Design, synthesis and biological activities of Dispiroimidazolidine-Pyrrolizine/pyrrolidine derivatives via 3 component 1,3-Dipolar cyclo -addition reaction.

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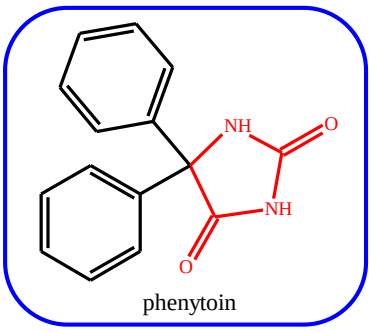
Abstract

Pyrrolizine/pyrrolidine scaffolds have long been described for their encouraging biological responses such as anti-cancer, anti-microbial, anti-viral, etc. Hydantoin, a versatile pharmacophore, has also been employed for developing a variety of bioactive molecules. Therefore, we anticipated to integrate these two privileged moieties into a single one for enriched biological applications. In this work, we developed an effective synthesis of Dispiroimidazolidine Pyrrolizine/pyrrolidine conjugates via 1, 3-cycloaddition reaction of azomethine ylides generated *in situ* by the 8-bromotryptanthrin and Acyclic/Cyclic α-amino acid with the Knoevenagel adduct derivatives (derived from the reaction of Hydantoin with substituted benzaldehydes) We further evaluated anti-bacterial, anti-fungal and cytotoxicity activity of all the compounds against *MCF-7* human breast cancer cells. Compound 3A-1 & 2, 3 B-1 & 2 and 3 A-9 & B-9 containing 4-flouro and nitro substituent on Phenyl ring and furyl with Bromo atom on Indolo[2,1-b]quinazoline-6,12-dione nucleus showed better activity having IC values 1.82 µg/ml,1.94 µg/ml & 1.88 µg/ml respectively.

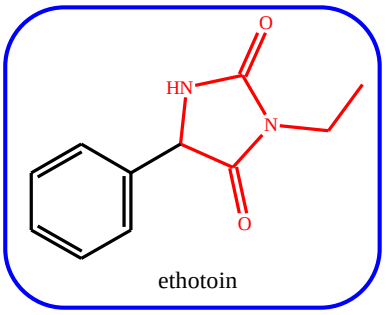
Introduction

Spiro- heterocyclic derivatives are thought-provoking research areas for organic and medicinal chemist due to their prominent role in lead drug identification and drug discovery and the presence of bridge atoms which provides structural rigidity, structural complexity and stereo-selectivity which increase binding affinity to bio- targets. The diverse structures of Spiro heterocyclic compounds are present and isolated form natural product and synthetic compounds (1-7). They possess widespread are biological properties like anti-cancer (8-11), anti-microbial (12-13), Anti-viral (14) photochromism (15-17) and hole transporting (18).

Hydantoin scaffold is an essential constituent of alkaloids, drug molecules (19-20), marine drug and various synthetic compounds possessing diverse bioactivities such as anti-cancer, antiarrhythmic, antiviral, antidepressant, and antithrombotic and shown in.Fig-1. (20-22)



phenytoin



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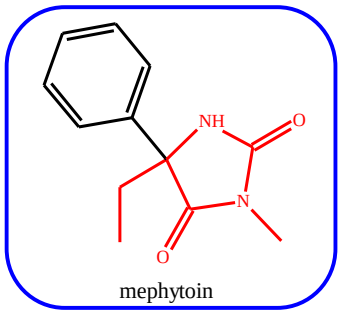
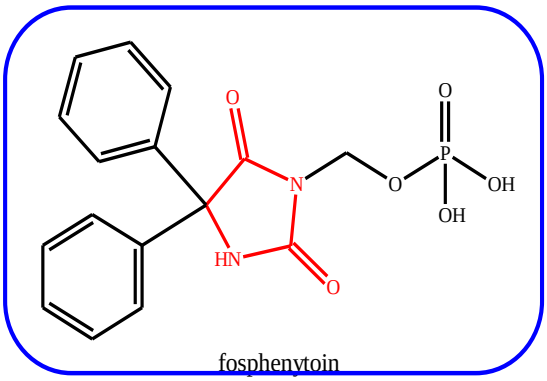
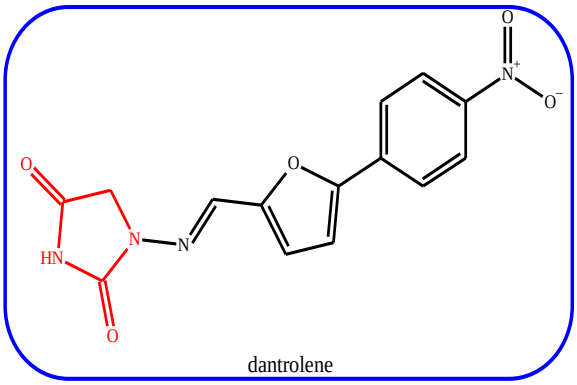


mephytoin

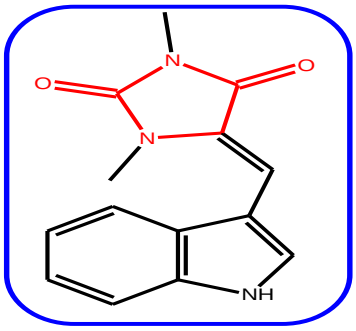


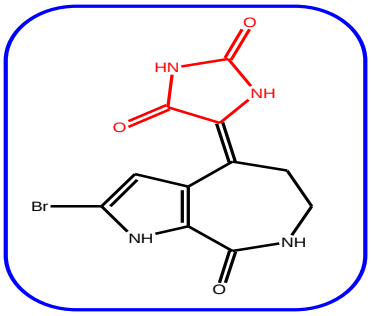
fosphenytoin



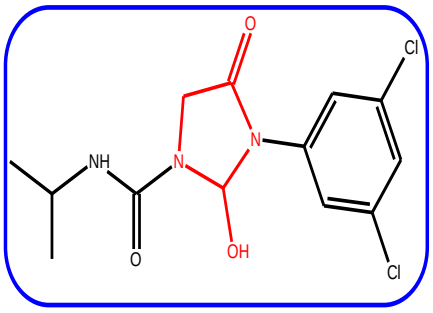
dantrolene

Approved Drug Molecules

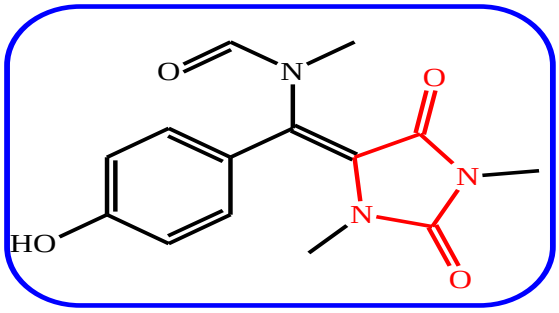


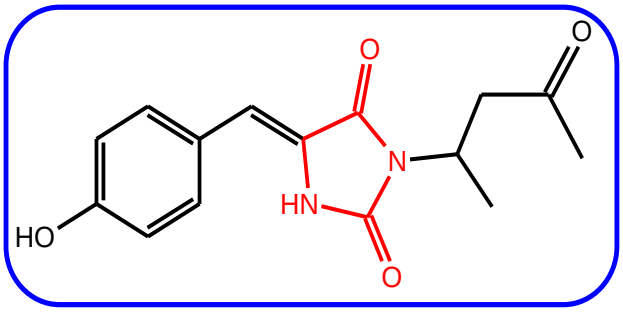


Alkaloids



Pesticide





Marine drug

Figure-01

Thus, in order to proliferation our curiosity in of novel Spiro-heterocyclic scaffold having characteristic feature and above mention biological application. We presume the molecular hybridization of into new hybrid architecture. we report herein the efficient synthesis in excellent

yields of a series of Dispiroimidazolidine-Pyrrolizine/pyrrolidine derivatives by the three-component 1,3-dipolar cycloaddition reaction of azomethine ylides generated *in situ* by the 8-bromotryptanthrin and Acyclic/Cyclic α-amino acid with the Knoevenagel adduct derivatives (derived from the reaction of Hydantoin with substituted benzaldehydes) The process is simple and mild reaction condition with chemo-, region- and stereo selectivity which served various aspects of medicinal and combinatorial chemistry (23-30) .fig-2

