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Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/isoxazolinylindol-2-ones

Hemlata Kaur, Sunil Kumar and Ashok Kumar*

Medicinal Chemistry Division, Department of Pharmacology,

L.L.R.M. Medical College, Meerut 250004, U.P. India

Corres author.ashokraj.kumar744@gmail.com (A.Kumar). Fax: +91 121 2760888
Tel.: 91-0121-2764084, Mob.: +919639241111

Abstract: A novel 3-[2-(substituted arylidenylamino chalconyl)-4-(substituted arylidenyl chalconyl)-5-spirooxa/ thiadiazolyl]-indol-2-ones (**3a-3h**), 3-Spiro-[1',3',4'-oxa/thiadiazolyl-2'-{1''-acetyl-5''-(substitutedphenyl-3''-amino)-4'-{1''-acetyl-5''-(substitutedphenyl pyrazolinyl)}]-5'-indol-2-ones (**4a-4h**) and 3-Spiro- [1',3',4'-oxa/thiadiazolyl-2'-{5''-(substitutedphenyl-3''-amino)-4'-{5''-(substitutedphenylisoxazolinyl) }]-5'-indol-2-ones (**5a-5h**) have been synthesized and screened for their antipsychotic and anticonvulsant activities. Structures of the compounds were established by elemental (C, H, N) and spectral (IR, ^{1}H-NMR and mass) analysis.
***Keywords*:** Arylidenyl/arylidenylaminochalconyl-indol-2-ones, Oxa/thiadiazolylpyrazolinyl/isoxazolinyl-indol-2-ones, Antipsychotic and Anticonvulsant activities: Acute toxicity.

Introduction

Psychoses is the mental disorder, with serious distortion of thought, behaviour, and capacity to recognize reality and of perception (delusions and hallucinations), affecting approximately 10% of world's population. All clinically effective antipsychotics (except Clozapine like) have potent post synaptic dopaminergic D2 receptor blocking action and antipsychotic potency has shown good Correlation with their capacity to bind to D_2 receptor. Blockade of dopamine action in corpus striatum is
responsible for the extrapyramidal symptoms (EPS) so often associated with antipsychotic drugs. In
addition to dopaminergic receptor blockade, some (atypical) antipsychotics like resperidone and clozapine also block 5HT system, which helps to lessen EP reactions and is related to their usefulness in improving negative symptoms. Some of the antipsychotic drugs such as chlorpromazine have a number of adverse drug reactions such as parkinsonism viz. tremor, muscular rigidity, excessive salivation, akinesia and many of the endocrinal and metabolic disturbances such as gynaecomastia, galactorrhea and aggravation of diabetes. Since epilepsy is very often associated with CNS psychiatric disorders, a drug with both antipsychotic as well as antiepileptic activity will be more beneficial. Therefore the need for more effective and less toxic antipsychotic drugs still exists. Indole derivatives have documented consistent advances in the design of novel antipsychotic as well as anticonvulsant agents. Indole derivatives have occupied unique place in medicinal and biological chemistry due to their diverse pharmacological display as antipsychotic[1, 2], and anticonvulsant [3, 4]. Furthermore, different derivatives of oxadiazole and thiadiazole have also been reported as antipsychotic[5, 6] and anticonvulsant[7-9] agents. Again, some pyrazoline and isoxazoline derivatives have also been reported to exhibit diverse biological activities such as antipsychotic[10-12] and anticonvulsant[13] agents. Based on these findings, we attempted to synthesize the title compounds presuming that the incorporation of oxadiazole, thiadiazole, pyrazoline and isoxazoline moieties in indole may impart prominent antipsychotic and anticonvulsant activity. All the newly synthesized compounds were screened for their antipsychotic and

anticonvulsant activities with the hope to get better antipsychotic and anticonvulsant agents.

Pharmacological Studies

All the compounds **3a-3h, 4a-4h** and **5a-5h** have been evaluated for antipsychotic activity. These compounds were also assayed in vitro for their anticonvulsant activity.

Antipsychotic activity

Effect on amphetamine induced stereo typed behaviour (SB)

It was done by the method of Castall and Naylor[14]. Before the administration of drugs, the animals were fasted for 12 h and were deprived of food during experiment. Amphetamine (4mg/kg, i.p.) was used to induce the stereotyped behaviour (SB) in albino rats. The intensity of SB was assessed for 60 min after test compounds treatment, using the following scoring system. Periodic sniffing= 1 Score, continuous sniffing = 2 Score, periodic biting, gnawing or licking =3 Score and continuous biting, gnawing or licking =4 Score. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group. Chlorpromazine (4mg/kg, i.p.) was used as standard and was injected 30 min. before the challenge, while propylene glycol (0.5 ml i.p.) or test compounds was given 20 min prior to the injection of amphetamine.

Induction of catalepsy

Albino rats were tested for catalepsy according to the method of Castall and Naylor[14]. The scoring was done as animal maintaining the impose posture 0-10 sec=0 score, 11-30 sec= 1 score, 31-60 sec =2 score, 61 to 120 sec=3 score, after injecting propylene glycol (0.5 ml, i.p.) or test compounds or haloperidol (0.5 mg/kg, i.p.) as standard.

Rotarod performance test

The rotarod performance was essentially the same as described by Dunham and Miya[15]. It is a measure of strength and coordinated movement of animals. The animals were given a training session on the rotarod (rotating at 6 rpm) a day before the test session. As soon as the rat fell off the rotarod, it was immediately placed back. Training was terminated when the rat remained on the rod continuously for 2 min. On the second day, after administration of test compound, the rats were given the trials on the rotarod at 60 min and the cumulated time spent on the rotarod was recorded with a cut off of 2 min.

Anticonvulsant activity

Maximum electroshock seizure (MES) test

This activity was performed by method of the Toman et al [16] on albino rats of the Charles foster strain of either sex, weighing, between 100-120 g. Rats were divided into the groups of 10 animals each and pregnancy was excluded in female rats. The rats were treated with the test compounds 30 mg/kg and phenytoin sodium 30 mg/kg i.p. After 1 hours they were subjected to the shock of 150 mA by convulsiometer through ear electrodes for 0.2 sec. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animals protected/ number of animals tested.

Acute toxicity study

The compounds were investigated for this acute toxicity (LD_{50}) in albino mice by following the method of smith[17]. Test compounds were administered orally in one group and the same volume of normal saline in another group of animals consisting six mice each in graded doses. During the study, the animals were allowed to take water and food adlibidum. After 24 h of drug administration percent mortality in each group was observed. From the data obtained LD_{50} was calculated.

