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DRUG SYNTHESIS

SYNTHESIS, PARTITION COEFFICIENTS AND ANTIBACTERIAL ACTIVITY OF 3´-PHENYL (SUBSTITUTED)-6´-ARYL-2´(1*H*)-*CIS*-3´,3´a -DIHYDROSPIRO[3-*H*-INDOLE-3,5´-PYRAZOLO (3´,4´-d)-THIAZOLO-2-(1*H*)-ONES]

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Abstract: Condensation of isatin with primary aryl amines gave a series of Schiff bases (**1**) which on reaction with thioglycolic acid in 1,4-dioxane afforded the formation of the corresponding 4- thiazolidinones (**2**). Compound **2** on condensation with substituted benzaldehydes in anhydrous sodium acetate furnished 3-aryl -5[1]-phenyl(substituted)spiro[3*H*-indole-3,2[1]-thiazolidines]-2-(1*H*), 4[1](5[1]*H*)-diones (**3**). The latter (**3**) on reaction with hydrazine hydrochloride in anhydrous sodium acetate gave 3'-phenyl(substituted)-6'-aryl-2'(1*H*)-cis-3',3'a-dihydrospiro[3*H*-indole-3,5'-pyrazolo(3',4'-d)-thiazolo-2-(1*H*)-ones] (4). The structure has been established on the basis of spectral data. The partition coefficient for n-octanol/water solvent system and *in vitro* antibacterial activity of the 2'(1*H*)-cis-3',3'a-dihydrospiro[3*H*-indole-3,5'-pyrazolo(3',4'-d)-thiazolo-2-(1*H*)-one] derivatives have been evaluated.

Keywords: isatin, thiazolidinones, pyrazole, i*n vitro* antibacterial activity, partition coefficient

In recent years, spirooxindoles are of great interest due to their exceptional biological activities (1). Spiroindole heterocycles, in which the indole ring is linked to the other heterocyclic system through the spirocarbon atom at C-3, show an increased spectrum of biological activities. A systematic investigation of this class of heterocycles has been carried out by Joshi and co-workers (2). Pyrazole (3) and thiazole (4) derivatives have also been known as useful therapeutic agents. It is also believed that the presence of an N-C-S linkage is responsible for the amoebicidal, anticonvulsant and fungicidal (5) activities. Since the work is in progress on isatin derivatives (6), it was thought worthwhile of incorporating pyrazole and oxindole skeletons through a thiazole ring *via* an N-C-S linkage at C-3 atom of indole ring with a hope to develop a series of spirooxindole heterocycles. In view of this above, an attempt have been undertaken for the synthesis of 3'-phenyl(substituted)-6'-aryl-2'(1*H*)-cis-3',3'a-dihydrospiro[3*H*-indole-3,5'-pyrazolo(3',4'-d)-thiazolo-2-(1*H*)-ones] from an easily available starting material, isatin, followed by determination of their partition coefficient for *n*-octanol/water solvent system and *in vitro* antibacterial activity.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. Purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on a Jasco FT/IR 410 spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra ($CDCl_3$) were run on a Bruker DPX 300-MHz spectrometer using TMS as internal reference (chemical shifts in δ ppm). Mass spectra were scanned on a Jeol JMS-600 spectrometer operating at 70 eV. C, H and N analyses were carried out on a Euro EA (Italy) analyzer.

Schiff bases (**1a-g)** were prepared following the reported method (7).

3'-Arylspiro[3*H*-indole-3,2'-thiazolidine]-2-(1*H*),4'-(5'-*H*)-diones (**2a-g**) :

An equimolar mixture of compound (**1a-g**) (0.001 mol) and thioglycolic acid (0.001 mol, 0.122 g) in 1,4-dioxane (50 mL) was refluxed for 10-12 h. The excess solvent was removed under reduced pressure and the liquified residue was poured into ice-cold water. The solid thus obtained was washed with sodium bicarbonate solution and crystallized from ethanol: **2a** (60%); m.p. 158°C; IR (cm^{-1}): 3361

