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Synthesis of novel derivatives of benzothiazole and benzothiazole isosters of expected activity against breast cancer

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ABSTRACT

Combination of benzothiazole and benzothiazole isosteres (benzoxazole and benzimidazole) with certain anticancer active heterocyclic compounds, in one molecule, to increase its anticancer activity, was done and the study of this combination regarding the anticancer activity was made.

In this study, substituted pyrazoles IIIa-c were prepared through diazotization of aminocompounds Ia-c followed by condensation with acetylacetone then hydrazinalysis of intermediates IIa-c (Scheme 1).

Scheme 2 includes the reaction of the amino group of Ia-c with 2-chloromethyl-1H- benzimidazole (IV) to afford new compounds Va-c.

The reaction of the amino group of Ia-c with pyrazolopyrimdine VIII gave the desired compounds IXa-c (Scheme 3).

The cytotoxicity of compounds IIIa-c, Va-c and IXa-c was evaluated against human breast carcinoma cell line (MCF7).

KEYWORDS

Benzothiazole;
Benzoxazole;
Benzimidazole;
Isosters;
Pyrazoles;
Anticancer.

INTRODUCTION

The biotransformation of benzothiazole plays an important role to activate or deactivate the benzothiazole molecule as anticancer agent, so the following figure 1 shows the main biotransformation of benzothiazole.

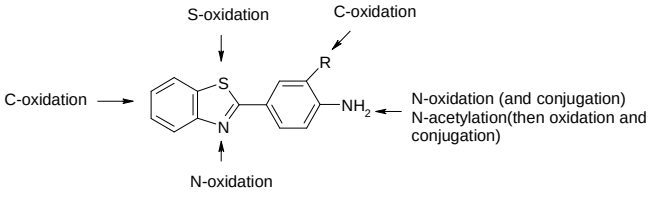


Figure 1

The mechanism action of benzothiazole involves induction of cytochrome enzyme (CYP1A1), catalyzed biotransformation of benzothiazole to generate electrophilic species, which covalently bind to DNA, exerting lethal damage to sensitive tumor cells, *in vitro* and *in vivo*[1-5].

The literature survey revealed that many benzothiazole isosteres have anticancer activity[6-18].

An idea of a great interest is to combine the pharmacologically active benzothiazole nucleus and its isostere with other nuclei having anticancer activity to disclose the activity of the resulting compounds.

Many compounds containing pyrazole[22-25] as a part of their structures have anticancer action. This directed us to the incorporation of these pharmacophores in

benzothiazole and benzothiazole isosteres nucleus to afford compounds of the expected action.

RESULT AND DISCUSSION

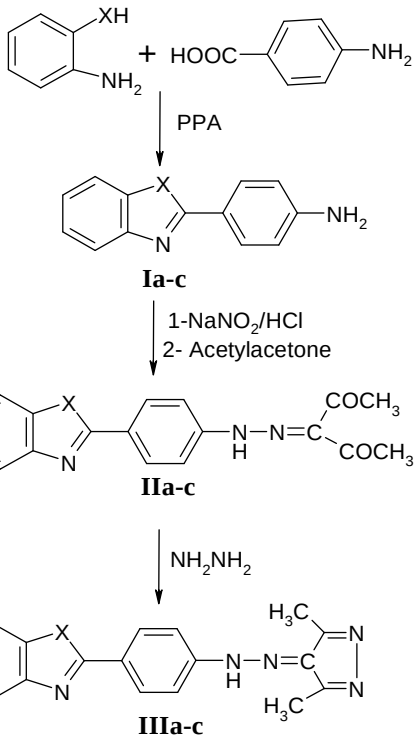
Chemistry

The starting materials (precursors) Ia-c were prepared via cyclodehydration reaction between *o*-phenylene diamine, 2-aminophenol or 2-aminothiophenol with 4-aminobenzoic acid (PABA) using polyphosphoric acid (PPA) as a dehydrating agent accord to reported condition[9-14]

Several dehydrating agents have been reported, however, PPA is the reagent of choice since it was documented that it gave good yield and this is the procedure that was adapted[9-11,14] (Scheme 1)

Diazotisation of compounds 1a-c followed by coupling of the diazonium salt with acetylacetone in basic medium gave compounds IIa-c. The basic medium of this reaction was achieved by using one equivalent of sodium acetate to convert acetylacetone into the monosodio derivative as a result of removal of one a-proton to yield an ambident anion[31].

