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ONE POT SYNTHESIS, ANTITUMOR, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SOME SCHIFF BASE HETEROCYCLES

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ABSTRACT

A series of Schiff bases of furan and thiophen rings has been synthesized in one step, in good and excellent yields, using acetic acid as catalyst. The synthesized products were evaluated for their anticancer activity toward breast (MDA-MB231) and colorectal (LoVo) human cell lines cancers. The in vitro antibacterial and antifungal potential of the products were also determined using tree bacterial strains (*Echerichia coli*, *Bacillus subtilis*, and *Micrococcus luteus*) and fungal strains (*Fusarium oxysporum f.sp albedinis FAO*). Significant activity against breast cancer cell lines and Fungal strains was observed.

Keywords: Schiff bases, Antitumor, MDA-MB231, LoVo, antibacterial, antifungal.

INTRODUCTION

New and successful strategies in the discovery of drugs for pharmaceutical and therapeutic applications are in a revolutionary period. Thus, compounds known as Schiff bases, bearing azomethine functional group –C=N–, have gained importance in pharmaceutical and medicinal industries due to their widespread potential biological activities such as anticancer [1], antibacterial and antifungal activities [2], anticonvulsant [3,4], antituberculosis [5,6], analgesic and anti-inflammatory [7]. On the other hand, Schiff bases with hydroxyl-substituent have been known to show good pharmaceutics [8,9] and antimicrobial properties [10]. Indeed, the presence of hydroxyl groups on the aromatic ring renders the Schiff bases as antioxidants to scavenge free radicals. Thus, Schiff bases bearing hydroxyl-substituent may be a key motif in diseases treatment related to free-radical hurt. In view of these, the aim of this paper is to evaluate the anti-tumor inhibition efficiency, antibacterial and antifungal activities of six hydroxyl-substituent Schiff bases obtained in one-pot reaction

from the acetic acid-catalyzed condensation of heteroaromatic aldehydes with aminobenzene derivatives. The list of synthesized and tested hydroxyl-substituent Schiff bases is given below.

MATERIAL AND METHODS

All commercial reagents were analytical grade and used without further purification. Melting points were determined by using a BUCHÏ 510 m.p. apparatus. The NMR spectra were obtained with a Bruker AC 300 spectrometer (CNRS). Molecular weights were determined on a JEOL JMS DX-300 Mass Spectrometer.

Synthesis of (E)-4-(furan-2-ylmethyleneamino) phenol (L1): A solution of furan-2-carbaldehyde (2g, 20.3mmol) and 4-aminophenol (2.3g, 20.3mmol) in 50ml of dry diethyl ether was stirred at room temperature for 8 days using a two drops of acetic acid as catalyst. The formed product was filtrated and washed with dry ether. The final purification was performed by re-crystallization from hot methanol to give pink powder. Yield 63.15% (2.4g, 12.82mmol). Mp 198-199°C. R_f = 0.5 (silica, CH_2Cl_2/MeOH, 9/1). ^{1}H NMR (300MHz, DMSO) δ ppm: 9.52 (s, 1H, OH); 8.39 (s, 1H, CH=N); 7.85 (d, 1H, furan-Hα); 7.15 (d, 2H, phenyl, C2H, C3H); 7.03 (d, 1H, furan-Hγ); 6.77 (d, 2H, phenyl, C3H, C5H); 6.65 (m, 1H, furan-Hβ). ^{13}C NMR (75 MHz, DMSO) δ ppm: 156.78 (1C, phenyl-C-OH); 152.78 (1C, C=N); 145.97 (2C, phenyl, C2 and C5) 142.75 (1C, furan-Cα); 122.86 (1C, furan-Cγ); 116.07 (2C, phenyl, C3 and C5); 112.82 (1C, furan-Cβ). m/z (M^+): 188.21. IR: ν(CH=N, imine) = 1630cm^{-1}

