Synthesis of Spiro-Pyrrolizine and Pyrrolidine derivative of Tryptanthrin and Evaluation of Their anti-bacterial, anti-fungal and anti-mycobacterial activities

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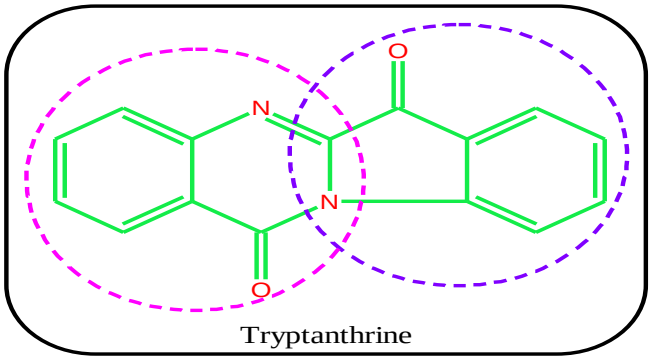
Abstract.

Multicomponent reaction of 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene) malononitrile and azomethine ylides formation from substituted aldehyde and α- amino acids (Proline and Sarcosine) to gives series of 8-bromo-12-oxo-3'-subtituted phenyl-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b] quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile and 8-bromo-1'-methyl-12-oxo-2'-subtituted phenyl-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine] -4',4'-dicarbonitrile in a quantitative yield. These compounds were screened for their anti-bacterial, anti- fungal and anti- mycobacterial activities. Best results were found in 8-bromo-3'-(4-fluorophenyl)-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b] quinazoline -6,2'-pyrrolizine]-1',1'-dicarbonitrile and 8-bromo-2'-(4-fluorophenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile with minimum inhibitory concentration (MIC) of 0.6 µg/ml against MTB.

Introduction

Multicomponent reaction is one pot transformation of three and more than three substrate with high atom economy and good yield. They are dynamic technique for synthesis of chiral complex and molecular hybrid skeleton. In recent years, for designing hybrid molecule with more than two pharmacophore in one molecular skeleton is unique emerging technique. (1)

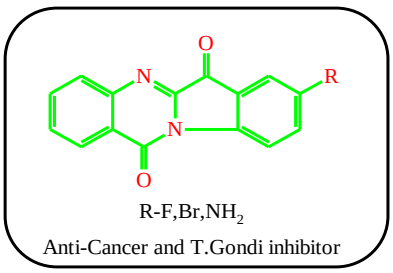
Tryptanthrin scaffold is one of the eye-catching classes of linear tetracyclic hetroaromatic compounds and containing indole and quinazoline core structure with carbonyl group at 6- and 12- position which shown in Fig -1.

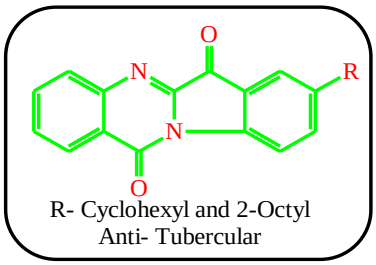


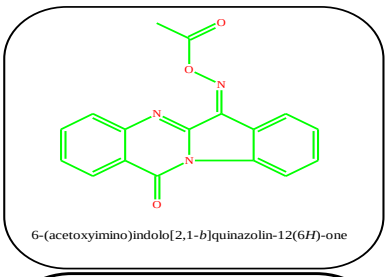
Tryptanthrine

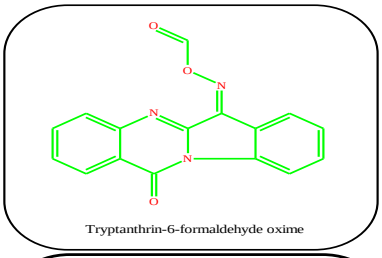
The quinazoline is ubiquitous in pharmaceutical (2-5), Natural product like lactones, alkaloids and terpenoids (6-8), dyes (9, 10), agrochemicals (11-13) and Material science like luminescent material (14,15) so Indolo[2,1-*b*]quinazoline-6,12-dione (Tryptanthrin) is important class of heterocycle containing promising pharmacophore. They have anti-inflammatory (16,17), Anti-fungal(18), Anti-microbial(19-22), anti-malarial (23-29), anti-viral(30), anti-cancer (31-42), anti-tubercular(43-46),Anti-trypanosomal (47), Anti-leishmanial activities(48),intestinal disorder (49), Photoelectric and surface activities (50-53).

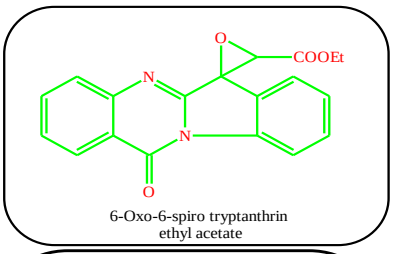
A large number of Indolo[2,1-*b*]quinazoline-6,12-dione derivatives are present in omniscience with different function groups are present at 6 & 8 position and also on indole & quinazoline core. It can be synthesized in lab and also naturally available which is shown in Fig-2