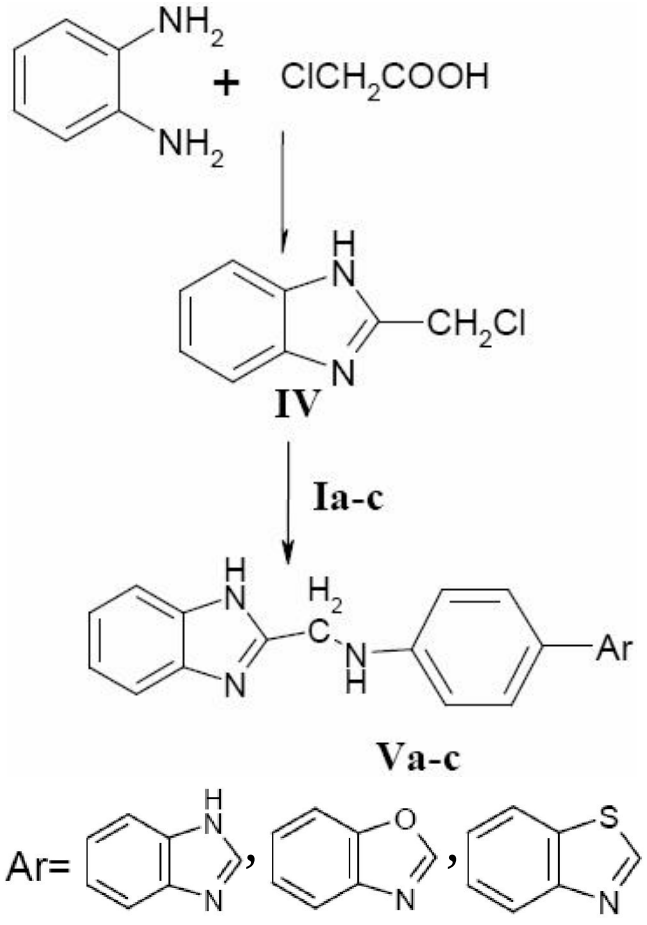
This conjugated base will be stabilised by resonance and reacted with the diazonium salt to yield compounds Ia-c.



Scheme 1

Compounds IIIa-c were synthesized through reaction of IIa-c with hydrazine hydrate. Compounds IIIa-c were confirmed by disappearance of (C=O)peak in IR of compounds IIa-c. (Scheme 1)

Compounds Va-c were prepared by nucleophilic substitution of 2-chloromethylbenzimidazole with amino group of Ia-c using Na_2CO_3 as base this was indicate in IR through appearance of peak at 1612-1610 (C=N) also in ^{1}HNMR peak at δ4.6-4.68(CH_2) (Scheme 2).