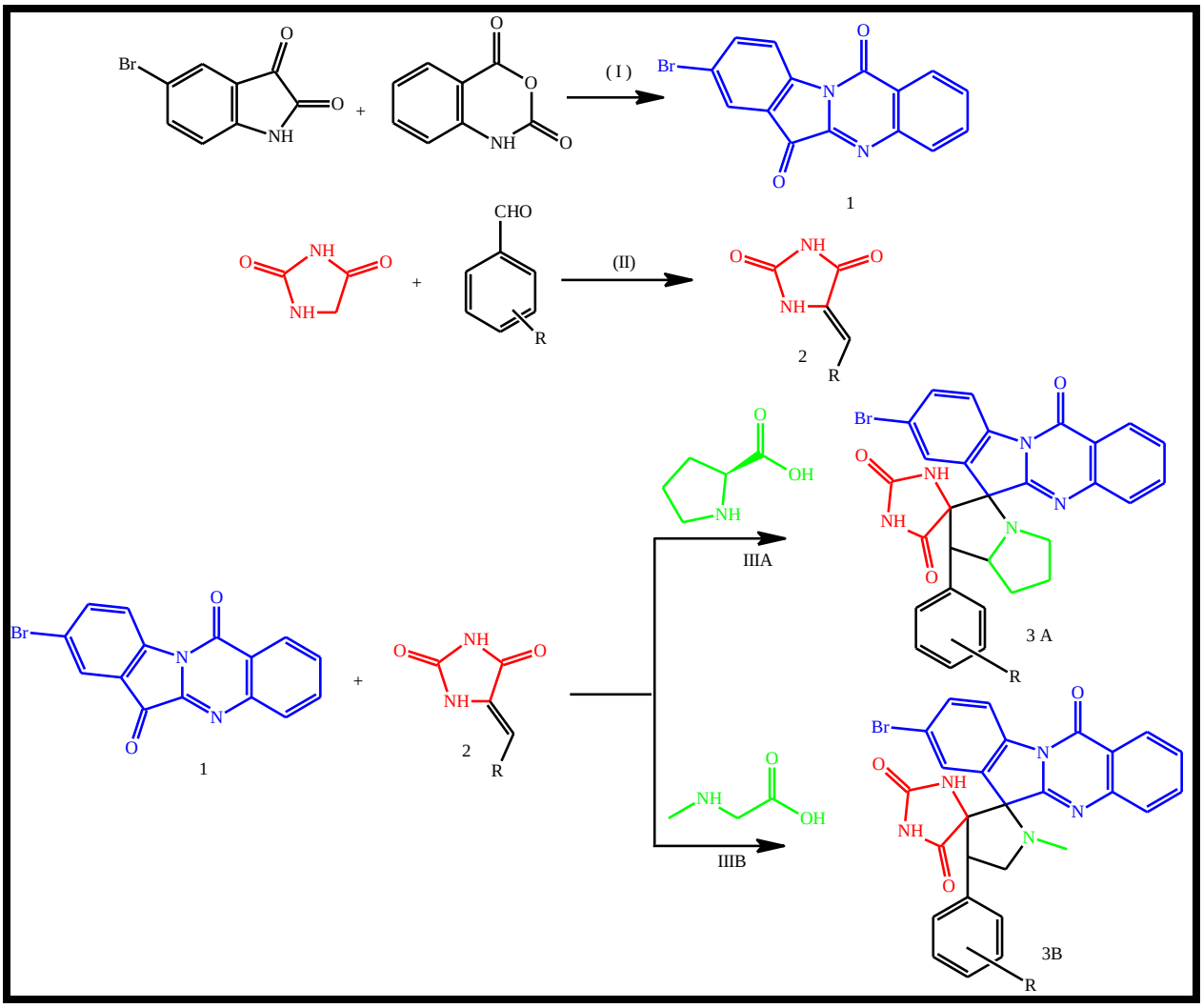


Figure-02

Reaction conditions I) Toluene, Triethyl amine, Reflux, 4 hrs ; II) Acetic acid, sodium acetate and different aldehyde ; III) Methanol, Reflux.
Where R means

3 A/B – 1	4-fluorobenzaldehyde
3 A/B – 2	4-nitrobenzaldehyde
3 A/B – 3	4-Methoxybenzaldehyde
3 A/B – 4	4- Hydroxy benzaldehyde

3 A/B – 5	3,4-dimethoxy benzaldehyde
3 A/B – 6	ISO-BUTYRALDEHYDE
3 A/B – 7	ISOVALERALDEHYDE
3 A/B – 8	PROPIONALDEHYDE
3 A/B – 9	FURFURAL

Chemistry

The synthesis of the prerequisite-A, 8-bromoindolo [2,1-b]quinazoline-6,12-dione / 8-Bromo tryptanthrin 1 was prepared according to the previously reported procedure in which 5-bromoisatin ,Isatoic anhydride and Triethyl amine in toluene under reflux condition (31). The Prerequisite-B, 5- substituted imidazolidine-2,4-dione derivatives 2 (1-9) is carried out from the appropriate aldehyde and Hydantoin in acetic acid. An Azomethine ylides were in situ generated from the reaction between 8-bromoindolo [2,1-b]quinazoline-6,12-dione (8-Bromo tryptanthrin 1) and alpha-amino acids(Proline & Sarcosine) The cycloaddition reaction of azomethine ylides with polarophiles 2 gives the substituted Dispiroimidazolidine-Pyrrolizine 3 A 1-9 and Dispiroimidazolidine-pyrrolidine 3 B 1-9 derivatives respectively. The purity of compounds was checked by TLC. The structure of all the synthesized compounds was confirmed by IR, (1 H & 13C) NMR and Mass spectral analysis. The result of elemental analysis of the synthesized compounds was in agreement with theoretical values.

Experimental section

All the melting points were taken in open capillaries and are uncorrected. The purity of compounds was checked routinely by pre-coated TLC plates with 0.25 mm layer of silica gel-60 with fluorescent indicator UV254 (Merck) and spots were visualized by exposing the dry plates in UV 254 and iodine vapors. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. IR spectra (n max in cm_1) were recorded on Shimadzu FTIR spectrophotometer using KBr technique. ^{1}H & ^{13}C NMR spectra on a Varian 300MHz NMR instrument using DMSO-d6 as solvent and TMS as internal reference (chemical shifts in d ppm). The elemental analysis (C, H, and N) of compounds was performed on Carlo Erbae 1108 elemental analyzer.

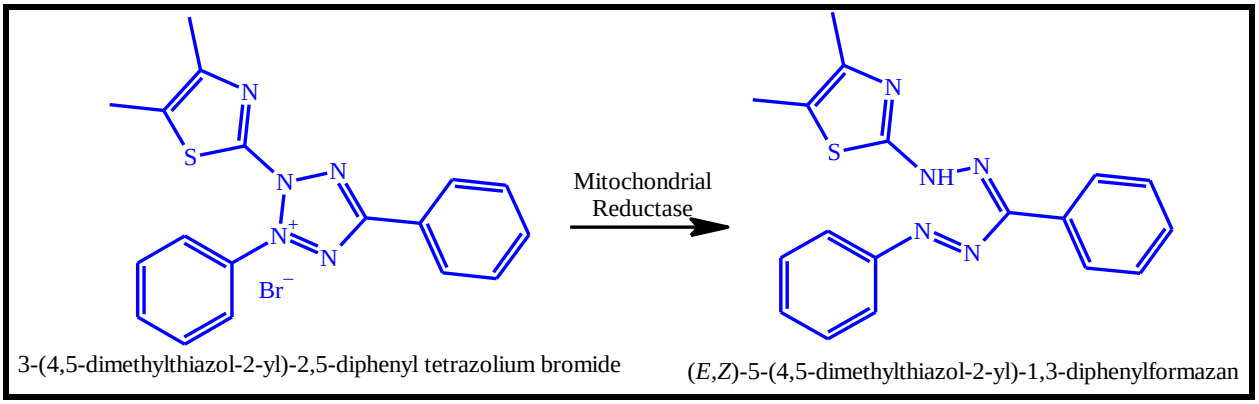
Biological activity

In vitro evaluation of antimicrobial and Cytotoxic activity

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan (32). Antibacterial activity was screened against Escherichia coli (MTCC-443), Pseudomonas aeruginosa (MTCC-1688), Klebsiella pneumonia (MTCC-109), Salmonella typhi (MTCC-98), Staphylococcus aureus (MTCC-96), Staphylococcus pyogenus (MTCC-442) and Bacillus subtilis (MTCC441). Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species C. albicans (MTCC 227), Aspergillus niger (MTCC 282) and Aspergillus clavatus (MTCC 1323). Nystatin and Griseofulvin was used as a standard antifungal agent. The

antimicrobial screening data are shown in Tables 3,4,5 & 6 and also depicted in Graphs. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs. Muellere Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 108 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains.

