b	S

Moreover, good antibacterial activity against *E.coli* (MIC 16 mg/ml) comparable to that of streptomycin (MIC 13 mg/mL) and ciprofloxacin (MIC 12.5 mg/mL) was exhibited by novel nalidixic acid based 1,2,4-triazole derivatives **LXI** [58].



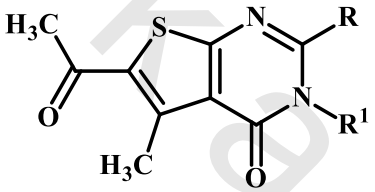
LXI

RESEARCH OBJECTIVES

It is well-known that azoles are constituents of many bioactive heterocyclic compounds with diverse biological and clinical applications. The incorporation of azoles is an important synthetic strategy in drug discovery.

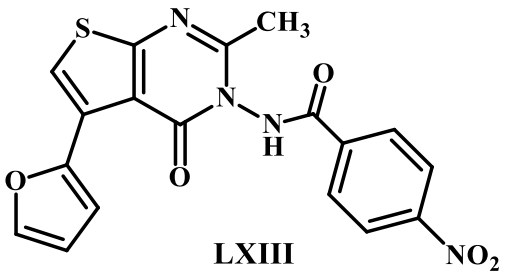
Besides, thienopyrimidines and their fused ring systems show potential bioactivities as they are bioisosteres of purines.

Among the thienopyrimidine derivatives, compounds **LXII a-c** exhibited significant antitumor and antioxidant activity [59] while compounds **LXIII** and **LXIV** showed significant antibacterial and antimycobacterial activity against all the microbial strains used when tested *in-vitro* [60].

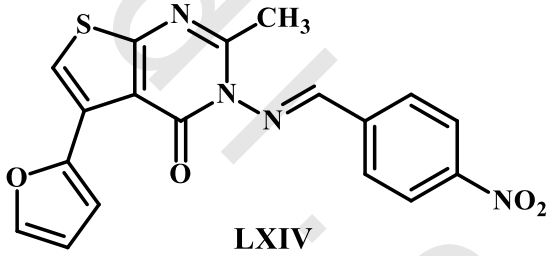


LXII a-c

No.	R	R^1
a	SH	NH_2
b	SH	H
c	CH_3	NH_2

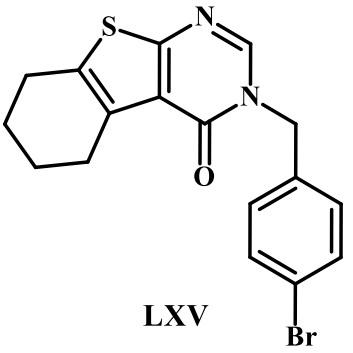


LXIII

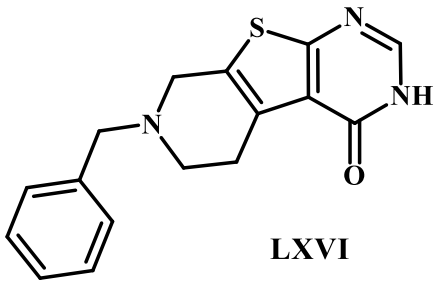


LXIV

Among the fused thienopyrimidine derivatives, compound **LXV** exhibited significant inhibitory activities against hepatocellular liver carcinoma (HepG2), breast adenocarcinoma (MCF-7) and gastric cancer (BCG-823) cell lines compared to the positive control 5-fluorouracil[61]. Moreover, compound **LXVI** showed very good anticancer activity against human breast adenocarcinoma MCF-7, colorectal carcinoma HCT116 and larynx carcinoma HEP2 with IC_{50} value of 0.67, 0.47 and 0.47 µg/ml, respectively compared with doxorubicin as reference drug with IC_{50} value of 0.70, 0.69 and 0.40 µg/ml, respectively [62].

