Pharmacophore 2015, Vol. 6 (1), 73-80 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

SYNTHESIS AND SCREENING OF 3-((5-((6-(PROPYLYLTHIO)-1H-BENZO[d] IMIDAZOL-2-YL) AMINO)-1, 3, 4-OXADIAZOL-2-YL) IMINO) SUBSTITUTED INDOLIN-2-ONES AS CYTOTOXIC, ANTI-OXIDANT AGENTS

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ABSTRACT

The present study involves the synthesis of 3-((5-((6-(propylthio)-1H-Benz [d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl)imino) substituted indolin-2-ones and evaluation for their cytotoxic, antioxidant activities. The compounds are screened for their cytotoxicity by MTT assay method for MCF-7, HeLa, HCT-116 and $HepG_2$ cell lines and antioxidant property by DPPH method. All the compounds showed their activity concentration dependent manner.

Keywords: Cytotoxic, Antioxidant, DPPH, MTT, Indolin-2-ones.

INTRODUCTION

Heterocycles from by far the largest of classical divisions of organic chemistry and are of immense biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastic are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituent around a core scaffold in defined three-dimensional representations.[1] In this study involves benzimidazole nucleus as scaffold and oxadiazole and isatin as substituents. There are few publications highlighting the cytotoxic and antioxidant activity of benzimidazole.[2,3]

The suggested synthetic plan to obtain the target compounds are shown in Scheme1. The N-(6-(propyl thio)-1H-Benz [d] imidazol-2-yl) hydrazine carboxamide (2) was obtained by treating Methyl (6-(propyl thio)-1H-Benz [d] imidazol-2-yl) carbamate (1) with hydrazine hydrate. N-(6-(propylthio)-1H-Benz[d]imidazol-2-yl)-1, 3, 4-oxadiazole-2, 5-diamine (3) was formed by reaction with cyanogen Bromide. N-(6-(propylthio)-1H-Benz[d]imidazol-2-yl)-1, 3, 4-oxadiazole-2, 5-diamine (3) was treated with corresponding isatins to get titled compounds.

MATERIAL AND METHODS

The chemicals and solvents are purchased (SD fine) was purchased from local wendors. Pre coated silica gel F_{254} (Merck) to check the purity of the reaction. Melting points were recorded on Thoshniwal melting point apparatus. IR spectra were recorded on Bruker Spectrophotometer using KBr pellet method. Mass spectra were recorded on ESI-MS spectrophotometer.^{1}HNMR spectra were recorded on Bruker Avance 300 MHz spectrophotometer on DMSO-d_6 as solvent.

Experimental

Synthesis of 3-((5-((6-(propylthio)-1H-Benz [d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-one (VI a-m)

Synthesis of N-(6-(propylthio)-1H-Benz [d] imidazol-2-yl) hydrazine carboxamide (II)

Methyl (6-(propylthio)-1H-Benz [d] imidazol-2-yl) carbamate (0.01 mol) was refluxed with hydrazine hydrate 99% (0.2 mole) in 20 ml of methanol for 2 hrs. The solvent was evaporated and poured into ice cold water and collected the product by filtration dried and purified with methanol.

Synthesis of N-(6-(propylthio)-1H-Benz [d] imidazol-2-yl)-1, 3, 4-oxadiazole-2, 5-diamine (V)

N-(6-(propylthio)-1H-Benz [d] imidazol-2-yl) hydrazine carboxamide (II, 0.1 mol) was dissolved in 25 ml of methanol and cooled the solution by keeping in ice bath. A cold suspension of cyanogen bromide (CNBr) (0.12 mol) in 25 ml of methanol was added over a period of 5min with rapid stirring. The reaction mixture was stirred for 0.75 hrs at room temperature, solid sodium bicarbonate (0.1 mol) was added in small portions to bring the pH 6.5 - 7.0. Stirring was continued for another 1hour. The solid separated was filtered, washed with cold water and dried. ESI-MS $[M+H]^+$ 291.

Synthesis of 3-((5-((6-(propylthio)-1H-Benz[d] imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substitutedindolin-2-ones (VI a-m)

To a warm solution of (N-(6-(propylthio)-1H-Benz[d]imidazol-2-yl)-1,3,4-oxadiazole-2,5-diamine (0.01 mol) in absolute ethanol (15 ml) appropriate indole-2,3-dione (0.01 mol) was added in the presence of glacial acetic acid (3 drops) and the reaction mixture was refluxed for 8-12 hr, then allowed to cool to room temperature. The solid separated was filtered, thoroughly washed with cold water, dried and recryastllized from ethanol. Compounds VI a-m were characterized by physical data, TLC, melting point, IR, Mass and ^{1}HNMR spectra. Melting points were determined in open capillary tubes on a Thomas Hoover melting point apparatus and were uncorrected.