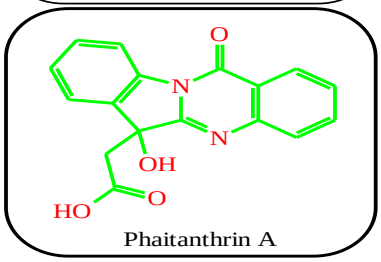


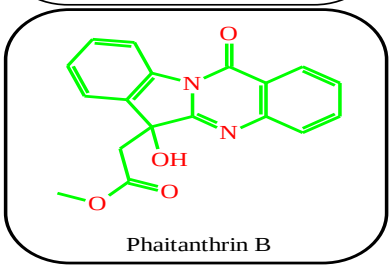


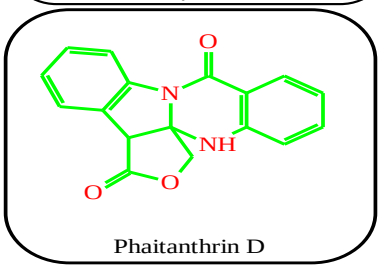


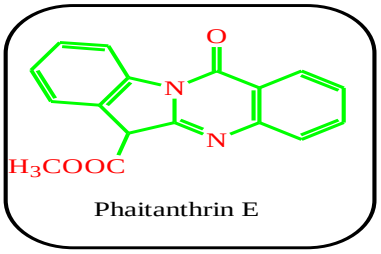








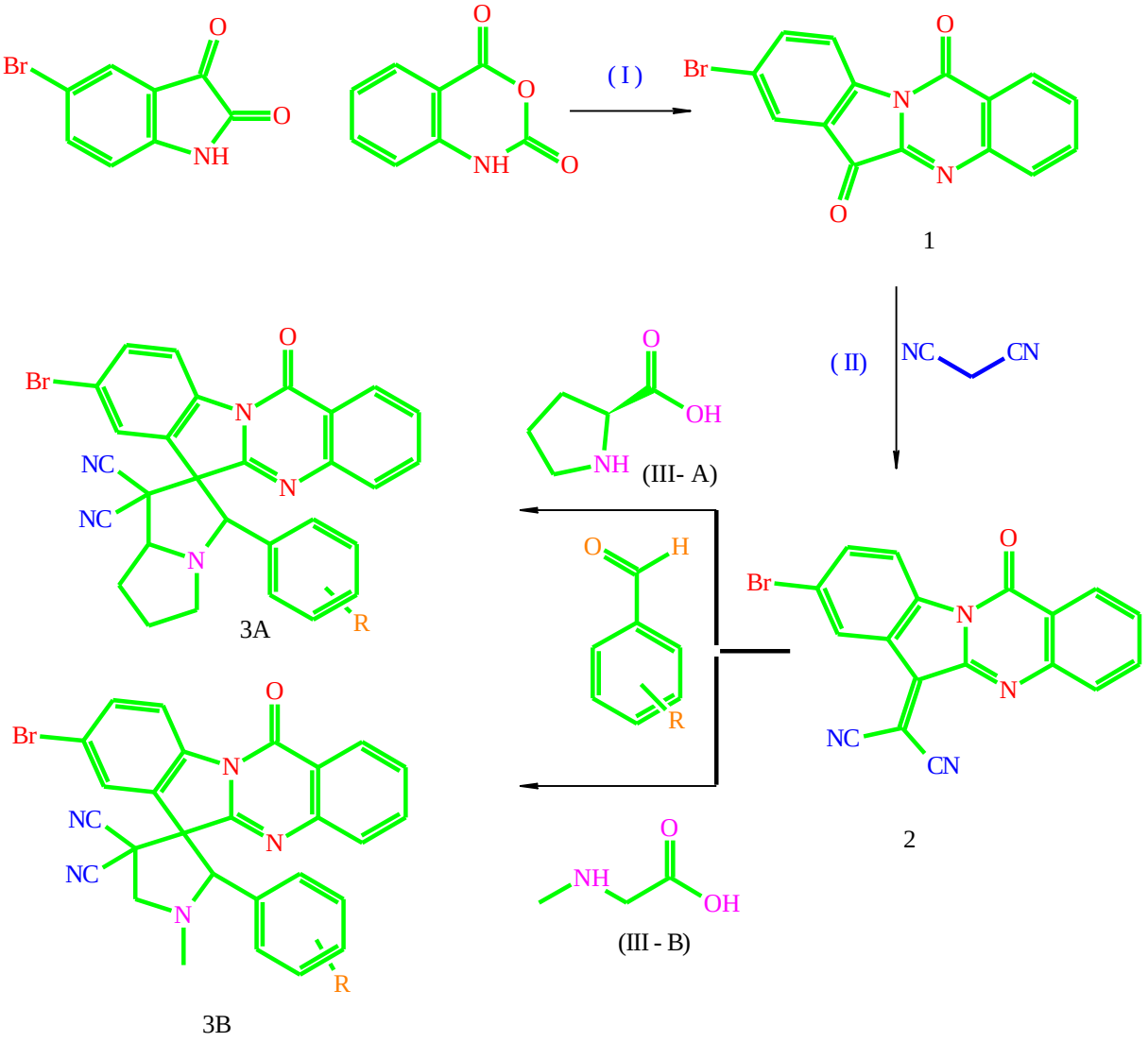




Furthermore some compound containing spiropyrrolizine and spiropyrrolidine nucleus (54-56) which can be a potential lead compound and have biological activities.
Based on the Biological activities of tryptanthrin and both spiropyrrolizine & spiropyrrolidine derivatives are incorporated in one nucleus and were synthesized.

However discovery of new lead compounds and pharmacological active sites which is an essential motif of medicinal chemist. It will produced multiple activities with one nucleus is most important motif of medicinal chemist.

An Essential motif of medicinal chemist is to discover new lead compound and pharmacological active sites which can cater multiple activities in one nucleus so designing new hybrid molecules through combinatorial and computational chemistry. In this context we were synthesized molecules and shown in Fig-3



Reaction conditions I) Toluene, Triethyl amine, Reflux, 4 hrs; II) DMSO, K2CO3 and Malononitrile ; III) Acetonitrile, Reflux temperature.

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

There are two most common methods for synthesis of tryptanthrin and it's derivatives. One is condensation in which Isatoic anhydride and isatin (50-51), anthranilamide and chloro

derivatives of Isatin(57), 2- amino benzaldehyde and o-methylisatin (58) and second one is Oxidation indigo(59-61) and isatin(62-63).

