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Synthesis, some reactions, cytotoxic evaluation and antioxidant study of novel benzimidazole derivatives

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ABSTRACT

A series of novel benzimidazole derivatives incorporating chalcone ***(3)****, pyrazolines****(4),(5), (16),*** *oxazoline****(6),*** *pyrimidines****(7-13),(17)*** *and oxirane****(15)*** *derivatives were synthesized and some of their reactions with some electrophiles and /or nucleophiles were studied . Some of the new derivatives were biologically evaluated as antioxidants and the results showed that the presence of the epoxide ring in* ***(15)*** *as well as the pyrimidine thione in* ***(7)*** *are responsible for their reactivity, rather than the presence of the pyrazoline ring system as in* ***(4a)*** *.On the other hand ,some of the synthesized compounds were tested as for their cytotoxic activity and the results were encouraging . All the synthesized compounds were characterized by elemental analysis as well as spectral data such as IR,* ^{1}*H-NMR and Mass spectra.*

Key words: Benzimidazole derivatives, Reactions with nucleophiles, Biological activity, Antioxidant and Cytotoxic activity.

INTRODUCTION

Benzimidazoles are an important group of heterocyclic compounds that are biologically active and of significant importance in medicinal chemistry. The benzimidazole ring is an important pharmacophore in modern drug discovery . The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry because its derivatives possessed various biological activities[1]such as antioxidant [2,3],antimicrorobial [4-6] ,anthelmintic [7],anticancer[8,9] ,antihypertensive[10,11] ,antineoplastic[12,13] , anti-inflammatory [14,15] , anti-analgesic [16] , antiprotozoal [17] , anti-hepatitis B virus [18] , antiulcer [19] , antiviral [20] ,antifungal [21,22] ,and anticonvulsant [23,24] activity.

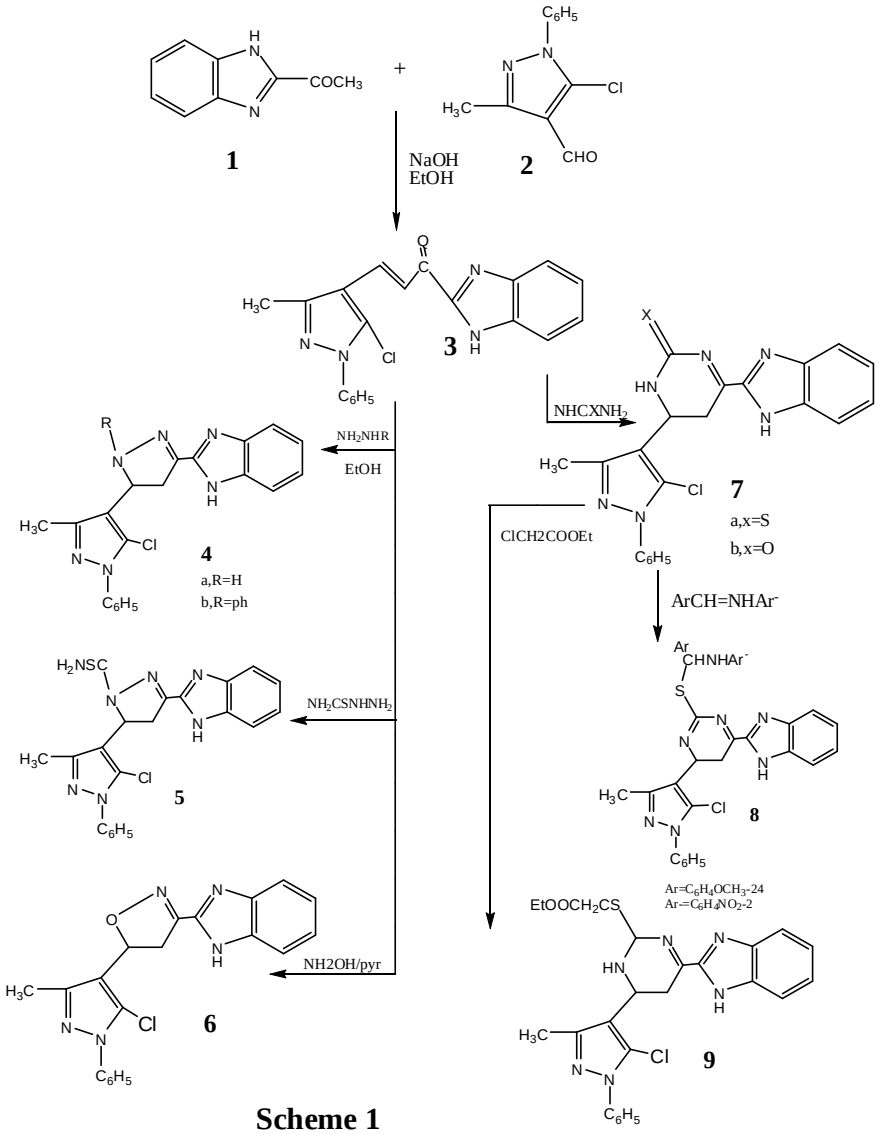
On the other hand , chalcones are very well known important starting materials for the synthesis of various classes of heterocyclic compounds such as pyrazolines , isoxazolines , pyrimidines and /or benzodiazepines [25,26] as well .Most of these compounds were found to be highly bioactive and were widely used in pharmaceutics.The bacteriostatic as well as bactericidal activity in the chalcone system is attributed to the presence of the enone function –C=C-C=O [27,28].

Hence it was thought interesting to prepare a benzimidazole moiety incorporating the enone function . In view of the above findings and in continuation of our research program [28-31]to find effective new antimicrobial and/or antitumor agents for the treatment of infectious diseases , the present study focused on the synthesis and biological evaluation of some benzimidazolo incorporating chalcone , pyrazoles , oxazole , pyrimidines and oxirane moieties in order to

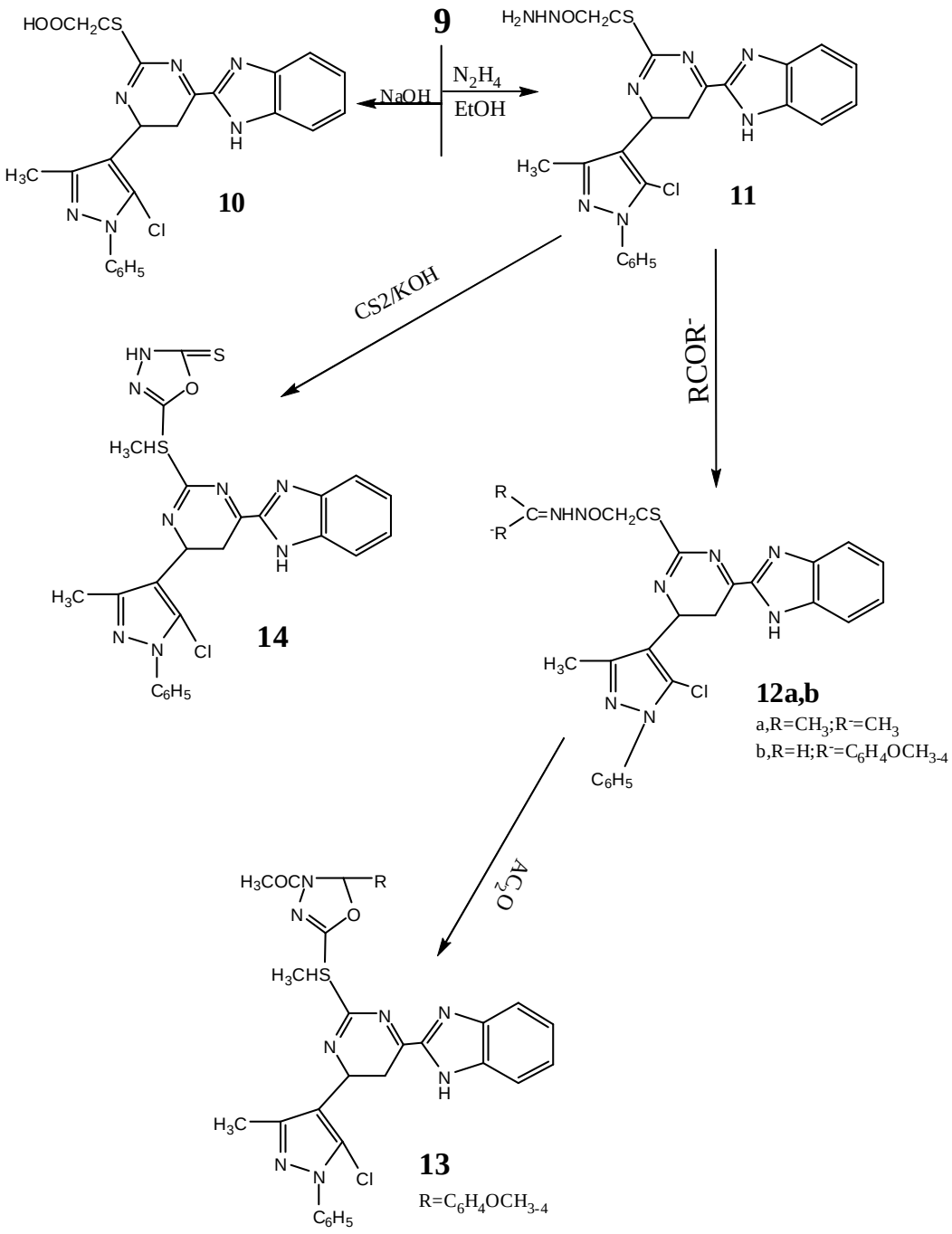
throw a more precise information about their chemical reactivity and study on benzimidazole chalcone combined molecule , and its biological activity as antioxidant and /or antitumor as well .