Scheme 2

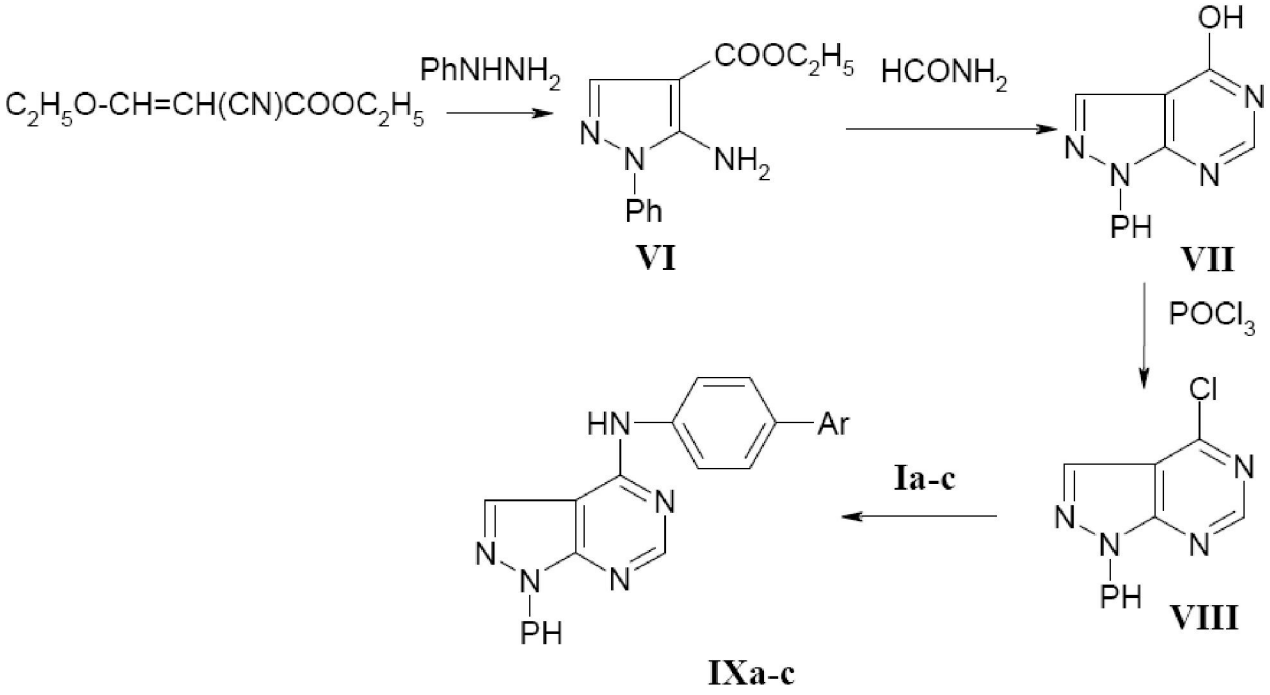
Nucleophilic substitution of compound VIII with Ia-c, was used for the preparation of IXa-c.

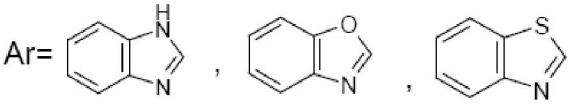
In ^{1}HNMR of compounds IXa-c, significant two single peaks appeared at δ 8.64(s, 1H, CH=N of pyrazole), δ 8.75 (s,1H, CH=N of pyrimidine) and also at δ 10.65 (s, *1H*, HN, D_2O exchangeable). (Scheme 3)

Anticancer

The cytotoxicity of compounds IIIa-c, Va-c and

IXa-c was evaluated against human breast carcinoma cell line (MCF7). For comparison purposes, the cytotoxicity of doxorubicin (DOX), as a standard antitumor drug, was evaluated under the same conditions. The IC_{50} and IC_{90} (dose of the compound which caused a 50% and 90% reduction of survival values) were shown in TABLE 1. The results are represented graphically in figure 2 and 3.