Results and Discussion

All the newly synthesized compounds (**3a-3h, 4a-4h** and **5a-5h)** were tested in vivo in order to evaluate their antipsychotic and anticonvulsant activities at a dose of 30 mg/kg i.p. and pharmacological data of all the newly synthesized compounds of this series have been reported in Table 1. All these compounds show substantive antipsychotic activity. These compounds were screened for their anticonvulsant activity against maximum electroshock induced seizures. While evaluating antipsychotic and anticonvulsant activities, compounds **3a-3h** exhibited different results. Compounds **3a-3h** showed good response (i. e. 1.2-2.0 score) against amphetamine induced stereotyped behaviour. These compounds also exhibited interesting results i.e. (106.8-114.8 sec.) in rotarod performance test, but showed moderate response in cataleptic behaviour. Among the compounds **3a-3h**, **3h** (having 4-NN'-dimethylaminophenyl moiety) showed very good antipsychotic activity towards all the parameters. The later compound also exhibited good anticonvulsant response (i.e. 50%). In next step compounds, i.e. compounds **4a-4h** markedly increase in antipsychotic as well as anticonvulsant activity. Compounds **4e-4h** showed potent results against amphetamine induced stereotyped behaviour (i.e. 0-0.6 score) and cataleptic behaviour (0-1.0 score). These compounds showed interesting results (94.8-100.8 sec.) in rotarod performance test. Compounds **4a-4d** also exhibited good antipsychotic activity but less than compounds **4e-4h.** Among the compounds **4a-4h**, the compound **4h** (having 4-NN'-dimethylaminophenyl

moiety at V^{th} position of pyrazoline ring) have shown most potent antipsychotic activity. This compound completely antagonized the stereotyped behaviour induced by amphetamine and did not produce any cataleptic behaviour. Compound **4h** exhibited most potent result (94.8 sec.) in rotarod performance test. Furthermore, compound **4h** exhibited 90% anticonvulsant activity which was more potnt than reference drug phenytoin sodium (30 mg/kg i.p.). On the other side i..e. compounds **5a-5h** (having isoxazoline ring) showed varying score (0.8-1.6 score) against amphetamine induced stereotyped behaviour and cataleptic behaviour (0-1.4 score). In addition to these parameters, the compound **5a-5h** also exhibited good performance in rotarod performance test. Moreover, compounds **5a, 5b, 5c, 5d, 5e, 5f, 5g** and **5h** elicited 50%, 40%, 60%, 80%, 50%, 50%, 70% and 80% anticonvulsant activity. Moreover, the compounds **4a-4h** (having pyrazolines ring) showed better response than compounds **5a-5h** (having isoxazoline ring). The newly synthesized compounds were also tested for approximate lethal dose LD_{50} and were found to exhibit a higher value of LD_{50} i.e. more than 1000mg/kg i.p. and among them compound **4h** exhibited maximum LD_{50} of more than 2000 mg/kg i.p. thus indicating that it was most safe.

5. Conclusion

While considering all the newly synthesized compounds of this series together, use may conclude that:

- Compounds having thiadiazole ring (i.e. **3e-3h, 4e-4h** and **5e-5h**) show better antipsychotic and anticonvulsant activity than the compounds having oxadiazole ring (i.e. **3a-3d, 4a-4d** and **5a-5d)**.
- Pyrazoline derivatives (i.e. **4a-4h**) exhibited better activity than isoxazoline derivatives**(i.e. 5a-5h)**. with isoxazoline ring.
- Compounds having 4-N $(CH_3)_2$ C_6H_4-substitution at V^{th} position of pyrazoline ring showed More potent activity than other substituted pyrazolines.

Experimental Protocols

Chemistry

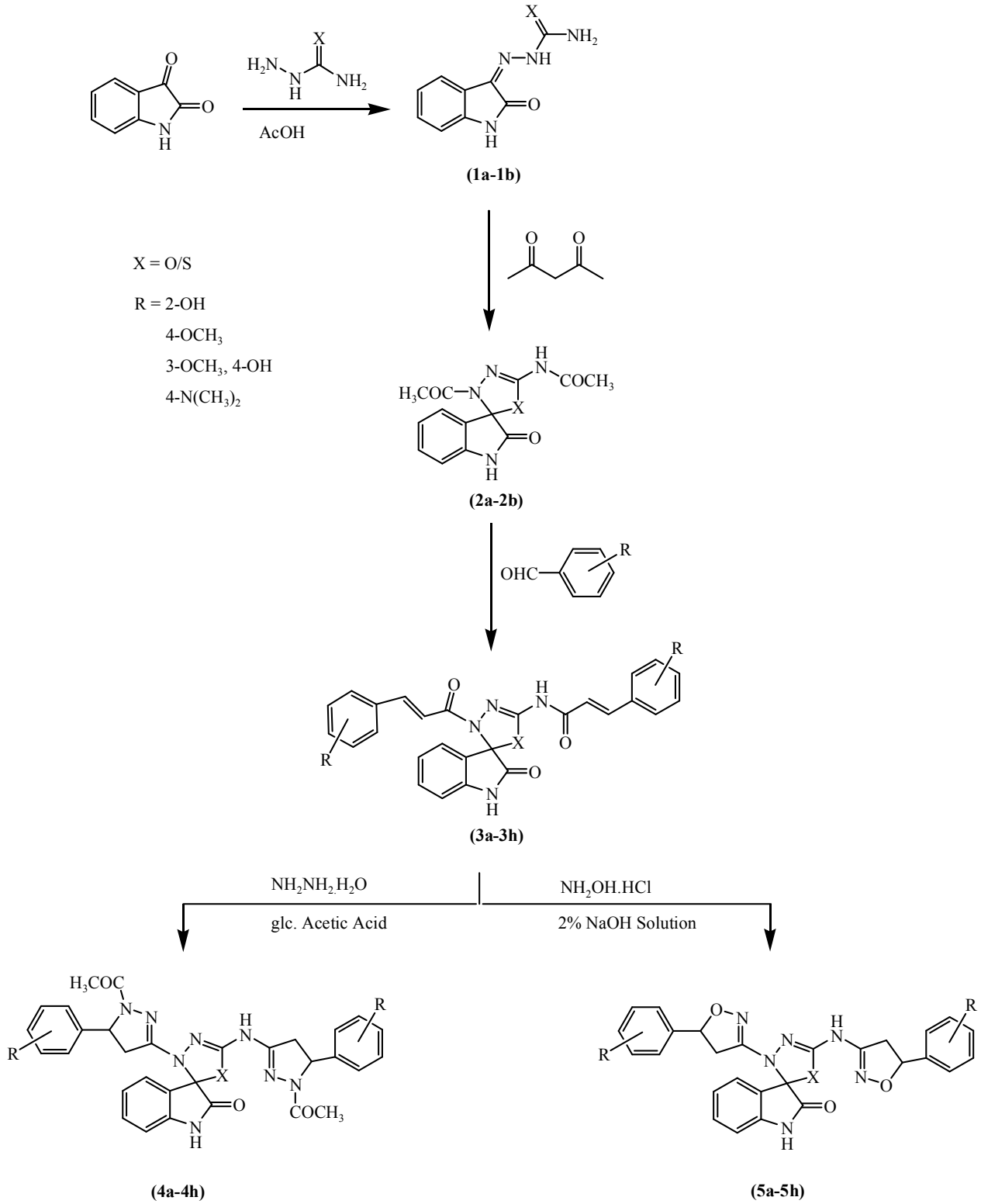
All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The progress of the reaction is monitored by TLC and product are purified through recrystalization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate of 0.5 mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions, and spots were visualized under iodine chamber. Elemental analysis (C,H, N) of all the compounds was done through Perkin-Elmer 2400 elemental analyzer and results were found within + 0.4% of theoretical values. Infra red (IR) spectra were recorded in KBr on Perkin-Elmerspectrum RX-I instrument and □max was recorded in cm-1. ^{1}H NMR spectra were recorded by Bruker AC-300 F instrument using a mixture of $CDCl_3$ and $DMSOd_6$ as solvent and tetramethyl silane (TMS) as internal reference standard. Mass spectra were determined on VG-70-S instrument.