MATERIALS AND METHODS

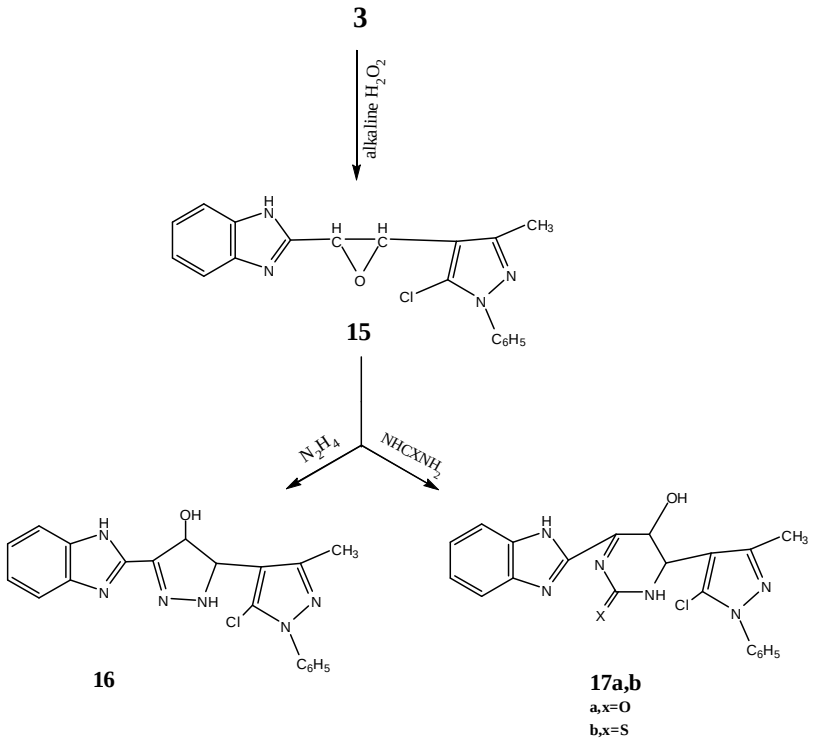
Melting points are determined on a Gallen Kemp melting point apparatus and are uncorrected. Elemental analysis (% C,H,N) is carried out by a Perkin-Elmer 2400 CHN analyser. IR spectra of compounds have been recorded on a Thermo-Nicolet FT-IR200 spectrometer in KBr disc(cm^{-1}). ^{1}H-NMR are spectra recorded on Bruker DRX(300 MHz) spectrophotometer using DMSO-d6as solvent and TMS as internal standard . Chemical shifts are reported inδppm . Mass spectra of synthesized compounds were carried out using Shimadzu GC–MS(Shimadzu 2010 plus) mass spectrometer direct probe method.



Scheme 1


9
HOOCH2CS
NaOH
N2H4
EtOH
H2NHNOCH2CS
10
11
CS2/KOH
RCOR-
14
12a,b
a,R=CH3;R-=CH3
b,R=H;R-=C6H4OCH3-4
Ac2O
13
R=C6H4OCH3-4

Scheme 2



Scheme 3

Synthesis of(1H-benzo[d]imidazol-2-yl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-5-yl)prop-2-en-1-one (3)
A mixture of 2-acetyl benzimidazole **(1)(**0.04 mol) and the aldehyde**(2)(**0.1 mol) were dissolved in ethanol(20 ml) the reaction mixture was stirred in ice bath ,then add 5ml of 10% aqeous NaOH drop wise through 30 min.The solid obtained was filtered off, washed well with dilute ethanol followed by crystallization from ethanol to give 3 as dark green crystals ; yield 75% ;m.p 189^{0}C.IR :3231 cm^{-1}(√NH), 3130, 3060, 2980, 2929, 2860 cm^{-1}(√ C-H), 16671 cm^{-1}(√ C=O),1604 cm^{-1}(√ C=N) .The ^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 10.50(s,1H,NH), 6.86-8.39 (m, 9H,Ar-H), 3.80(d,1H,CH_α), 2.50(d,1H, CH_β),2.23(s,3H,CH_3) . MS: 361 $1^{+\cdot}$(M-1)(12.1%), 191.5(2%), 145(2.2%), 76(8.5%) ,50(100%).Anal. of $C_{20}H_{15}N_4O$ Cl(362.5) (%) calcd: C, 66.20; H, 4.13; N, 15.44; Cl, 9.79. Found:C, 66.21; H, 4.21; N, 15.45Cl, 9.88.

Synthesis of2-(5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzo[d] imidazole(4a),2-(5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol -4-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzo[d]imidazole(4b)
A mixture of **3**(0.01 mol),and hydrazines, namely hydrazine hydrate and/or phenylhydrazine (0.01 mol) in ethanol (30 ml)was refluxed for 6 hrs. After concentration and cooling the solid obtained was crystallized from ethanol togive 4a and/or 4b respectively .4a as dark green crystals ; yield 68% ;m.p 200^{0}C.IR spectrum of **4a**:3232 cm^{-1}(√NH), 3200 cm^{-1}(√NH), 3126, 3060, 2980, 2929,2890, 2860 cm^{-1}(√ C-H), 1626 cm^{-1}(√ C=N),1601 cm^{-1}(√ C=C) .^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.20(s,1H,NH), 10.59(s,1H,NH), 6.88-7.86 (m, 9H,Ar-H), 3.47(t,1H,CHCH$_2$), 2.99(d,2H, CH$_2$CH),1.31(s,3H,CH_3) . MS: 375$1^{+\cdot}$(M-1)(2.04%), 191.5(2%),224(0.5%), 167(3.9%) ,153(0.3%) 144(1%), 94(2.1%) ,55(100%).Anal.$C_{20}H_{17}N_6$ Cl(376.5) (%) calcd: C, 63.74; H, 4.25; N, 22.30 ;Cl, 9.42. Found:C, 63.75; H, 4.26; N, 22.32;Cl, 9.42.**4b** as black crystals ; yield 56% ; m.p 215^{0}C .IR :3275 cm^{-1}(√NH), 3200 cm^{-1}(√NH), 3126, 3050, 2980, 2929,2890 cm^{-1}(√ C-H), 1613cm^{-1}(√ C=N),1599cm^{-1}(√ C=C) .^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.2(s,1H,NH), 6.12-8.7 (m, 14H,Ar-H), 2.98(t,1H,CHCH$_2$), 2.27(d,2H, CH$_2$CH),1.46(s,3H,CH_3) .MS: 452$1^{+\cdot}$(M+1)(4.11%), Anal. $C_{26}H_{21}N_6$ Cl(452.5) (%) calcd: C, 68.95; H, 4.64;N, 18.56; Cl, 7.84. FoundC, 68.99; H, 4.65;N, 18.53; Cl, 7.82.

Synthesis of 3-(1H-benzo[d]imidazol-2-yl)-5-(5-chloro-4-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide(5)

A mixture of **3**(0.01 mol),thiosemicarbazide(0.01 mol;0.8 gm dissolved in 1 ml water containing sodium acetate(0.01 mol,0.8 g) in ethanol (30 ml)was refluxed for 6 hrs. After concentration and cooling the product that obtained was collected by filtration , washed well with dilute ethanol followed by crystallization from ethanol to give **5** as green crystals ; yield 69% ;m.p 202^{0}C.IR : 3399,3232 cm^{-1}(√NH_2,NH), 3162,3136, 3067, 2959,2927, 2881 cm^{-1}(√ C-H), 1613 cm^{-1}(√ C=N),1597 cm^{-1}(√ C=C),1249 cm^{-1}(√ C=S) .^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 12.20(s,1H,NH), 11.2(s,2H,NH_2),6.84-8.58 (m, 9H,Ar-H), 2.99(t,1H,CHCH$_2$), 2.47(d,2H, CH$_2$CH),1.23(s,3H,CH_3) . MS: 435 Ɩ$^{+\cdot}$(M)$^{+\cdot}$ (60.12%), 365(100%),192(2%), 155(3%) ,129(5%) 144(1%), 77(49.6%) . Anal.$C_{21}H_{18}N_7S$ Cl(435.5) (%) calcd: C, 57.86; H, 4.13; N, 22.50; S, 7.34 ;Cl, 8.15 Found:C, 57.90; H, 4.15; N, 22.48; S, 7.35;Cl, 8.12.