Evaluation of Cytotoxic Activity

In vitro anticancer activity against MCF-7, HeLa, HCT-116 and HepG2 cancer cell line was determined using 96 well tissue culture plates. The method followed in the evaluation was standard MTT assay method.[4,5] The cell suspension of 1×105 cells/ml was prepared in complete growth medium. The drug solution was serially diluted at concentration of 10 µg/ml to 100 µg/ml with complete growth medium containing 1 µg/ml, 3 µg/ml, 10 µg/ml, 30 µg/ml and 100 µg/ml concentrations (<2%DMSO solution).The 100 µl of cell suspension was added to each well of 96-well tissue culture plates. The cells were allowed to grow in a CO_2 incubator (37^0C, 5% CO_2, 90% relative humidity) for 24 hrs. The test drug solutions in complete growth medium (100µl) were added after 24hrs incubation to the wells containing a cell suspension. After 48hrs of treatment with different concentrations of test drug solutions, the cells were incubated with 20 µl of MTT (2.5 mg/ml) for 2 hrs. After 24 hrs medium was removed and 80µl of lysis buffer was added to each well the plate was wrapped in aluminum.

Evaluation of Antioxidant Activity

α,α-Diphenyl picrylhydrazyl (DPPH 1 ml of 0.135 mM in methanol), a stable free radical was used for the evaluation of the antioxidant activity of the test compounds.[6] To 1ml of the test compound (at different concentrations), 1ml of DPPH solution were added, mixed thoroughly and absorbance (optical density) read at 517 nm against methanol as blank. The reduction in percentage of free radical Concentration (OD) with different concentrations of test compounds was calculated and compared with ascorbic acid as standard. Results were expressed as IC_{50} values (concentration of test required to scavenge 50 % free radicals.)

Characterization

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1,3,4-oxadiazol-2-yl) imino) indolin-2-one (4a)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34 (s,1H),7.5-7.6 (s,1H),7.71-7.78 (d,1H), 7.9 (d,1H),11.50(s, 1H, NH), and 13.5 (s, 1H, NH). ESI-MS: (m/z) 420$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-methylindolin-2-one (VI b)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st).^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.85 (t, 3H), 1.62 (m,2H),2.81(t, 2H),6.9-8 (m,6H, Ar),7.11-7.18(d,1H,Ar), 7.26 (d,1H,Ar),7.34(s,1H),7.45-7.55(s,1H),7.69-7.78 (d,1H), 11.00(s, 1H, NH), and 13.00 (s, 1H, NH). ESI-MS: (m/z) 434$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 7-methylindolin-2-one (VI c)

IR (KBr, cm^{-1})3328.53 cm^{-1} (N-H), 2949.53cm^{-1} (aliphatic C-Hst), 1707.13 cm^{-1} (C=Ost), 1623.99 cm^{-1} (C=O st), 1269.50 cm^{-1} (C-N st), 1095.75 cm^{-1} (C-F st), 690.21 cm^{-1} (C-S st). ^{1}HNMR (DMSO-d_6 400 MHz) δ = 0.85 (t, 3H), 1.62 (m,2H),2.81(t, 2H),6.9-8 (m,6H, Ar),7.11-7.18(d,1H,Ar),7.26(d,1H,Ar),7.34(s,1H),7.45-7.55 (s,1H),7.69-7.78(d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH)ESI-MS: (m/z) 434$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-fluoro indolin-2-one (VI d)

IR (KBr, cm^{-1}) 3328.53 cm^{-1} (N-H), 2949.53cm^{-1} (aliphatic C-Hst), 1707.13 cm^{-1} (C=Ost), 1623.99 cm^{-1} (C=O st), 1269.50 cm^{-1} (C-N st), 1095.75 cm^{-1} (C-F st), 690.21 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ=1.1 (t,3H), 1.75(m,2H),2.95(t,2H),7.5-8.5(m,6H,Ar),7.16-7.22(d,1H,Ar),7.32(d, 1H, Ar), 7.38(s,1H),7.7-7.8(s,1H),7.75-7.79(d,1H), 11.70(s, 1H, NH), and 13.7 (s, 1H, NH).ESI-MS: (m/z) 438$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-carboxy indolin-2-one (VI e))