Synthesis of (E)-4-(thiophen-2-ylmethyleneamino) phenol (L2): A solution of thiophen-2-carbaldehyde (2.1g, 18.07mmol) and 4-aminophenol (1.97g, 18.07mmol) in 50ml of dry diethyl ether (90ml) was continued under stirring at room temperature for 6 days using two drops of catalyst (acetic acid). The formed product was filtrated and washed with dry ether. The final purification was performed by re-crystallization from hot ethanol to give a yellow powder. Yield 68.06% (2.5g, 12.29mmol). Mp 204-205°C. R_f = 0.60 (silica, CH_2Cl_2/MeOH, 9/1) ^{1}H NMR (300MHz, DMSO) δ ppm: 9.53 (m, 1H, OH); 8.48 (s, 1H, CH=N); 7.52 (d,1H, thiophen-Hα); 7.48 (d, 1H, thiophen-Hγ); 7.22 (t, 1H, thiophen-Hβ); 7.15 (d, 2H, phenyl-C2H, C6H); 6.96 (d, 2H, phenyl-C3H, C5H). ^{13}C NMR (75 MHz, DMSO) δ ppm: 156.71 (1C, phenyl-OH); 150.99 (1C, CH=N); 132.85 (1C, thiophen-Cα); 130.55 (1C, thiophen-Cγ); 122.92 (1C, thiophen-Cβ); 122.92 (2C, phenyl, C2 and C6); 116.20 (2C, phenyl, C3 and C5). m/z (M^+): 204.18. IR: ν(CH=N, imine) = 1615cm^{-1}.

Synthesis of (E)-N-(furan-2-ylmethylene)-2-methylaniline (L3): This product was prepared by mixing *ortho*-toluidine (2.23g, 20mmol) and furan-2-carbaldehyde (2g, 20mmol) in 50ml of dry diethyl ether. The reaction mixture was stirred for 7 days at room temperature using acetic acid as catalyst. The reaction completion was confirmed by TLC and the product was purified on silica gel column flash-chromatography using CH_2Cl_2/MeOH. The resulting product was precipitated in petrol ether, filtrated and dried to get pure product as brown powder. Yield 56.97% (2.1g, 11.33 mmol). Mp 62-63°C. R_f = 0.77 (silica, CH_2Cl_2/MeOH, 9/1) ^{1}H NMR (300MHz, CDCl3) δ ppm: 8.17 (s, 1H, CH=N); 7.61 (d, 1H, furan-Hα); 7.23 (d,1H, phenyl, C3H); 7.19 (t, 1H, phenyl, C5H); 7.14 (t, 1H, phenyl, C4H); 7.00 (d,1H, phenyl, C6H); 6.91 (t, 1H, furan-Hγ); 8.74 (m,1H, furan-Hβ); 2.51 (s, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl3) δ ppm: 148.07 (1C, C=N); 145.67 (1C, furan-Cα); 131.99 (1C, phenyl-C5-CH_3); 130.39 (1C, phenyl-C3); 126.75 (1C, phenyl-C4); 125.92 (1Cphenyl-C5); 117.85 (1C, furan-Cγ); 116.02 (1C, phenyl-C6); 112.20 (1C, furan-Cβ); 17.95 (1C, CH_3). m/z (M^+): 185.91. IR: ν(CH=N, imine) = 1630cm^{-1}

Synthesis of (E)-2-methyl-N-(thiophen-2-ylmethylene) aniline (L4): The synthesis of **(L4)** was carried out, in a similar procedure as it is described above, by mixing *ortho*-toluidine (1.4g, 13.37mmol) and thiophen-2-carbaldehyde (1.5g, 13.37mmol) in 50ml of dry diethyl ether. The reaction mixture was stirred for 7 days using acetic acid as catalyst. The reaction completion was confirmed by TLC. The product was purified by silica gel column flash-chromatography using CH_2Cl_2/MeOH to give brown powder. Yield 55.73% (1.5g, 7.45mmol). Mp 39-40°C. R_f = 0.8 (silica, CH_2Cl_2/MeOH, 9/1) ^{1}H NMR (300MHz, CDCl3) δ ppm: 8.47 (s, 1H, CH=N); 7.52 (d, 1H, thiophene-Hα) 7.48 (d, 1H, thiophene-Hγ); 7.25 (d, 1H, phenyl-C3H), 7.22 (t, 1H, phenyl-C5H); 7.16 (t, 1H, phenyl-C4H); 7.13 (d, 1H, phenyl-C5H); 6.96 (t, 1H, thiophene-Hβ). 2.39 (s, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl3) δ ppm: 152.28 (1C, C=N); 131.81 (1C, thiophene-Cα); 130.23 (1C, thiophene-Cγ); 127.73 (1C, phenyl-C3); 127.27 (1C, phenyl-C5); 126.71 (1C, phenyl-C4); 125.82 (1C, phenyl-C6); 117.77 (1C, thiophene-Cβ); 17.88 (1C, CH3). m/z (M^+): 202.19. IR: ν(CH=N, imine) = 1616cm^{-1}.