Synthesis of3-(1H-benzo[d]imidazol-2-yl)-5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydroisoxazole (6)

A mixture of **3**(0.01 mol),hydroxylamine hydrochloride(0.01 mol) in pyridine (30 ml)was refluxed for 6 hrs. The reaction mixture was poured into ice and HCl and the solid filtered off , washed well with dilute ethanol followed by crystallization from ethanol to give **(3)** as dark brown crystals ; yield 65% ;m.p 215^{0}C.IR : 3376cm^{-1}(√NH), 3130, 3060,2960, 2920, 2880cm^{-1}(√ C-H), 1598 cm^{-1}(√ C=N) .^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.44(s,1H,NH), 6.85-7.86 (m, 9H,Ar-H), 3.43(t,1H,CHCH$_2$), 2.50(d,2H, CH$_2$CH),1.23(s,3H,CH_3) . MS: 377Ɩ$^{+\cdot}$(M)$^{+\cdot}$ (4.0%),239(58.1%), 192(3%),141(40.6%), 131(11.4%) ,82(2%) 72(1%), 63(100%),56(70.8%) . Anal.$C_{20}H_{16}N_5$ Cl(377.5) (%) calcd: C, 63.57; H, 4.23;N, 18.54; Cl, 9.40. Found:C, 63.62; H, 4.29;N, 18.53; Cl, 9.35.

Synthesis of 6-(1H-benzo[d]imidazol-2-yl)-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidine-2(1H)-thione(7a),4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidin-2(1H)-one (7b).

A mixture of **3**(0.01 mol),withthiourea and/orurea(0.01 mol) in absolute ethanol (30 ml) containing sodium ethoxide (prepared from 0.2 gm sodium dissolved in 5 ml absolute ethanol) was refluxed for 6 hrs. After concentration and cooling the product that obtained was collected, washed well with dilute ethanol followed by crystallization from ethanol to give **7a** and/or**7b. 7a** as green crystals ; yield 76% ;m.p 235^{0}C.IR spectrum of **7a**: 3402cm^{-1}(√NH), 3160, 3020, 3009,2981, 2926cm^{-1}(√ C-H),2660(C-SH), 1622 cm^{-1}(√ C=N),1594 cm^{-1}(√ C=C),1249 cm^{-1}(√ C=S).The ^{1}H-NMR(300 MHz ,DMSO-d6): showed signal bands δppm at 11.45,11.02 (2xs,2x1H,2xNH), 7.07-8.00 (m, 9H,Ar-H), 2.56(t,1H,CHCH$_2$), 2.19(d,2H, CH$_2$CH),1.23(s,3H,CH_3) . MS: 418Ɩ$^{+\cdot}$(M-2)(0.16%), 345(14%), 303(100%), 282(7%) ,238(12%) ,193(11.5%), 152(31.9%),. 123(84.4%),78(58%),.Anal.$C_{21}H_{17}N_6SCl$(420.5) (%) calcd: C, 59.92; H, 4.04; N, 19.97; S, 7.62;Cl, 8.44.Found:C, 59.99; H, 4.05; N, 19.95; S, 7.59;Cl, 8.40.

7b as green crystals ; yield 64% ;m.p 220^{0}C.IR :showed absorption bands at 3401cm^{-1}(√NH), 3130, 3069,3004,2980, 2925, 2828cm^{-1}(√ C-H), 1677 cm^{-1}(√ C=O), 1629 cm^{-1}(√ C=N),1594 cm^{-1}(√ C=C). ^{1}H-NMR(300 MHz ,DMSO-d6): showed signal bands δppm at 11.44,9.57(2xs,2x1H,2xNH), 6.83-7.88 (m, 9H,Ar-H), 2.51(t,1H,CHCH$_2$), 2.21(d,2H, CH$_2$CH),1.29(s,3H,CH_3) . MS: 406Ɩ +$^{\cdot}$(M+1)(4.0%), 386(50%),364(59%), 272(77%) ,239(37%) ,120(18%), 63(100%),. Anal.$C_{21}H_{17}N_6OCl$(404.5) (%) calcd: C, 62.29; H, 4.20; N, 20.76;Cl, 8.77. Found:C, 62.35; H, 4.22; N, 20.75;Cl, 8.75.

Synthesis of N-((4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidin-2-ylthio)(p-methoxyphenyl)methyl)-2-nitroaniline (8)

A mixture of **7a**(0.01 mol),and Schiff base namelyN-(4-methoxybenzylidene)-2-nitroaniline prepared from refluxing (0.01) mol of o-nitro aniline and 4- methoxybenzaldehyde in 15 ml of absolute ethanol) in 30 ml of absolute ethanol was refluxed for 6 hrs. After concentration and cooling the product that obtained was collected ,washed well with dilute ethanol followed by crystallization from ethanol to give**8** as dark orange crystals ; yield 76% ;m.p 245^{0}C. IR : 3461cm^{-1}(√NH),3069, 2987, 2921, 2850, cm^{-1}(√ C-H), 1612 cm^{-1}(√ C=N),1591 cm^{-1}(√ C=C).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.39,9.87 (2xs,2x1H,2xNH), 6.88-7.86 (m, 17H,Ar-H), 3.76(s,3H,OCH_3-Ar),3.37(t,1H,CHCH$_2$), 2.44(d,2H, CH$_2$CH),1.64(s,3H,CH_3) . MS: 675Ɩ$^{+\cdot}$(M-2)(3.16%), 380(0.06%),321(0.21%), 282(7%) ,220(0.12%) ,193(0.1%), 152(31.9%),. 123(84.4%),57(100%),. Anal.$C_{35}H_{29}N_8O_2S$ Cl(676) (%) calcd: C, 62.08; H, 4.28; N, 16.55; S, 4.73;Cl, 5.24.Found;C, 62.11; H, 4.31; N, 16.61; S, 4.76;Cl, 5.25.

Synthesis of ethyl 2-(6-(1H-benzo[d]imidazol-2-yl)-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydropyrimidin-2-ylthio)acetate(9)

A mixture of **7a**(0.01 mol),and ethylacetoacetate (0.01 mol) in presence of dry aceton containing anhydrous K_2CO_3 were refluxed for 20 hrs. After evaporation of the excess solvent , the reaction mixture was poured into ice/ 10%HCl(15 ml) filtered off dried and, crystallized from ethanol to give**9** as dark yellow crystals ; yield 66% ;m.p 260^{0}C.IR : 3273cm^{-1}(√NH),3069, 2921, 2853, cm^{-1}(√ C-H),1725 cm^{-1}(√ C=O ester), 1617cm^{-1}(√ C=N).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 9.87 (s,1H,NH), 6.85-8.81 (m, 9H,Ar-H),4.31(q,2H,$\underline{CH_2}CH_3$), 3.43(t,3H, $\underline{CH_3}CH_2$),3.04(t,1H,$\underline{CH}CH_2$), 3.001(d,2H, $\underline{CH_2}CH$),1.06(s,3H,CH_3) . MS: 506ł$^{+\cdot}$(M)(4.05%), 423(3.6%) ,211(3.1%) ,196(3.3%), 182(3.4%),. 155(3.35%),57(100%),. Anal.$C_{25}H_{23}N_6O_2S$ Cl(506.5) (%) calcd: C, 59.23; H, 4.54; N, 16.58; S, 6.31;Cl, 7.008.Found;C, 59.22; H, 4.55; N, 16.60; S, 6.32;Cl, 7.99.

Synthesis of 2-(4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydro pyrimidin-2-ylthio)acetic acid(10)

A suspension of **9** in ethanolic sodium hydroxide solution (prepared from dissolving 0.01 mole of sodium hydroxide in 1ml of water then mixed with 15ml of absolute ethanol)was refluxed for 2 hr.then evaporated to half its volume , acidified with dilute HCl .The solid that separated was collected , washed with dilute ethanol and recrystallised from ethanol to give**10** as yellow crystals ; yield 61% ;m.p 245^{0}C.IR : 3420(br),3363(br)cm^{-1}(√OH/NH),2954, 2920, 2850 cm^{-1}(√ C-H),1710cm^{-1}(√ C=O , of an acid), 1605cm^{-1}(√ C=N).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 10.80(s, 1H, OH),10.21(s,1H,NH),7.21-8.87 (m, 9H,Ar-H),3.63(s,2H,$\underline{CH_2}CO$), 3.45(t,3H, $\underline{CH}CH_2$),2.50(d,1H,CH$\underline{CH_2}$), 1.06(s,3H,CH_3) . MS: 478ł$^{+\cdot}$(M)(3.23%), 345(14%) , base peak (100% for $C_{14}H_{15}N_4O_2S$) .Anal.$C_{23}H_{19}N_6O_2S$ Cl(506.5) (%) calcd: C, 57.68; H, 3.97; N, 17.55; S, 6.68;Cl, 7.41.Found;C, 57.70; H, 3.99; N, 17.54; S, 6.79;Cl, 7.45.