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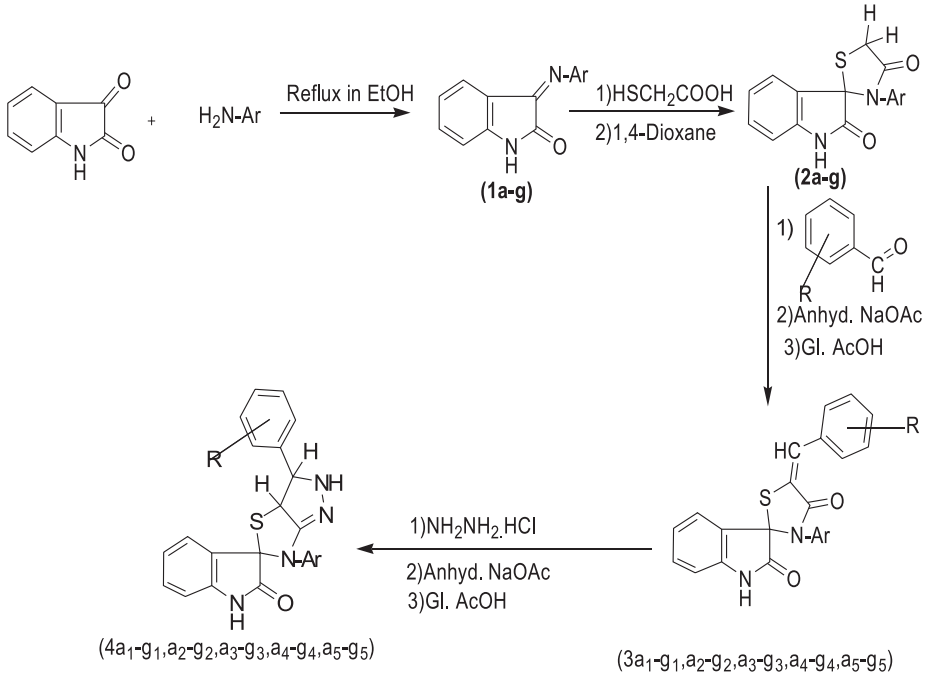


1,2,3,4,a; Ar = Phenyl
b; Ar = 4-Cl phenyl
c; Ar =4-Br phenyl
d; Ar = 2-NO_2phenyl
e; Ar = Naphthyl
f; Ar = 4-COOH phenyl
g; Ar = 2-OCH_3 phenyl
3,4a_1-g_1; R = H
a_2-g_2; R = 2-Cl
a_3-g_3; R = 2-OH
a_4-g_3; R = 4-OCH_3
a_5-g_5; R =4-NO_2

Scheme.

(NH), 3045 (CH-arom.), 1736 (C=O); ^{1}H-NMR: δ (ppm): 3.52 (2H, s, CH_2), 6.78-7.46 (9H, m, ArH), 8.74 (1H, s, NH); MS: (m/z) 296 (M^+). Analysis ($C_{16}H_{12}N_2SO_2$). C, H, N (Found: C, 64.69; H, 4.22; N, 9, 38. $C_{23}H_{17}N_3O_3S$ calcd. for: C, 64.85; H, 4.08; N, 9.45 %).

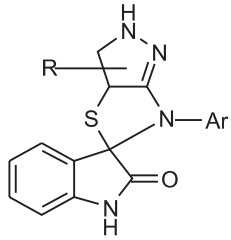
3-Aryl-5^1-phenyl(substituted)spiro[3*H*-indole-3,2^1-thiazolidine]-2-(1*H*),4^1-(5^1-*H*)-diones (**3a$_1$-g$_1$,a$_2$-g$_2$,a$_3$-g$_3$ a$_4$-g$_4$, a$_5$-g$_5$**)

An equimolar mixture of compound **2a$_1$** (0.001 mol), substituted benzaldehydes (0.001 mol) and anhydrous sodium acetate (0.001 mol, 0.082 g) in glacial acetic acid (20 mL) was refluxed for 3 h. The reaction mixture was concentrated and poured into ice-cold water. The solid thus separated was filtered, washed with water and crystallized from glacial acetic acid: **3a$_1$** (70%); m.p. 212^{o}C. (Found: C, 71.67; H, 4.34; N, 7.47. $C_{23}H_{17}N_3O_3$ calcd. for: C, 71.86; H, 4.19; N, 7.29%); ν_{max} : 3447 (NH), 3026 (CH-arom.), 1722 (C=O), 1482 cm^{-1} (C=C); 1H NMR δ (ppm): 6.12 (1H, s, CH), 6.76-7.45 (13H, m, ArH), 8.81 (1H, s, NH); MS [m/z]: 384 (M^+).