Synthesis of (E)-2-(furan-2-ylmethyleneamino)phenol (L5): This compound was prepared by condensation of furan-2-

carbaldehyde (3g, 31.22mmol) and 2-aminophenol (3.41g, 31.25mml) in ether as solvent. The reaction was kept under stirring for 7 day using acetic acid as catalyst. The reaction completion was confirmed by TLC. The solvent was concentrated and the resulting product purified by silica gel column flash-chromatography usingCH_2Cl_2/MeO to give brown powder as 76.9% Yield (4.5g, 24.03mmol). Mp 68-69°C. R_f = 0.85 (silica, CH_2Cl_2/MeOH, 9/1) ^{1}H NMR (300MHz, CDCl3) δ ppm: 8.49 (s, 1H, C<u>H</u>=N); 7.63 (d, 1H, furan-Hα); 7.25 (d, 1H, furan-Hγ); 7.17 (t, phenyl, C4<u>H</u>); 7.07 (s, phenyl, C3<u>H</u>); 7.01 (d, 1H, phenyl, C6<u>H</u>); 6.88 (t, phenyl, C5<u>H</u>); 5.26 (m, 1H, furan-Hβ). ^{13}C NMR (75 MHz, CDCl3) δ ppm: 146.09 (1C, CH=N); 144.74 (1C, furan-Cα); 129.01 (1C, furan-Cγ); 120.10 (1C, phenyl-C4); 116.54 (1C, phenyl, C3); 115.75 (1C, phenyl-C6); 115.27 (1C, phenyl-C5); 110.17 (1C, furan-Cβ). m/z (M^+): 188.04 IR: ν(CH=N, imine) = 1605cm^{-1}.

Synthesis of (E)-2-(thiophen-2-ylmethyleneamino) phenol (L6): A solution of 2-aminophenol (0.48g, 4.45mmol) and thiophen-2-carbaldehyde (0.5g, 4.45mmol) dissolved in dry diethyl ether was stirred for 7 days using acetic acid as catalyst. The formed product was filtered and washed with cold diethyl ether to give light brown powder. Yield 86.23% (0.78g, 3.86mmole). Mp 177-178°C. R_f = 0.39 (silica, CH_2Cl_2/MeOH, 9/1) ^{1}H NMR (300MHz, CDCl3) δ ppm: 8.88 (s, 1H, C-OH); 6.62 (d, 1H, thiophen-Hα); 6.59 (d, 1H, thiophen-Hγ); 6.56 (s, 1H, CH=N, imine); 6.53 (t, 2H, phenyl-C3H, C5H); 6.49 (d, 1H, phenyl-C6H); 6.38(d, 1H, phenyl-C2H); 6.35(m, 1H, thiophen-Hβ). m/z (M^+): 204.17 IR: ν(CH=N, imine) = 1603cm^{-1}.

Evaluation of Anticancer Activity: The synthesized compounds **L1-L6** were evaluated for their anticancer activity toward breast (MDA-MB231) and colorectal (LoVo) human cell lines cancers using MTT tests.

General terms [11]: MTT tests were performed in order to rapidly, i.e. within 3 days, measure the effect of compounds on the overall cell growth. The test measures the number of metabolically active living cells that are able to transform the yellow product 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (herein referred as MTT) into the blue product formazan dye by mitochondrial reduction. The amount of formazan obtained at the end of the experiment, measured by means of a spectrophotometer (Plate Reader Victor X4 Microplate reader (Perkin Elmer), is directly proportional to the number of living cells. To perform the assay, cells were allowed to grow in 96-well microplates with a flat bottom following addition of an amount of 100 µl of cell suspension per well with 4,500 cells/well. Cell lines were seeded in Glutamax-containing RPMI supplemented with 10% Fetal Bovine Serum (PAA) and 1% penicillin + streptomycin mix (Invitrogen).