Synthesis of 2-(4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydro pyrimidin-2-ylthio)acetohydrazide(11)

A mixture of **9**(0.01 mol),and hydrazine hydrate(0.01 mol) in ethanol (20 ml)was refluxed for 6 hrs. After concentration and cooling the product was collected ,washed well with dilute ethanol and recrystallized from ethanol togive **11** as yellowish crystals ; yield 68% ;m.p 285^{0}C. IR : 3300,3275cm^{-1}(√NH_2,NH),3178,3091, 2921, 2851, cm^{-1}(√ C-H),1667 cm^{-1}(√ C=O amide), 1586 cm^{-1}(√ C=N). ^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.9, 11.6,11.4 (3xs,4H,2x1H,1x2H,2xNH, NH_2), 7.2-8.9 (m, 9H,Ar-H),3.45(s,3H,CH_2CO),3.04(q,2H,$\underline{CH_2}CH_3$), 2.50(t,3H, $\underline{CH_3}CH_2$),2.007(d,2H, $\underline{CH_2}CH$),1.06(s,3H,CH_3) . MS: 492ł$^{+\cdot}$(M)(10.3%), 360.9(12.1%) , 123(11.6%),. 118.7(12.2%),74.9(1.3%),58(13.8%),and the base peak at 50.5(100%). Anal.$C_{23}H_{21}N_8OS$ Cl(492.5) (%) calcd: C, 56.04; H, 4.26; N, 22.74; S, 6.49;Cl, 7.20.Found;C, 56.10; H, 4.31; N, 22.69; S, 6.50;Cl, 7.30.

Reaction of 11 with carbonyl compounds :Synthesis of2-(4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidin-2-ylthio-N^1(propan-2-ylidene)acetohydrazide(12a)

A suspension of **11**(0.01 mol)in dry acetone (30 ml)was heated on a water bath for 6 hrs . After concentration and cooling the residue was collected ,washed well with dilute ethanol and recrystallized from ethanol togive **12a** as orange crystals ; yield 71% ;m.p 255^{0}C. IR : 3276 cm^{-1}(√NH), 3109,3001, 2959, 2926,2845, cm^{-1}(√ C-H),1678cm^{-1}(√ C=O amide), 1614cm^{-1}(√ C=N),1537 cm^{-1}(√C=C). ^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 10.65,10.05 (2xs,2H,2xNH), 6.75-8.72 (m, 9H,Ar-H),3.45(s,2H,S$\underline{CH_2}$CO) ,1.031.06,1.08(3xs,3x3H,3xCH_3) . MS: 532.9ł$^{+\cdot}$(M+1) (2.01%), 302.5(10.9%), 195(7.3%),193(3.7%),148(25.7%),127(8.3%) 120(35.9%), 82(5.5%),77(7.2%), 55(100%). Anal.$C_{26}H_{25}N_8OS$ Cl(492.5) (%) calcd: C, 58.58; H, 4.73; N, 21.02; S, 6.49;Cl, 6.02.Found;C, 58.50; H, 4.75; N, 21.04; S, 6.50;Cl, 6.05.

Reaction of 11 with anisaldehyde :Formation of2-(4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidin-2-ylthio-N^1(4-methoxy benzylidene)acetohydrazide(12b)

A mixture of **11**(0.01 mol) and anisaldehyde (0.01 mol) in 30 ml of absolute ethanol containing sodium ethoxide (formed by dissolving 0.4 gm of sodium metal in 5 ml of absolute ethanol)was refluxed for 6 hrs . After concentration and cooling the product was collected ,washed well with dilute ethanol and recrystallized from ethanol togive **12b** as darkorange crystals ; yield 51% ;m.p 300^{0}C. IR : 3396,3258cm^{-1}(√NH), 3111,3050, 2850 cm^{-1}(√ C-H),1671cm^{-1}(√ C=O amide), 1614 cm^{-1}(√ C=N),1586cm^{-1}(√C=C). ^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 10.39,10.02(2xs, 2H, 2xNH), 7.12-8.87 (m, 13H,Ar-H), 3.48(s,3H,OCH_3), 3.29 (s,1H,N=CH),2.51(s,2H,S$\underline{CH_2}$CO) ,2.70(s,2H,S-$\underline{CH_2}$),2.50(t,1H, $\underline{CH}CH_2$),2.30(d,2H, $\underline{CH_2}CH$),1.06(s,3H,CH_3) . MS: 610ł$^{+\cdot}$(M)(10%),465(9.9%) 382(12%) ,262(14%), 140(19%),125(23%) 111(30.1%), 97(36%), 85(26%), 75(39%), 57(100%).

Anal.$C_{31}H_{27}N_8O_2S$ Cl(610.5) (%) calcd: C, 60.93; H, 4.42; N, 18.21; S, 5.31;Cl, 5.82.Found;C, 60.94; H, 4.43; N, 18.21; S, 5.31;Cl, 5.82.

Formation of 1-[5-(4-(1H-benzo[d]imidazol-2-yl)-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydro pyrimidin-2-ylthio)-2-(4-methoxy phenyl)-1,3,4-oxadiazol-3(2H)-yl]ethanone (13)

A suspension of **12**(0.01 mol)in 15 ml acetic anhydride was heated on a water bath for 2 hrs . The solvent was evaporated (under reduced pressure) and the residue was treated with petroleum ether (b.p.60-80 ^{0}C), collected then with dilute ethanol and recrystallized from ethanol togive **13** as green crystals ; yield 65% ;m.p 275^{0}C. IR : 3204cm^{-1}(√NH), 3005, 2981, 2933cm^{-1}(√ C-H),1713cm^{-1}(√ C=O ketone $COCH_3$), 1613cm^{-1}(√ C=N).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.68(s,1H, NH), 7.2-8.98 (m, 13H,Ar-H), 4.33(s,1H,N-CH-O),3.45(s,3H,OCH_3) ,1.031.06,1.08(3xs,3x3H,3xCH_3) . MS: 652$^{1+\cdot}$(M)(3.7%), 456(5%) ,422(3.6%), 348(0.3%), 221(0.1%), 169(3.9%),155(4.9%),145(1.8%), 111(34%),97(41%),70(45%), 57(100%).Anal.$C_{33}H_{29}N_8O_3S$ Cl(652.5) (%) calcd: C, 60.68; H, 4.44; N, 17.16; S, 4.90;Cl, 5.44.Found;C, 60.69; H, 4.45; N, 17.20; S, 4.91;Cl, 5.54.

Reaction of 11 with CS_2 in KOH:Formation of 2-[4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidin-2-ylthio)-]1,3,4-oxadiazol-5-thione (14)

A mixture of **11**(0.01 mol), carbon disulphide (8ml)and aqueous KOH (10ml,10%) was heated on a water bath for 2 hrs . After evaporation of solvent (under reduced pressure) , the product was neutralized with dilute HCl , then extracted with ether and the solvent was evaporated (under reduced pressure) .The residue was collected and washed well with dilute ethanol and thenrecrystallized from ethanol togive **14** as green crystals ; yield 75% ;m.p 302^{0}C. IR : 3394cm^{-1}(√NH), 3001, 2959, 2919,2850cm^{-1}(√ C-H),1627cm^{-1}(√ C=N),1540 cm^{-1}(√C=C),1190 cm^{-1}(√C=S) .^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 8.89,8.77(2xs,2x1H,2x NH), 6.68-8.03 (m, 9H,Ar-H),3.35(t,1H,N-CH-CH_2),2.71(d,2H,CH_2CH),2.52(s,2H,S-CH_2), ,1.39(s,3H,CH_3) . MS: 534$^{1+\cdot}$(M)(3.2%), 476(3.1%) ,432(3.6%), 400(5%), 375(4.9%), 344(2.9%), 302(8.7%), 209(10.1%), 165(16%),121(46.1%), 106(31.3%) ,91(45%), 81(31%), 65(32.3%), 55(100%).Anal.$C_{24}H_{21}N_8OS_2$ Cl(536.5) (%) calcd: C, 53.67; H, 3.94; N, 20.86; S, 11.94;Cl,6.60.Found;C, 53.70; H, 3.93; N, 20.85; S, 11.93;Cl,6.60.

Reaction of the chalcone 3 with H_2O_2in alkaline NaOH: Synthesis of2-(3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)oxiran-2-yl)-1H-benzo[d]imidazole(15)

A suspension of **3**(0.01 mol) in acetone(30ml) and methanol (15ml)was treated with 8% aqueous sodium hydroxide (12 ml) while cooling and stirring then hydrogen peroxide (15ml ,30%)was added (on portions) .The solution was stirred while cooling for 2 hrs ,then left side overnight.The product was collected ,washed well with dilute ethanol and recrystallized from ethanol togive **15** as light brown crystals ; yield 75% ;m.p 220^{0}C. IR : 3225cm^{-1}(√NH), 3107, 2990, 2920,2860,2820cm^{-1}(√ C-H),1690cm^{-1}(√ C=O aroyl), 1598cm^{-1}(√ C=N),1290 cm^{-1}(epoxy linkage).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 11.42(s, 1H, NH), 6.88-7.87 (m, 9H,Ar-H), 4.01(d, 1H,CO-CH-O),3.89(d,1H, O-CH-C) ,1.16(s,3H,CH_3) . MS: 378$^{1+\cdot}$(M)(2.9%), 350(2.7%) ,310(69%), 193(6.2%), 187(5%), 157(3%), 130(19.4%),57(100%).Anal.$C_{20}H_{15}N_4O_2$ Cl(378.5) (%) calcd: C, 63.40; H, 3.96; N, 14.79; Cl, 9.73.Found;C, 63.41; H, 4.01; N, 14.81; Cl, 9.40.