3'-Phenyl (substituted) 6'-aryl-2'(1*H*)-cis-3',3'a-dihydrospiro[3*H*-indole-3,5'-pyrazolo (3',4'-d)-thiazolo-2-(1*H*)-ones] (**4a$_1$-g$_1$,a$_2$-g$_2$,a$_3$-g$_3$,a$_4$-g$_4$,a$_5$-g$_5$**)

An equimolar mixture of compound **3a$_1$** (0.001 mol) hydrazine hydrochloride (0.001 mol) and anhydrous sodium acetate (0.001 mol, 0.082 g) in minimum amount of glacial acetic acid (20 mL) was heated under reflux for 6 h and cooled to room temperature. The solid thus separated was filtered, washed thoroughly with water and crystallized from

Table 1. Physical and preparative data for 3′-phenyl (substituted)-6′-aryl-2′(1*H*)-*cis*-3′,3′a-dihydrospiro [3-*H*-indole-3,5′-pyrazolo(3′,4′-d)-thiazolo-2-(1*H*)-ones].



Code	Ar	R	Molecular Formula*	Molecular weight**	M.p (°C)	Yield (%)	Log P***
4 a$_1$	C_6H_5	C_6H_5	$C_{23}H_{18}N_4OS$	398	182	56	1.26
a$_2$	C_6H_5	C_6H_4Cl	$C_{23}H_{17}N_4OSCl$	432.5	198	58	1.22
a$_3$	C_6H_5	C_6H_5O	$C_{23}H_{18}N_4O_2S$	414	196	48	1.25
a$_4$	C_6H_5	C_6H_7O	$C_{24}H_{20}N_4O_2S$	428	192	60	ND
a$_5$	C_6H_5	$C_6H_4NO_2$	$C_{23}H_{17}N_5O_3S$	443	187	62	1.12
b$_1$	C_6H_4Cl	C_6H_5	$C_{23}H_{17}N_4OSCl$	432.5	204	56	1.10
b$_2$	C_6H_4Cl	C_6H_4Cl	$C_{23}H_{16}N_4OSCl_2$	467	206	55	1.31
b$_3$	C_6H_4Cl	C_6H_5O	$C_{23}H_{17}N_4O_2SCl$	448.5	192	49	ND
b$_4$	C_6H_4Cl	C_6H_7O	$C_{24}H_{19}N_4O_2SCl$	462.5	209	50	1.41
b$_5$	C_6H_4Cl	$C_6H_4NO_2$	$C_{23}H_{17}N_5O_3SCl$	477.5	206	55	1.31
c$_1$	C_6H_4Br	C_6H_5	$C_{23}H_{17}N_4OSBr$	479	176	63	1.24
c$_2$	C_6H_4Br	C_6H_4Cl	$C_{23}H_{16}N_4OSBrCl$	513.5	162	61	1.45
c$_3$	C_6H_4Br	C_6H_5O	$C_{23}H_{17}N_4O_2SBr$	495	158	69	1.38
c$_4$	C_6H_4Br	C_6H_7O	$C_{24}H_{19}N_4O_2SBr$	509	161	71	1.40
c$_5$	C_6H_4Br	$C_6H_4NO_2$	$C_{23}H_{17}N_5O_3SBr$	525	157	56	1.35
d$_1$	$C_6H_4NO_2$	C_6H_5	$C_{23}H_{17}N_5O_3S$	445	204	48	1.14
d$_2$	$C_6H_4NO_2$	C_6H_4Cl	$C_{23}H_{16}N_5O_3SCl$	479.5	190	62	1.17
d$_3$	$C_6H_4NO_2$	C_6H_5O	$C_{23}H_{17}N_5O_4S$	461	207	57	ND
d$_4$	$C_6H_4NO_2$	C_6H_7O	$C_{24}H_{19}N_5O_4S$	475	210	51	1.35
d$_5$	$C_6H_4NO_2$	$C_6H_4NO_2$	$C_{23}H_{17}N_6O_5S$	491	192	49	1.45
e$_1$	$C_{10}H_7$	C_6H_5	$C_{27}H_{20}N_4OS$	450	186	61	ND
e$_2$	$C_{10}H_7$	C_6H_4Cl	$C_{27}H_{19}N_4OSCl$	482.5	190	56	1.21
e$_3$	$C_{10}H_7$	C_6H_5O	$C_{27}H_{20}N_4O_2S$	464	188	47	1.11
e$_4$	$C_{10}H_7$	C_6H_7O	$C_{28}H_{22}N_4O_2S$	478	178	49	1.20
e$_5$	$C_{10}H_7$	$C_6H_4NO_2$	$C_{27}H_{19}N_5O_3S$	493	172	52	1.17
f$_1$	$C_7H_5O_2$	C_6H_5	$C_{24}H_{18}N_4O_3S$	442	176	64	1.26
f$_2$	$C_7H_5O_2$	C_6H_4Cl	$C_{24}H_{17}N_4O_3SCl$	476.5	188	49	1.22
f$_3$	$C_7H_5O_2$	C_6H_5O	$C_{24}H_{18}N_4O_4S$	458	169	47	1.32
f$_4$	$C_7H_5O_2$	C_6H_7O	$C_{25}H_{20}N_4O_4S$	472	182	52	ND
f$_5$	$C_7H_5O_2$	$C_6H_4NO_2$	$C_{24}H_{17}N_5O_5S$	487	168	46	ND
g$_1$	C_7H_7O	C_6H_5	$C_{24}H_{20}N_4O_2S$	430	172	48	1.19
g$_2$	C_7H_7O	C_6H_4Cl	$C_{24}H_{19}N_4O_2SCl$	464	202	52	1.26
g$_3$	C_7H_7O	C_6H_5O	$C_{24}H_{20}N_4O_3S$	446	166	46	1.14
g$_4$	C_7H_7O	C_6H_7O	$C_{25}H_{22}N_4O_3S$	460	164	51	1.23
g$_5$	C_7H_7O	$C_6H_4NO_2$	$C_{24}H_{19}N_5O_4S$	475	170	53	1.11