The detailed experimental procedure was the following: after a 24-hour period of incubation at 37°C, the culture medium was replaced by 100 µl of fresh medium in which the tested compound was previously dissolved, at the following concentrations: 10^{-8}, 5.10^{-8}, 10^{-7}, 5.10^{-7}, 10^{-6}, 5.10^{-6}, 10^{-5}, 5.10^{-5} and 10^{-4} g/ml. Each experiment was performed in sestuplicates. Cells were then incubated at 37°C in a Binder incubator under 5% CO_2-containing humidified atmosphere.

After 72 hours of incubation, with or without the compound to be tested, the medium was replaced by 100 µl of HBSS (without phenol red) containing MTT at a concentration of 1 mg/ml. The micro-wells were subsequently incubated during 3 hours at 37° C and centrifuged at 1300 rpm during 10 minutes. Medium was removed and formazan crystals formed were dissolved in 100 µl DMSO. The micro-wells were shaken for 5 minutes and read on a spectrophotometer at wavelengths of 570 nm (maximal formazan absorbance).

For each experimental condition, the mean optical density was calculated, allowing the determination of the percentage of living cells in comparison to the control.

Evaluation of antibacterial and antifungal activities

The in vitro antibacterial and antifungal activites was tested by the agar diffusion technique (ADT).

General terms [12]: ADT has been investigated using susceptibility test of NCCLS (National Committee for Clinical Laboratory Standards) recommended by the WHO and the French standard NF - U - 47-107 AFNOR 2004.

The agar media were inoculated with test organisms and a solution of the tested compound in DMSO/EtOH (50/50) was added to different concentration in the culture media. The growth is followed by a count of bacteria and yeast colonies and measurement of mycelium diameter. The inhibition percentage of a molecule is equal to the ratio of the colonies number or the mycelium diameter of the culture in presence of a dose of the tested compound over the colonies number or the mycelium diameter of the reference culture multiplied by 100. The minimum inhibition

concentration (MIC) is the least dose of the compound which caused inhibition of the micro organism growth.

Calculates the concentration IC50 was done using the same bacterial inocula mentioned above with decreasing concentration of the tested products. DO was measured of each culture at 625 nm.

$$\text{Inhibition percentage} = \left(\frac{\text{Do - Dx}}{\text{Do}}\right) \text{ x } 100$$

Do : diameter of the mycelial growth of the culture witness.
Dx : diameter of the mycelial growth in the presence of the product to be tested.

RESULTS AND DISCUSSION

Linker Synthesis: The synthesis of target drugs was illustrated in scheme 1. The condensation of furan-2-carbaldehyde or thiophen-2-carbaldehyde with aminobenzene derivatives in dry diethyl ether, using acetic acid as catalyst, offered desired products in high yield. Structure of compounds had been assigned using resonance frequency of protons on the basis of their integration and multiplicity pattern. Indeed, the broad and weak NH_2 peak is usually shown in a region at 4-6 ppm [13], this signal disappears in the spectra of formed Schiff bases. The aromatic carbon of Schiff bases were attributed by comparing the experimental chemical shifts with those calculated from the incremental method [14]. The ^{13}C-NMR spectral data and the molecular peak of the target products are in accord with the proposed structures.

Biological Assays

The target drugs described in this manuscript were evaluated for their biological activities against:

- Human cancer cell lines such as : breast (MDA-MB231) and colorectal (LoVo) cancers.
- Fungal strains (*Fusarium oxysporum f.sp albedinis*) isolated from a date palm having a vascular fusariose.
- Bacterial strains (*Echerichia coli*, *Bacillus subtilis*, and *Micrococcus luteus*).