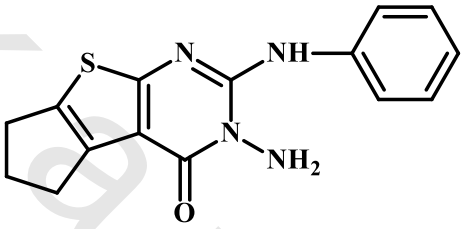


LXV



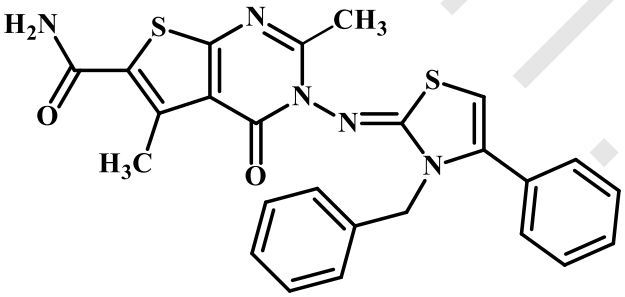
LXVI

On the other hand, compound **LXVII** was proved to possess remarkable broad spectrum antimicrobial activity against *P.aeruginosa*, *S. aureus*, *B.subtilis* and *C.albicans*. In addition, it showed promising antiviral activity with 80% reduction of the viral plaque number [63].



LXVII

Recently we reported new series of thienopyrimidine derivatives, their biological evaluation revealed that compound **LXVIII** exhibited dual anticancer and antimicrobial activities [64].



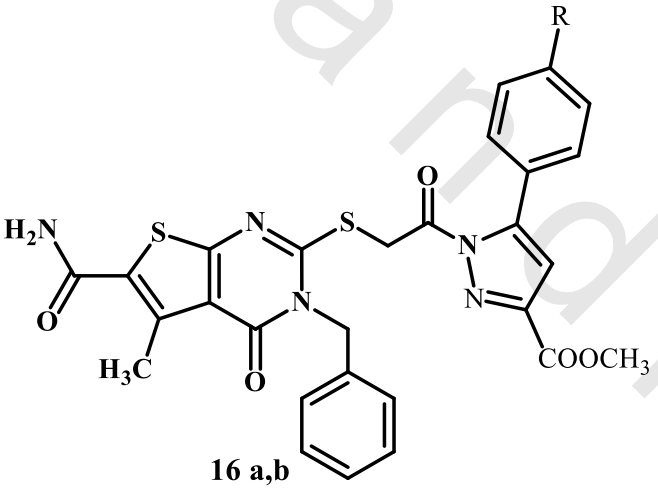
LXVIII

The increasing number of neoplastic diseases together with the accompanied high mortality rates has stimulated the search for new structure leads that might be of value in designing novel anticancer drugs.

Patients suffering from neoplastic disorders and receiving chemotherapeutic treatment are more likely to get microbial infections due to subsequent depression of the immune system.

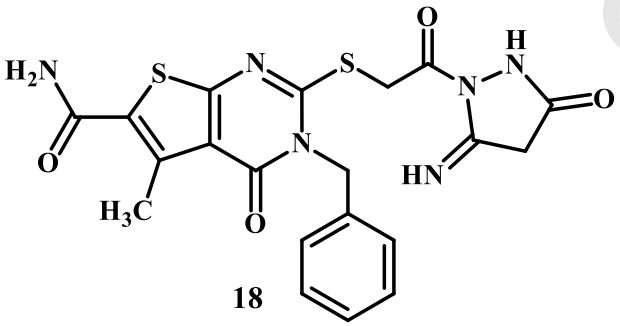
The combination of two pharmacophores on the same scaffold is a well-established approach to the synthesis of more potent drugs [65,66]. Motivated by these facts and as a continuation of our research program on the synthesis of novel bioactive heterocyclic compounds, the objectives of the present investigation have been directed toward the design and synthesis of hybrid molecules that incorporate the thienopyrimidine-6-carboxamide scaffold linked to various azole moieties through different atom spacers.

Among the new pyrazole containing thienopyrimidine derivatives the pyrazole ring in compounds **16a,b**, **18** and **19** is separated by a three atom spacer, while is separated by six and five atom spacer as in compounds **9a-c** and **27a-c**, respectively.