The Cytotoxic activities of newly synthesized compounds 3A 1-9 and 3 B 1-9 were carried out by MTT colorimetric assay (33). It is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, coloured (dark purple) formazan product. The cells are then solubilized with an organic solvent (eg. DMSO, isopropanol), and the released, solubilized formazan reagent is measured spectrophotometrically. Since reductions of MTT can only occur in metabolically active cells the level of activity is a measure of the viability of the cells



3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

(*E*,*Z*)-5-(4,5-dimethylthiazol-2-yl)-1,3-diphenylformazan

Materials:
MCF-7 (Human breast cancer),Dulbecco`s Modified Eagle Media (DMEM) with low glucose -Cat No-11965-092 (Gibco, Invitrogen), Fetal bovine serum (FBS) -Cat No -10270106 (Gibco, Invitrogen), Antibiotic – Antimycotic 100X solution (Thermofisher Scientific)-Cat No-15240062, Positive Control- Doxorubicin, Negative Control- Cells with media

Protocol- Cytotoxicity
The cells were seeded in a 96-well flat-bottom microplate and maintained at 37oC in 95% humidity and 5% CO2 overnight. Different concentration (100, 50, 25, 12.5, 6.25, 3.125µg/ml) of samples were treated. The cells were incubated for another 48 hours. The wells were washed twice with PBS and 20 µL of the MTT staining solution was added to each well and the plate was incubated at 37oC.After 4h, 100 µL of DMSO was added to each well to dissolve the formazan crystals, and absorbance was recorded with a 570 nm using microplate reader (33).

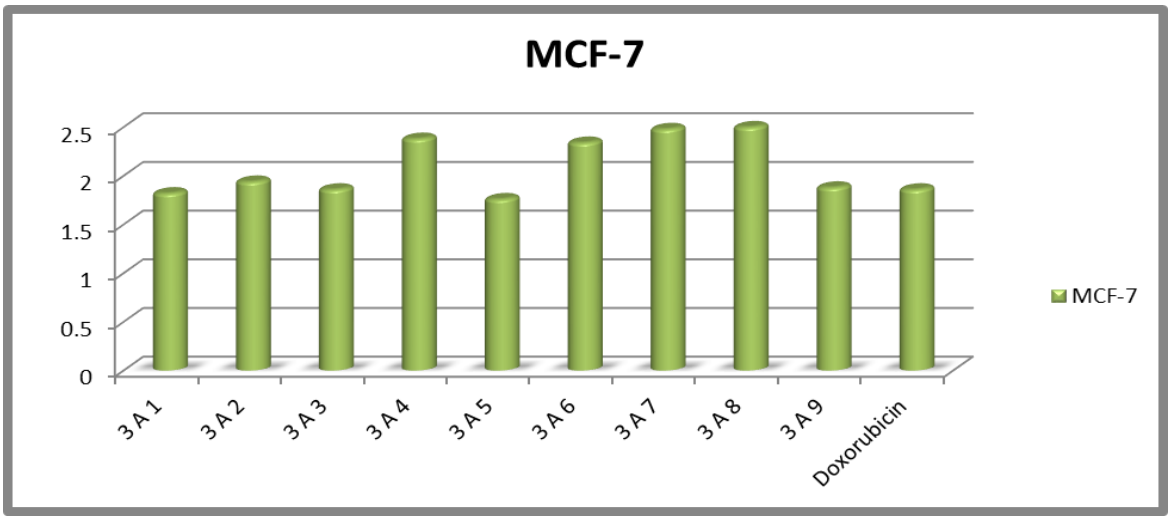
Formula:
Surviving cells (%) = Mean OD of test compound /Mean OD of Negative control ×100

Using graph Pad Prism Version5.1, we calculate the IC 50 of compounds
Results

The IC50value of compounds (µg/ml)

Sample	MCF-7	
	Mean	SD
3 A 1	1.82	0.01
3 A 2	1.94	0.03
3 A 3	1.86	0.03
3 A 4	2.38	0.02
3 A 5	1.76	0.02
3 A 6	2.34	0.03
3 A 7	2.48	0.01
3 A 8	2.5	0.02
3 A 9	1.88	0.03
Doxorubicin	1.86	0.03

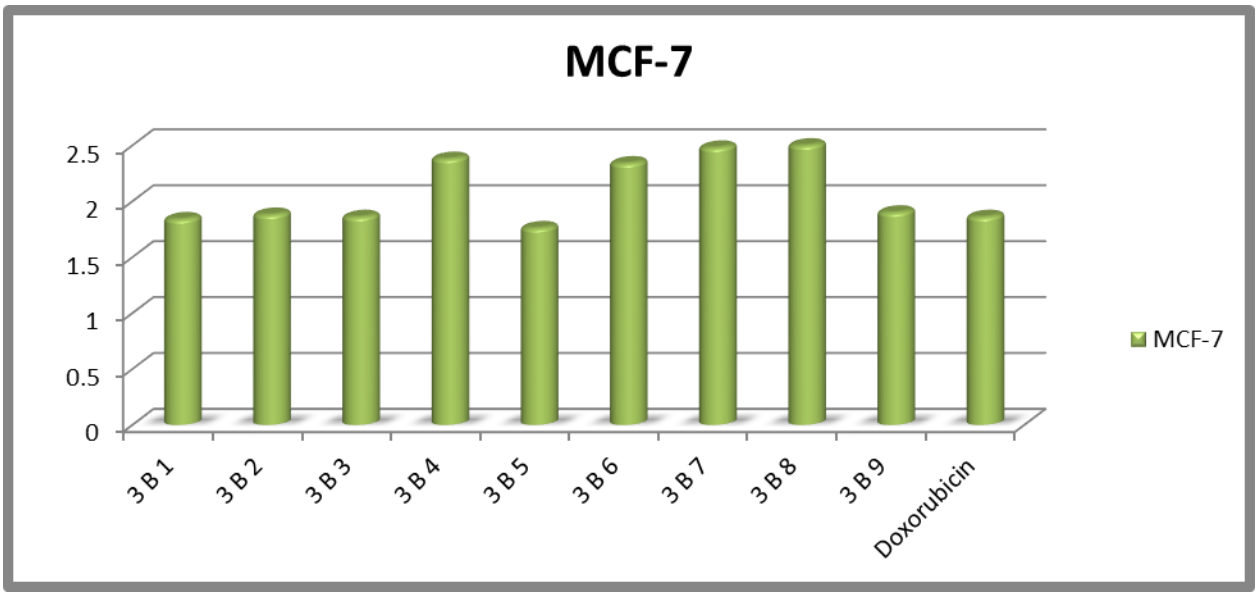
Table-01



IC50value of compounds (µg/ml)

Sample	MCF-7	
	Mean	SD
3 B 1	1.84	0.01
3 B 2	1.88	0.03
3 B 3	1.86	0.03
3 B 4	2.38	0.02
3 B 5	1.76	0.02
3 B 6	2.34	0.03
3 B 7	2.48	0.01
3 B 8	2.5	0.02
3 B 9	1.9	0.03
Doxorubicin	1.86	0.03

Table-02



IC50value of compounds (µg/ml)

The cytotoxic activities data are shown in Tables 3 also depicted in Graph 5-6

Results and discussion

Analytical results

A series of Dispiroimidazolidine-Pyrrolizine/pyrrolidine derivatives has been synthesized as per outlined synthetic Fig-2. IR, (^{1} H & ^{13}C) NMR and mass spectral data are in well coordinate with the proposed structures of all newly synthesized compounds. Here, In this synthetic research work, an effort has been made to synthesis of 8-bromoindolo [2,1-b]quinazoline-6,12-dione via Condensation reaction. The yield and Purity of compound 1 was Good without column chromatography and also mass spectrum gives molecular ion peak at m/z 327.87 for IR spectrum displayed stretching vibration at 1684 and 1618 cm-^{1} for Ketone and 3080 and 2975 aromatic functional groups, while ^{1} H NMR spectrum showed of aromatic ring at 8.529-8.501 (d, 1H), 8.403-8.429 (d, 1H), 8.034-8.011 (2H), 7.921- 7.782 (2H) 7.707-7.658 (1H),which proved the synthetic core nucleus.
Condensation of Hydantoin and Aliphatic/Aromatic aldehyde in presence of sodium acetate and acetic acid as solvent gave 5-substituted imidazolidine-2,4-dione (2, 1-9).

1,3 cyclo- addition reaction of compounds 1, different 5-substituted imidazolidine-2,4-dione and Proline/ Sarcocine generated the final Dispiroimidazolidine-Pyrrolizine/pyrrolidine derivatives (3 A, 1-9/ 3B ,1-9).

Biological results

The literature survey disclosed that insertion of electron withdrawing groups at positions 6 and 8 increased activities from of Tryptanthrin. Based on these opinions led to the instigation that a series of some distinctive novel moieties. From in vitro antibacterial activity data, it is confirmed that compounds containing strong electron withdrawing (Fluorine group and Nitro group) i.e. 3A-1,2 & 3B-1,2 exhibited excellent activity against all microbial strains, while compounds 3A-9 & 3B-9 exhibited comparable activity against all microbial strains. From in vitro antifungal activity data, it is found that compound 3A-1 and 2 & B-1 and 2 is displaying highest activity against all fungal strains. Overall, all the compounds have displayed significant antibacterial and antifungal activity.