The reaction scheme of title compound 3a-9/b-9 is depicted in Scheme 1. In a typical experimental procedure, the mixture of 5-bromo Isatin, Isatoic anhydride and Triethyl amine in toluene under reflux condition to give 8-bromoindolo[2,1-b]quinazoline-6,12-dione/8-Bromo tryptanthrin 1, followed by reaction with malononitrile and potassium carbonate in DMSO as a solvent at ambient temperature to give 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene)malononitrile 2. In present study, the 1,3 cycloaddition reaction of an azomethine ylide formation from substituted aldehyde and alpha-amino acids(Proline & Sarcocine) with 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene)malononitrile 2. in Acetonitrile was stirred at reflux temperature to give 8-bromo-12-oxo-3'-subtituted phenyl and alkyl-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b] quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A 1-9 and 8-bromo-1'-methyl-12-oxo-2'-subtituted phenyl and alkyl-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B 1-9, respectively. The purity of compounds was checked by TLC. The structure of all the synthesized compounds was confirmed by IR, (^{1} H & ^{13}C) 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 antituberculosis activity

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan (65). 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 1 and 2 and also depicted in Graph 1-4 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 anti-mycobacterial activities of newly synthesized compounds were assessed against M. tuberculosis ATTC 2729415 using the micro plate Alamar Blue assay (MABA)(66). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile de-ionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.
The anti-mycobacterial screening data are shown in Tables 3 also depicted in Graph 5-6

Results and discussion

Analytical results

A series of pyrrolidine/pyrrozine derivatives has been synthesized as per outlined synthetic Fig-3. 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 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.
2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene)malononitrile (2) showed broad stretching bands around 1692 & 1620 cm1 for Ketone and 2245 for nitrile function group while ^{1} H NMR spectrum showed. δ= 7.71 (t, J= 6.1 Hz, 1H), 7.81-7.91 (m, 2H), 8.01 (d, J= 7.1 Hz, 1H), 8.44 (d, J= 8.8 Hz, 1H), 8.52 (d, J= 6.1 Hz, 1H), 8.58 (s, 1H) ppm; which proved the synthetic nucleus,

Multicomponent reaction of compounds 2, various substituted Aldehyde and Proline/ Sarcocine produces the final pyrrolidine/pyrrozine derivatives 3 a-9/ 3b-9.

Biological results

The literature survey revealed that introduction of electron withdrawing groups at positions 8 greatly increased activities from that of Tryptanthrin, along with substitution at the 6th position being most favorable. These observations led to the conception that a series of some different novel. 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

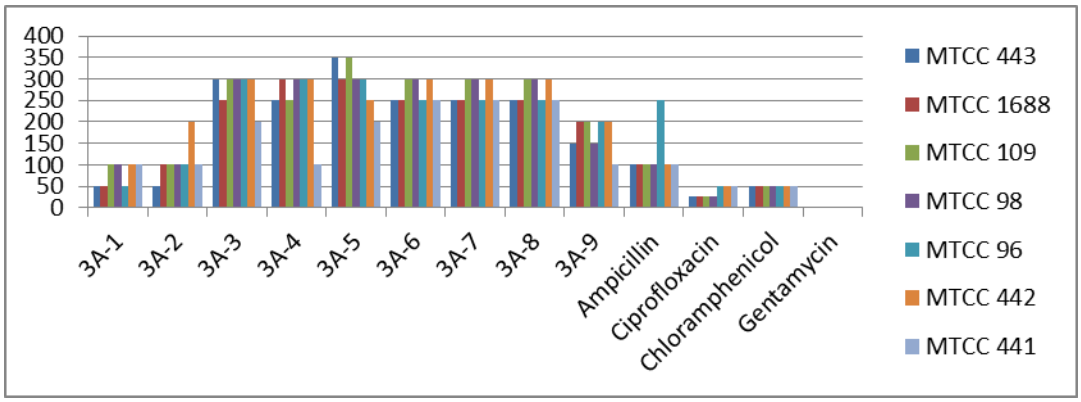
activity against all microbial strains, while compounds 3A-9 & 3B-9 exhibited comparable activity against all microbial strains. From in vitro antifungal activity data, it is found that compound 3A-1 and 2 & B-1 and 2 is displaying highest activity against all fungal strains. Overall, all the compounds have displayed significant antibacterial and antifungal activity.

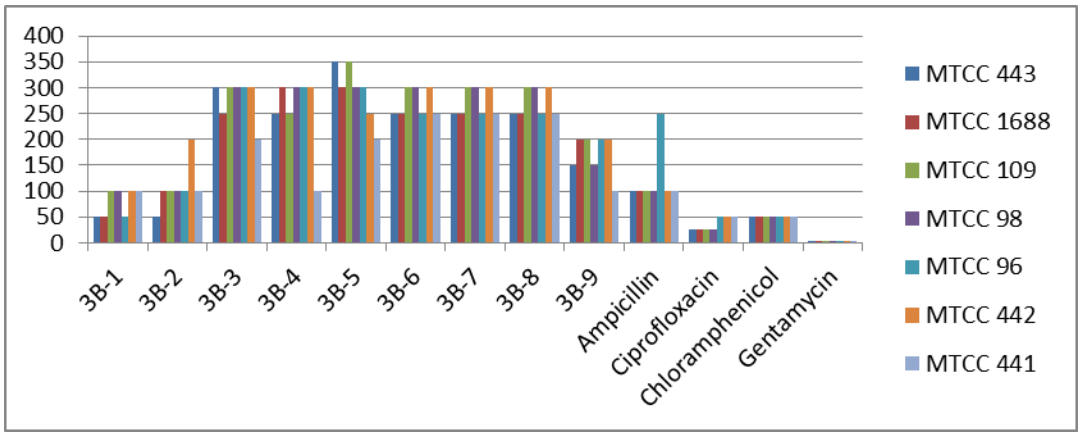
In general, the order of antibacterial activity of the substituents at the 3'th position of pyrrolizine and pyrrolidine derivative is F > NO2>OH ~ Furyl> OMe >Isobutyl>Isopropyl>Ethyl and also due to presence of Bromo atom at position 8 in the compounds 3A 1-9 is responsible for good activity. The in vitro antibacterial and antifungal screening results are summarized in Tables 1 and 2 and also in graph. The hopeful results from the antibacterial and antifungal studies encouraged us to go for preliminary screening of synthesized compounds against M. tuberculosis H37Rv, which is summarized in Table 3 and also in graph. Compound 3A-1 & 2, 3 A-9 & B-9 containing 5-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 (0.6 µg/ml) and compounds 3A-2,6,7,8 and B-2,6,7,8 showed good activity (1.6 µg/ml).