Reaction of the 15 with hydrazine hydrate:Synthesis 3-(1H-benzo[d]imidazol-2-yl)-5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-4-ol (16)

A mixture of **15** (0.01 mol), hydrazine hydrate (0.01 mol) in absolute ethanol (30 ml) was refluxed for 6hrs.After concentration and cooling the residue was collected and treated with petroleum ether (b.p.40-60 ^{0}C),then with dilute ethanol and recrystallized from ethanol togive **16** as orange crystals ; yield 81% ;m.p 250^{0}C. IR : 3420 cm^{-1}(√OH),3365,3200cm^{-1}(2x√NH cyclic), 3061, 2979, 2922,2852 (√ C-H),1612cm^{-1}(√ C=N),1530cm^{-1}(√ C=C).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 12.43(s,1H,OH), 11.50(d,1H,NH-CH),11.2(s, 1H, NH cyclic), 6.88-7.85(m, 9H,Ar-H),3.12(d, 1H,-CH-OH),2.51(d,1H, -CH-NH) ,1.22(s, 3H, CH_3) . MS: 391$^{1+\cdot}$(M-1)(2.9%), 375(13.8%) , 307(1.7%), 293(17.6%),181(10.2%),153(4%), 131(2.5%),122(10.1%),116(9.4%), 105(17.4%), 92 (21.8%), 77(100%) .Anal.$C_{20}H_{17}N_6O$ Cl(392.5) (%) calcd: C, 61.15; H, 4.36; N, 21.39; Cl, 9.02.Found;C, 61.20; H, 4.34; N, 21.38; Cl, 9.00.

Reaction of the 15 with urea and /or thiourea:Synthesisof4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-hydroxy-5,6-dihydropyrimidin-2(1H)-one (17a) and 4-(1H-benzo[d]imidazol-2-yl)-6-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-hydroxy-5,6-dihydropyrimidin-2(1H)-thione (17b)

A mixture of **15** (0.01 mol), urea and/or thiourea (0.01 mol) in absolute ethanol (30 ml) was refluxed for 6hrs. After concentration and cooling theproduct was collected and washed well with dilute ethanol and recrystallized from

ethanol togive **17a and /or 17b** respectively . **17a** as yellow crystals ; yield 78% ;m.p 265^{0}C. IR : 3400 cm^{-1}(√OH),3330cm^{-1}(√NH), 3069, 2987, 2921,2850 cm^{-1} (√ C-H),1655 cm^{-1}(√ C=O),1612 cm^{-1}(√ C=N),1603cm^{-1}(√ C=C).^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 12.49(s,1H,OH), 12.45(d,1H,NH),11.43(s, 1H, NH), 6.88-7.85(m, 9H,Ar-H), 3.45(d, 1H, -CH-OH),2.51(d,1H, -CH-NH) ,1.83(s, 3H, CH_3) . MS: 423$^{1+\cdot}$(M+2)(3.69%), 382(5.6%) , 328(2%), 213(4%),192(2%),186(2%), 157(5%),113(8.4%),116(9.4%) ,96 (1.2%),77(16.2%) , 57(100%) .Anal.$C_{21}H_{17}N_6O_2$ Cl(420.5) (%) calcd: C, 59.92; H, 4.04; N, 19.97; Cl, 8.44.Found;C, 60.01; H, 4.05; N, 20.03; Cl, 8.51.

17b as orange crystals ; yield 63% ;m.p 295^{0}C. IR : 3353cm^{-1}(√NH), 3096, 2987, 2921,2820 cm^{-1} (√ C-H),1615 cm^{-1}(√ C=N),1548 cm^{-1}(√ C=C),1249 cm^{-1}(√ C=S),.^{1}H-NMR(300 MHz ,DMSO-d6): δppm at 12.05 (d,1H,NH), 11.11 (s, 1H, NH), 6.83-7.98(m, 9H,Ar-H), 3.41(d, 1H, -CH-OH),2.11(d,1H, -CH-NH) ,1.03(s, 3H, CH_3) . MS: 435$^{1+\cdot}$(M)(4.11%), 372(4.1%) , 214(2.3%),192(6.7%),186(7.5%), 96 (3.7%),77(65%) , 57(100%) .Anal.$C_{21}H_{17}N_6OS$ Cl(463.5) (%) calcd: C, 57.73; H, 3.89; N, 19.24;S, 7.31;Cl, 8.13.Found;C, 57.72; H, 3.91; N, 19.25;S, 7.31; Cl, 8.20.

RESULT AND DISCUSSION

Chemistry

The chalcone derivative **(3)** was prepared by the conventional method [23,24] from the interaction of the aceto [d] imidazol-2-yl)ethanone **(1)** with 5-chloro-3-methyl-1-phenyl-1H1-pyrazole-4-caboaldehyde**(2)** in alkaline ethanolic medium . Treatment of chalcone **(3)** with hydrazines namely hydrazine hydrate and /or phenyl hydrazine afforded the corresponding pyrazoline derivatives**(4a,4b)** ,while treatment of **(3)**with thiosemicarbazide affordedthe corresponding 3-(1H-benzo[d]imidazol-2-yl)-5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide**(5) .** The assigned structures for **(3), (4a, b)**and**(5)**were confirmed on the basis of IR,^{1}H-NMR and mass spectral analysis the IR spectra of **(4a,4b)**showed bands in the region 3232,3275 cm^{-1}for √NH , in the region 3126-2860cm^{-1}for √C-H,in the region 1626-1613cm^{-1}for √C=N and in the region 1599-1601cm^{-1}for √C=C. The ^{1}H-NMR for **(4a)** showed the signals of NH as two signlets at δ 11.2,10.59,the multiplet at 6.88-7.86 ppm for the aromatic protons and signals of the methyl protons at 1.31, while the signals of **(4b)** were signalsat δ 11.2 ppm as asinglet for NH, at 6.12-8.7 ppm for the 9 aromatic protons and methyl protons appeared as singlet at 1.46. The mass spectra of **(4a)** and **(4b)**showed the molecular ion peaks at m/z 375 and m/z 453 which are agreed well with the proposed structure . The IR spectrum of **(5)**reveled absorption bands at the region 3399,3232 cm^{-1}for √NH_2,NH , in the region 3162-2881cm^{-1}for √C-H,in the region 1613cm^{-1}for √C=N , in the region 1597cm^{-1}for √C=C,and in the region 1249cm^{-1}for √C=S. The ^{1}H-NMR reveled two signlets at δ12.2,11.2 for the NH, a multiplet at 6.8-8.5 ppm for the aromatic protons and singlet at 1.2 for the methyl protones. The mass spectrum showed the molecular ion peaks at 453 and the base peak at m/z 365.

Treatment of the chalcone **(3)** with hydroxyl amine hydrochloride affected 1,3 cyclocondensation to the corresponding 3,5 diaryl-1,2-oxazole derivative **(6) .**The IR spectrum of **(6)**reveled absorption bands at the region 3376,3130-2880 cm^{-1}characteristic for √ NH and √C-H respectively.The ^{1}H-NMR showed signals at δ11.44 assignlets for the NH, a multiplet at 6.85-7.87 ppm for the 9 aromatic protons and singlet at 1.23.for the methyl protones. The chalcone derivative **(3)** on the treatment with thiourea and /or urea in refluxing ethanol afforded the corresponding 4,6-diaryl-5,6-dihydro pyrimidin-2(1H)-thione**(7a)** or its pyrimidin-2(1H)-one derivative **(7b)**respectively . The structures of compounds **(7a,b)** were elucidated on the basis of elemental analysis as well as spectral data .IR spectrum of **(7a)**showed bands in the region 3402,3333 cm^{-1}for √NH , in the region 3160-2926cm^{-1}for √C-H,in the region 1622,1594cm^{-1}for √C=N and √C=C and a characteristic absorption band at 1249for √C=S. The ^{1}H-NMR showed signalsat δ 11.45,11.02 ppmas two signlets for cyclic NH groups ,a multiplet at 7.07-8.00 ppm for the 9 aromatic protons and a signlet of the methyl protons at 1.23 ppm. The mass spectrumof **(7a)** showed the molecular ion peaks atm/z 418 for M-1^{1+}and the base peak at m/z 303.