General procedure for the synthesis of Isatin-3-semi/thiosemicarbazone **1a-1b**

A solution of semicarbazide and thiosemicarbazide (2.0 mol) in glacial acetic acid (26 ml) and isatin or indole 2, 3 dione (2.0 mol) and the mixture was refluxed for 3 hours. After cooling the solid mass was collected by filtration, washed well with water, dried and recrystallized from appropriate solvent to give compounds **1a-1b** respectively.

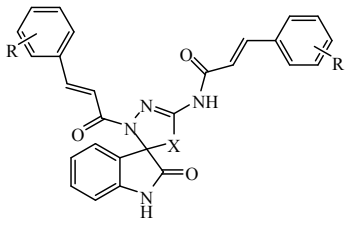
Isatin-*3-semicarbazone* **(1a).** Yield 88% (methanol); m.p. 262 ^{0}C. IR (KBr, □max in cm^{-1}): 3422 (NH), 3350 (NH2), 1688, 1682 (C=O), 1632 (C=N), 1613 (C═C of aromatic ring). ^{1}H-NMR (CDCl3) □ in ppm: 6.72-7.61 (m, 4H, Ar-H), 8.32 (s, 2H, NH2), 8.60 (brs, 1H, NH.CO), 8.75 (brs, 1H NH.CO). MS: [M]+ at *m/z* 204.18. Anal. calcd. for C9H8N4O2: C, 52.94; H, 3.95; N, 27.44: Found: C, 52.90; H, 3.96; N, 27.43%

Isatin-3-thiosemicarbazone **(1b).** Yield 85% (ethanol); m.p. 266 ^{0}C. IR (KBr, □max in cm^{-1}): 3420 (NH), 3348 (NH2), 1689 (C=O), 1630 (C=N), 1615 (C═C of aromatic ring), 1292 (N-N), 1130 (C=S); ^{1}H-NMR (CDCl3) □ in ppm: 6.79-7.60 (m, 4H, Ar-H), 8.30 (s, 2H, NH2), 8.50 (brs, 1H NH.C=S); 8.65 (brs, 1H, NH.CO); MS: [M]+ at *m/z* 220.24. Anal. calcd. for C9H8N4OS: C, 49.08; H, 3.66; N, 25.44: Found : C, 40.10; H, 3.68 ; N, 25.45%

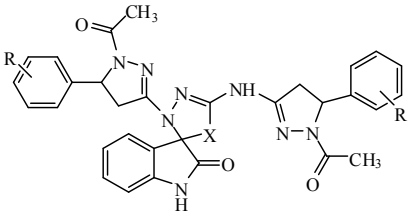


Synthetic route of pyrazolinyl/isoxazolinyl indol-2-ones derivatives

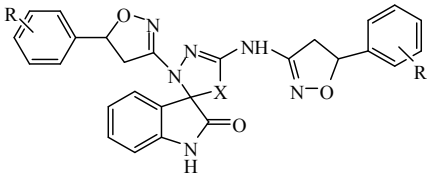
TABLE 1. Antipsychotic and anticonvulsant activities of compounds synthesized 3a-3h, 4a-h and 5a-h.



(3a-3h)



(4a-4h)



(5a-5h)

Com. No	R	X	Dose mg/kg i.p.	Catalepsy Scored [c]	Amphetamine induced SB (Mean Score) [d]	MES % seizures protection [e]	Rotarod Test [f] Mean Sec.	ALD_{50} [g] mg/kg
P.G. [a]	-	-	0.5 ml	0.0	3.8	0	120.0	
CPZ [a]	-	-	4.0	-	0.0	-	100.0	
HPL [b]	-	-	0.5 ml	1.8	-	0		
P.S. [b]	-	-	30	-	-	80***		
3a.	2-OH	O	30	2.8	2.0	20	114.8	>1000
3b	4-OCH_3	O	30	2.6	1.8	20	114.0	>1000
3c.	3-OCH_3	O	30	2.6	1.6	30	112.2	>1000
3d.	4-OH 4-$N(CH_3)_2$	O	30	2.4	1.6	30	110.8	>1000
3e.	2-OH	S	30	2.4	1.4	40	110.6	>1000
3f.	4-OCH_3	S	30	2.2	1.4	20	110.0	>1000
3g.	3-OCH_3	S	30	2.4	1.2	30	108.4	>1000
3h.	4-OH 4-$N(CH_3)_2$	S	30	2.0	1.2	50*	106.8	>1000
4a.	2-OH	O	30	1.2	0.8	40	104.4	>1000
4b.	4-OCH_3	O	30	1.2	0.6	50*	102.6	>1000
4c.	3-OCH_3	O	30	1.0	0.4	60**	102.8	>1000
4d.	4-OH 4-$N(CH_3)_2$	O	30	0.8	0.2	50*	102.0	>1000
4e.	2-OH	S	30	1.0	0.6	50*	100.8	>1000
4f.	4-OCH_3	S	30	0.8	0.4	40	100.4	>1000
4g.	3-OCH_3	S	30	0.4	0.2	60**	100.2	>1000
4h.	4-OH 4-$N(CH_3)_2$	S	30	0.0	0.0	90***	94.8	>2000
5a.	2-OH	O	30	1.4	1.6	50*	106.6	>1000
5b.	4-OCH_3	O	30	1.2	1.4	40	104.8	>1000
5c.	3-OCH_3	O	30	1.2	1.2	60**	102.0	>1000
5d.	4-OH 4-$N(CH_3)_2$	O	30	0.8	1.0	80***	98.4	>1000
5e.	2-OH	S	30	1.0	1.2	50*	102.6	>1000
5f.	4-OCH_3	S	30	1.0	1.2	50*	100.6	>1000
5g.	3-OCH_3	S	30	0.8	1.0	70***	102.4	>1000
5h.	4-OH 4-$N(CH_3)_2$	S	30	0.0	0.8	80***	98.8	>1000

*P < .05, **P < .01, ***P < .001

All the compounds were tested at the dose of 30 mg/kg i.p.