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	50	50	100	100	50	100	100
3A-2	4-Nitrophenyl	50	100	100	100	100	200	100
3A-3	4-Methoxyphenyl	300	250	300	300	300	300	200
3A-4	4-hydroxyphenyl	250	300	250	300	300	300	100
3A-5	3,4-dimethoxy phenyl	350	300	350	300	300	250	200
3A-6	Isopropyl	250	250	300	300	250	300	250
3A-7	Isobutyl	250	250	300	300	250	300	250
3A-8	Ethyl	250	250	300	300	250	300	250
3A-9	Furyl	150	200	200	150	200	200	100
3B-1	4-Flourophenyl	50	50	100	100	50	100	100
3B-2	4-Nitrophenyl	50	100	100	100	100	200	100
3B-3	4-Methoxyphenyl	300	250	300	300	300	300	200
3B-4	4-hydroxyphenyl	250	300	250	300	300	300	100
3B-5	3,4-dimethoxy phenyl	350	300	350	300	300	250	200
3B-6	Isopropyl	250	250	300	300	250	300	250
3B-7	Isobutyl	250	250	300	300	250	300	250
3B-8	Ethyl	250	250	300	300	250	300	250
3B-9	Furyl	150	200	200	150	200	200	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
Gentamy		0.05	1	0.05	1	0.25	0.5	0.5

cin								

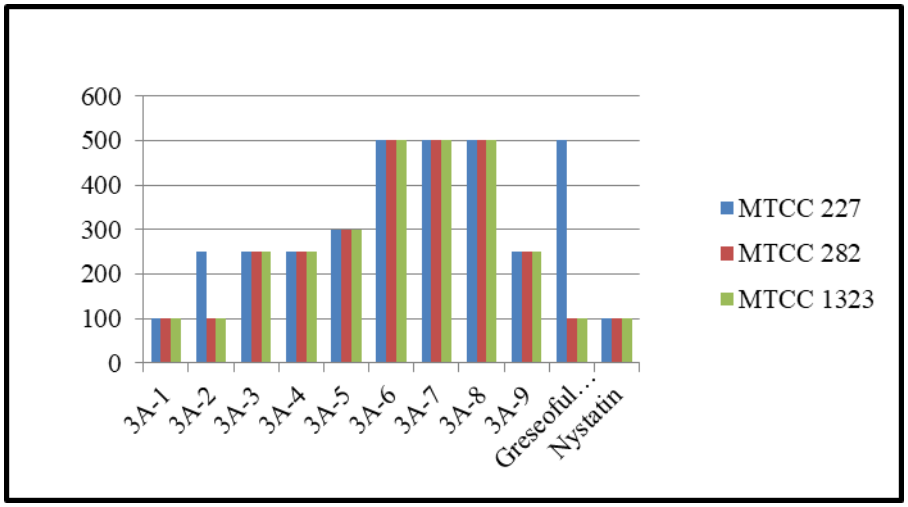
E.c. = E. coli (MTCC-443); P.a.= P. aeruginosa (MTCC-1688); Kl.pn.= Kl. pneumoniae (MTCC-109); S.ty. =S. typhi (MTCC-98); S.a.= S. aureus (MTCC-96); S.py.= S. pyogenus (MTCC-442); B.s.= B. subtilis (MTCC-441).

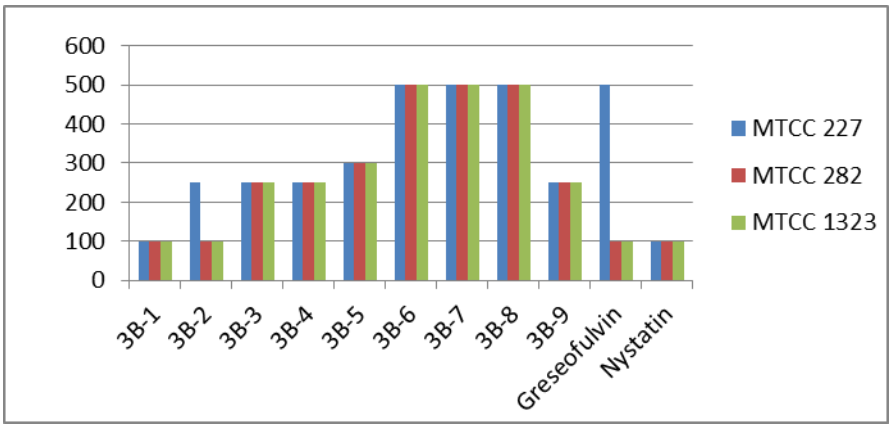




Entry	R	C.albicans	A.niger	A.Clavatus
		MTCC 227	MTCC 282	MTCC 1323
3A-1	4-Flourophenyl	100	100	100
3A-2	4-Nitrophenyl	250	100	100
3A-3	4-Methoxyphenyl	250	250	250
3A-4	4-hydroxyphenyl	250	250	250
3A-5	3,4-dimethoxy phenyl	300	300	300
3A-6	Isopropyl	500	500	500
3A-7	Isobutyl	500	500	500
3A-8	Ethyl	500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