Scheme 3

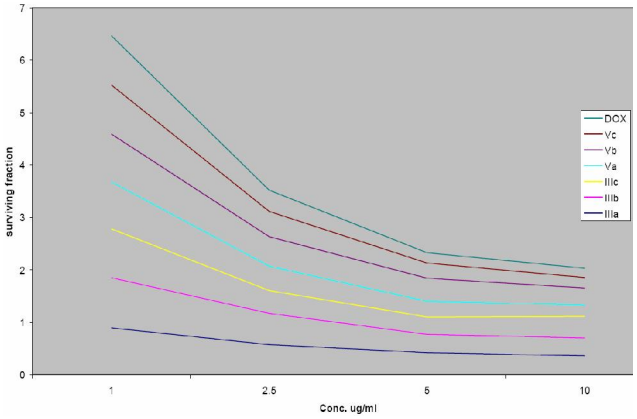


Figure 2

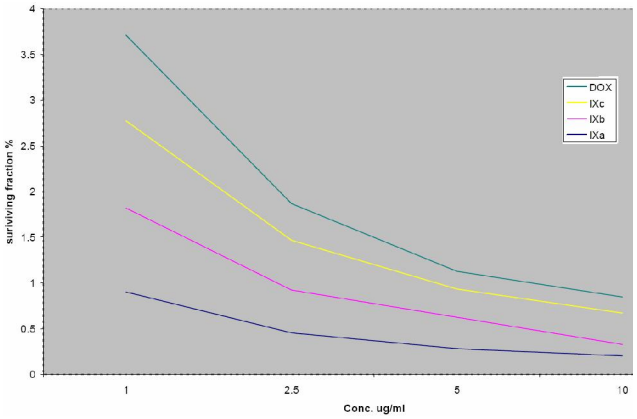


Figure 3

All the tested compounds were found to possess potential antitumor activities against the tested tumor cell line, with $IC_{50's} < 10$ ug/ml (TABLE 1). The results in TABLE 1 demonstrate the sensitivity of individual cell lines. Compounds IIIc, and IX b are the most potent compounds.

EXPERIMENTAL

Chemistry

Melting points were determined in open capillary tubes on a Sonar melting point apparatus and were

uncorrected. Reaction progress was monitored by thin layer chromatography on silica gel sheets (Merck silica gel-G) and the purity of the compounds was ascertained by single spot on TLC sheet. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in Bruker Avance II 300 NMR spectrometer using appropriate deuterated solvents and are expressed in part per million (d, ppm) downfield from tetramethylsilane (internal standard). Infrared (IR) spectra were recorded on a Shimadzu FTIR spectrometer. Mass and element analysis were carried in micr analytical centre in Cairo university. Anticancer activity was carried out in pharmacology department in faculty of veterinary medicine in Cairo University.

General procedure for the synthesis of 2(4-aminophenyl) benzimidazoles (1a), 2(4-aminophenyl) benzoxazoles (1b) and 2(4-aminophenyl) benzothiazole (1c)[14, 9-11]

A mixture of *o*-phenylene diamine, 2-aminophenol or 2-aminothiophenol (0.05mol), 4- aminobenzoic acid (0.05mol) and polyphosphoric acid (85 g) was heated in an oil-bath at 220 °C for 3 hs.

The reaction mixture was cooled then poured onto ice-cooled 10 % sodium carbonate solution (1 liter). The formed solid product was collected, washed with water and crystallized from aqueous methanol to yield compounds Ia-c

Yield and m.p. as reported

	Yield	m.p.
Ia	80 %	245-247
Ib	60%	185-187
Ic	50%	155-157

General procedure for the synthesis of IIa-c

To an ice cooled solution of the corresponding amino compounds Ia-c (0.01mol) in hydrochloric acid (2.5 ml) and distilled water (5ml), a solution of sodium nitrite (0.013mol) in distilled water (5ml) was added portion wise. This solution was added portion wise to a well-stirred cold solution of acetylacetone (0.01 mol) in 50% aqueous ethanol (10ml) containing sodium acetate (0.9g, 0.011mol). The reaction mixture was kept in ice for 2 hrs and then filtered. The product was dried and crystallized from ethanol.