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34 (s,1H),7.5-7.6(s,1H),7.71-7.78 (d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH) ESI-MS: (m/z) 478$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-chloro indolin-2-one (VI f)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 1.0 (t, 3H), 1.67 (m,2H),2.87(t, 2H),7-8.2 (m,6H,Ar), 7.12-7.2(d,1H,Ar), 7.28 (d,1H,Ar),7.34 (s,1H), 7.5-7.6 (s,1H),7.72-7.8 (d,1H), 11.60(s, 1H, NH), and 13.55 (s, 1H, NH) ESI-MS: (m/z) 454$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 7-chloro indolin-2-one (VI g)

IR (KBr, cm^{-1}): 2963.04 cm^{-1} (aliphatic C-Hst), 1723.15 cm^{-1} (C=Ost), 1619.89 cm^{-1} (C=O st), 1267.34 cm^{-1} (C-N st), 1094.71 cm^{-1} (C-F st), 676.04 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 1.0 (t, 3H), 1.67 (m,2H),2.87(t, 2H),7-8.2 (m,6H,Ar), 7.12-7.2 (d,1H,Ar), 7.28 (d,1H,Ar),7.34(s,1H),7.5-7.6(s,1H),7.72-7.8 (d,1H), 11.60(s, 1H, NH), and 13.55 (s, 1H, NH). ESI-MS: (m/z) 454$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-bromo indolin-2-one (VI h)

IR (KBr, cm^{-1}) 3450.07 cm^{-1} (N-H), 2922.15cm^{-1} (aliphatic C-Hst), 1594.62 cm^{-1} (C=Ost), 1297.98 cm^{-1} (C-N st), 1029.18cm^{-1} (C-Brst), 629.33 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ=0.99 (t, 3H),1.66 (m,2H),2.86(t, 2H),7-8.1 (m,6H, Ar),7.12-7.19 (d,1H,Ar), 7.29 (d,1H,Ar), 7.35 (s,1H),7.55-7.65(s,1H),7.75-7.79(d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH) ESI-MS: (m/z) 499$[M]^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 7-fluoro indolin-2-one (VI i)

IR (KBr, cm^{-1}) 34321.35 cm^{-1} (N-H), 1622.98 cm^{-1} (C=Ost), 1269.16 cm^{-1} (C-N st), 1094.70 cm^{-1} (C-Brst), 689.84 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.99 (t, 3H), 1.66 (m,2H),2.86(t, 2H),7-8.1 (m,6H, Ar),7.12-7.19 (d,1H,Ar),

7.29(d,1H,Ar),7.35(s,1H),7.55-7.65(s,1H),7.75-7.79(d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH) ESI-MS: (m/z) 438[M]$^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-nitro indolin-2-one (VI j)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34 (s,1H), 7.5-7.6 (s,1H), 7.71-7.78(d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH) ESI-MS: (m/z) 465[M]$^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 7-nitro indolin-2-one (VI k)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR (DMSO-d_6 400 MHz) δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34(s,1H),7.5-7.6(s,1H),7.71-7.78(d,1H),11.50(s, 1H, NH), and 13.5 (s, 1H, NH) ESI-MS: (m/z) 465[M]$^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 5-carboxy indolin-2-one (VI l)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR(DMSO-d_6 400 MHz) δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34 (s,1H),7.5-7.6 (s,1H), 7.71-7.78 (d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH)ESI-MS: (m/z) 465[M]$^+$

3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) 7-carbomethoxy indolin-2-one (VI m)

IR (KBr, cm^{-1}) 3471.60 cm^{-1} (N-H), 3055.03 cm^{-1} (arom C-H st), 2962.18cm^{-1} (aliphatic C-Hst), 1728.13 cm^{-1} (C=Ost), 1278.00 cm^{-1} (C-N st), 695.31 cm^{-1} (C-S st). ^{1}HNMR (DMSO-d_6 400 MHz) (δ = 0.9 (t, 3H), 1.65 (m,2H),2.85(t, 2H),7-8 (m,6H, Ar), 7.12-7.18(d,1H,Ar),7.28(d, 1H, Ar), 7.34(s,1H),7.5-7.6(s,1H),7.71-7.78 (d,1H), 11.50(s, 1H, NH), and 13.5 (s, 1H, NH)ESI-MS: (m/z) 478[M]$^+$

RESULTS AND DISCUSSION

The synthesis of the titled compounds started with Methyl (6-(propylthio)-1H-Benz [d] imidazol-2-yl carbamate which was treated with hydrazine hydrate using methanol as a solvent to get N-(6-(propylthio)-1H-Benz[d]imidazol-2-yl) hydrazine carboxamide (II). This compound was treated with cyanogen bromide with caution to get cyclized and the compound N-(6-(propylthio)-1H-Benz[d]imidazol-2-yl)-1,3,4-oxadiazole-2, 5-diamine (III) was formed. The compound (III) was treated with corresponding isatins to get Schiff base of the compound i.e. title compounds (IVa-m). The compounds are evaluated for their cytotoxicity and antioxidant properties by using standard protocols.