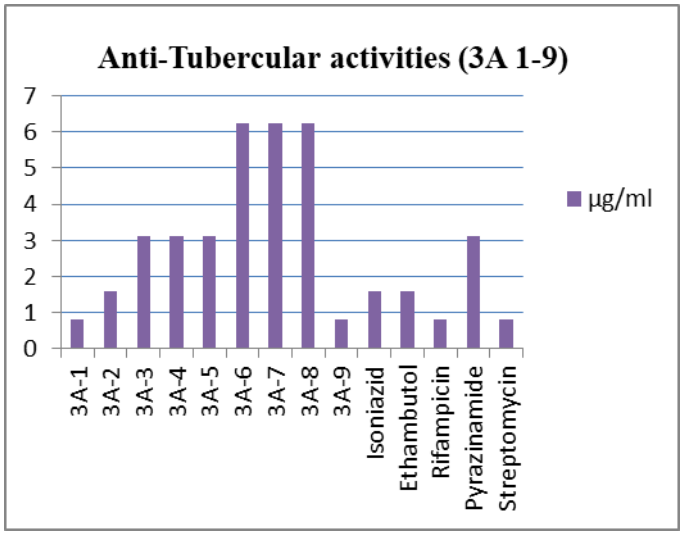
3B-6	Isopropyl	500	500	500
3B-7	Isobutyl	500	500	500
3B-8	Ethyl	500	500	500
3B-9	Furyl	250	250	250
Greseofulvin		500	100	100
Nystatin		100	100	100

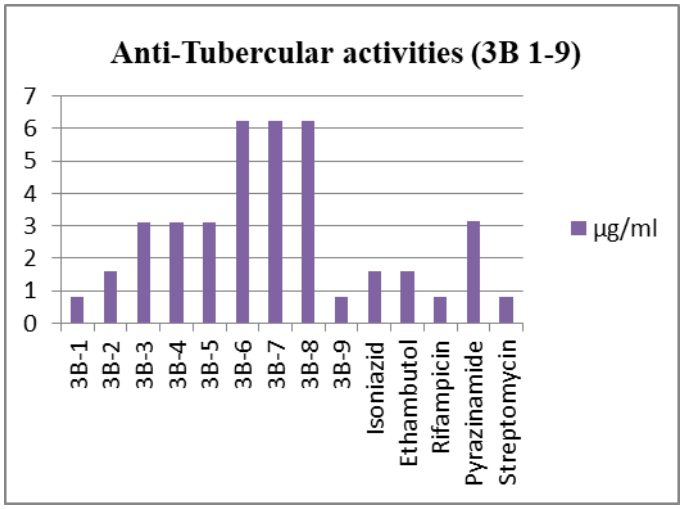




Entry	R	M.tuberculosis H37 RV ATCC N0-27294
		MTCC 200
3A-1	4-Flourophenyl	0.8 µg/ml
3A-2	4-Nitrophenyl	1.6 µg/ml
3A-3	4-Methoxyphenyl	3.12 µg/ml
3A-4	4-hydroxyphenyl	3.12 µg/ml
3A-5	3,4-dimethoxy phenyl	3.12 µg/ml

3A-6	Isopropyl	6.25 µg/ml
3A-7	Isobutyl	6.25 µg/ml
3A-8	Ethyl	6.25 µg/ml
3A-9	Furyl	0.8 µg/ml
3B-1	4-Flourophenyl	0.8 µg/ml
3B-2	4-Nitrophenyl	1.6 µg/ml
3B-3	4-Methoxyphenyl	3.12 µg/ml
3B-4	4-hydroxyphenyl	3.12 µg/ml
3B-5	3,4-dimethoxy phenyl	3.12 µg/ml
3B-6	Isopropyl	6.25 µg/ml
3B-7	Isobutyl	6.25 µg/ml
3B-8	Ethyl	6.25 µg/ml
3B-9	Furyl	0.8 µg/ml
Isoniazid		1.6 µg/ml
Ethambutol		1.6 µg/ml
Rifampicin		0.8 µg/ml
Pyrazinamide		3.125 µg/ml
Streptomycin		0.8 µg/ml





General procedure

Preparation of 8-bromoindolo[2,1-b]quinazoline-6,12-dione /8-bromo tryptanthrin 1.(67).

Title compounds was prepared using reported procedure. 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 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene)malononitrile 2 (68)

The title compound 2 is prepared as reported procedure with minor modification. Compound 1(15.2 mmol), Malanonitrile (22.9 mmol), powder potassium carbonate (30.5 mmol) were mix in DMSO (50 ml) and stirred the reaction mass at ambient temperature till reaction complies on TLC. After reaction complies, quench the reaction mass in ice+ water and extracted the product in ethyl acetate. Washed the organic layer with brine solution and concentrated the mass under vacuum gave red color compound which was further column purified to get title product.

Spectral data of 2: Red solid, yield 45%; mp > 260 ^{0}C;
MS: m/z [390.92]$^+$;
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group)
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6] δ= 7.71 (t, J= 6.1 Hz, 1H), 7.81-7.91 (m, 2H), 8.01 (d, J= 7.1 Hz, 1H), 8.44 (d, J= 8.8 Hz, 1H), 8.52 (d, J= 6.1 Hz, 1H), 8.58 (s, 1H) ppm;
^{13}C-NMR [100 MHz, d, ppm, DMSO-d6]: 71.5(C2), 116.3(C1,C3), 117.9 – 142.7 (C10,C11,C12,C12,C13,C14,C15,C17,C18,C19,C20,C21,C22),153.1(C7),161.5(C9),166.2 (C16),
Anal. Calcd. for C19H10BrN4O (390.22): C, 58.48; H, 2.58;N, 14.36. Found: 57.72 H 1.77 N 14.93

Preparation of 8-bromo-12-oxo-3'-subtituted phenyl-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b] quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A and 8-bromo-1'-methyl-12-oxo-2'-subtituted phenyl-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B

Compound 2 (1.0 mol), substituted aromatic aldehyde (1.05 mol) and Proline (3A,1.10 mol) or Sarcosine (3B, 1.10 ml) were mixed in Acetonitrile (20 ml). The reaction mixture was refluxed till completion of reaction. The progress of reaction was monitored on TLC. After reaction completion, the solvent was removed under reduced pressure and resulting solid was isolated with water then purified using flash column chromatography.