The IR spectrum of **(7b)**reveled absorption bands at the region 3401,3310-2828,1677,1629 cm^{-1}correspondingto √ NH , √C-H,√C=O and √C=N. The ^{1}H-NMR of **(7b)** reveled two signlets at δ11.4,9.57 for two signlets for cyclic NH groups ,a multiplet at 6.83-7.88 ppm for the 9 aromatic protons and a signlet of the methyl protons at 1.29 ppm. The mass spectrumof **(7b)** showed the molecular ion peaks at m/z 406 for M+1^{1+}and the base peak at m/z 63.

Addition of compound **(7a)**to a Schiff base in the presence of sodium ethoxide affected alkylation of the active olefinic bond of the Schiff base to give the corresponding α-aroyl amino benzylidene thiopyrimidine derivative**(8)** .

The IR spectrum of **(8)**showed absorption bands at 3461cm^{-1}for √NH , in the region 3169-2850cm^{-1}for √C-H,at 1612√C=N, and1594cm^{-1}for √C=C. The ^{1}H-NMR of **(8)**showed two signals at δ11.39,9.87 for two signlets for the two NH groups ,a multiplet at 6.88-7.86 ppm for the aromatic protons and a signlet of the methyl protons at 1.46. The mass spectrum showed the molecular ion peaks at m/z 675 for M-2Ι^{+}and the base peak at m/z 57.

Alkylation of **(7a)**with ethylchloroacetate in dry acetone containing anhydrous potassium carbonate occurred at the thione group only and not in the NH group to give the corresponding ethyl 2-(6-(1H-benzo[d]imidazol-2-yl)-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydropyrimidin-2-ylthio)acetate**(9)** .This was in agreement with the previous findings [25-27].The IR spectrum of **(9)**showed absorption bands at 3273cm^{-1}for √NH , in the region 3090-2853cm^{-1}for √C-H,at 1725 cm^{-1}for √C=O ester , and1617cm^{-1}for √C=N.The mass spectrum showed the molecular ion peaks at m/z 506 for M-1Ι^{+}. The ^{1}H-NMR reveled a multiplet at 7.2-8.8 ppm for the 9 aromatic protons and three signlets at 9.67,4.31 and 1.06 due to NH,CO$\underline{CH_2}$ and CH_3 protons respectively.

Refluxing **(9)**in alcoholic sodium hydroxide gave the corresponding thioacetic acid **(10).** The IR spectrum of **(10)**showed absorption bands at 3420cm^{-1}for √OH, 3363cm^{-1}for √NH , in the region 3090-2850cm^{-1}for √C-H,at 1710 cm^{-1}for √C=O acid , and1605cm^{-1}for √C=N.The mass spectrum showed the molecular ion peak at m/z 478 for M-1Ι^{+}. The ^{1}H-NMR reveled a multiplet at 7.21-8.87 ppm for the aromatic protons and four signlets at 1.03 ,2.50,9.67 and 10.39 due toCH_3 ,CO$\underline{CH_2}$, NH and OH protons respectively. Moreover refluxing **(9)** with hydrazine hydrate in ethanol afforded the corresponding 5,6-dihydropyrimidin-2-thioacetohydrazide derivative **(11) .** The IR spectrum of **(11)**showed absorption bands at 3300,3275,3178,2851,1667 and 1617cm^{-1} due to for stretching absorption bands of √NH_2 ,√NH , √C-H,√C=O , and √C=N respectively.The ^{1}H-NMR reveled signlets at 11.9,11.6 and 8.9 ppm for NH_2 , and two NH ,7.2-8.9 ppmmultiplet for the aromatic protons, 1.03 ,3.45 two singlets one for the $CH_3$and the other for CO$\underline{CH_2}$.The mass spectrum showed the molecular ion peak at m/z 492 for MΙ^{+}, and the base peak m/z 50 for C_4H_2.

The reaction of the hydrazine derivative **(11)**with carbonyl compounds was investigated .Thus, **(11)**reacted with acetone and /or anisaldehyde to give the hydrazide derivatives **(12a)**and /or **(12b) .**The IR spectrum of **(12a)**showed absorption bands at 3330,3003-2850,1655 and 1605cm^{-1} due to absorption bands of √√NH , √C-H,√C=O , and √C=N respectively.The ^{1}H-NMR showed signals at δ 10.8,10.28 ppm corresponding tothe 9 aromatic protons and at 1.34,1.36 ppm the two singlets for the protons of the two methyl groups. The IR spectrum of **(12b)**showed absorption bands at 3252,3396cm^{-1}for √NH , 1614cm^{-1}for √C=N, On the other hand , interaction of compound 4,6-diaryl pyrimidin-2-yl thio-N-arylidene acetohydrazide **(12b)**with acetic anhydride affected rearrangement , followed by cyclization to the corresponding 1,3,4-oxadiazol derivative **(13)**. The IR spectrum of **(13)**showed absorption bands at 3204cm^{-1}for √NH , in 1713 cm^{-1}for √C=O ketone , and1613cm^{-1}for √C=N.The ^{1}H-NMR of **(13)** reveled athe NH protons as asinglet at 11.68 ppm, a multiplet at 7.2-8.9 ppm for the aromatic protons ,methoxy protons CO$\underline{CH_3}$ and as singlet at 3.45 ,1.91,1.03 respectively.Onthe other hand , treatment of the hydrazino derivative **(11)** with carbon disulphide in the presence of aqueous potassium hydroxide affected cyclization to the corresponding 1,3,4-oxadiazole-5-thione derivative **(14)**.The IR spectrum of **(14)**agreed well with the proposed structure , it reveled absorption bands at 3394,3001-2850, 1667 and 1627,1190cm^{-1} due to √NH , √C-H,√C=N , and √C=S respectively.The ^{1}H-NMR of **(14)** showed signals at 8.89,8.77 as two signlets for the two NH cyclic, a singlet at 2.51 for –SCH_2- , a multiplet at 6.68-8.03 ppm for the 9 aromatic protons .The mass spectrum of **(14)** showed the molecular ion peaks at m/z 534 for MΙ^{+} and the base peak m/z 55 for $C_3H_5NΙ^{+}$.

The reaction of chalcone **(3)**with hydrogen peroxide in alkaline medium affected the formation of the corresponding oxirane derivative **(15)** .This was in agreement with the pervious findings [29] .The IR spectrum of **(15)** reveled the presence of stretching absorption bands of √NH ,√C-H ,√C=O ,√C=N , and √C-Cl at 3225,3107-2820, 1690 , 1598,608cm^{-1} and the epoxy linkage at 1290 cm^{-1}.The ^{1}H-NMR showed signals at 11.42 as signlet for the NH , 6.88-7.87 as multiplet for the aromatic protons, the system of the oxirane ring as a doublet at 3.89-4.01 ppm .The mass spectrum of **(15)** showed the molecular ion peaks at m/z 378 for MΙ^{+} and the base peak m/z 57 for CH_3-CH_2-N_2.

The reaction of **(15)**with hydrazine hydrate in refluxing ethanol yielded the corresponding 4-hydroxy pyrazol derivative. The IR spectrum of **(16)** reveled the presence of absorption bands of √OH , √NH , √C-H ,√C=N , and √C=C at 3420,3265,3200,3061-2852, 1612 and 1530cm^{-1}respectively.The ^{1}H-NMR showed signals at 12.43 as a signlets for the OH and a doublet for the NH at the pyrazole ring and at 11.02 ppm a singlet for the cyclic NH , 6.88-

7.85 as multiplet for the aromatic protonsppm .The mass spectrum of **(16)** showed the molecular ion peaks at m/z 391 for M⁺, at m/z 375 M-OH and the base peak m/z 77 for C_6H_5.

The reaction of **(15)** with urea and /or thiourea in refluxing ethanol affected the cyclization to the corresponding 4-hydroxy pyrimidin-2-one **(17a)** and / or 4-hydroxy pyrimidin-2-thione **(17b)** via opening of the epoxide ring followed by recyclization . The IR spectrum of **(17a)** reveled the presence of absorption bands at 3400,3330,3069-2850,1655, 1612 and 1603cm^{-1} corresponding to √OH , √NH , √C-H,√C=O(amide) ,√C=N , and √C=C respectively.The ^{1}H-NMR showed signals at 12.49,12.45,11.43 as two doublet and a signlets, 6.88-7.86 as multiplet for the aromatic protons .The mass spectrum of **(17a)** showed the molecular ion peaks at m/z 423 for M+2⁺, and the base peak m/z 57 for $C_2H_5N_2$. . The IR spectrum of **(17b)** reveled the presence of absorption bands at 3353 cm^{-1}for √NH ,3069-2820 for √C-H , 1615 for √C=N and 1249cm^{-1}√C=S respectively.The ^{1}H-NMR showed signals at 12.05,11.11 as two signlets, 6.83-7.93 as multiplet for the aromatic protons .The mass spectrum of **(17b)** showed the molecular ion peaks at m/z 435 for M⁺ , and the base peak m/z 57 for $C_2H_5N_2$

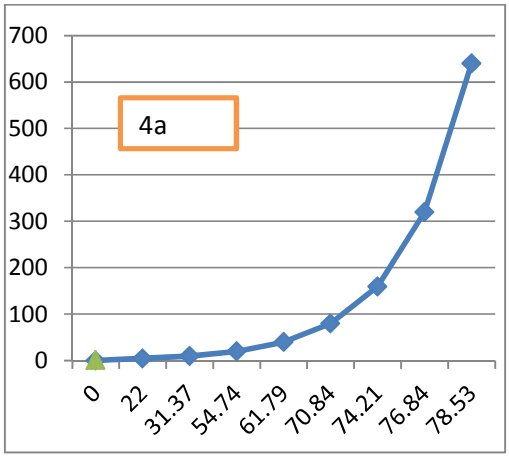
Antioxidant Testing:
The newly prepared compounds **4a,7a,15** are tested for antioxidant property by DPPH method .