The in vitro cytotoxicity data of 3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-ones (VI a-m) on MCF-7, HeLa, HCT-116, $HepG_2$ was presented in the Table 2 and Figure 1. The IC_{50} values of all these synthetic compounds for MCF-7 were found between 23.21 and 59.86. Among the compounds of the series, Compound VI l (R=5-COOH) which has got better growth inhibition and got an IC_{50} value as 23.21 µM. Compounds VI e (R=5-$COOCH_3$) and VI i (R=7-F) are next in order having IC_{50}values as 26.85 µM and 36.97 µM respectively. Compound VI g (R=7-Cl) was least active among them with an IC_{50} value as 67.52 µM. The IC_{50} values of all these synthetic compounds for HeLa were found between 26.63 and 69.21. Among the compounds of the series, Compound VI l (R=7-$COOCH_3$) which has got better growth inhibition and got an IC_{50} value as 26.63 µM. Compounds VI e (R =5-COOH) and VI a(R=H) are next in order having IC_{50} values as 29.21 µM and 33.98 µM respectively. Compounds VI g (R=7-Cl), VI c (R=7-CH3), VI d R= (R =5-F) were least active among them with an IC_{50} values as 77.32 µM, 69.21 µM and 69.26 µM respectively. The IC_{50}

values of all these synthetic compounds for HCT-116 were found between 57.05 and 201.68. Among the compounds of the series, Compound VI l (R=5-COOH) showed better activity when compared with the standard showing IC_{50} value as 57.05 µM. Compounds VI f (R=5-Cl) and VI a (R=H) is next in the series with an IC_{50} values as 58.40 µM and 66.77 µM respectively. Compound VI m (R=7-$COOCH_3$) was least active among them with an IC_{50} value as 201.68 µM. The IC_{50} values of all these synthetic compounds for $HepG_2$ were found between 68.19 and 192.93.Among the series, VI l (R=5-COOH) showed good activity with an IC_{50} value as 68.19 µM. Compounds VI c (R=7-CH_3) and VI h (R=5-Br) were next in order with an IC_{50} values as 81.21 µM, 91.25 µM respectively. Compound VI j (R=5-NO_2) was least active among them with an IC_{50} value as 185.46 µM.

The IC_{50} values of all these synthetic compounds for antioxidant activity were found between 98.25 and 178.21. Among the series, VI g (R=7-Cl) was active with an IC_{50} value as 98.25 µM. Compound VI j (R=5-NO_2) was next in order with an IC_{50} values as 99.32 µM. Compound VI b (R=5-CH_3) was least active among them with an IC_{50} value as 178.21 µM.

CONCLUSION

In summary a new series of Benzimidazole molecules were synthesized, characterized and screened for cytotoxic and antioxidant activities. Among the synthesized compounds 7-chloro substitution increases antioxidant activity and 5-carboxy substitution increases cytotoxic activity.

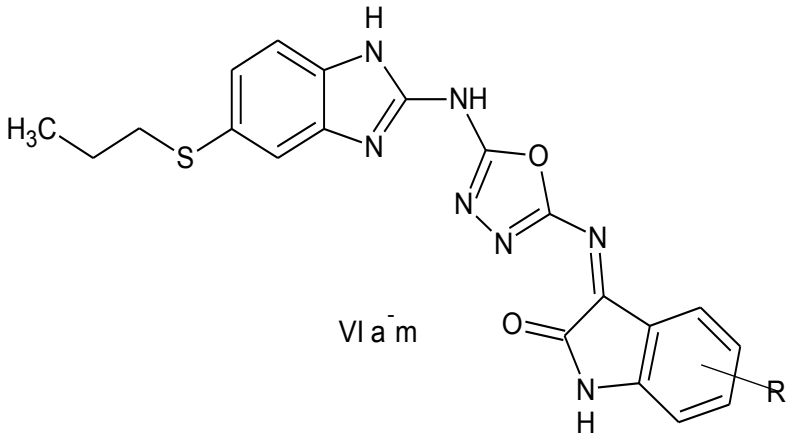
CONFLICT OF INTEREST

The authors express no conflict of interest.