[a] P.G. = Propylene glycol, CPZ = Chlorpromazine. [b] HPL = Haloperidol , P.S. = Phenytoin sodium.

[c] Score of cataleptic behaviour with reference to propylene glycol treated group of rats; Haloperidol (0.5 ml i.p.)induced group 1.8 with reference to control group.

[d] Protection against amphetamine (4mg/kg) induced stereotyped bahaviour (SB). [e] Percentage protection against convulsions in Maximal Electroshock Seizure test.

[f] Time spent on the rod (in sec.) in rotarod performance test. [g] LD_{50} of the compounds 3a-3h, 4a-4h and 5a-5h.

General procedure for the synthesis of 3-[2'-acetylamino-4'-(acetyl)-1, 3, 4-oxa/thiadiazolyl]-indol-2-ones 2a-2b.

A mixture of compounds **1a/1b** (0.2 mol) and freshly distilled acetic anhydride (50 ml) was heated to 110-120 ^{0}C for 4 h and after removal of acetic anhydride from the reaction mixture with the help of rotary vaccum evaporator, a solid mass was obtained which was recrystallized from suitable solvents to give compounds **2a/2b.**

3-[2'-acetylamino-4'-(acetyl)-1, 3, 4-oxadiazolyl]-indol-2-one **(2a)**. Yield 84% (acetone); m.p. 287 ^{0}C. IR (KBr, □max in cm^{-1}): 3426 (-NH), 1752 (C=O, COCH3), 1690 (C=O, CONH), 1641 (C=N), 1618 (C═C of aromatic ring), 1295 (N-N), 1012 (C-O-C); ^{1}H-NMR (CDCl3) □ in ppm: 2.18 (s, 3H, N-COCH3), 2.80 (s, 3H, NH-COCH3) 6.82-7.61 (m, 4H, Ar-H), 8.43 (s, 1H, NHCOCH3), 8.75 (brs, 1H, NHCO). MS: [M]+ at *m/z* 220.24. Anal. calcd. for C13H12N4O4: C, 54.17; H, 4.20; N, 19.44: Found : C, 54.18; H, 4.19; N, 19.46%

3-[2'-acetylamino-4'-(acetyl)-1, 3, 4-thiadiazolyl]-indol-2-one **(2b)**: Yield 81% (methanol); m.p. 290 ^{0}C. IR (KBr, □max in cm^{-1}): 3423 (-NH), 1755 (C=O, COCH3), 1691 (C=O, CONH), 1643(C=N), 1615 (C═C of aromatic ring), 1294 (N-N), 698 (C-S-C). ^{1}H-NMR (CDCl3) □ in ppm: 2.16 (s, 3H, N- COCH3), 2.70 (s, 3H, NH-COCH3), 6.86-7.62 (m, 4H, Ar-H), 8.40 (s, 1H, NHCOCH3), 8.68 (brs, 1H, NHCO). MS: [M]+ at *m/z* 220.24. Anal. calcd. for C13H12N4O3S : C, 51.31 ; H, 3.97 ; N, 18.41: Found : C, 51.30; H, 3.99; N, 18.40%

General procedure for the synthesis of 3-[2-(Substitutedarylidenylamino chalconyl)-4-(substituted arylidenyl chalconyl)-5-spiro-oxdiazolyl]-indol-2-ones 3a-3h.

A solution of compound **2a/2b** (0.4 mol) in absolute ethanol (100 ml) in 2% NaOH and various substituted aromatic aldehydes (0.1 mol) was refluxed for 8-12 hours, concentrated, cooled and poured onto ice. The solid thus obtained was filtered, washed with water and recrystallised from appropriate solvent to furnish compounds **3a-3d/3e-3h**.

3-[2-(2'-Hydroxyarylidenylaminochalconyl)-4-(2'-hydroxyarylidenylchalconyl)-5-spirooxadiazolyl]-indol-2-one **(3a).** Yield 79% (DMF); m.p. 243 ^{0}C. IR (KBr, □max in cm^{-1}): 3438 (-NH), 3432 (OH) 1685, 1681 (C=O), 1643 (C=N), 1631 (CH=CHAr), 1610 (C═C of aromatic ring),1293 (N-N), 1012 (C-O-C),. ^{1}H-NMR (CDCl3) □ in ppm: 6.77 (d, 2H, 2 x COCH=CH), 6.81-7.77 (m, 12H, Ar-H), 8.60 (s , 2H, 2 x =CH-Ar), 8.85 (s, 1H, NHCO), 8.90 (brs, 1H, NH of indole exchangeable with D2O), 11.10 (s, 2H, 2 x OH). MS: [M]+ at *m/z* 494.49; Anal. calcd. for C27H20N4O6 : C, 65.32; H, 4.06 ; N, 11.29: Found : C, 65.33; H, 4.07; N, 11.28 %

3-[2-(4-methoxyarylidenylaminochalconyl)-4-(4-methoxyarylidenylchalconyl)-5-spirooxadiazolyl]-indol-2-one **(3b).** Yield 80% (methanol); m.p. 257 ^{0}C. IR (KBr, □max in cm^{-1}): 3431 (NH), 1686, 1679 (C=O), 1642 (C=N), 1633 (CH=CHAr), 1612 (C═C of aromatic ring), 1294 (N-N), 1225 (OCH3), 1013 (C-O-C). ^{1}H-NMR (CDCl3) □ in ppm: 3.37 (s, 6H, 2 x OCH3), 6.79 (d 2H, 2 x COCH=CH), 6.82-7.69 (m, 12H, Ar-H), 8.61 (d , 2H, 2x =CH-Ar),8.84 (s, 1H, NHCO), 8.92 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 522.55; Anal. calcd. for C29H24N4O6: C, 66.41; H, 4.61 ; N, 10.68: Found : C, 66.43; H, 4.64 ; N, 10.66 %