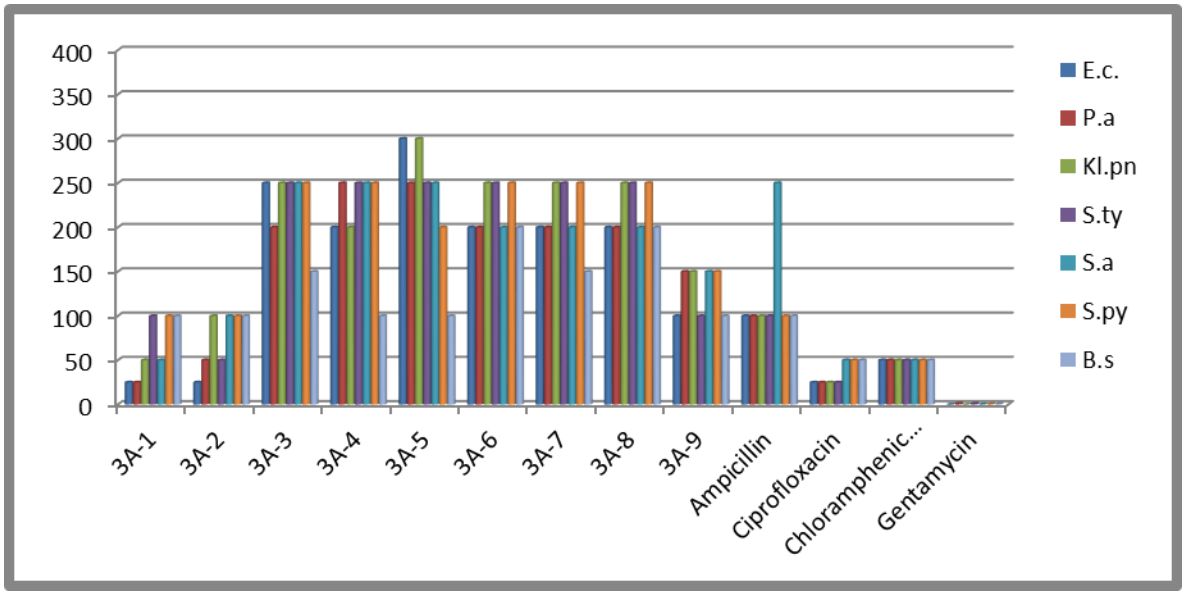
In general, the order of antibacterial activity of the substituents at the 1st position of pyrrolizine and pyrrolidine derivative is F > NO2>OH ~ Furyl> OMe >Isobutyl>Isopropyl>Ethyl and also due to presence of Bromo atom at position 8 in the compounds 3A, 1-9 and 3B 1,9 is responsible for good activity. The in vitro antibacterial and antifungal screening results are summarized in Tables 3, 4, 5 & 6 and also in graphs. The hopeful results from the antibacterial and antifungal studies encouraged us to go for preliminary screening of synthesized compounds against MCF-7 (Human Brest cancer, which is summarized in Table 1 & 2 and also in graphs. Compound 3A-1 & 2, 3 B-1 & 2 and 3 A-9 & B-9 containing 4-flouro and nitro substituent on Phenyl ring and furyl with Bromo atom on Indolo[2,1-b]quinazoline-6,12-dione nucleus showed better activity (1.82 µg/ml,1.94 µg/ml & 1.88 µg/ml) and compounds 3A-3,6,7,8 and B-3,6,7,8 showed good activity.

Anti-bacterial activities of compounds (Table-03)

Entry	R	E.c.	P.a	Kl.pn	S.ty	S.a	S.py	B.s
		MTCC 443	MTCC 1688	MTCC 109	MTCC 98	MTCC 96	MTCC 442	MTCC 441
3A-1	4-Flourophenyl	25	25	50	100	50	100	100
3A-2	4-Nitrophenyl	25	50	100	50	100	100	100
3A-3	4-Methoxyphenyl	250	200	250	250	250	250	150
3A-4	4-hydroxyphenyl	200	250	200	250	250	250	100
3A-5	3,4-dimethoxy phenyl	300	250	300	250	250	200	100
3A-6	Isopropyl	200	200	250	250	200	250	200
3A-7	Isobutyl	200	200	250	250	2000	250	150
3A-8	Ethyl	200	200	250	250	200	250	200
3A-9	Furyl	100	150	150	100	150	150	100
Ampicillin		100	100	100	100	250	100	100
Ciprofloxacin		25	25	25	25	50	50	50
Chloramphenicol		50	50	50	50	50	50	50

Gentamycin		0.05	1	0.05	1	0.25	0.5	0.5

E.c. = E. coli (MTCC-443); P.a.= P. aeruginosa (MTCC-1688); Kl.pn.= Kl. pneumoniae (MTCC-109); S.ty. =S. typhi (MTCC-98); S.a.= S. aureus (MTCC-96); S.py.= S. pyogenus (MTCC-442); B.s.= B. subtilis (MTCC-441).

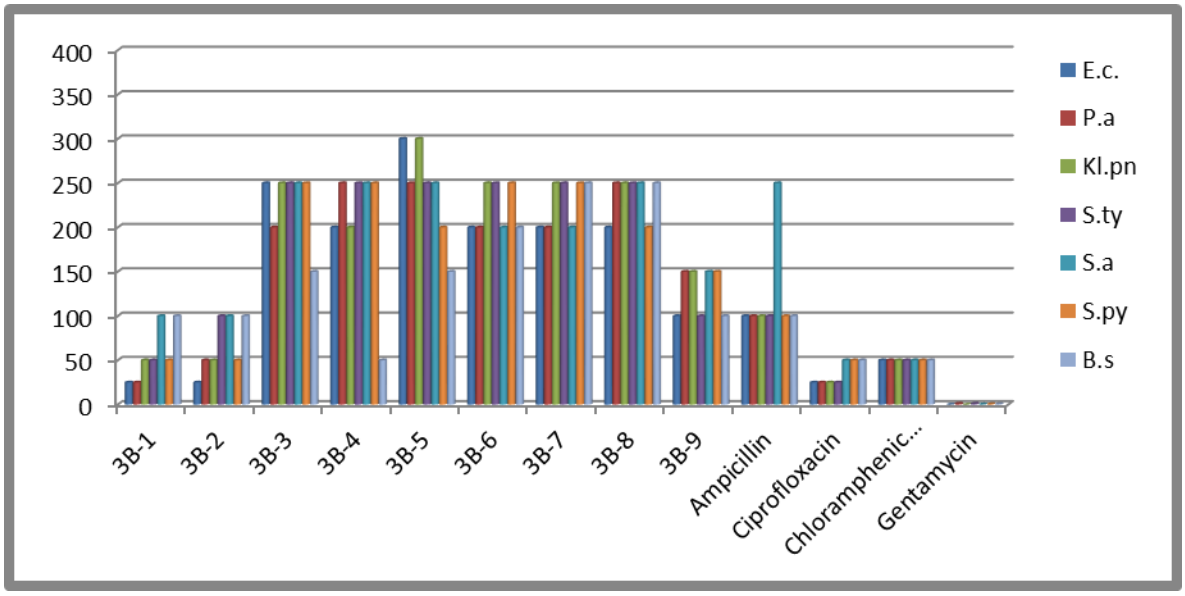


Anti-bacterial activities of compounds (Table-04)

Entry	R	E.c.	P.a	Kl.pn	S.ty	S.a	S.py	B.s
		MTCC 443	MTCC 1688	MTCC 109	MTCC 98	MTCC 96	MTCC 442	MTCC 441
3B-1	4-Flourophenyl	25	25	50	50	100	50	100
3B-2	4-Nitrophenyl	25	50	50	100	100	50	100
3B-3	4-Methoxyphenyl	250	200	250	250	250	250	150
3B-4	4-hydroxyphenyl	200	250	200	250	250	250	50
3B-5	3,4-dimethoxy phenyl	300	250	300	250	250	200	150
3B-6	Isopropyl	200	200	250	250	200	250	200
3B-7	Isobutyl	200	200	250	250	200	250	250
3B-8	Ethyl	200	250	250	250	250	200	250
3B-9	Furyl	100	150	150	100	150	150	100
Ampicillin		100	100	100	100	250	100	100
Ciprofloxacin		25	25	25	25	50	50	50
Chloramphenicol		50	50	50	50	50	50	50
Gentamycin		0.05	1	0.05	1	0.25	0.5	0.5