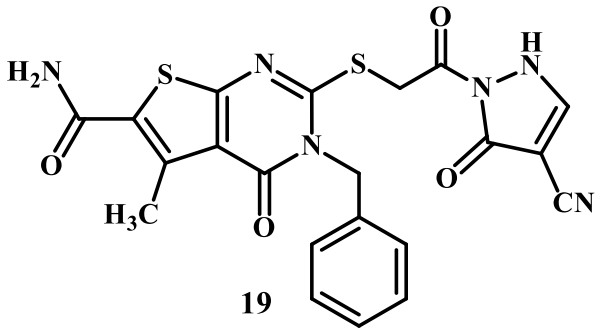


16 a,b

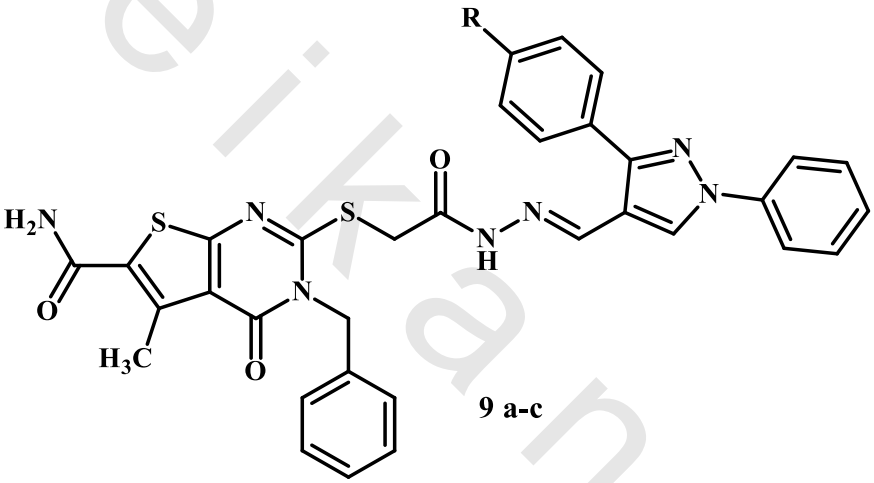
Compound ID	R
16a	H
16b	CH_3



18

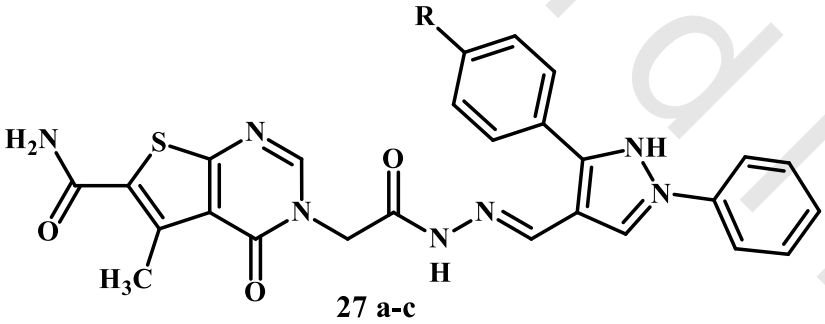


19



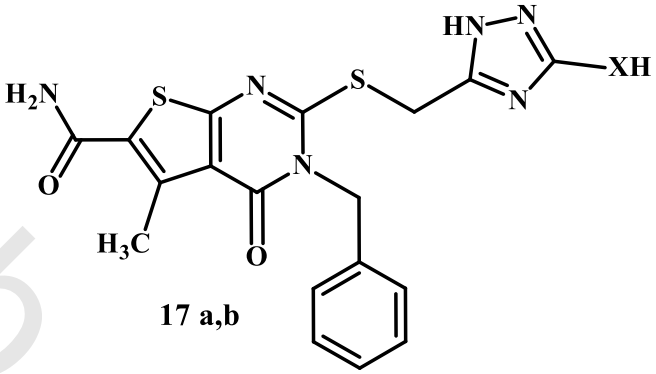
9 a-c

Compound ID	R
9a, 27a	H
9b, 27b	Br
9c, 27c	CH_3



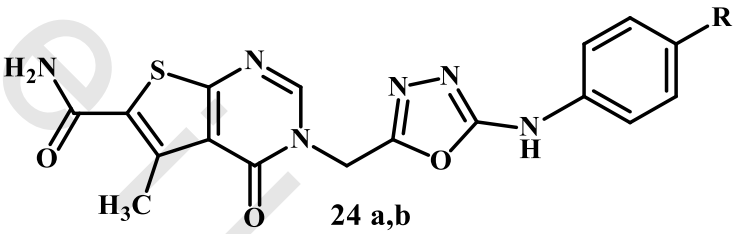
27 a-c

In addition, some hybrid molecules were designed to incorporate thienopyrimidine linked either to triazole ring **17a,b** at position 2 separated by two atom spacer or oxadiazole **24a,b** and thiadiazole rings **25** at position 3 separated by one atom spacer.