3-[2-(4-hydroxy-3-methoxyarylidenylamino chalconyl)-4-(4-hydroxy-3-methoxyarylidenylchalconyl) -5-spiro-oxadiazolyl]-indol-2-one (**3c).** Yield 79% (ethanol); m.p. 245 ^{0}C. IR (KBr, □max in cm^{-1}):, 3427 (-NH), 3424 (OH) 1687, 1682 (C=O), 1644 (-C=N), 1630 (CH=CHAr), 1611 (C═C of aromatic ring), 1293 (N-N), 1230 (OCH3), 1011 (C-O-C). ^{1}H-NMR (CDCl3) □ in ppm: 3.32 (s, 6H, 2 x OCH3), 6.82 (d, 2H, 2 x COCH=CH), 6.88-7.78 (m, 10H, Ar-H), 8.64 (s , 2H, 2 x =CH-Ar), 8.83 (s, 1H, NHCO), 8.91 (brs, 1H, NH of indole exchangeable with D2O), 11.12 (s, 2H, 2 x OH). MS: [M]+ at *m/z* 554.55; Anal. calcd. for C29H24N4O8 : C, 62.59; H, 4.35; N, 10.07: Found : C, 62.61; H, 4.34; N, 10.08%

3-[2-(4-NN'-dimethylaminophenylamino chalconyl)-4-(NN'-dimethylaminophenylchalconyl)-5-spiro-oxadiazolyl]-indol-2-one **(3d).** Yield 80% (acetone); m.p. 249 ^{0}C. IR (KBr, □max in cm-1): 3430 (-NH), 1684, 1680 (C=O), 1641 (-C=N), 1634 (CH=CHAr),1614 (C═C of aromatic ring), 1293 (N-N), 1013 (C-O-C). ^{1}H-NMR (CDCl3) □ in ppm: 1.30 (s, 12H, 2 x N(CH3)2), 6.71 (d, 2H, 2 x COCH=CH), 6.74-7.80 (m, 12H, Ar-H), 8.64 (s , 2H, 2 x =CH-Ar), 8.86 (s, 1H, NHCO), 8.96 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 548.63; Anal. calcd. for C31H30N6O4: C, 67.62 ; H, 5.49; N, 12.26: Found : C, 67.63; H, 5.48 ; N, 12.27 %

3-[2-(2'-Hydroxyarylidenylaminochalconyl)-4-(2'-hydroxyarylidenylchalconyl)-5-spirothiadiazolyl]-indol-2-one (**3e).** Yield 78% (DMF); m.p. 250 ^{0}C. IR (KBr, □max in cm^{-1}): 3434, 2565 (-NH), 3430 (OH), 1684, 1678 (C=O), 1645 (-C=N), 1632 (CH=CHAr), 1613 (C═C of aromatic ring), 1294 (N-N), 702 (C-S-

C). ^{1}H-NMR (CDCl3). in ppm: 6.75 (d, 2H, 2 x COCH=CH), 6.79-7.80 (m, 12H, Ar-H), 8.63 (s , 2H, 2 x =CH-Ar), 8.88 (s, 1H, NHCO), 8.95 (brs, 1H, NH of indole exchangeable with D2O), 11.15 (s, 2H, 2x OH). MS: [M]+ at *m/z* 510.56; Anal. calcd. for C27H20N4O5S: C, 63.27; H, 3.93; N, 10.93: Found : C, 63.30; H, 3.97; N, 10.92%

3-[2-(4-methoxyarylidenylaminochalconyl)-4-(4-methoxyarylidenylchalconyl)-5-spirothiadiazolyl]-indol-2-one **(3f).** Yield 76% (ethanol); m.p. 256 ^{0}C. IR (KBr, max in cm^{-1}): 3435 (- NH), 1683, 1677 (C=O), 1646 (-C=N), 1631 (CH=CHAr), 1615 (C=C of aromatic ring), 1014 (C-S-C), 1292 (N-N), 1221 (OCH3). ^{1}H-NMR (DMSOd6) in ppm: 3.40 (s, 6H, 2 x OCH3), 6.73 (d 2H, 2 x COCH=CH), 6.78-7.77 (m, 12H, Ar-H), 8.60 (s , 2H, 2 x =CH-Ar), 8.85 (s, 1H, NHCO), 8.90 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 538.61; Anal. calcd. for C29H24N4O5S: C, 64.43; H, 4.47; N, 10.36 : Found : C, 64.42; H, 4.46; N, 10.35%

3-[2-(4-hydroxy-3-methoxyarylidenylamino chalconyl)-4-(4-hydroxy-3-methoxyarylidenylchalconyl)-5-spiro-thiadiazolyl]-indol-2-one (**3g).** Yield 81% (methanol); m.p. 253 ^{0}C. IR (KBr, max in cm^{-1}): 3434 (-NH), 3426 (OH), 1685, 1679 (C=O), 1647 (-C=N), 1629 (CH=CH), 1616 (C=C of aromatic ring), 1293 (N-N), 1222 (OCH3), 697 (C-S-C); ^{1}H-NMR (DMSOd6) in ppm: 3.39 (s, 6H, 2 x OCH3), 6.85(d 2H, 2 x COCH), 6.85-7.87 (m, 10H, Ar- H), 8.63 (s , 2H, 2 x =CH-Ar), 8.82 (s, 1H, NHCO), 8.99 (brs, 1H, NH of indole exchangeable with D2O), 11.22 (s, 2H, 2 x OH),. MS: [M]+ at *m/z* 570.61; Anal. calcd. for C29H24N4O7S: C, 60.83 ; H, 4.22; N, 7.78 : Found : C, 60.85; H, 4.23; N, 7.79%

3-[2-(4-NN'-dimethylaminophenylamino chalconyl)-4-(4-NN'-dimethylaminophenylchalconyl)-5-spiro- thiadiazolyl]-indol-2-one (**3h).** Yield 79% (methanol); m.p. 249 ^{0}C. IR (KBr, max in cm^{-1}): 3430 (-NH), 1690, 1682 (C=O), 1646 (-C=N), 1633 (CH=CH), 1612 (C=C of aromatic ring), 1295 (N-N), 701 (C-S-C). ^{1}H-NMR (CDCl3) in ppm: 1.33 (s, 12H, 2 x N(CH3)2), 6.80 (2 x d 2H, 2 x COCH=CH), 6.83-7.79 (m, 12H, Ar-H), 8.60 (s , 2H, 2 x =CH-Ar), 8.85 (s, 1H, NHCO), 8.90 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 564.70; Anal. calcd. for C31H30N6O5S: C, 65.70; H, 5.34 ; N, 14.83: Found : C, 65.69 ; H, 5.36; N, 14.84%

***General procedure for the synthesis of 3-Spiro-[1', 3',4'-oxadiazolyl-2'-{1''-acetyl-5''-(2-hydroxy-phenyl -3''-amino)-4'-{1''-acetyl-5''-(2-hydroxy-phenyl) pyrazolinyl}]-5'-indol-2-ones* 4a-4d.**