The compounds 3A – 1 to 9 and 3B – 1 to 9 were prepared as per General method for the preparation of different substituted spiropyrrolidine and spiropyrrolidine derivative (Scheme 1).

Preparation of 8-bromo-3'-(4-fluorophenyl)-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b]quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A -1

Red solid solid, Yield 38%, mp > 260 ^{0}C;
MS: m/z [553.12];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group)
^{1}H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.25-2.42(2H, T), 1.73 (2H, m), 1.87(2H, t), 2.45(1H,t),4.2(1H,s), 7.26-8.52 (11H, m, ArH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.9 -62.4 (C11,C19,C20,C21,C22,C23, C24),112.7 (C25,C27), 117.2- 147.8 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16, C17,C30,C31, C32,C33,C34,C35), 161.3 (C4),167.2 (C2)
Anal. Calcd. for $C_{29}H_{19}BrFN_5O$ (552.41): C, 63.05; H, 3.47; N, 12.68.
Found: C, 62.85; H, 3.22; N, 12.39%.

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

Red solid solid, Yield 42%, mp > 260 ^{0}C;

MS: m/z [580.23];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group), 1520,1340 (Aromatic NO_2)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.25-2.42(2H, T), 1.73 (2H, m), 1.87(2H, t),2.45(1H,t),4.2(1H,s), 7.26-8.39 (11H, m, AreH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 21.9-61.9 (C11,C19,C20,C21,C22,C23, C24),111.7 (C25,C27), 118.9- 148.2 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16, C17,C30,C31, C32,C33,C34,C35), 161.8 (C4),167.8(C2)
Anal. Calcd. for $C_{29}H_{19}BrN_6O_3$ (579.41): C, 60.12; H, 3.31; N, 14.50. Found:
C, 60.03; H, 3.22; N, 14.39%.

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

Red solid solid, Yield 45%, mp > 260 ^{0}C;
MS: m/z [565.84];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group),1240 (-C-O – Stretching, aromatic ether) 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.25-2.42(2H, T), 1.73 (2H, m), 1.87(2H, t),2.45(1H,t)3.92(3H,S),4.12(1H,s), 6.90-8.13 (11H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.7-62.5 (C11,C19,C20,C21,C22,C23, C24,C37),111.6 (C25,C27), 118.2- 146.6 (C5,C6,C7,C8,C9,C10,C12, C13,C14,C15, C16, C17,C30,C31,C32,C33,C34,C35), 161.2 (C4),166.4(C2)
Anal. Calcd. for $C_{30}H_{22}BrN_5O_2$ (564.44): C, 63.84; H, 3.93; N, 12.41. Found:
C, 63.59; H, 3.64; N, 12.13%.

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

Red solid solid, Yield 42%, mp > 260 ^{0}C;
MS: m/z [551.27];
IR [nmax, cm_1, KBr]: 3300,1380(-OH group),3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.25-2.42(2H, T), 1.73 (2H, m), 1.87(2H, t),2.45(1H,t),8.85(1H,OH),,4.12(1H,s), 6.82-8.13 (11H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 21.4-62.5 (C11,C19,C20,C21,C22,C23, C24),111.5 (C25,C27), 118.9- 156.8 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16, C17,C30,C31, C32,C33,C34,C35), 161.2 (C4),167.2(C2)
Anal. Calcd. for $C_{29}H_{20}BrN_5O_2$, (550.42): C, 63.28; H, 3.66; N, 12.72. Found:
C, 63.12; H, 3.37; N, 12.17%.

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

Red solid solid, Yield 41%, mp > 260 ^{0}C;
MS: m/z [595.43];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group),1240 (-C-O – Stretching, aromatic ether) 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.25-2.42(2H, T), 1.73 (2H, m), 1.87(2H, t),2.45(1H,t)3.92(3H,S),3.82(3H,S),4.12(1H,s), 6.89-8.13 (10H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.5-62.3 (C11,C19,C20,C21,C22,C23, C24,C37,C39),111.3 (C25,C27), 117.9- 147.9(C5,C6,C7,C8,C9,C10,C12,C13,C14, C15, C16, C17,C30,C31,C32,C33,C34,C35), 161.6 (C4),166.7(C2)
Anal. Calcd. for $C_{31}H_{24}BrN_5O_3$, (594.47): C, 62.63; H, 4.07; N, 11.78. Found:
C, 62.39; H, 3.79; N, 11.53%.

8-bromo-3'-isopropyl-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b]quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A-6

Red solid solid, Yield 44%, mp > 260 ^{0}C;
MS: m/z [501.76];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.35-2.54(2H, T), 1.68 (2H, m), 1.52(2H, t),2.26(1H,t),0.9(6H, d),1.48(1H,m),3.15(1H,s), 7.58-8.13 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 19.6.5-63.9 (C11,C19,C20,C21,C22,C23, C24,C30,C31,C32),111.8 (C25,C27), 118.6- 147.4(C5,C6,C7,C8,C9,C10,C12,C13,C14, C15, C16, C17,), 161.2 (C4),166.7(C2)
Anal. Calcd. for $C_{26}H_{22}BrN_5O$ (500.40): C, 62.41; H, 4.43; N, 14.00. Found:
C, 62.03; H, 4.12; N, 13.86%.