Antitumor activity: Study results showed an anti-proliferative activity of hydroxyl-substituent Schiff bases especially against breast cancer cell lines. This is evident by the range of IC50 values (Table 1) which present an inhibitory activity at micromolar concentration. This result is probably related to the high radical-scavenging property of hydroxyl-substituent Schiff bases [15]. It is known that "free radicals are omnipresent in our body and are generated by normal physiological processes. These radicals can inflict cellular damage which contributes to cancer" [16]; several defenses have evolved both to protect our cells from radicals such as antioxidant scavengers. Indeed, the large conjugate system, the high radical-scavenging property and low steric hindrance in the framework of hydroxyl-substituent Schiff base benefit these products to trap radicals [15]. Accordingly, Schiff bases without hydroxyl-substituent (**L3** and **L4**) did not show any interestingly activity against any of the two cancer cell lines examined. This result highlights the interest of hydroxyl-substituent Schiff bases in the treatment of the radical-related disease. An example of the curves of the active compounds against MDA-MB-231 proliferation in normoxie conditions is shown in Figure 2.

We also noted that the hydroxyl-substituent radical at *ortho* position (**L5** and **L6**) may be covered by the lone electron pair from the N atom resulting in supplementation of an electron for the hydroxyl radical. This overlapping prevents these products to trap radicals. For the hydroxyl-substituent radical at *para* position (**L1** and **L2**), no aforementioned electron-supplementation effect takes place [17].
The results revealed that hydroxyl-substituent Schiff bases are promising in the treatment of diseases caused by free radicals, and provide more information for designing novel drugs.

Antibacterial and antifungal activity: The results revealed that all drugs did not exhibit any significant effect against tree bacterial strains examined (IC50 > 320 µg/ml for **L3** and **L4)** and (IC50 > 2000 µg/ml for **L1**, **L2**, **L5** and **L6**), whereas these compounds are significantly active against Fungal strains, especially towards: **L2**, **L4** and **L6** (Table 1) with thiophen ring. It is found that the negative charges of the sulfur and imine groups contribute positively in favor of an antifungal activity, more than antibacterial activity [18-20]. This is in good agreement with the mode of antifungal action of the compounds bearing ($X^{\delta-}$---$Y^{\delta-}$) pharmacophore site. Indeed, the fungal activity of **L2** is very substantial, and decreases slightly in case of **L4** and **L6** because of hydroxyl or methyl groups attached to *ortho* position of the N atom creating thus an additional ($X^{\delta-}$---$Y^{\delta+}$) pharmacophore site which is in disfavor of an antifungal activity (Figure 2).

The greater activity of pharmacophore site is due to their physicochemical properties and their ability to penetrate the fungal cell envelope and reach its cellular action site.

CONCLUSION

In the present work, a series of new furan and thiophen based Schiff bases were synthesized and characterized by spectral studies. All the synthesized compounds were first evaluated for their anti-tumor activities against two human cancer cell lines including breast (MDA-MB231) and colorectal (LoVo) cancers. The Compounds were also screened against tree bacterial strains (*Echerichia coli, Bacillus subtilis*, and *Micrococcus luteus*) and against fungal strains (*Fusarium oxysporum f.sp albedinis*). Hydroxyl-substituent Schiff bases exhibited excellent activity against the two cancer cell lines examined, whereas compounds bearing ($X^{\delta-}$---$Y^{\delta-}$) pharmacophore site are significantly active against Fungal strains.

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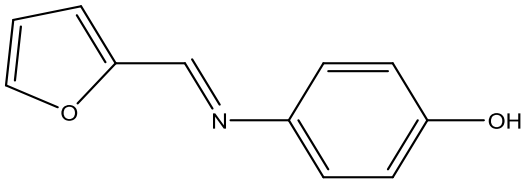
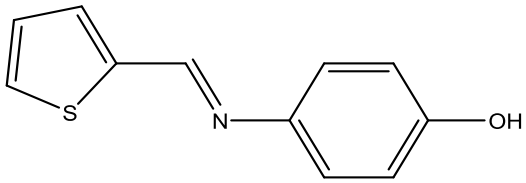