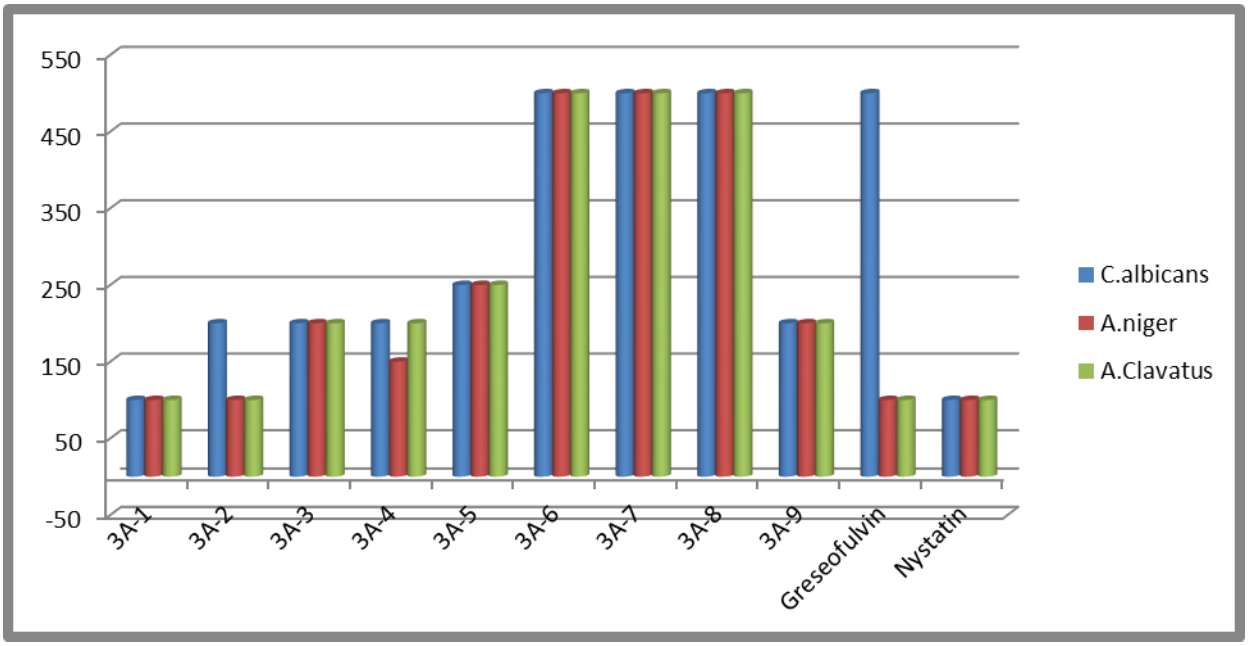
E.c. = E. coli (MTCC-443); P.a.= P. aeruginosa (MTCC-1688); Kl.pn.= Kl. pneumoniae

(MTCC-109); S.ty. =S. typhi (MTCC-98); S.a.= S. aureus (MTCC-96); S.py.= S. pyogenus (MTCC-442); B.s.= B. subtilis (MTCC-441).



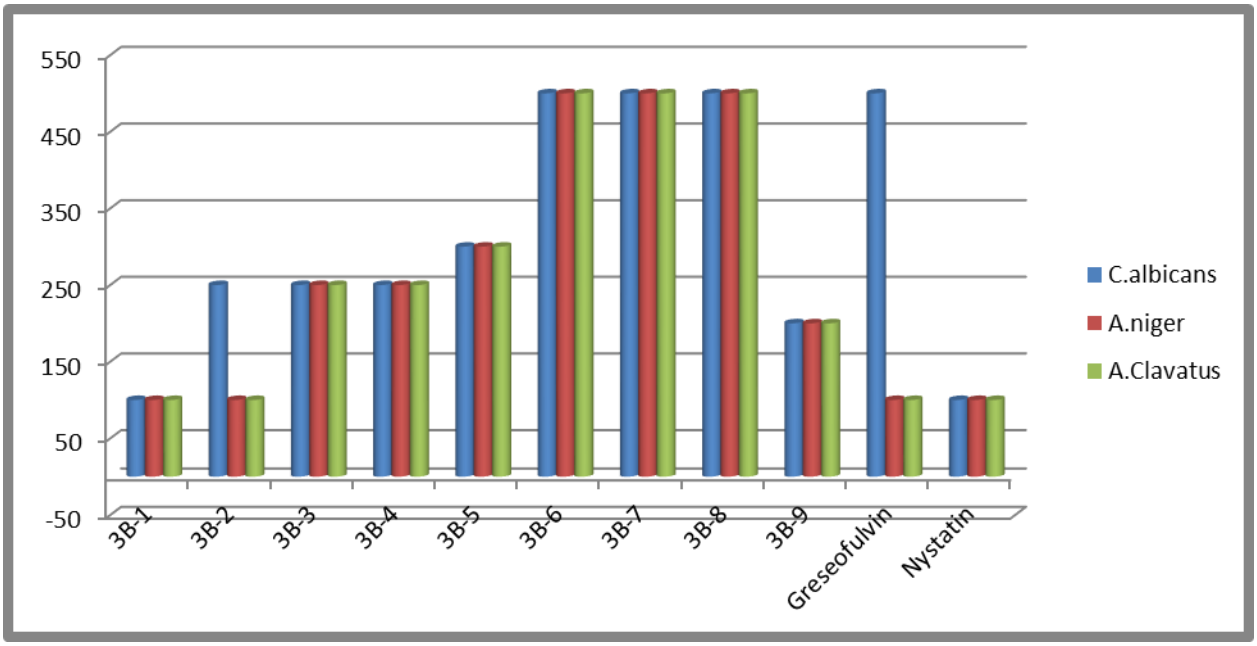
Anti-fungal Activities of compounds (Table-05)

Entry	R	C.albicans	A.niger	A.Clavatus
		MTCC 227	MTCC 282	MTCC 1323
3A-1	4-Flourophenyl	100	100	100
3A-2	4-Nitrophenyl	200	100	100
3A-3	4-Methoxyphenyl	200	200	200
3A-4	4-hydroxyphenyl	200	150	200
3A-5	3,4-dimethoxy phenyl	250	250	250
3A-6	Isopropyl	500	500	500
3A-7	Isobutyl	500	500	500
3A-8	Ethyl	500	500	500
3A-9	Furyl	200	200	200
Greseofulvin		500	100	100
Nystatin		100	100	100



Anti-fungal Activities (Table-06)

Entry	R	C.albicans	A.niger	A.Clavatus
		MTCC 227	MTCC 282	MTCC 1323
3B-1	4-Flourophenyl	100	100	100
3B-2	4-Nitrophenyl	250	100	100
3B-3	4-Methoxyphenyl	250	250	250
3B-4	4-hydroxyphenyl	250	250	250
3B-5	3,4-dimethoxy phenyl	300	300	300
3B-6	Isopropyl	500	500	500
3B-7	Isobutyl	500	500	500
3B-8	Ethyl	500	500	500
3B-9	Furyl	200	200	200
Greseofulvin		500	100	100
Nystatin		100	100	100



General procedure

Preparation of 8-bromoindolo[2,1-b]quinazoline-6,12-dione /8-bromo tryptanthrin 1.
5-Bromo Isatin(44.2 mmol), Isatoic anhydride(48.6mmol), Triethyl amine(221.2mmol) were mixed in Toluene (100 ml). The reaction mass was reflux for 4.0 hrs. Yellowish green solid formation was obtained during reaction maintaining at reflux temperature. The progress of reaction was monitored by TLC. After completion of reaction mass cooled it to ambient temperature and filtered the reaction mass under vacuum and washed the wet cake with ethyl acetate. Further the title product is purified using alcohol.

Spectral data of 1: Yellowish solid, yield 52%; m.p. 274-276^{0}C;
MS: m/z [327.87]+;
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1684, 1618(Aromatic Ketone)
^{1}H- NMR [400 MHz, d, ppm, CDCl3] 8.529-8.501 (d, 1H), 8.403-8.429 (d, 1H), 8.034-8.011 (2H), 7.921- 7.782 (2H) 7.707-7.658 (1H).
^{13}C-NMR[100MHz,d,ppm,DMSO-d6] 118.2 – 144.5 (C5,C6,C7,C8,C9,C10,C12,C13, C14,C15 ,C16,C17), 152.8-(C2),161.3-(C4),188.3- (C11)
Anal. Calcd. for $C_{15}H_7BrN_2O_2$ (327.14): C, 55.07; H, 2.16;N, 8.56,
Found: C, 55.02; H, 2.13;Br,24.44,N, 8.54, O,9.76

Preparation of different 5- substituted imidazolidine-2,4-dione (2-1-9)
Hydantoin(1.0 m.eq.), nine different aldehyde (1.05 m.eq.), Sodium acetate (1.1 m.eq.) were mixed in Acetic acid (20 times) and stirred the reaction mass at reflux temperature till reaction complies on TLC. After reaction complies, quench the reaction mass in ice + water and filtered the product and wash with water. The crude product is purified in ethanol and water solvent system.