8-bromo-3'-isobutyl-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b]quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A -7

Red solid solid, Yield 43%, mp > 260 ^{0}C;
MS: m/z [515.63];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.35-2.54(2H, T), 1.68 (2H, m), 1.52(2H, t),2.26(1H,t),1.08(6H, d),1.58(1H,m),1.64(2H,m)3.15(1H,s), 7.58-8.13 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.5-62.8 (C11,C19,C20,C21,C22,C23, C24,C30,C31,C32,C33),111.8 (C25,C27), 117.9- 146.8(C5,C6,C7,C8,C9,C10,C12, C13,C14, C15, C16, C17,), 160.8 (C4),166.8(C2)
Anal. Calcd. for $C_{27}H_{24}BrN_5O$ (514.43): C, 63.04; H, 4.70; N, 13.61. Found:
C, 62.87; H, 4.38; N, 13.24%.

8-bromo-3'-ethyl-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b]quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3 A-8

Red solid solid, Yield 41%, mp > 260 ^{0}C;
MS: m/z [487.45];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.35-2.54(2H, T), 1.68 (2H, m), 1.52(2H, t),2.26(1H,t),0.91(3H, t),1.42(2H,m), 3.15(1H,s), 7.58-8.13 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 10.9-62.8 (C11,C19,C20,C21,C22,C23, C24,C30,C31),112.4 (C25,C27), 118.9- 147.3(C5,C6,C7,C8,C9,C10,C12,C13,C14, C15, C16, C17,), 160.6 (C4),166.4(C2)
Anal. Calcd. for $C_{25}H_{20}BrN_5O$ (486.37): C, 61.74; H, 4.41; N, 14.40. Found:
C, 61.56; H, 4.28; N, 14.13%.

8-bromo-3'-(furan-2-yl)-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b]quinazoline-6,2'-pyrrolizine]-1',1'-dicarbonitrile 3A-9

Red solid solid, Yield 35%, mp > 260 ^{0}C;
MS: m/z [525.68];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),1280 (-0- Ether streaching)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.35-2.54(2H, T), 1.68 (2H, m), 1.52(2H, t),2.26(1H,t), 4.14(1H,s), 6.87-8.28 (10H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 21.8-61.4 (C11,C19,C20,C21,C22,C23, C24),111.8 (C25,C27), 107.9- 147.3(C5,C6,C7,C8,C9,C10,C12,C13,C14, C15, C16, C17,C31,C32,C33,C34), 160.7 (C4),165.8(C2)
Anal. Calcd. for $C_{27}H_{18}BrN_5O_2$ (524.38): C, 61.84; H, 3.46; N, 13.36. Found:
C, 61.64; H, 3.18; N, 12.94%.

8-bromo-2'-(4-fluorophenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-1

Red solid solid, Yield 43%, mp > 260 ^{0}C;
MS: m/z [527.83];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone),
2245(Nitrile group), 760-895 (-CH2 group).
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.37(3H,s),3.12-2.96(2H,m), 4.2(1H,s), 7.26-8.52 (11H, m, AreH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 22.6 -65.7 (C11,C19,C20,C21,C27),112.4 (C22,C24), 114.8-161.3 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16,C17,C28,C29, C30,C31,C32,C33), 161.2 (C4),167.4 (C2)
Anal. Calcd. for $C_{27}H_{17}BrFN_5O$ (526.37): C, 61.61; H, 3.26; N, 13.31. Found:
C, 58.03; H, 3.22; N, 18.90%.

8-bromo-2'-(4-nitrophenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3B-2

Red solid solid, Yield 42%, mp > 260 ^{0}C;
MS: m/z [554.84];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group), 1520,1340 (Aromatic NO_2)

1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.32(3H,s), 3.09-2.83 (2H, m), , 4.14(1H,s), 7.26-8.39 (11H, m, AreH).
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 23.1 -66.7 (C11,C19,C20,C21,C27),111.8 (C22,C24), 116.2-147.3 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16,C17,C28,C29, C30,C31,C32,C33), 160.8 (C4),166.8 (C2)
Anal. Calcd. for $C_{27}H_{17}BrN_6O_3$ (553.38): C, 58.60; H, 3.10; N, 15.19. Found:
C, 58.38; H, 2.87; N, 14.93%.

8-bromo-2'-(4-methoxyphenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3B-3

Red solid solid, Yield 45%, mp > 260 ^{0}C;
MS: m/z [539.58];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group),1240 (-C-O – Stretching, aromatic ether) 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28(3H,s),3.06-2.86 (2H, m), 3.92(3H,S),4.12(1H,s), 6.90-8.13 (11H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 23.8 -67.1 (C11,C19,C20,C21,C27,C35),111.6 (C22,C24), 114.5-158.1 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16,C17,C28,C29, C30,C31,C32,C33), 161.2 (C4),166.4 (C2)
Anal. Calcd. for $C_{28}H_{20}BrN_5O_2$ (538.41): C, 62.46; H, 3.74; N, 13.01. Found:
C, 62.26; H, 3.67; N, 12.79%.

8-bromo-2'-(4-hydroxyphenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-4

Red solid solid, Yield 42%, mp > 260 ^{0}C;
MS: m/z [525.73];
IR [nmax, cm_1, KBr]: 3300,1380(-OH group),3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.26(3H,s),3.12-2.89 (2H, m), 8.79(1H,OH),,4.18(1H,s), 6.79-8.18 (11H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 21.9 -66.9 (C11,C19,C20,C21,C27),111.8 (C22,C24), 115.3-157.7 (C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16,C17,C28,C29, C30,C31,C32,C33), 160.2 (C4),166.5 (C2)
Anal. Calcd. for $C_{27}H_{18}BrN_5O_2$ (524.38): C, 61.84; H, 3.46; N, 13.36. Found:
C, 61.63; H, 3.12; N, 12.96%.