To a solution of **3a-3d/3e-3h** (0.03 mol) in methanol, hydrazine hydrate (99%) (0.03 mol) and few drops of glacial acetic acid were added. The reaction mixture were refluxed for 10 hours, distilled and cooled. The separated solid was filtered, washed with water and recrystallised from suitable solvent to give compound **4a-4d/4e-4h.**

*3-Spiro-[1', 3',4'-oxadiazolyl-2'-{1''-acetyl-5''-(2-hydroxy- phenyl -3''-amino)-4'-{1''-acetyl-5''-(2-hydroxy- phenyl) pyrazolinyl}]-5'-indol-2-one (***4a).** Yield 77% (ethanol); m.p. 170 ^{0}C. IR (KBr, max in cm^{-1}): 3432 (NH), 3428 (OH), 1698, 1690 1665 (C=O), 1640 (C=N), 1620 (C=C of aromatic ring), 1490 (N-N), 1010 (C-O-C). ^{1}H-NMR (CDCl3) in ppm: 3.40 (s, 6H, 2 x N-CO CH3), 3.75 (d, 4H, 2 x CHCH2), 5.75 (t, 2H, 2 x CHCH2), 6.90-7.92 (m, 12H, Ar-H), 8.87 (s, 1H , NH), 8.92 (brs, 1H, NH of indole exchangeable with D2O), 11.22 (s, 2H, 2 x OH). MS: [M]+ at *m/z* 606.63; Anal. calcd. for C31H28N8O6: C, 61.18; H, 4.64; N, 18.41: Found : C, 61.21; H, 4.63; N, 18.43%

3-Spiro-[1', 3', 4'-oxadiazolyl-2'-{1''-acetyl-5''-(4-methoxyphenyl-3''-amino)-4'-{1''-acetyl-5''-(4-methoxyphenyl) pyrazolinyl}]-5'-indol-2-one **(4b).** Yield 79% (acetone); m.p. 181 ^{0}C. IR (KBr, max in cm^{-1}): 3433 (NH), 1699, 1692 1666 (C=O), 1641 (C=N), 1619 (C=C of aromatic ring), 1493 (N-N), 1222 (OCH3), 1011 (C-O-C). ^{1}H-NMR (CDCl3) in ppm: 3.43 (s, 6H, 2 x OCH3), 3.49 (s, 6H, 2 x N-CO CH3), 3.73 (d, 4H, 2 x CHCH2), 5.74 (t, 2H, 2 x CHCH2), 6.89-7.90 (m, 12H, Ar-H), 8.88 (s, 1H , NH), 8.90 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 634.68; Anal. calcd. for C33H32N8O6 : C, 62.26 ; H, 5.07; N, 17.60: Found : C, 62.24 ; H, 5.08 ; N, 17.61%

3-Spiro-[1', 3', 4'-oxadiazolyl-2'-{1''-acetyl-5''-(4-hydroxy-3-methoxy-phenyl -3''-amino)-4'- {1''-acetyl-5''-(4-hydroxy-3-methoxy-4-hydroxy phenyl) pyrazolinyl}]-5'-indol-2-one **(4c).** Yield 78% (DMF); m.p. 167 ^{0}C. IR (KBr, max in cm^{-1}): 3430 (NH), 3426 (OH), 1696, 1689 1667 (C=O), 1643 (C=N), 1621 (C=C of aromatic ring), 1494 (N-N), 1223 (OCH3), 1014 (C-O-C). ^{1}H-NMR (CDCl3) in ppm: 3.41 (s, 6H, 2 x OCH3), 3.48 (s, 6H, 2 x N-CO CH3), 3.76 (d, 4H, 2 x CHCH2), 5.78 (t, 2H, 2 x CHCH2), 6.82-7.88 (m, 10H, Ar-H), 8.83 (s, 1H, NH), 8.92 (brs, 1H, NH of indole exchangeable with D2O), 11.25 (s, 2H, 2x OH). MS: [M]+ at *m/z* 666.68; Anal. calcd. for

C33H32N8O8: C, 59.28 ; H, 4.82; N, 17.76: Found : C, 59.29; H, 4.81; N, 17.75 %

3-Spiro-[1', 3',4'-oxadiazolyl-2'-{1''-acetyl-5''-(4-NN'-dimethylaminophenyl -3''-amino)-4'- {1''-acetyl-5''-(4-NN'-dimethylaminophenyl)pyrazolinyl}]-5'-indol-2-one **(4d).** Yield 72% (acetone); m.p. 179 ^{0}C. IR (KBr, max in cm^{-1}): 3431 (NH), 1697, 1691 1664 (C=O), 1642 (C=N), 1618 (C=C of aromatic ring), 1495 (N-N), 1015 (C-O-C). ^{1}H-NMR (DMSOd6) in ppm: 1.29 (s, 12H, 2 x N(CH3)2), 3.43 (s, 6H, 2 x N-CO CH3), 3.78 (d, 4H, 2 x CHCH2), 5.77 (t, 2H, 2 x CHCH2), 6.87-7.80 (m, 12H, Ar-H), 8.80 (s, 1H , NH), 8.95 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 660.76; Anal. calcd. for C35H38N10O4: C, 63.43; H, 5.78; N, 21.13 : Found : C, 63.42; H, 5.71; N, 21.12%

3-Spiro-[1', 3', 4'-thiadiazolyl-2'-{1''-acetyl-5''-(2-hydroxyphenyl -3''-amino)-4'-{1''-acetyl- 5''-(2-hydroxyphenyl) pyrazolinyl}]-5'-indol-2-one **(4e).** Yield 74% (ethanol); m.p. 275 ^{0}C. IR (KBr, max in cm^{-1}): 3434 (NH), 3429 (OH), 1699, 1688, 1663 (C=O), 1622 (C=C of aromatic ring), 1639 (C=N), 1494 (N-N), 699 (C-S-C); ^{1}H-NMR (CDCl3) in ppm: 3.42 (s, 6H, 2 x N-CO CH3), 3.72 (d, 4H, 2 x CHCH2), 5.73 (t, 2H, 2 x CHCH2), 6.86-7.86 (m, 12H, Ar-H), 8.83 (s, 1H , NH), 8.94 (brs, 1H, NH of indole exchangeable with D2O), 11.18 (s, 2H, 2x OH). MS: [M]+ at *m/z* 622.69; Anal. calcd. for C31H28N8O5S : C, 59.60; H, 4.52 ; N, 17.94: Found : C, 59.59; H, 4.55; N, 17.95%