Spectral data of (Z)-5-(4-fluorobenzylidene)imidazolidine-2,4-dione(2a):
yield 65%; mp > 260 ^{0}C;
MS: m/z [207.6]$^+$;
IR [nmax, cm_1, KBr]: 3322, 1735, 1659, 910
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 7.72 (d, 2H), 7.40 (d, 2H), 5.91 (s, 1H), 6.01 (s, NH), 12.3 (s, NH);
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 152.9 (C1), 162.4(C3),113.7-123.6 (C4,C8), 116.7-131.6(C9,C10,C11,C12,C13,C14)
Anal. Calcd. for $C_{10}H_7FN_2O_2$ (206.18): C, 58.26; H, 3.42;N, 13.59. Found: C,58.18; H ,3.12; N 13.35

Spectral data of (Z)-5-(4-nitrobenzylidene)imidazolidine-2,4-dione(2b):
yield 72%; mp > 260 ^{0}C;
MS: m/z [234.6]$^+$;
IR [nmax, cm_1, KBr]: 3320, 1739, 1653, 1588, 903
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 8.46 (d, 2H), 8.12 (d, 2H), 5.95 (s, 1H), 6.12 (s, NH), 12.35 (s, NH);
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 155.6 (C1), 166.7(C3),114.2-125.5 (C4,C8), 126.8-149.6(C9,C10,C11,C12,C13,C14)
Anal. Calcd. for $C_{10}H_7N_3O_4$ (233.18): C, 51.51; H, 3.03;N, 18.02. Found: C,51.32; H 2.93; N, 17.86

Spectral data of (Z)-5-(4-methoxybenzylidene)imidazolidine-2,4-dione(2c): ,
yield 65%; mp > 260 ^{0}C;
MS: m/z [219.5]$^+$;
IR [nmax, cm_1, KBr]: 3325, 1745, 1659, 1276, 905
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 8.27 (d, 2H), 7.18 (d, 2H), 5.98 (s, 1H), 6.15 (s, NH), 12.38 (s, NH); 3.86 (S, 3H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 153.8 (C1), 165.3(C3),113.9-123.8 (C4,C8), 115.8-161.9(C9,C10,C11,C12,C13,C14), 58.4 (C16).
Anal. Calcd. for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.55; H,4.62;N, 12.84. Found: C,60.28; H, 4.28; N, 12.49

Spectral data of (Z)-5-(4-hydroxybenzylidene)imidazolidine-2,4-dione(2d): ,
yield 63%; mp > 260 ^{0}C;
MS: m/z [205.8]$^+$;
IR [nmax, cm_1, KBr]: 3328, 3250, 1735, 1654, 920
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 7.54 (d, 2H), 6.84 (d, 2H), 6.06 (s, 1H), 6.22 (s, NH), 12.35 (s, NH); 9.74 (S, 1H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 153.3 (C1), 162.4(C3),114.2-123.8 (C4,C8), 117.2-158.5(C9,C10,C11,C12,C13,C14)
Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.19): C, 58.82; H,3.95;N, 13.72. Found:C, 58.68; H,3.78; N 13.59

Spectral data of (Z)-5-(3,4-dimethoxybenzylidene)imidazolidine-2,4-dione(2e): ,
yield 68%; mp > 260 ^{0}C;
MS: m/z [249.4]$^+$;
IR [nmax, cm_1, KBr]: 3329, 1752, 1663, 1272, 830
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 7.38 (S, 1H), 7.26 (S, 1H), 7.09 (S, 1H), 5.97 (s, 1H), 6.12 (s, NH), 12.37 (s, NH); 3.86 (S, 3H), 3.84 (S, 3H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 153.7 (C1), 165.1(C3),113.8-123.4 (C4,C8), 112.7-150.5(C9,C10,C11,C12,C13,C14), 58.7 (C16, C18).
Anal. Calcd. for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87;N, 11.29. Found:C, 57.86; H, 4.67; N, 10.97

Spectral data of (Z)-5-(2-methylpropylidene)imidazolidine-2,4-dione(2f): ,
yield 63%; mp > 260 ^{0}C;
MS: m/z [155.8]$^+$;
IR [nmax, cm_1, KBr]: 3339, 1766, 1669
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 5.98 (s, 1H), 6.14 (s, NH), 12.34 (s, NH); 2.42 (m, 1H), 1.23 (d, 6H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 152.8 (C1), 163.7(C3),113.9-124.6 (C4,C8), 20.8-27.6 (C9,C10,C11)
Anal. Calcd. for $C_7H_{10}N_2O_2$ (154.17): C, 54.54; H, 6.54;N, 18.17. Found: C, 54.28; H, 6.18; N, 17.95

Spectral data of (Z)-5-(3-methylbutylidene)imidazolidine-2,4-dione(2g): ,
yield 58%; mp > 260 ^{0}C;
MS: m/z [169.7]$^+$;
IR [nmax, cm_1, KBr]: 3343, 1768, 1662
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 6.04 (s, 1H), 6.12 (s, NH), 12.35 (s, NH); 1.92 (t, 2H), 1.82 (m, 1H), 1.05 (d, 6H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 153.7 (C1), 163.4(C3),114.2-131.8 (C4,C8), 22.5-35.4 (C9,C10,C11,C12)
Anal. Calcd. for $C_8H_{12}N_2O_2$ (168.20): C, 57.13; H,7.19;N, 16.66. Found: C,56.88 ; H, 6.89; N, 16.24

Spectral data of (Z)-5-propylideneimidazolidine-2,4-dione(2h): ,
yield 54%; mp > 260 ^{0}C;
MS: m/z [141.5]$^+$;
IR [nmax, cm_1, KBr]: 3340, 1763, 1665
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 6.02 (s, 1H), 6.09 (s, NH), 12.33 (s, NH); 2.12 (m, 2H), 1.07 (d, 3H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 153.9 (C1), 163.7(C3),113.9-132.4 (C4,C8), 12.6-15.8 (C9,C10)
Anal. Calcd. for $C_6H_8N_2O_2$ (140.14): C, 51.42; H, 5.75;N, 19.99. Found: C,51.09; H, 5.48 ; N, 19.78

Spectral data of (Z)-5-(furan-2-ylmethylene)imidazolidine-2,4-dione(2i): ,
yield 53%; mp > 260 ^{0}C;
MS: m/z [179.4]$^+$;
IR [nmax, cm_1, KBr]: 3347, 1768, 1668
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 6.94 (s, 1H), 6.12 (s, NH), 12.38 (s, NH); 7.56 (d, 1H), 6.94 (t, 1H), 8.23 (d, 1H)
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 152.8 (C1), 162.8(C3), 111.7-131.3 (C4, C8), 113.8-150.6 (C10,C11,C12,C13)
Anal. Calcd. for $C_8H_6N_2O_3$ (178.15): C, 53.94; H, 3.39;N, 15.73. Found: C,53.68; H, 3.05; N, 15.48

Preparation of 8''-bromo-1'-substituted-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3A and 8''-bromo-1'-methyl-4'-substitued-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione3 B

8-Bromotryptanthrin (1.0 m.eq.), 5- substituted imidazolidine-2,4-dione 2 (1.0 m.eq.) and Proline (3A) and Sarcosine (3B) (1.0 m.eq.) were mixed in dry methanol (30 times). The reaction mixture was refluxed till completion of reaction. The progress of reaction was monitored on TLC. After reaction completion, cooled the reaction mass to 0-5^{o}C & stirred for 2.0 hrs. The product is filtered and washed with chilled methanol. Dried the material under vacuum at 40-45^{o}C. The structures of compounds were identified with IR, (^{1}H and ^{13} C) NMR and Mass.

The compounds 3A – 1 to 9 and 3B – 1 to 9 were prepared in the same fashion using appropriate spiro-pyrrolizine and spiro-pyrrolidine derivative (Scheme 1).

8''-bromo-1'-(4-fluorophenyl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A -1)

Off white solid, Yield 65%, mp. > 250 ^{o}C; MS: m/z [587.2];
IR [nmax, cm_1, KBr]: 1601,1618,1709,3411
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.34-2.48 (t,2H), 1.62-1.74 (m,4H), 2.68(m,1H),3.72(d,1H), 7.12-8.23 (m, 11H, AreH), 10.84 (s,NH), 11.10 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 21.8 – 82.4 (C3,C7,C8,C9,C10,C11,C12), 158.6 (C13),165.3(C2),162.6(C16), 180.6(C4), 118.3-149.2 (C17,C18,C19,C20,C21,C22,C23,C24, C25,C26,C27,C28,C32,C33,C34,C35,C36,C37)
Anal. Calcd. for $C_{29}H_{21}BrFN_5O_3$ (586.42): C,59.40 ; H, 3.61; N, 11.94. Found: C, 59.09; H, 3.16; N, 11.69.