* All compounds gave satisfactory elemental analysis (± 0.4% of the theoretical values).
** Molecular weight determination by mass spectra. ***ND (Not determined).

Table 2. Antibacterial activity data (zone of inhibition*) of 3′-phenyl (substituted)-6′-aryl-2′ (1*H*)-*cis*-3′,3′a-dihydrospiro [3-*H*-indole-3, 5′-pyrazolo (3′, 4′-d)-thiazolo-2-(1*H*)-ones] in the concentration of 100 µg/mL.

Compound Code	*S. a.*	*A. p.*	*E. c.*	*K. a.*
4 a$_1$	14	16	17	18
a$_2$	17	15	16	16
a$_3$	19	17	19	18
a$_4$	14	14	14	14
a$_5$	13	13	13	11
b$_1$	14	13	15	14
b$_2$	21	21	23	23
b$_3$	16	16	15	14
b$_4$	19	19	20	19
b$_5$	24	23	25	24
c$_1$	13	11	12	12
c$_2$	20	20	21	20
c$_3$	23	22	22	23
c$_4$	19	20	20	20
c$_5$	24	22	18	19
d$_1$	17	16	17	16
d$_2$	23	21	22	21
d$_3$	12	13	13	13
d$_4$	21	22	20	21
d$_5$	21	21	20	20
e$_1$	19	20	21	20
e$_2$	14	12	13	13
SSe$_3$	21	22	21	22
e$_4$	15	15	14	15
e$_5$	16	15	17	15
f$_1$	14	14	15	14
f$_2$	15	15	14	14
f$_3$	15	14	14	14
f$_4$	18	17	17	17
f$_5$	14	11	12	13
g$_1$	16	15	17	16
g$_2$	17	17	17	18
g$_3$	14	13	14	14
g$_4$	12	11	12	10
g$_5$	14	16	16	19
Ampicillin trihydrate	26	28	32	28
DMSO	00	00	00	00

*Diameter of the hole was 6 mm. ***S. a.*** = *Staphylococcus aureus*, ***A. p.*** = *Actinomycus pyoginus*, ***E. c.*** = *Escherichia coli*, ***K. a.*** = *Klebsiella aeroginus*.

glacial acetic acid: **4a$_1$** $\nu_{max.}$ 3402 (NH), 3078 (CH-arom.), 1732 (C=O) ,1624 (C=N), 1328 cm^{-1}(CN) 1H NMR δ (ppm): 3.70(1H, d, CH), 4.30(1H, d, CH), 6.74-7.43 (13H, m, ArH), 8.87(1H, s, NH), 9.35 (1H, s, NH) ;. [*m*/*z*] 398 (M^+): Anal. ($C_{23}H_{18}N_4SO$). C,H,N. (Found : C, 72.28; H, 4.52; N, 10.66. calcd. for: C, 72.52; H, 4.82; N, 10.57%)

RESULTS

Schiff bases (**1a-g),** which served as a starting material (7) for various spiroindole heterocycles of diverse biological activities are obtained with good yield (76-88%) by condensation of isatin with various arylamines (Scheme). 3′-Aryl spiro[3*H*- indole-