ACKNOWLEDGEMENT

The authors are thankful to Laila Implex, Vijayawada, Andhra Pradesh and IICT, Hyderabad for providing spectra.

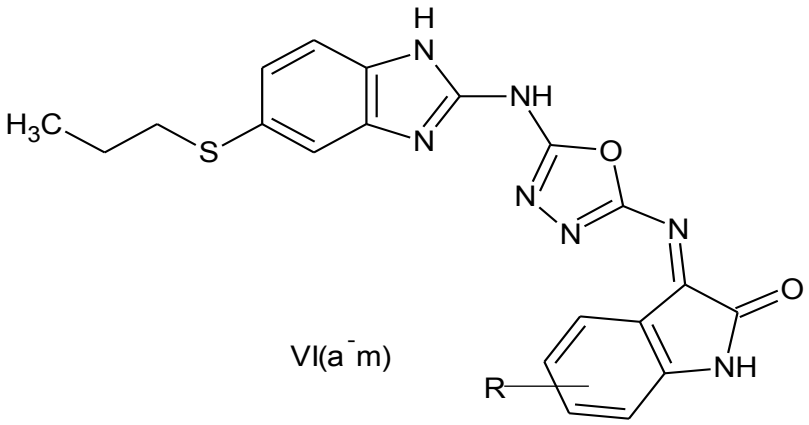
Table 1: Physical data of 3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-ones (VI a-m)



S. No.	Compound Name	R	Molecular formula	Molecular weight	Melting range (°C)	Percentage yield
1	4 a	H	$C_{20}H_{17}N_7O_2S$	419	169-170	77
2	4 b	5-CH3	$C_{21}H_{19}N_7O_2S$	433	171-173	75
3	4 c	7-CH3	$C_{21}H_{19}N_7O_2S$	433	173-175	78
4	4 d	5-F	$C_{20}H_{16}FN_7O_2S$	437	176-178	65
5	4 e	5- $COOCH_3$	$C_{22}H_{19}N_7O_4S$	477	177-179	54
6	4 f	5-Cl	$C_{20}H_{16}ClN_7O_2S$	453	195-196	71
7	4 g	7-Cl	$C_{20}H_{16}ClN_7O_2S$	453	183-185	65
8	4 h	5-Br	$C_{20}H_{16}BrN_7O_2S$	498	195-196	68

9	4 i	7-F	$C_{20}H_{16}FN_7O_2S$	437	176-178	59
10	4 j	5-NO_2	$C_{20}H_{16}N_8O_4S$	464	182-184	55
11	4 k	7- NO_2	$C_{20}H_{16}N_8O_4S$	464	183-185	55
12	4 l	5-COOH	$C_{21}H_{17}N_7O_4S$	464	183-185	66
13	4 m	7-$COOCH_3$	$C_{22}H_{19}N_7O_4S$	477	187-189	55