(*E*)-4-((furan-2-ylmethylene)amino)phenol **(L1)**



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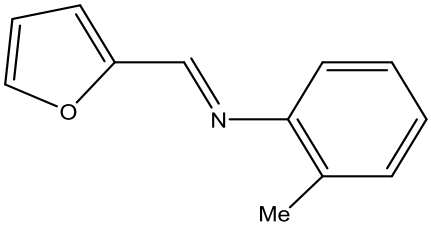
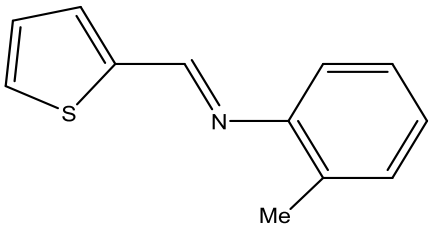
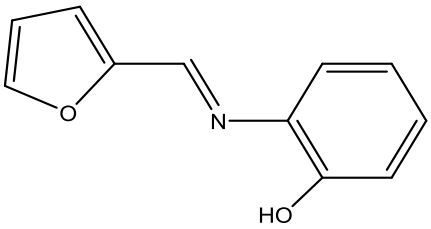


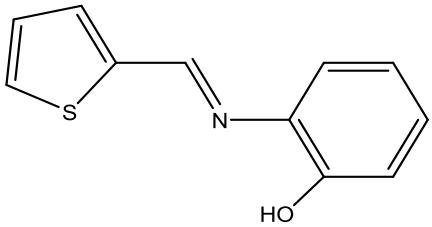
(*E*)-1-(furan-2-yl)-*N*-(*o*-tolyl)methanimine **(L3)**



(*E*)-1-(thiophen-2-yl)-*N*-(*o*-tolyl)methanimine **(L4)**

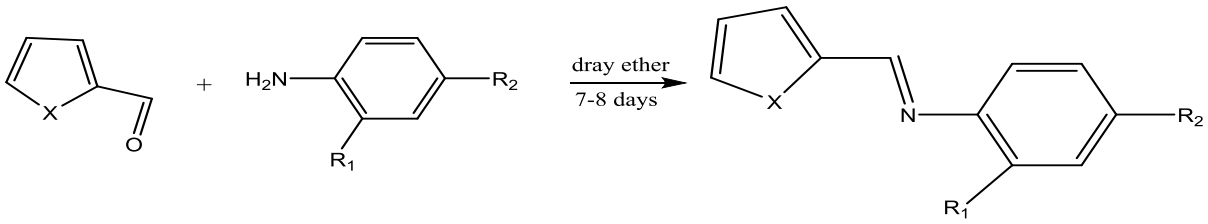


(*E*)-2-((furan-2-ylmethylene)amino)phenol **(L5)**



(*E*)-2-((thiophen-2-ylmethylene)amino)phenol **(L6)**

Figure 1: Structure of hydroxyl-substituent and non hydroxyl-substituent Schiff bases tested.



X = O;	R_1 = H;	R_2 = OH	**(L1)**
X = S;	R_1 = H;	R_2 = OH	**(L2)**
X = O;	R_1 = CH_3;	R_2 = H	**(L3)**
X = S;	R_1 = CH_3;	R_2 = H	**(L4)**
X = O;	R_1 = OH;	R_2 = H	**(L5)**
X = S;	R_1 = OH;	R_2 = H	**(L6)**

Scheme 1: Methodology of synthesized products.