3-{[4-(1H-Benzimidazol-2-yl)phenyl]-hydrazono}pentan-2,4-dione (IIa)

Yield 80%; m.p.>300 °C; IR (KBr): 3298 (NH), 2919 (CH aliphatic) 1674 (C=O) and 1634 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 2.49 (s, 6H, C*H*$_3$), δ 3.43 (S, H, NH of benzimidazole D$_2$O exchangeable) δ 7.50–7,82 (m, 6H, ArH), δ 8.34-8.37 (d, 2H, Ar-H) and δ 12.63 (s, *H*, HN-N=C, D2O exchangeable) ppm; EIMS: *m/z* 320 [M$^{+\cdot}$](20%) Anal.Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found; C, 67.23; H, 5.09; N,17.55%.

3-{[4-(1H-Benzoxazol-2-yl)phenyl]-hydrazono}pentane-2,4-dione (IIb)

Yield 75%; m.p.>300 °C; IR (KBr): 3438 (NH), 2920 (CH aliphatic) 1673 (C=O) and 1622 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 2.48 (s, 6H, C*H*$_3$), δ 7.32–7,88 (m, 6H, ArH), δ 8.22-8.24 (d, 2H, Ar-H) and δ 13.73 (s, *H*, HN-N=C, D$_2$O exchangeable) ppm; EIMS: *m/z* 321 [M$^{+\cdot}$](18%); Anal.Calcd for $C_{18}H_{16}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found; C, 67.16; H, 4.59; N,13.20%.

3-{[4-(1H-Benzothiazol-2-yl)phenyl]-hydrazono}pentane-2,4-dione (IIc)

Yield 75%; m.p.>300 °C; IR (KBr): 3439 (NH), 2923 (CH aliphatic) 1675 (C=O) and 1626 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 2.45 (s, 6H, C*H*$_3$), δ 7.44–8.05 (m, 6H, ArH), δ 8.12-8.14 (d, 2H, Ar-H) and δ 13.76 (s, *H*, HN-N=C, D$_2$O exchangeable) ppm; EIMS: *m/z* 337 [M$^{+\cdot}$](15%) Anal. Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45. Found; C, 64.12; H, 4.31; N, 12.29%.

General procedure for the synthesis of IIIa-c

A mixture of compound IIa-c (0.01mol) and 99% hydrazine hydrate (0.011mol) in ethanol (20ml) was refluxed for 6 hs. The reaction mixture was evaporated. The residue was washed with water, dried and crystallized from DMF.

N-(4-Benzimidazol-2-ylphenyl)-N^{-}(3,5-dimethylpyrazol-4-ylidine) hydrazine (IIIa)

Yield 74%; m.p.>300 °C; IR (KBr): 3418,3190 (2NH), and 1626 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 2.50 (s, 6H, C*H*$_3$), δ 3.80 (S, H, NH of benzimidazole D$_2$O exchangeable) δ 7.52–8.01 (m, 6H,

ArH), δ 8.44-8.47 (d, 2H, Ar-H) and δ 12.65 (s, *H*, HN-N=C, D_2O exchangeable) ppm; EIMS: *m/z* 316 [$M^{+\cdot}$](35%); Anal.Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found; C, 68.38; H, 4.88; N,26.38%.

N-(4-Benzoxazol-2-yl-phenyl)-N⁻(3,5-dimethylpyrazol-4-ylidine)hydrazine (IIIb)

Yield 74%; m.p.>300 °C; IR (KBr): 3199 (NH), and 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 2.48 (s, 6H, C*H*$_3$), δ 7.48–7.94 (m, 6H, ArH), δ 8.32-8.35 (d, 2H, Ar-H) and δ 12.95 (s, *H*, HN-N=C, D_2O exchangeable) ppm; EIMS: *m/z* 317 [$M^{+\cdot}$](30%) Anal.Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found; C, 68.28; H, 4.78; N,22.24%.