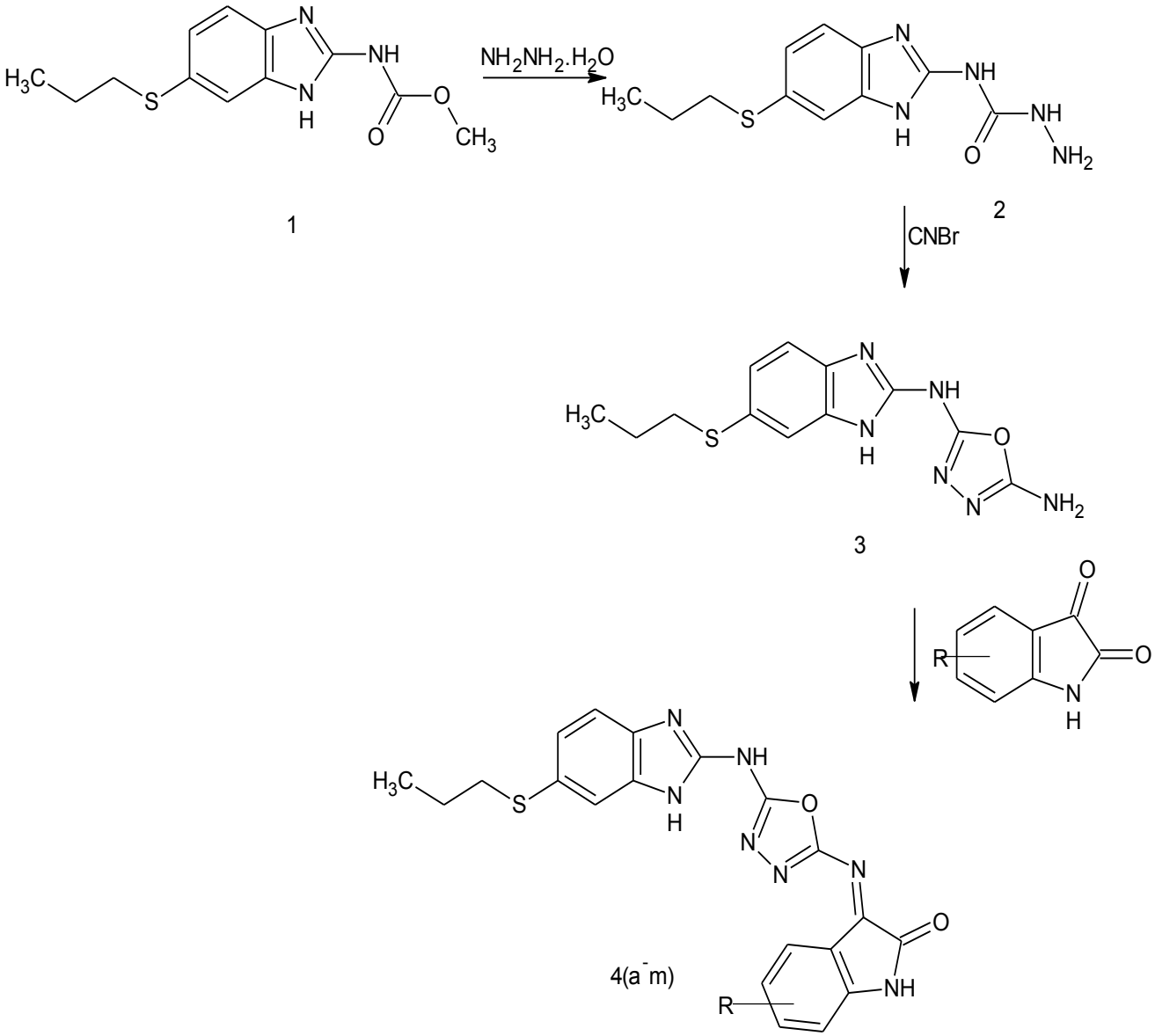
Table 2: In vitro cytotoxic activity data of 3-((5-((6-(propylthio)-1H-Benz[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-ones (VI a-m)



VI(a-m)

S. No.	Compound Name	R	IC_{50}(µg/ml)*				
			MCF-7	HeLa	HCT-116	$HepG_2$	oxidant
1	4 a	H	42.88	33.98	110.84	146.18	114.23
2	4 b	5-CH_3	55.38	65.88	110.18	177.67	178.21
3	4 c	7-CH_3	59.418	69.21	103.58	91.25	129.32
4	4 d	5-F	59.86	69.26	66.77	100.42	145.56
5	4 e	5-$COOCH_3$	26.85	36.75	157.06	180.67	136.23
6	4 f	5-Cl	55.02	65.22	58.40	105.36	129.36
7	4 g	7-Cl	67.52	77.32	84.06	149.48	98.25
8	4 h	5-Br	56.26	63.26	119.24	81.21	118.23
9	4 i	7-F	36.97	46.95	109.62	103.33	115.23
10	4 j	5-NO_2	49.67	52.87	87.71	185.46	99.32
11	4 k	7-NO_2	48.96	52.96	99.85	192.93	124.65
12	4 l	5-COOH	23.21	29.21	57.05	68.19	131.25
13	4 m	7-$COOCH_3$	59.63	26.63	201.68	117.66	114.23
14	Standard	Cisplatin	14.97	14.08	12.19	7.54	--
15	Standard	Ascorbic acid	--	--	--	-	5.83

*Values are expresses as means (n=4)



Scheme-1: Synthesis of 3-((5-((6-(propylthio)-1H-benzo[d]imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-ones (4a-m)

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Cite This Article: K, Blessi Priyanka and G, Sammaiah (2015), "synthesis and screening of 3-((5-((6-(propylylthio)-1h-benzo[d] imidazol-2-yl) amino)-1, 3, 4-oxadiazol-2-yl) imino) substituted indolin-2-ones as cytotoxic, anti-oxidant agents", ***Pharmacophore***, Vol. 6 (1), 73-80.