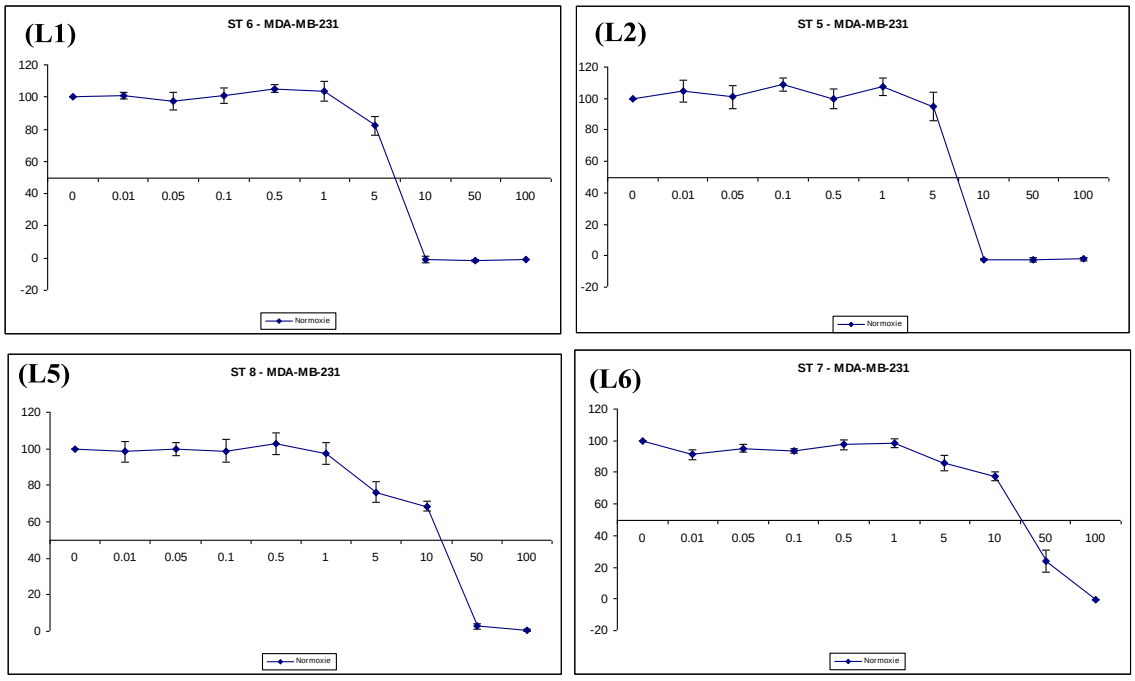
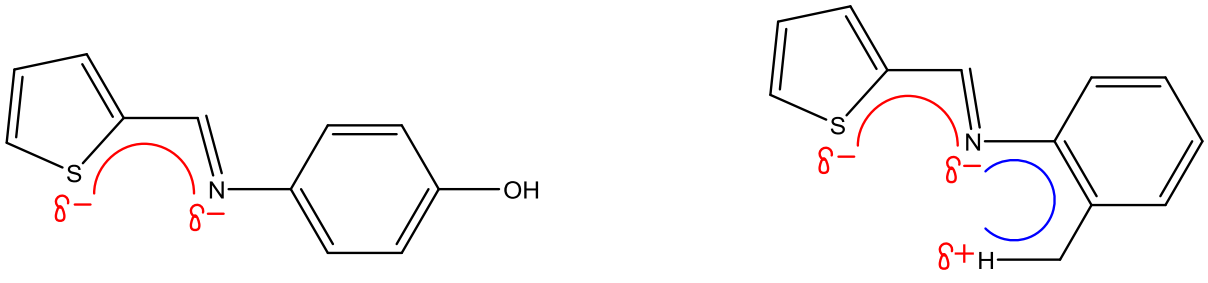


Figure 2: Curves of active compounds against MDA-MB-231 proliferation in Normoxie conditions.



(L2) **(L4)** and **(L6)**

Figure 3: Favor and disfavor pharmacophore site of an antifungal activity.

Table 1: IC50 values of compounds (**L1–L6**) against breast and colorectal cancer cell lines as determined by MTT assay. N/A means non applicable because IC50 >100 µg/ml.

	MDA-MB231	**LOVO**
Compounds	IC50 (µg/ml)	IC (µg/ml)
L1	6.9	14.6
L2	7.3	23.8
L3	N/A	N/A
L4	N/A	N/A
L5	30.5	23.5
L6	7.3	10

Table 2: MIC values of compounds (**L1–L6**) against *Fusarium oxysporum f.sp albedinis.*

	20 µl	**80 µl**	**160 µl**	**Inhibition (%)= (D°-Dx)/D° x 100**			**MIC (µg/ml)**
L1	3,50	1,2	0,8	30	76	84	128
L2	1,2	1,00	0,8	76	80	84	60
L3	3,2	1,3	1,00	36	74	80	120
L4	2	1,3	0,7	60	74	86	72
L5	5	3,4	1,00	0	32	80	500
L6	1,8	0,8	0,5	64	84	90	72

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