N-(4-Benzothiazol-2-yl-phenyl)- N⁻ (3,5-dimethylpyrazol-4- ylidine) hydrazine (IIIc)

Yield 74%; m.p.>300 °C; IR (KBr): 3224 (NH), and 1656 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 2.48 (s, 6H, C*H*$_3$), δ 7.48–8,25 (m, 6H, ArH), and δ 12.65 (s, *H*, HN-N=C, D_2O exchangeable) ppm; EIMS: *m/z* 334 [$M^{+\cdot}$ +1], 21.37%. EIMS: *m/z* 333 [$M^{+\cdot}$](27%)Anal.Calcd for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.01. Found; C, 65.02; H, 4.79; N, 21.24%.

General procedure for the synthesis of Va-c

A well stirred mixture of Ia-c (0.01mol), anhydrous potassium carbonate (0.01mol) and 2-chloromethyl-1H-benzimidazoles (IV) (1.66, 0.01mol) in ethanol (100 ml) was heated under reflux for 24 hs. The reaction mixture was filtered while hot and the solvent was removed by distillation under reduced pressure. The residue obtained was washed with water, filtered, dried and crystallized from butanol.

N-(1H-Benzimidazol-2-ylmethyl)-2-(4-aminophenyl)- 1H-benzimidazole (Va)

Yield 74%; m.p.>300 °C; IR (KBr): 3300 (NH), 2919(CH aliphatic) and 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 3.5-4-5 (broad, 3H, 3NH, D_2O exchangeable), δ 4.65 (s, 2H, CH_2) and δ 6.88-8.09 (m, 12H, Ar-H) ppm; Anal.Calcd for $C_{21}H_{17}N_5$:C, 74.32; H, 5.05; N, 20.63. Found; C, 74.22; H, 5.02; N, 20.71%.

N-(1H-Benzimidazol-2-ylmethyl)-2-(4-aminophenyl) benzoxazole (Vb)

Yield 74%; m.p.>300 °C; IR (KBr): 3456, 3296 (2NH), 3051(CH aromatic) and 1610 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 3.5-4-5 (broad, 2H, 2NH, D_2O exchangeable), δ 4.60 (s, 2H, CH_2) and δ 6.69-7.92 (m, 12H, Ar-H) ppm; Anal.Calcd for $C_{21}H_{16}N_4O$:C, 74.10; H, 4.74; N, 16.46. Found; C, 74.20; H, 4.52; N,16.33%.

N-(1H-Benzimidazol-2-ylmethyl)-2-(4-aminophenyl) benzothiazole (Vc)

Yield 74%; m.p.>300 °C; IR (KBr): 3450, 3292 (2NH), 3050(CH aromatic) and 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 3.5-4-5 (broad, 2H, 2NH, D_2O exchangeable), δ 4.68 (s, 2H, CH_2) and δ 6.65-7.92 (m, 12H, Ar-H) ppm; EIMS: *m/z* 356 [$M^{+\cdot}$], 91.56%; Anal.Calcd for $C_{21}H_{16}N_4S$: C, 70.76; H, 4.52; N, 15.72. Found; C, 70.79; H, 4.52; N,15.95%.

General procedure for the synthesis of IXa-c

A well stirred mixture of Ia-c (0.01mol), anhydrous potassium carbonate (0.01mol) and compound VIII (2.3g, 0.01mol) in ethanol (100 ml), was heated under reflux for 12 hrs. The mixture was filtered while hot and the solvent was removed by distillation under reduced pressure. The obtained residue was washed with water, filtered, dried and crystallized from DMF.

[4-(1*H*-Benzimidazol-2-yl)1-phenyl] (1-phenyl-1H-pyrazolo [3,4-d]pyrimidin-4-yl) amine (IXa)

Yield 74%; m.p.>300 °C; IR (KBr): 3427 br. band (NH) and 1605 (N=C); ^1H NMR (300 MHz, DMSO-d6): δ 3.37 (s, *1H*, HN, D_2O exchangeable, NH of imidazole) ppm; δ 7.37–8,05 (m, 13H, ArH), δ 8.18 s, 1H, CH=N of pyrazole), δ 8.32 (s, 1H, CH=N of pyrimidine) and δ 12.22 (s, *1H*, HN, D_2O exchangeable) ppm ; Anal.Calcd for $C_{24}H_{17}N_7$: C, 71.45; H, 4.25; N, 24.30. Found; C, 71.59; H, 4.64; N,24.44%.