3-Spiro-[1', 3', 4'-thiadiazolyl-2'-{1''-acetyl-5''-(4-methoxyphenyl -3''-amino)-4'-{1''-acetyl- 5''-(4-methoxyphenyl) pyrazolinyl}]-5'-indol-2-one **(4f).** Yield 70% (acetone); m.p. 184 ^{0}C. IR (KBr, max in cm^{-1}): 3430 (NH), 1697, 1688, 1665 (C=O), 1638 (C=N), 1491 (N-N), 1624 (C=C of aromatic ring), 1226 (OCH3), 700 (C-S-C). ^{1}H-NMR (CDCl3) in ppm: 3.41 (s, 6H, 2 x OCH3), 3.47 (s, 6H, 2 x N-CO CH3), 3.74 (d, 4H, 2 x CHCH2), 5.72 (t, 2H, 2 x CHCH2), 6.89-7.90 (m, 12H, Ar-H), 8.89 (s, 1H , NH), 8.90 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 650.75; Anal. calcd. for C33H32N8O5S: C, 60.72 ; H, 4.94; N, 17.17 : Found : C, 60.71; H, 4.93 ; N, 17.13%

3-Spiro-[1', 3', 4'-thiadiazolyl-2'-{1''-acetyl-5''-(4-hydroxy-3-methoxyphenyl -3''-amino)-4'- {1''-acetyl-5''-(4-hydroxy-3-methoxyphenyl) pyrazolinyl}]-5'-indol-2-one **(4g).** Yield 76% (methanol) m.p. 167-169 ^{0}C. IR (KBr, max in cm^{-1}): 3439 (NH), 3430 (OH), 1699, 1691 1664 (C=O), 1646 (C=N), 1625 (C=C of aromatic ring), 1497 (N-N), 1226 (OCH3), 697 (C-S-C). ^{1}H-NMR (DMSOd6) in ppm: 3.42 (s, 6H, 2 x OCH3), 3.46 (s, 6H, 2 x N-CO CH3), 3.71 (d, 4H, 2 x CHCH2), 5.76 (t, 2H, 2 x CHCH2), 6.78-7.73 (m, 10H, Ar-H), 8.83 (s, 1H , NH), 8.94 (brs, 1H, NH of indole exchangeable with D2O), 11.26 (s, 2H, 2 x OH),. MS: [M]+ at *m/z* 682.22; Anal. calcd. for C33H32N8O7S: C, 57.89; H, 4.71; N, 16.36: Found : C, 57.87; H, 4.68; N, 16.38%

3-Spiro-[1', 3',4'-thiadiazolyl-2'-{1''-acetyl-5''-(NN'-dimethylamino phenyl -3''-amino)-4'- {1''-acetyl-5''-(NN-dimethylaminophenyl) pyrazoline}]-5'-indol-2-one **(4h).** Yield 75% (ethanol); m.p. 182 ^{0}C. IR (KBr, max in cm^{-1}): 3435 (NH), 3432 (OH), 1697, 1688 1666 (C=O), 1640 (C=N), 1623 (C=C of aromatic ring), 1496 (N-N), 698 (C-S-C). ^{1}H-NMR (CDCl3) in ppm: 1.55 (s, 12H, 2 x N(CH3)2), 3.48 (s, 6H, 2 x N-CO CH3), 3.75 (d, 4H, 2 x CHCH2), 5.75 (t, 2H, 2 x CHCH2), 6.83-7.93 (m, 12H, Ar-H), 8.84 (s, 1H , NH), 8.89 (brs, 1H, NH of indole exchangeable with D2O),. MS: [M]+ at *m/z* 676.83; Anal. calcd. for C35H38N10O3S: C, 61.93; H, 5.64; N, 20.63: Found : C, 61.94; H, 5.67; N, 20.62%

General procedure for the synthesis of 3-Spiro-[1', 3',4'-oxadiazolyl-2'-{5''-(substitutedphenyl-3''-amino)-4'-{1''-acetyl-5''-(substitutedphenylisoxazolinyl)}-5'-indol-2-ones **5a-5d.**

To a solution of **3a-3d/3e-3h** (0.03 mol) in methanol (100ml), hydroxyl amine (0.03 mol) was added. The reaction mixture was refluxed for 10 hours in presence of 2% NaOH solution. The resulting mixtures were concentrated and poured onto ice. The completion of reaction was monitored by TLC. The solid thus obtained were filtered, washed and recrystallized with appropriate solvent to furnish compounds **5a-5d/5e-5h**.

3-Spiro-[1', 3', 4'-oxadiazolyl-2'-{5''-(2-hydroxy phenyl-3''-amino)-4'-{5''-(2-hydroxyphenyl)}-isoxazolinyl]-5'-indol-2-one **(5a).** Yield 77% (methanol); m.p. 164 ^{0}C. IR (KBr, max in cm^{-1}): 3433 (NH), 3428 (OH), 1689 (C=O), 1643 (C=N), 1614 (C=C of aromatic ring), 1492 (N-N), 1230 (C-O-N), 1016 (C-O-C). ^{1}H-NMR (DMSOd6) in ppm: 3.82 (t, 2H, 2 x CH of isoxazoline ring), 5.87 (d, 4H, 2 x CH2 of isoxazoline ring), 6.79-7.98 (m, 12H, Ar-H), 8.70 (s, 1H, NH), 8.90 (brs, 1H, NH of indole exchangeable with D2O), 11.24 (s, 2H, 2x OH). MS: [M]+ at *m/z* 524.52; Anal. calcd. for C29H22N6O6: C, 61.59; H, 4.21; N, 15.96: Found : C, 61.58 ; H, 4.23; N, 15.95 %

3-Spiro-[1',3',4'-oxadiazolyl-2'-{5''-(4-methoxyphenyl-3''-amino)-4'-{5''-(4-methoxyphenyl) }isoxazolinyl]-5'-indol-2-one **(5b).** Yield 74% (acetone); m.p. 193 ^{0}C. IR (KBr, max in cm^{-1}): 3430

(NH), 1691 (C=O), 1641 (C=N), 1616 (C=C of aromatic ring), 1494 (N-N), 1233 (C-O-N), 1226 (OCH3), 1017 (C-O-C). ^{1}H-NMR (CDCl3) □ in ppm: 3.37 (s, 6H, 2 x OCH3), 3.79 (d, 4H, 2 x CH2 of isoxazoline ring), 5.84 (t, 2H, 2 x CH of isoxazoline ring), 6.90-7.99 (m, 12H, Ar- H), 8.69 (s, 1H, NH), 8.95 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 552.58; Anal. calcd. for C29H26N6O6: C, 62.81; H, 4.73 ; N, 15.15: Found : C, 62.83 ; H, 4.72; N, 15.18%