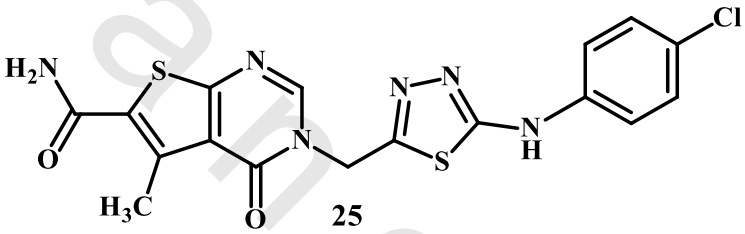
17 a,b

Compound ID	X
17a	O
17b	S



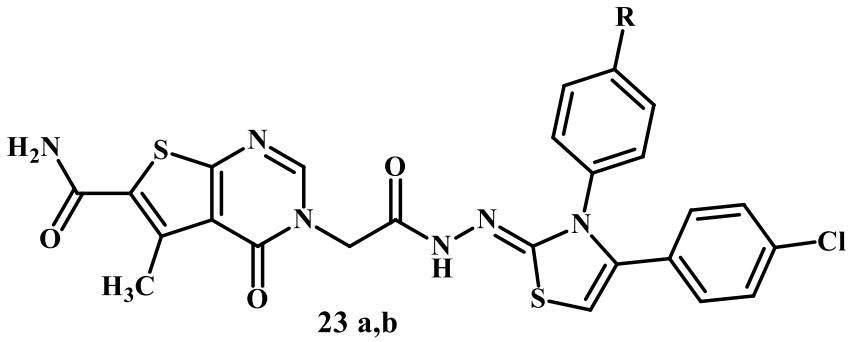
24 a,b

Compound ID	R
24a	Cl
24b	OCH_3



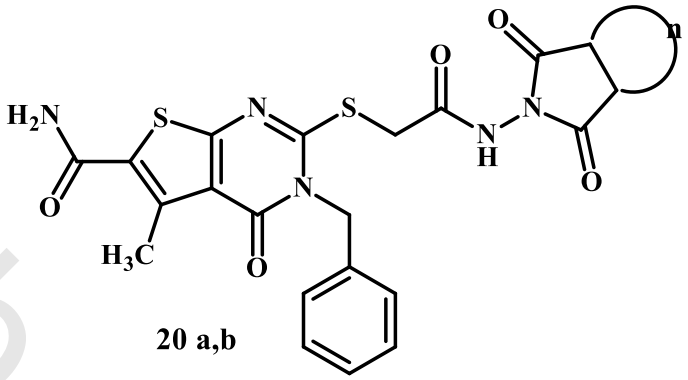
25

Additionally, several heterocyclic compounds containing other azoles such as thiazoline [67,68] and pyrrole [69,70] as well as fused azole such as indole [71,72] and isoindole [73,74] showed promising anticancer and/or antimicrobial activities. Therefore, similar thienopyrimidine derivatives **23a,b, 20a,b** and **11** were synthesized hoping comparative activity.



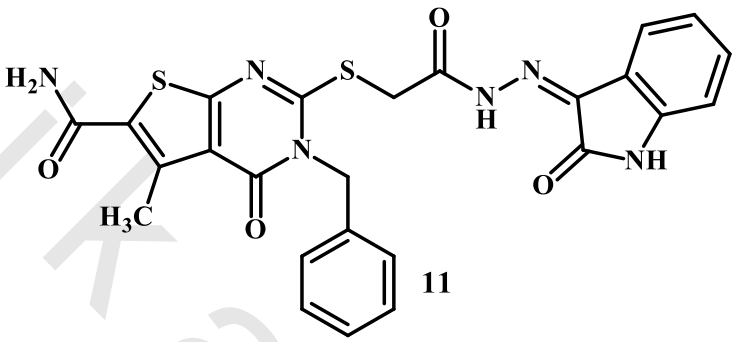
23 a,b

Compound ID	R
23a	Cl
23b	OCH_3



20 a,b

Compound ID	n
20a	0
20b	C_4H_4



11

The newly synthesized compounds were tested *in-vitro* for their anticancer activity, as well as for their antimicrobial activity aiming at finding out new candidates that might have dual anticancer and antimicrobial activities.

Molecular modeling concept was applied on number of compounds in an attempt to gain better insight about their molecular interactions.

Docking studies were designed to help understanding of the mode of action of the active compound and its interaction with target enzyme.

The integrity of the structure of the newly synthesized compounds would be substantiated by microanalytical, IR, ^{1}H-NMR, ^{13}C-NMR and/or MS data.