(4-Benzoxazol-2-yl-phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amine (IXb)

Yield 70%; m.p.>300 °C; IR (KBr): 3407 (NH) 3047(CH aromatic) and 1586 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 6.32–8.05 (m, 13H, Ar-H), δ 8.19(s, 1H, CH=N of pyrazole), δ 8.32(s, 1H, CH=N of pyrimidine) and δ 12.25 (s, *1H*, HN, D2O exchangeable) ppm; Anal. Calcd for $C_{24}H_{16}N_6O$: C, 71.28; H, 3.93; N, 20.78. Found; C, 70.99; H, 4.00; N,20.66%.

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(4-Benzothiazol-2-yl-phenyl) (1-phenyl-1H-pyrazolo [3,4-d]pyrimidin-4-yl) amine (IXc)

Yield 74%; m.p.>300 °C; IR (KBr): 3266 (NH) 3105-3025(CH aromatic) and 1633 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ 6.77–8.58 (m, 13H, Ar-H), δ 8.64(s, 1H, CH=N of pyrazole), δ 8.75(s, 1H, CH=N of pyrimidine) and δ 10.65 (s, *1H*, HN, D2O exchangeable) ppm; EIMS: *m/z* 420 [$M^{+\cdot}$] (100%); Anal.Calcd for $C_{24}H_{16}N_6S$: C, 68.55; H, 3.84; N, 19.99. Found; C, 68.45; H, 4.00; N,20.12%.

Anticancer activity studies[31]

Anticancer activity studies were done at Cairo University, National Cancer Institute, Cancer Biology Department, Pharmacology Unit. Compounds IIIa-c, Va-c and IXa-c were tested at concentrations between 1 and 10 ug/ml using SulfoRhodamine-B (SRB) assay for cytotoxic activity against breast carcinoma cell line (MCF7)

Measurement of potential cytotoxicity by SRB assay Potential cytotoxicity of the compounds was tested using the method of Skehan et al. [37], as follows: Cells were plated in 96 multiwell plate (104 cells/well) for 24 hrs before treatment with the compound(s) to allow attachment to the wall of the plate. Different concentrations of the compounds (0, 1, 2.5, 5 and 10 ug/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 hrs at 37 °c in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with SulfoRhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound.

The following TABLE 1 shows IC50 (Dose of the compound which reduced survival to 50%)

Results

The percentage of cell survival was calculated as follows:

Survival fraction= O.D. (treated cells)/O.D. (control cells)

The IC50 values (the concentration required to produce 50%inhibition of cell growth) were calculated using sigmodial dose response curve fitting models (GraphPad, Prizm software incorporated). Each concentration was repeated 3 times. (TABLE 1)

TABLE 1 : *In-vitro* cytotoxicity of 12 synthesized compounds

Compound	Viable cells (%) Concentration (µg/ml) 1	2.5	5	10	IC50 (µg/ml)	IC90 (ug/ml)
IIIa	0.895	0.573	0.421	0.360	1	3.67
IIIb	0.945	0.595	0.349	0.342	1.18	3,50
IIIc	0.932	0.435	0.332	0.413	1.09	2.32
Va	0.897	0.467	0.299	0.213	1.03	2.40
Vb	0.912	0.564	0.441	0.324	1.04	3.75
Vc	0.937	0.482	0.289	0.199	1.13	2.37
IXa	0.899	0.452	0.279	0.201	1.02	2.33
IXb	0.921	0.469	0.343	0.125	1.07	2.40
IXc	0.954	0.544	0.311	0.343	1.18	2.93
DOX	0.938	0.403	0.194	0.177	0.297	0.83

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