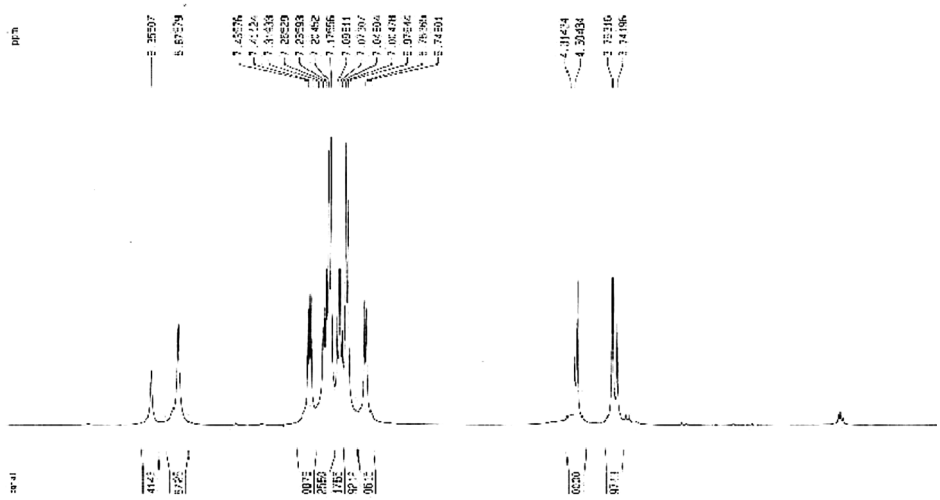


Figure 1.

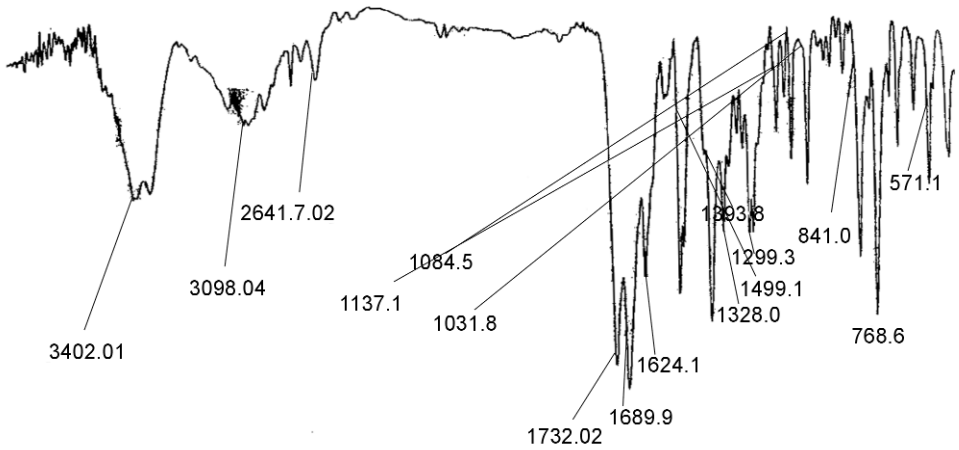


Figure 2. IR spectra compound $4a_1$.

3,2´- thiazolidine]-2(1*H*),4´-(5´*H*)-diones (**2a-g**) are prepared with 52-65 % yields by reacting thioglycolic acid with respective 3-iminooxindoles (**1a-g)** in refluxing 1,4-dioxane for 10-12 h.

Spiro[3*H*-indole-3,2´-thiazolidine] **(2a-g$_1$)**, on condensation with respective substituted benzaldehydes in the presence of anhydrous NaOAc and glacial acetic acid afforded 3-aryl-5´-phenyl(substituted)spiro[3*H*-indole-3, 2^x-thiazolidine]-2-(*1H*),4´-(5´*H*)diones **(3a$_1$-g$_1$,a$_2$-g$_2$,a$_3$-g$_3$,a$_4$-g$_4$,a$_5$-g$_5$)** with 57-71% yields. When **3a$_1$** was heated with hydrazine hydrochloride in the presence of anhydrous NaOAc and glacial acetic acid for 6 h, compound **4a$_1$** was obtained as colored solid with 56% yield.