8''-bromo-1'-(4-nitrophenyl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-2)

Pale yellow solid, Yield 68%, mp.> 250 ^{0}C; MS: m/z [614.7];

IR [nmax, cm_1, KBr]: 1592,1615,1709,3412
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.34-2.46(t,2H), 1.68-1.75 (m,4H), 2.63(m,1H), 3.65 (d,1H), 7.45-8.56 (m, 11H, AreH), 10.82 (s,NH), 11.13 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.4 – 87.5 (C3,C7,C8,C9,C10,C11,C12), 154.3 (C13),168.4(C2),159.8(C16), 178.3(C4), 112.4-143.4(C17,C18,C19,C20,C21,C22,C23,C24, C25,C26,C27,C28,C32,C33,C34,C35,C36,C37)
Anal. Calcd. for $C_{29}H_{21}BrN_6O_5$ (613.43): C, 56.78; H, 3.45; N, 13.70. Found : C, 56.48; H, 3.13; N, 13.39.

8''-bromo-1'-(4-methoxyphenyl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-3)

White solid, Yield 72%, mp.>250 ^{0}C; MS: m/z [599.2];
IR [nmax, cm_1, KBr]: 1598,1615,1708,3409
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.31-2.43(t,2H), 1.63-1.74 (m,4H), 2.67(m,1H), 3.71 (d,1H), 3.84 (s,3H), 7.05-8.22 (m, 11H, AreH), 10.85 (s,NH), 11.15 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 19.8 – 84.9 (C3,C7,C8,C9,C10,C11,C12,C39), 157.5 (C13),167.9(C2),158.3(C16), 180.7(C4), 113.7-156.8(C17,C18,C19,C20,C21,C22,C23,C24, C25,C26,C27,C28,C32,C33,C34,C35,C36,C37)
Anal. Calcd. for $C_{30}H_{24}BrN_5O_4$ (598.46): C, 60.21; H, 4.04; N, 11.70. Found: C, 59.95; H, 3.89; N, 11.28.

8''-bromo-1'-(4-hydroxyphenyl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-4)

Off white solid, Yield 67%, mp.>250 ^{0}C; MS: m/z [585.3];
IR [nmax, cm_1, KBr]: 1592,1620,1704,3412,3450.
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.34-2.47(t,2H), 1.62-1.75 (m,4H), 2.64(m,1H), 3.73 (d,1H), 9.88 (s,1H), 6.72-8.15 (m, 11H, AreH), 10.82 (s,NH), 11.13 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.6 – 84.5 (C3,C7,C8,C9,C10,C11,C12), 155.6 (C13),168.4(C2),159.2(C16), 181.4(C4), 118.4-152.4(C17,C18,C19,C20,C21,C22,C23,C24, C25,C26,C27,C28,C32,C33,C34,C35,C36,C37)
Anal. Calcd. for $C_{29}H_{22}BrN_5O_4$, (584.43): C, 59.60; H, 3.79; N, 11.98. Found: C, 59.28; H, 3.34; N, 11.68.

8''-bromo-1'-(3,4-dimethoxyphenyl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-5)

White solid, Yield 73%, mp.>250 ^{0} C; MS: m/z [629.6];
IR [nmax, cm_1, KBr]: 1596,1618,1703,3406
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.32-2.44(t,2H), 1.62-1.73 (m,4H), 2.63(m,1H), 3.65 (d,1H), 3.82 (s,3H), 3.78 (s,3H), 7.08-8.19 (m, 11H, AreH), 10.87 (s,NH), 11.18 (s,NH).

^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.5 – 83.6 (C3,C7,C8,C9,C10,C11,C12,C39,C41), 155.9 (C13),167.6(C2),157.2(C16), 180.7(C4), 111.4-153.4(C17,C18,C19,C20,C21, C22, C23, C24, C25,C26,C27,C28,C32,C33,C34,C35,C36,C37)
Anal. Calcd. for $C_{31}H_{26}BrN_5O_5$, (628.48): C, 59.24; H, 4.17; N, 11.14. Found: C, 58.97; H, 3.89; N, 10.88.

8''-bromo-1'-isopropyl-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-6)

Off white solid, Yield 57%, mp.> 250 ^{0}C; MS: m/z [535.8];
IR [nmax, cm_1, KBr]: 1468, 1590,1618,1710,3412
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.36-2.48(t,2H), 1.65-1.79 (m,4H), 2.28(m,1H), 2.17 (d,1H), 1.45 (m,1H), 0.94 (d,6H), 7.62-8.21 (m, 7H, AreH), 10.82 (s,NH), 11.15 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 15.4 – 80.4 (C3,C7,C8,C9 ,C10,C11, C12,C32,C33 ,C34), 154.3 (C13),165.3(C2),158.8(C16), 181.3(C4), 116.3-143.7(C17,C18,C19,C20,C21, C22, C23, C24, C25,C26,C27,C28)
Anal. Calcd. for $C_{26}H_{24}BrN_5O_3$ (534.41): C,58.44; H, 4.53; N, 13.11. Found: C, 58.14; H, 4.26; N, 12.87.

8''-bromo-1'-isobutyl-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A -7)

Off white solid, Yield 55%, mp.>250 ^{0}C; MS: m/z [549.2];
IR [nmax, cm_1, KBr]: 1462, 1595,1614,1714,3419

^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.34-2.47(t,2H), 1.63-1.72 (m,4H), 2.18(m,1H), 2.26 (d,1H), 1.65 (m,1H),1.17(t,2H), 0.96 (d,6H), 7.56-8.28 (m, 7H, AreH), 10.85 (s,NH), 11.17 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 19.8 – 82.7 (C3,C7,C8,C9 ,C10,C11, C12,C32,C33 ,C34,C35), 153.8 (C13),165.8(C2),158.2(C16), 180.8(C4), 119.7-151.4(C17,C18,C19,C20,C21, C22, C23, C24, C25,C26,C27,C28)
Anal. Calcd. for $C_{27}H_{26}BrN_5O_3$ (548.44): C, 59.13; H, 4.78; N, 12.77. Found: C, 58.89; H, 4.36; N, 12.34.

8''-bromo-1'-ethyl-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3 A-8)

White solid, Yield 52%, mp.>250 ^{0}C; MS: m/z [521.8];
IR [nmax, cm_1, KBr]: 1466, 1597,1613,1718,3412
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.32-2.49(t,2H), 1.62-1.78 (m,4H), 2.12(m,1H), 2.36 (d,1H), 1.52 (m,2H), 1.04 (d,3H), 7.52-8.32 (m, 7H, AreH), 10.78 (s,NH), 11.21 (s,NH).

^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 10.3 – 80.4 (C3,C7,C8,C9 ,C10,C11, C12,C32,C33), 154.2 (C13),164.9(C2),159.6(C16), 181.2(C4), 117.3-152.1(C17,C18,C19,C20,C21, C22, C23, C24, C25,C26,C27,C28)
Anal. Calcd. for $C_{25}H_{22}BrN_5O_3$ (520.39): C, 57.70; H, 4.26; N, 13.46. Found: C, 57.37; H, 4.02; N, 13.18.

8''-bromo-1'-(furan-2-yl)-5',6',7',7a'-tetrahydro-1'H,12''H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione (3A-9)

Black solid, Yield 43%, mp.>250 ^{0}C; MS: m/z [525.8];
IR [nmax, cm_1, KBr]: 1592,1618,1713,3416
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.38-2.53(t,2H), 1.58-1.82 (m,4H), 2.74(m,1H), 4.08 (d,1H), 6.18-7.34 (m,3H), 7.52-8.34 (m, 7H, AreH), 10.72 (s,NH), 11.26 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 10.3 – 75.7 (C3,C7,C8,C9 ,C10,C11, C12), 153.7 (C13),165.1(C2),160.1(C16), 180.7(C4), 102.8-151.3(C17,C18,C19,C20,C21, C22, C23, C24, C25,C26,C27,C28,C33,C34,C35,C36)
Anal. Calcd. for $C_{27}H_{18}BrN_5O_2$ (524.38): C, 58.08; H, 3.61; N, 12.54. Found: C, 57.84; H, 3.27; N, 12.28.

8''-bromo-4'-(4-fluorophenyl)-1'-methyl-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3 B-1

Off white solid, Yield 62%, mp. > 250 ^{o}C; MS: m/z [561.7];
IR [nmax, cm_1, KBr]: 1605,1613,1704,3411
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.32 (s,3H),2.49-2.56 (d,2H),3.82(d,1H), 7.14-8.27 (m, 11H, AreH), 10.84 (s,NH), 11.14 (s,NH).

^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 33.9 – 88.2 (C3,C7,C8,C9,C29), 159.9 (C13), 165.9(C2), 157.9(C10), 181.2(C4), 114.8-153.1 (C14,C15,C16,C17,C18,C19,C20,C21,C22, C23 ,C24, C25,C30,C31,C32,C33,C34,C35)
Anal. Calcd. for $C_{27}H_{19}BrFN_5O_3$ (560.38): C, 57.87; H, 3.42; N, 12.50. Found: C, 57.43; H, 3.19; N, 12.19.