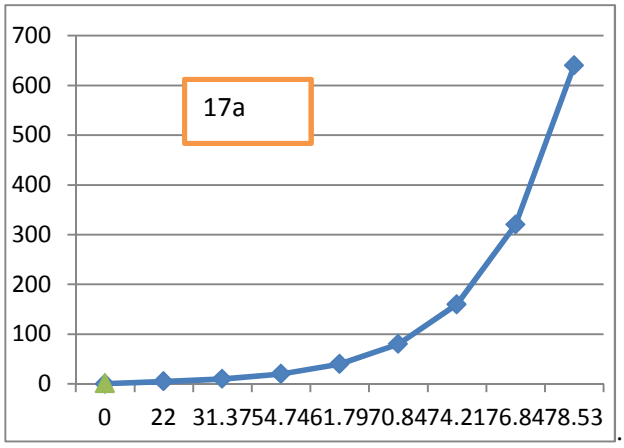
Reduction of 1,1- diphenyl-2-picrylhydrazyl (DPPH) Free Radical (DPPH method) The nitrogen centered stable free radical DPPH has often been used to characterize antioxidant . It is reversibly reduced and the odd electron in the DPPH free radical gives strong absorption maximum at 517 nm which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1- diphenyl-2-picrylhydrazine . The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced by this reaction has been used to measure the antioxidant properties of the tested newly derivatives. The solutions of the tested compounds (in ethanol) (100µM) were added to DPPH (100µM , in ethanol) . The tubes were kept at an ambient temperature for 25 minutes and the absorbance was measured at 517 nm . The difference between the test and the control experiments (Ascorbic), was taken and expressed as the percentage scavenging of the DPPH radical .

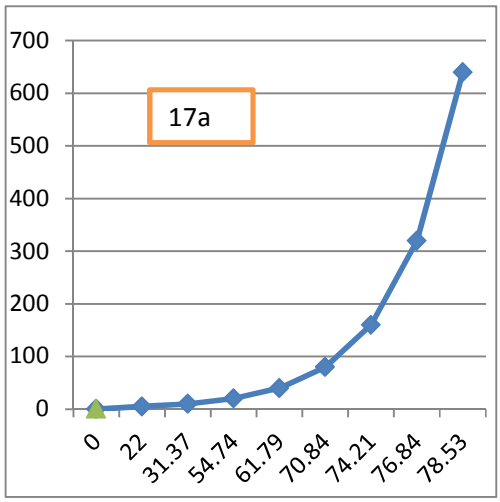
Table (1): Antioxidant Activity of the Target Compounds

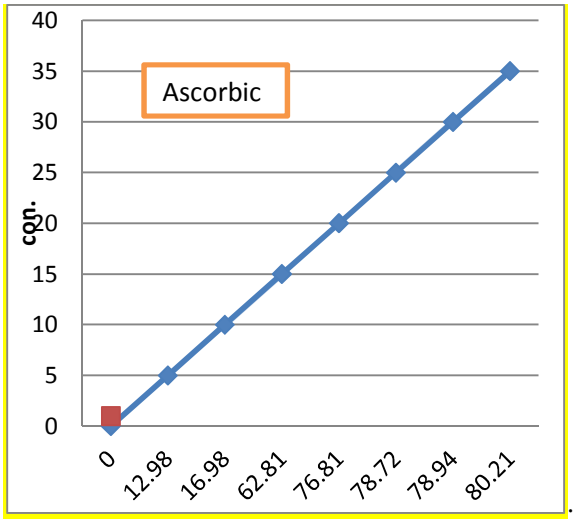
Sample con. µg	DPPH scavenging % inhibition at 100µM				
	Tested compounds			Standard ref .(Ascorbic)	
	4a	17a	15	Sample conc. µg	DPPH scavenging %
640	82.74	85.26	78.53	-	-
320	74.53	77.05	76.84	35	80.21
160	72.32	73.62	74.21	30	78.94
80	62.63	70.21	70.84	25	78.72
40	51.37	60.95	61.79	20	76.81
20	43.79	51.68	54.74	15	62.81
10	32.51	41.16	31.37	10	16.98
5	22.32	30.11	22.00	5	12.98
0	0	0	0	0	0

C = 100 µM
It is clear from the results that compounds **7a,15** exhibit significant antioxidant property in DPPH method at 100 µM concentration (Table) when compared with the standard reference Ascorbic acid .









Cytotoxicity Evaluation

Some of the newly prepared compounds were tested to determine their cytotoicity in the human hepatocellular liver carcinoma cell line HEPG-2 , against breast carcinoma cells MCF-7 cell line and against colon carcinoma cell lines HCT, using a modified method [27] .Thus , compounds **6,7b,11,12b** were tested against HEPG-2, compounds **4a,8,16,17a** against MCF-7 and compounds 5,9,13 and 14 against HCT cell line respectively . The cells were routinely cultured in Eagle's minimum essential media supplemented with 10% foetal bovine serum , 1% L-glutamine solution , and a non-essential amino acid solution .The investigated compounds were dissolved in a very small amount of DMSO, and a small volume was added to the cell culture . The tested compounds were prepared in triplicates at concentration ranging from 1.56 to 50 µg . The following types of controls were included : determination of 100% viability and 0% viability (the cells were treated with 10% DMSO),no cell control ,control for the determination of a possible interaction of the tested compounds with the reagent , control of the setting incubation medium and control of the toxicity of DMSO . The results are expressed as inhibitory concentration that reduces the cell viability to 50% of the maximal (control) viability (IC_{50}) . The results (**Table 2**) showed that compound **4a** was inactive toward the breast cancer cells (MCF-7)(> 50) , while compounds **8,16b,17a** exhibited cytotxic activity against MCF-7 with IC_{50} of 2.4, 30.8,2.6 µg/ml . Compounds **6,7b,11,12b** exerted activity against HEPG-2 cancer cells with IC_{50} of 33,19.3,33.8 respectively . Compounds **5,9,13,4** exhibited cytotoxic activity against HCT cancer cells with IC_{50} of 9.1,5.0,3.9,7.7 µg/ml . It is notable that **8 and 17a** are the most potent cytotoxic agents against MCF-7 with IC_{50}2.4 ,2.6 µg/ml , while **11,7b** are the most potent against HEPG-2 with IC_{50} 9,19.3 µg/ml and compound **13,9,14 and 15** the most potent against HCT with IC_{50} of 3.9,8.0,7.7 and 9.1 µg/ml .This is presumably due to a high lipophilicity of the benzimidazole moiety which enhances its absorption to the

cancer cells .However ,cytotxic activity of **4a,17a** has not reported in the literature. Hence , the benzimidazole analogs **8,17a,11,7b,5,9,13,14** are new series of cytotoxic agents .

Table (2): Cytotoxic activity of benzimidazole derivatives (4a,5,6,7b,8, 9,12b,13,14,16b)

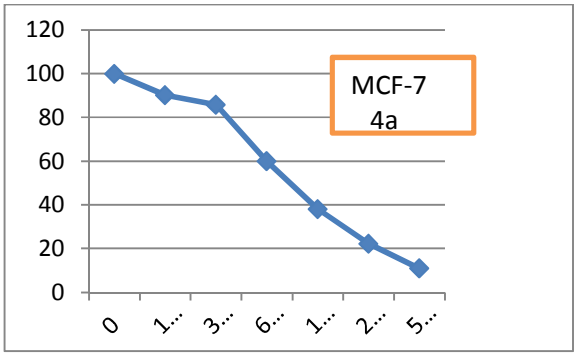
Cell lines[a]	IC50 (µg/ml)[b,c]											
	4a	**5**	**6**	**7b**	**8**	**9**	**11**	**12b**	**13**	**14**	**16b**	**17a**
MCF-7	>50	NT	NT	NT	2.4	NT	NT	NT	NT	NT	30.8	2.6
Hep G-2	NT	NT	33	19.3	NT	NT	9.0	33.8	NT	NT	NT	NT
HCT	NT	9.1	NT	NT	NT	5.0	NT	NT	3.9	7.7	NT	NT