3-Spiro-[1',3',4'-oxadiazolyl-2'-{5''-(4-hydroxy3-methoxyphenyl-3''-amino)-4'-{5''-(4- hydroxy-3-methoxyphenyl)}isoxazolinyl)]-5'-indol-2-one **(5c).** Yield 79% (acetone); m.p. 210 ^{0}C. IR (KBr, □max in cm^{-1}): 3436 (NH), 3427 (OH), 1690 (C=O), 1644 (C=N), 1615 (C=C of aromatic ring), 1493 (N-N), 1232 (C-O-N), 1227 (OCH3), 1010 (C-O-C). ^{1}H-NMR (CDCl3) □ in ppm: 3.41 (s, 6H, 2 x OCH3), 3.83 (d, 4H, 2 x CH2 of isoxazoline ring), 5.88 (t, 2H, 2 x CH of isoxazoline ring), 6.93-7.98 (m, 10H, Ar-H), 8.71 (s, 1H, NH), 8.92 (brs, 1H, NH of indole exchangeable with D2O), 11.19 (s, 2H, 2 x OH). MS: [M]+ at *m/z* 584.58; Anal. calcd. for C29H26N6O8: C, 59.38; H, 4.47; N, 14.33: Found : C, 59.39; H, 4.46; N, 14.32%

3-Spiro-[1',3',4'-oxadiazolyl-2'-{5''-(NN'-dimethylaminophenyl-3''-amino)-4'-{5''-(4- NN'-dimethylaminophenyl)}-isoxazolinyl]-5'-indol-2-one **(5d).** Yield 73% (methanol); m.p. 189 ^{0}C. IR (KBr, □max in cm^{-1}): 3429 (NH), 1688 (C=O), 1639 (C=N), 1617 (C=C of aromatic ring), 1495 (N-N), 1239 (C-O-N), 1014 (C-O-C). ^{1}H-NMR (CDCl3)□ in ppm: 1.78 (s, 12H, 2 x N(CH3)2), 3.81 (d, 4H, 2x CH2 of isoxazoline ring), 5.86 (t, 2H, 2x CH of isoxazoline ring), 6.88-7.97 (m, 12H, Ar-H), 8.68 (s, 1H, NH), 8.92 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 578.66; Anal. calcd. for C31H32N8O4 : C, 64.12; H, 5.55 ; N, 19.30 : Found : C, 64.10 ; H, 5.54 ; N, 19.33 % *6.1.5.*

3-Spiro-[1',3',4'-thiadiazolyl-2'-{5''-(2-hydroxyphenyl-3''-amino)-4'-{5''-(2-hydroxyphenyl) }isoxazolinyl]-5'-indol-2-one **(5e).** Yield 74% (ethanol); m.p. 267 ^{0}C. IR (KBr, □max in cm^{-1}): 3434 (NH), 3430 (OH), 1687 (C=O), 1635(C=N), 1619 (C=C of aromatic ring), 1492 (N-N), 1228 (C-O-N), 1015 (C-O-C). ^{1}H-NMR (DMSOd6) □ in ppm: 3.85 (d, 4H, 2x CH2 of isoxazoline ring), 5.83 (t, 2H, 2x CH of isoxazoline ring), 6.89-7.86 (m, 12H, Ar-H), 8.73 (s, 1H, NH), 8.98 (brs, 1H, NH of indole exchangeable with D2O), 11.27 (s, 2H, 2 x OH). MS: [M]+ at *m/z* 540.59; Anal. calcd. for : C29H22N6O5S C, 59.77 ; H, 4.09; N, 15.49: Found : C, 59.76; H, 4.04; N, 15.50%

3-Spiro-[1',3',4'-thiadiazolyl-2'-{5''-(4-methoxyphenyl-3''-amino)-4'-{5''-(4-methoxypheny)}-isoxazolinyl]-5'-indol-2-one **(5f).** Yield 75% (DMF); m.p. 195 ^{0}C. IR (KBr, □max in cm^{-1}): 3435 (NH), 1692 (C=O), 1638 (C=N), 1620 (C=C of aromatic ring), 1490 (N-N), 1234 (C-O-N), 1223 (OCH_3), 1017 (C-O-C); ^{1}H-NMR (CDCl3) □ in ppm: 3.45 (s, 6H, 2 x OCH3), 3.84 (d, 4H, 2x CH2 of isoxazoline ring), 5.82 (t, 2H, 2x CH of isoxazoline ring), 6.85-7.96 (m, 12H, Ar-H), 8.69 (s, 1H, NH), 8.93 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 568.64; Anal. calcd. for C29H26N6O5S : C, 61.04 ; H, 4.59; N, 14.73 : Found : C, 61.06; H, 4.60; N, 14.72 %

3-Spiro-[1',3',4'-thiadiazolyl-2'-{5''-(4-hydroxy-3-methoxyphenyl-3''-amino)-4'-{5''-(4- hydroxy-3-methoxyphenyl)}- isoxazolinyl]-5'-indol-2-one **(5g).** Yield 71% (acetone); m.p. 216 ^{0}C. IR (KBr, □max in cm^{-1}): 3432 (NH), 3427 (OH), 1693 (C=O), 1637 (C=N), 1619 (C=C of aromatic ring), 1489 (N-N), 1232 (C-O-N), 1224 (OCH3), 1018 (C-O-C). ^{1}H-NMR (CDCl3)□ in ppm: 3.44 (s, 6H, 2 x OCH3), 3.86 (2 x d, 4H, CH2 of isoxazoline ring), 5.80 (t, 2H, CH of isoxazoline ring), 6.98- 7.89 (m, 10H, Ar-H), 8.73 (s, 1H, NH), 8.90 (brs, 1H, NH of indole exchangeable with D2O), 11.19 (s,2H, 2 x OH). MS: [M]+ at *m/z* 600.64; Anal. calcd. for C29H26N6O7S: C, 57.80; H, 4.35; N, 13.95:Found : C, 57.83 ; H, 4.32; N, 13.93 %

3-Spiro-[1',3',4'-thiadiazolyl-2'-{5''-(4-NN'-dimethylaminophenyl-3''-amino)-4'-{5''-(4-NN'-dimethyl aminophenyl)}-isoxazolin]-5'-indol-2-one **(5h).** Yield 72% (methanol); m.p. 194 ^{0}C. IR(KBr, □max in cm^{-1}): 3437 (NH), 3433 (OH), 1688 (C=O), 1640 (C=N), 1621 (C=C of aromatic ring), 1492 (N-N), 1235 (C-O-N), 1016 (C-O-C); ^{1}H-NMR (CDCl3) □ in ppm: 1.80 (s, 12H, 2 x N(CH3)2), 3.78 (d, 4H, 2x CH2 of isoxazoline ring), 5.87 (t, 2H, 2x CH of isoxazoline ring), 6.71-7.88 (m, 12H, Ar-H), 8.67 (s, 1H, NH), 8.89 (brs, 1H, NH of indole exchangeable with D2O). MS: [M]+ at *m/z* 594.73; Anal. calcd. for C31H32N8O3S: C, 62.40; H, 5.41 ; N, 18.78: Found : C, 62.42; H, 5.43; N,18.77%

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