8-bromo-2'-(3,4-dimethoxyphenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-5

Red solid solid, Yield 41%, mp > 260 ^{0}C;
MS: m/z [569.33];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 1692, 1620(Aromatic Ketone), 2245(Nitrile group),1240 (-C-O – Stretching, aromatic ether) 760-895 (-CH2 group)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28(3H,s),3.15-2.91 (2H, m),3.96(3H,S),3.79(3H,S),4.18(1H,s), 6.84-8.13 (10H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 22.6 -66.5 (C11,C19,C20,C21,C27, C35,C37),111.6(C22,C24),111.8-149.2(C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16, C17,C28,C29, C30,C31,C32,C33), 160.8 (C4),166.8 (C2)
Anal. Calcd. for $C_{29}H_{22}BrN_5O_3$ (568.43): C, 61.28; H, 3.90; N, 12.32. Found:
C, 60.89; H, 3.28; N, 11.96%.

8-bromo-2'-isopropyl-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-6

Red solid solid, Yield 43%, mp > 260 ^{0}C;
MS: m/z [475.56]
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.21(3H,s),2.58 (1H,d),3.11-2.93 (2H,S),1.58(1H, m),0.93(6H, d),7.53-8.18 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.3 -67.5 (C11,C19,C20,C21,C27, C28,C29,C30),111.8(C22,C24),116.9-147.2(C5,C6,C7,C8,C9,C10,C12,C13,C14,C15, C16, C17), 160.9 (C4),166.4 (C2)
Anal. Calcd. for $C_{24}H_{20}BrN_5O$ (474.36): C, 60.77; H, 4.25; N, 14.76. Found:
C, 60.39; H, 4.08; N, 14.38%.

8-bromo-2'- isobutyl -1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-7

Red solid solid, Yield 45%, mp > 260 ^{0}C;
MS: m/z [489.54];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.29(3H,S),1.18 (2H,d), 1.58(1H, m),0.94(6H, d),1.58(1H,m),3.12 -2.91 (2H,d), 7.49-8.17 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 20.3 -67.5 (C11,C19,C20,C21,C27, C28,C29,C30),111.8(C22,C24),116.9-147.2(C5,C6,C7,C8,C9,C10,C12,C13,C14,C15, C16, C17), 160.9 (C4),166.4 (C2)
Anal. Calcd. for $C_{25}H_{22}BrN_5O$ (488.39): C, 61.48; H, 4.54; N, 14.34. Found:
C, 61.18; H, 4.29; N, 14.06%.

8-bromo-2'- ethyl -1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3B-8

Red solid solid, Yield 42%, mp > 260 ^{0}C;
MS: m/z [461.56];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group), 1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.28(3H,S),3.11-2.93(2H,d),1.46 (2H,m), 0.92(3H, t), 2.73(1H,m), 7.47-8.18 (7H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 11.6 -67.5 (C11,C19,C20,C21,C27, C28,C29),111.6(C22,C24),116.2-142.6(C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16, C17), 160.3 (C4),166.8 (C2)
Anal. Calcd. for $C_{23}H_{18}BrN_5O$ (460.34): C, 60.01; H, 3.94; N, 15.21. Found:
C, 59.78; H, 3.67; N, 15.07%.

8-bromo-2'-(furan-2-yl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile 3 B-9

Red solid solid, Yield 38%, mp > 260 ^{0}C:
m/z [499.46];
IR [nmax, cm_1, KBr]: 3080, 2975 (Aromatic C-H), 2880(-CH-, Aliphatic) 1692, 1620(Aromatic Ketone), 2245(Nitrile group), 760-895 (-CH2 group),1280 (-0- Ether streaching)
1H- NMR [400 MHz, d, ppm, DMSO-d6]: 2.24(3H,S), 3.14-2.96 (2H, m),4.18(1H,s), 6.65-8.26 (10H, m, AreH)
^{13}C NMR [100 MHz, d,ppm, DMSO-d6]: 18.9 -67.2 (C11,C19,C20,C21, C27),111.2(C22,C24),109.2-142.2(C5,C6,C7,C8,C9,C10,C12,C13,C14,C15,C16,C17, C29,C30,C31,C32), 160.9 (C4),166.3 (C2)
Anal. Calcd. for $C_{25}H_{16}BrN_5O_2$ (498.34): C, 60.26; H, 3.24; N, 14.05. Found:
C, 59.87; H, 2.93; N, 13.89%.

Conclusion

8-bromo-3'-(4-fluorophenyl)-12-oxo-5',6',7',7a'-tetrahydro-1'H,3'H,12H-spiro[indolo[2,1-b] quinazoline -6,2'-pyrrolizine]-1',1'-dicarbonitrile and 8-bromo-2'-(4-fluorophenyl)-1'-methyl-12-oxo-12H-spiro[indolo[2,1-b]quinazoline-6,3'-pyrrolidine]-4',4'-dicarbonitrile derivatives **(3A 1-9 & 3B 1-9)** were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures of newly synthesized compounds. The Condensation reaction for preparation of 8-bromo tryptanthrin **(1)** from Bromoisatin & Isatoic anhydride and 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene)malononitrile **(2)** from 8-bromo tryptanthrin and Malononitrile. 1,3-cycloaddtion reaction of 2-(8-bromo-12-oxoindolo[2,1-b]quinazolin-6(12H)-ylidene) malononitrile (2) and azomethine ylides formation from substituted aldehyde 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. While the compound 3 A-1 and 3 B-1 displayed encouraging antitubercular activity compared to standards.

Acknowledgements

The author (M.B.Patel) wishes to express his thanks to Dr.Vaibhav B. Valodkar and Mr. Nikunj C. Patel for providing necessary research facilities. Maratha Mandal's Central Research Laboratory, Belgaum, Karnataka for extending help for assessment of biological activity.

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