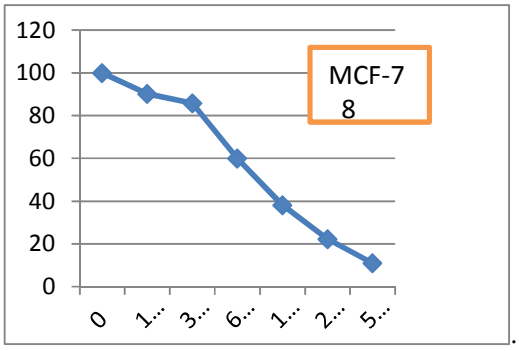
NT: indicates not tested

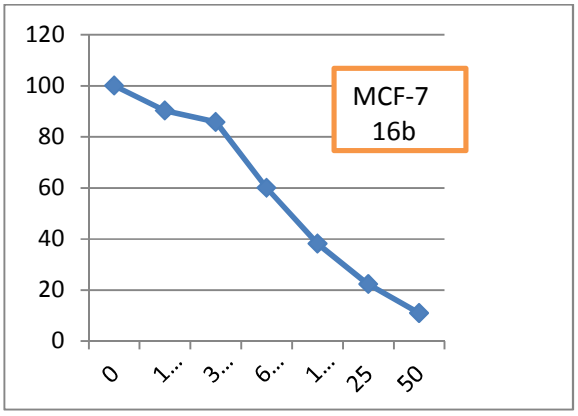
[a] *Cancer cell lines were hepatocellular carcinoma cell line (Hep G-2); colon carcinoma cell line (HCT); breast carcinoma cell line (MCF-7).*

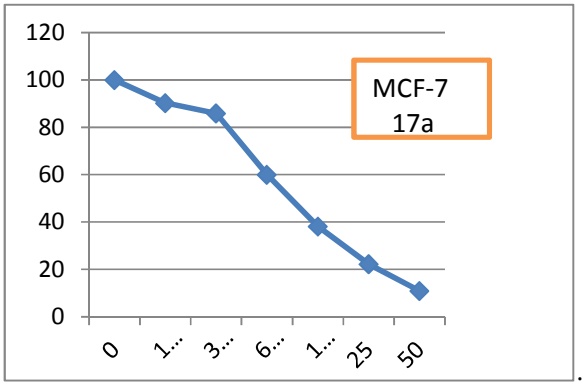
[b] *When IC50 > 50 µg/ml denotes inactive compound.*

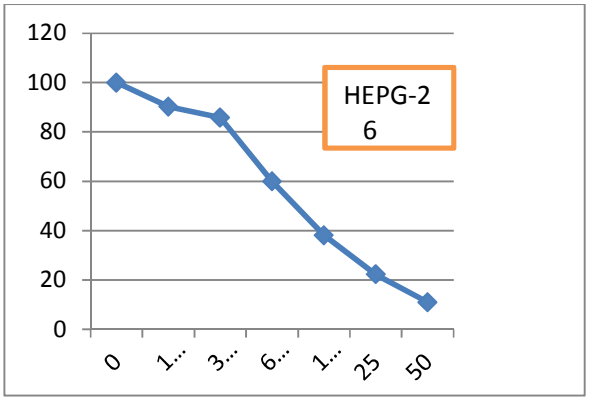
[c] *The assays were performed in triplicate.*

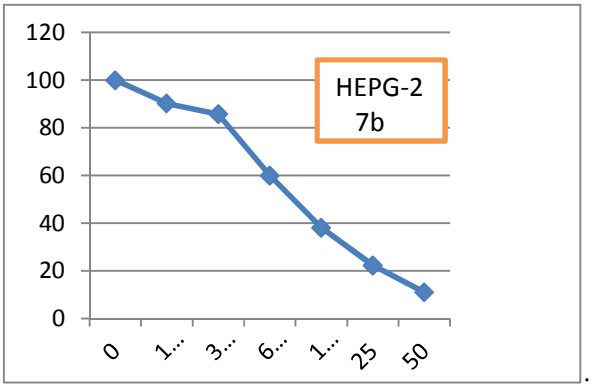


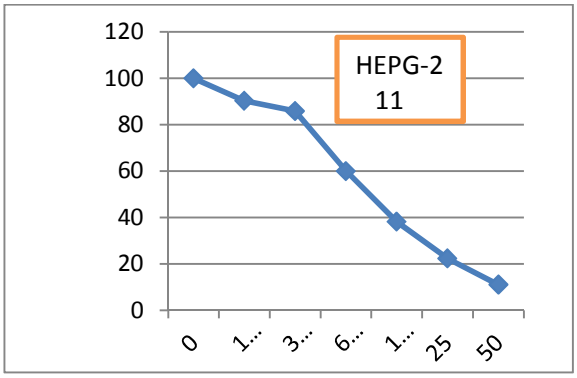


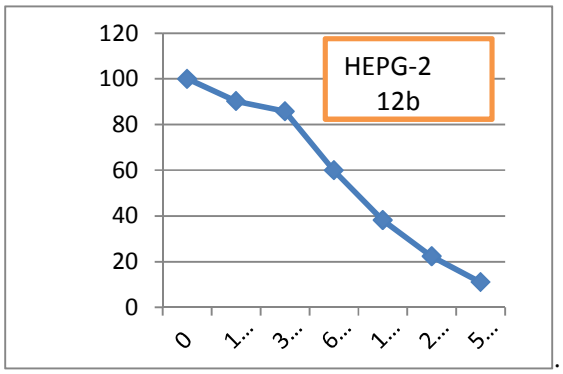


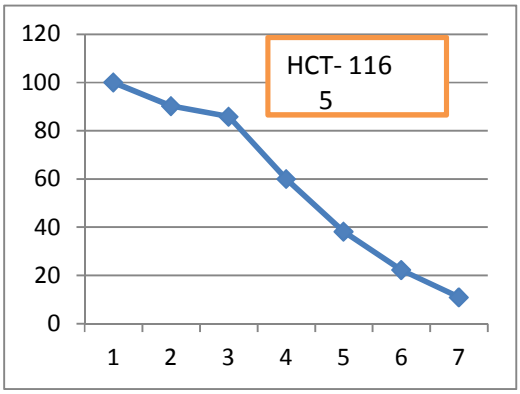


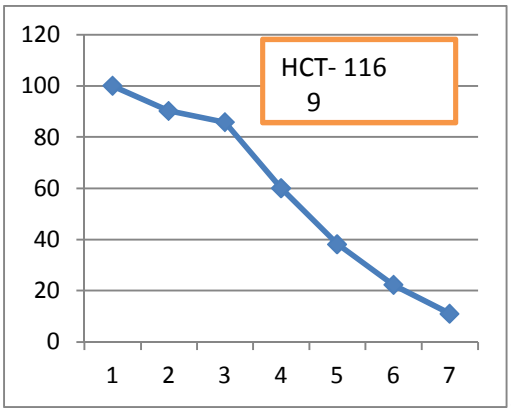


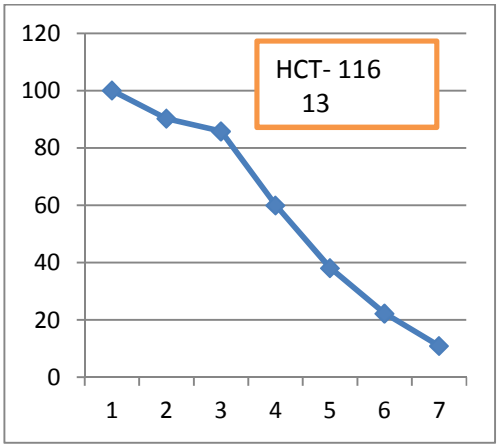


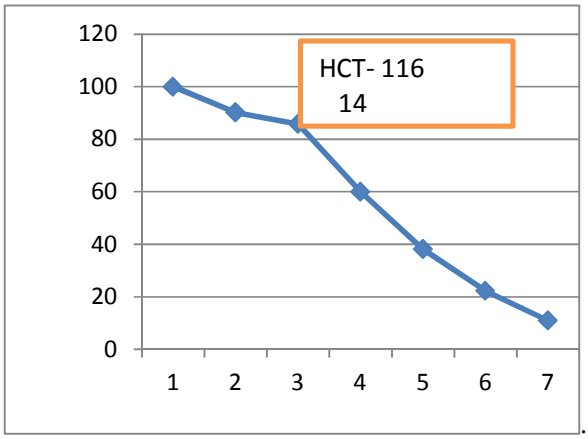












Structure – activity relationship

According to the results of the bio activities , it is noted that where-as compound 7b display the highest antioxidant , it also displayed cytotoxic activity against HEPG-2 cell .This is presumably due to a hydrophobic effect of sterically hindered benzimidazolo-thiopyrimidine group that enhances the penetration of compound 7b to the cancer cell.

CONCLUSION

The synthesis of target novel chalcone (3) , pyrazolo(4a,b,5), isoxazole(6) , pyrimidines (6-14), oxirane (15), hydroxyl pyrazolines (16) and hydroxyl pyrimidines (17a,b) was achieved according to the steps indicated . These reactions are simple , easily carried under normal reaction conditions . Most of the newly synthesized substituents were found to exhibit significant activity as antioxidant or anticancer agents . The findings demonstrate a new potential for some derivatives as lead comounds for further development as medicinal agents.

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