8''-bromo-1'-methyl-4'-(4-nitrophenyl)-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3B-2

Pale yellow solid, Yield 59%, mp.> 250 ^{0}C; MS: m/z [588.4];
IR [nmax, cm_1, KBr]: 1590,1612,1705,3408
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.36 (s,3H), 2.54-2.72 (d,2H),3.88(d,1H), 7.56-8.37 (m, 11H, AreH), 10.88 (s,NH), 11.15 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 35.9 – 84.5 (C3,C7,C8,C9,C38), 159.2 (C13), 164.6(C2), 155.7(C10), 180.4(C4), 115.3-152.9 (C14,C15,C16,C17,C18,C19,C20,C21,C22, C23 ,C24, C25,C29,C30,C31,C32,C33,C34)

Anal. Calcd. for $C_{27}H_{19}BrN_6O_5$ (587.39): C, 55.21; H, 3.26; N, 14.31. Found: C, 54.92; H, 2.93; N, 14.03.

8"-bromo-4'-(4-methoxyphenyl)-1'-methyl-12"H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione 3B-3

White solid, Yield 67%, mp.>250 ^{0}C; MS: m/z [573.6];
IR [nmax, cm_1, KBr]: 1593,1614,1706,3405
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28 (s,3H), 2.58-2.77 (d,2H), 3.83(d,1H), 3.72(s,3H), 6.98-8.17 (m, 11H, AreH), 10.79 (s,NH), 11.21 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 34.7 – 86.4 (C3,C7,C8,C9,C29,C37), 158.8(C13), 167.1(C2), 157.3(C10), 180.9(C4), 112.7-155.8 (C14,C15,C16,C17,C18,C19,C20,C21,C22, C23 ,C24, C25,C30,C31,C32,C33,C34,C35)
Anal. Calcd. for $C_{28}H_{22}BrN_5O_2$ (572.42): C, 58.75; H, 3.87; N, 12.23. Found: C, 58.36; H, 3.67; N, 11.89.

8"-bromo-4'-(4-hydroxyphenyl)-1'-methyl-12"H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione 3 B-4

Off white solid, Yield 62%, mp.>250 ^{0}C; MS: m/z [559.6];
IR [nmax, cm_1, KBr]: 1590,1618,1702,3408,3445.
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.29 (s,3H), 2.55-2.82 (d,2H), 3.82(d,1H), 6.54-8.21 (m, 11H, AreH), 8.96(s,1H), 10.77 (s,NH), 11.23 (s,NH).

^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 35.2 – 86.7 (C3,C7,C8,C9,C29), 158.9 (C13), 165.7(C2), 157.5(C10), 180.5(C4), 117.1-152.8 (C14,C15,C16,C17,C18,C19,C20,C21,C22, C23 ,C24, C25,C30,C31,C32,C33,C34,C35)
Anal. Calcd. for $C_{27}H_{20}BrN_5O_4$ (558.39): C,58.08; H, 3.61; N, 12.54. Found: C, 57.78; H, 3.22; N, 12.18.

8"-bromo-4'-(3,4-dimethoxyphenyl)-1'-methyl-12"H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione 3 B-5

White solid, Yield 65%, mp.>250 ^{0} C; MS: m/z [603.8];
IR [nmax, cm_1, KBr]: 1592,1614,1709,3406
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.23 (s,3H), 2.49-2.78 (d,2H), 3.75(d,1H), 3.82(s,3H), 3.94(s,3H), 7.12-8.18 (m, 10H, AreH), 10.77 (s,NH), 11.23 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 33.9 – 86.8 (C3,C7,C8,C9,C29,C37,C39), 159.1(C13), 167.7(C2), 156.1C10), 180.3(C4), 111.9-154.3 (C14,C15,C16,C17,C18,C19,C20,C21,C22, C23 ,C24, C25,C30,C31,C32,C33,C34,C35)
Anal. Calcd. for $C_{29}H_{24}BrN_5O_5$ (602.45): C, 57.82; H, 4.02; N, 11.63. Found: C, 57.38; H, 3.85; N, 11.38.

8''-bromo-4'-isopropyl-1'-methyl-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3 B-6

Off white solid, Yield 52%, mp.> 250 ^{0}C; MS: m/z [509.4];
IR [nmax, cm_1, KBr]: 1463, 1594,1613,1715,3416
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28 (s,3H), 2.17-2.48 (d,2H), 2.52(d,1H), 0.93(d,6H), 1.57 (m,1H), 7.58-8.21 (m, 7H, AreH), 10.83 (s,NH), 11.21 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 19.5 – 88.1 (C3,C7,C8,C9,C29,C30,C31,C32), 159.8 (C13), 165.6(C2), 155.4(C10), 181.4(C4), 114.9-154.2 (C14,C15,C16,C17,C18, C19, C20, C21, C22,C23 ,C24, C25)
Anal. Calcd. for $C_{24}H_{22}BrN_5O_3$ (508.38): C, 56.70; H, 4.36; N, 13.78. Found: C, 56.35; H, 3.83; N, 13.48.

8''-bromo-4'-isobutyl-1'-methyl-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3 B-7

Off white solid, Yield 48%, mp.>250 ^{0}C; MS: m/z [523.6];
IR [nmax, cm_1, KBr]: 1464, 1598,1613,1718,3459
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.21 (s,3H), 2.14-2.46 (d,2H), 2.49(m,1H), 0.96(d,6H), 1.21 (t,2H),1.68 (m,1H), 7.52-8.18 (m, 7H, AreH), 10.84 (s,NH), 11.19 (s,NH).

^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 22.8– 85.6 (C3,C7,C8,C9,C29,C30,C31,C32,C33), 158.9 (C13), 165.8(C2), 155.8(C10), 180.6(C4), 115.1-153.6 (C14,C15,C16,C17,C18, C19, C20, C21, C22,C23 ,C24, C25).
Anal. Calcd. for $C_{25}H_{24}BrN_5O_3$ (522.40): C, 57.48; H, 4.63; N, 13.41. Found: C, 57.08; H, 4.25; N, 13.12.

8''-bromo-4'-ethyl-1'-methyl-12''H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6''-indolo[2,1-b]quinazoline]-2,5,12''-trione 3B-8

White solid, Yield 45%, mp.>250 ^{0}C; MS: m/z [495.8];
IR [nmax, cm_1, KBr]: 1463, 1592,1618,1714,3418
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28 (s,3H), 2.12-2.56 (d,2H), 2.46(m,1H), 0.97(d,3H), 1.62 (m,2H), 7.57-8.21 (m, 7H, AreH), 10.82 (s,NH), 11.16 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 10.8– 84.7 (C3,C7,C8,C9,C29,C30,C31), 159.3 (C13), 165.4(C2), 154.8C10), 181.2(C4), 114.9-152.5 (C14,C15,C16,C17,C18, C19, C20, C21, C22,C23 ,C24, C25).
Anal. Calcd. for $C_{23}H_{20}BrN_5O_3$ (494.35): C, 55.88; H, 4.08; N, 14.17. Found: C, 55.38; H, 3.79; N, 13.91.

8"-bromo-4'-(furan-2-yl)-1'-methyl-12"H-dispiro[imidazolidine-4,3'-pyrrolidine-2',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione 3 B-9

Black solid, Yield 40%, mp.>250 ^{0}C; MS: m/z [533.6];
IR [nmax, cm_1, KBr]: 1595,1614,1718,3414
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.23 (s,3H), 2.49-2.76 (d,2H), 3.96(t,1H),6.25-8.26 (m, 10H, AreH), 10.86 (s,NH), 11.23 (s,NH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 34.7– 82.5 (C3,C7,C8,C9,C29), 158.8 (C13), 165.2(C2), 155.2C10), 180.3(C4), 104.2-152.2 (C14,C15,C16,C17,C18, C19, C20, C21, C22,C23 ,C24, C25,C31,C32,C33,C34).
Anal. Calcd. for $C_{25}H_{18}BrN_5O_4$ (532.35): C, 56.41; H, 3.41; N, 13.16. Found: C, 56.17; H, 3.13; N, 12.84.

Conclusion

8"-bromo-1'-substituted-5',6',7',7a'-tetrahydro-1'H,12"H-dispiro[imidazolidine-4,2'-pyrrolizine-3',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione and 8"-bromo-1'-methyl-4'-substitued-12"H-di spiro[imidazolidine-4,3'-pyrrolidine-2',6"-indolo[2,1-b]quinazoline]-2,5,12"-trione (3A 1-9 & 3B 1-9) were synthesized and characterized for their structure elucidation. Chemical and spectral data supported the structures of newly synthesized compounds. The Condensation reaction for preparation of 8-bromo tryptanthrin from Bromoisatin & Isatoic anhydride and azomethine ylides formation from Dispiroimidazolidine-Pyrrolizine and Dispiroimidazolidine-pyrrolidine and α- amino acids (Proline and Sarcosine) to afford Compounds (3 A1-9 and 3 B 1-9) which showed significant antibacterial and antifungal activity.The most potent cytotoxic compound against breast cancer cells (MCF-7) in our study was found to be **3A-1 & 3B-1** with IC50 value of 182 μg/ml.

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