Similarly, **4b$_1$-g$_1$, a$_2$-g$_2$, a$_3$-g$_3$, a$_4$-g$_4$, a$_5$-g$_5$** compounds are prepared by reacting respective spiro[3*H*-indole-3, 2^x-thiazolidine]-2-(1H),4´-(5´*H*) diones **3b$_1$-g$_1$, a$_2$-g$_2$, a$_3$-g$_3$, a$_4$-g$_4$, a$_5$-g$_5$** with NH_2NH_2·HCl under identical reaction conditions. The synthesized compounds **(4a$_1$-g$_1$, a$_2$-g$_2$, a$_3$-g$_3$, a$_4$-g$_4$, a$_5$-g$_5$)** were characterized by melting points, spectral data and elemental analysis.

DISCUSSION AND CONCLUSION

A large number of 2'(1*H*)-cis-3',3'a-dihydrospiro[3*H*-indole-3,5'-pyrazolo(3',4'-d)-thiazolo-2-(1*H*)-one] derivatives **(4a$_1$-g$_1$, a$_2$-g$_2$, a$_3$-g$_3$, a$_4$-g$_4$, a$_5$-g$_5$)** have been prepared and evaluated for they partition coefficient and *in vitro* antibacterial activity.The partition coefficient of selected compounds determined was by classical shake flask method (8) using *n*-octanol and aqueous phosphate buffer (pH 7.4) and the results are presented in Table 1. All the compounds tested are shown to be ideal drug candidates, as it was suggested that an ideal drug candidate

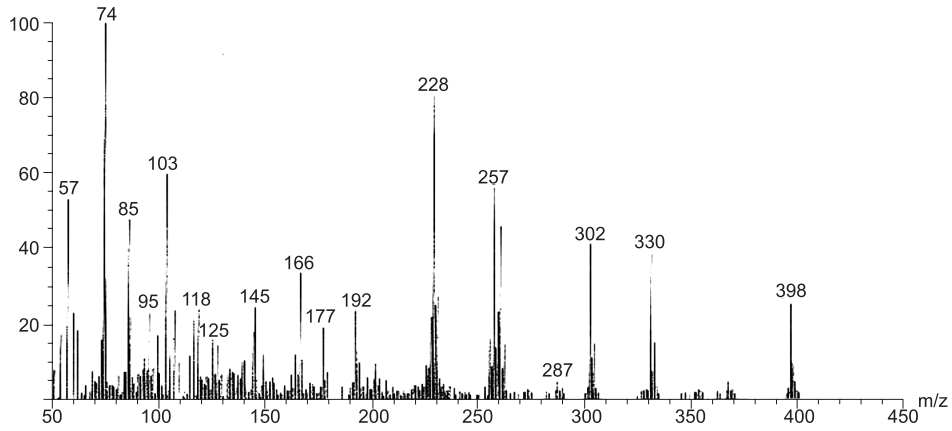


Figure 3.

should have log P value in the range 1 to 2. The *in vitro* antibacterial activities of compounds (**4a$_{1}$-g$_{1}$, a$_{2}$-g$_{2}$, a$_{3}$-g$_{3}$, a$_{4}$-g$_{4}$, a$_{5}$-g$_{5}$**) were determined by agar cup plate method (9), the results of which are summarized in Table 2. The antibacterial data in Table 2 clearly show that the halogen containing group is by far most active substituted R and Ar group. The methoxy group generally confer weak antibacterial activity. The nitro compounds has modest activity, but their hydroxyl substitution are weakly active to inactive, among the nitro compounds only the carboxylic derivatives possess moderate antibacterial activity. These generalizations hold as well for a variety of other "Ar" group series in which the effect on variety the "R" group has been extensively examined.

However, there is some dependence between the "Ar" and "R" groups in practical cases. This is illustrated in Table 2. These data reveal that there is an interplay between effect of Ar and R groups, evidenced by a change in rank order of activity of the various "Ar" groups for a given "R" group, but in each series of compound with common „Ar" groups, those with the halogen are always the most active.

However, the tested compounds were less active in comparison to ampicillin trihydrate (standard drug).

In conclusion, a number of spirooxindole heterocycles were synthesized and their partition coefficient in *n*-octanol/water system were determined and also assayed for their *in vitro* antibacterial activity.

Even though, 2'(1*H*)-cis-3',3'a-dihydrospiro [3*H*-indole-3,5'-pyrazolo(3',4'-d)-thiazolo-2-(1*H*)-one] derivatives (**4a$_{1}$-g$_{1}$, a$_{2}$-g$_{2}$, a$_{3}$-g$_{3}$, a$_{4}$-g$_{4}$, a$_{5}$-g$_{5}$**) are less active with reference to ampicillin trihydrate-drug, the data reported in this article may be a helpful guide for the medicinal chemist who are working in the area.

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