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New strategy for the green synthesis and biological evolution for the synthesis of 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid derivative.

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ABSTRACT

A series 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid were prepared by the reaction of (2-oxoindolin-3-ylideneamino)benzoic acid with thia glycolic acid in the presence of benzene. Herein key substitute isatin, isatin is a versatile substitute act as a biological and pharmacological compound. Isatin showing biological properties such as-anticancer, anticonvulsant, antimicrobial, antifungal and analgesic etc. An isatin derivative showing potent anticonvulsant activity at low concentration of synthesized compound of all derivatives. Herein formed Schiff base are found to be most potent anticonvulsant agent. The spectral study of newly synthesized compounds was characterized on the basis of elemental analysis, IR, H^1 NMR and mass spectra.

Keywords: Isatin, Isatin derivative, Schiff base, Biological and pharmacological activity

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INTRODUCTION

Isatin (1H-indole-2, 3-dione) is an organic heterocyclic compound. It's containing two type of carbonyl group one is lactum and another is keto. The isatin derivative possesses wide range of biological and pharmaceutical importance like antibacterial[1] , antifungal[2] , antidepresent[3], anti inflammatory[4].

The isatin derivative compound synthesized via Schiff base from Schiff reaction, the reacting species for synthesis of Schiff base are substituted aromatic aniline and isatin. The Schiff base is a compound having –C=N- bond where nitrogen atom jointed with the aryl or alkyl group directly. Schiff bases are the nitrogen analogs of aldehyde and ketone, in this type of compound C=O group is replace by -C=N-R group[5]. Schiff base contain both aliphatic and aromatic group but aromatic Schiff base compound are more stable because of conjugation and the other hand aliphatic Schiff base are less stable so they goes to polymerization[6].

Isatin derivative compound having many medicinal properties, it has distinct and discontinuous distribution of peripheral tissue and body fluidand isatin conjoint site are widely distributed also. We understood more about the function and site of action with the develop of new pharmacological agent to contract its activity. The derivative of substituted isatin having aroused great attention in recent year due to their bioactive properties. It has been observed that incorporation of certain bioactive and pharmacological in the existing drug molecules sometimes exert a profound influence on the biological activity of the parent molecules these are compound **(1)** and **(2)**.After this the reaction further goes to forward direction to be synthesized the final product are-(7a-e) .Identification of the chemical structures of the synthesized compounds were confirmed by the help of their IR, MS and H^1NMR spectral data. The medicinal activity synthesized compounds were tested by cup-plate method.

MATERIAL AND METHOD

General

Reagents and solvents (they are used in these reactions) were obtained from natural sources or commercial sources and used without further purification. Melting points were determined by the Toshniwal apparatus and reported uncorrected. The spectral and elemental analyses of synthesized compounds have been carried out at the National Chemical Laboratory Pune (Maharashtra) and Regional Sophisticated Instrumentation Centre Chandigarh (Punjab). The purity of compounds was checked on thin layer chromatography (TLC) of silica mesh 120-160 in various non-aqueous solvent system, e.g. Benzene, dichloromethane etc. Proton nuclear magnetic resonance (H^1 NMR) spectra were recorded on a Bru-ker NMR spectrophotometer (Germany) (400MHz) in deuterated dimethyl sulfoxide (DMSO-d6) or deuterated chloroform solution at room temperature. Me_4Si was used as an internal reference. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer. The microwave-assisted reactions were carried out in a commercial multimode MW oven it has equipped with inverter technology and also attached with a magnetic stirrer and reflux condenser, operating at 1000W generating 2400 MHz frequency. Mass spectra of synthesized compounds were recorded on Kratos 50 mass spectrometer is work at 70 eV.

Experimental section:-

Synthesis of substituted amino salicylic acid(3a-e)-

These compounds were synthesized from nitration with further reduction.

(i) ***Nitration of salicylic acid:[14]*** **-** Substituted salicylic acid (1a-e) (0.01) mole treated with con.HNO_3/H_2SO_4 , In this reaction both acids mixed with each other and added salicylic acid drop by drop , finally nitrated product (2a-e) were obtained[15].

(ii) ***Reduction with $SnCl_2$[16]:*** **-** The formally synthesized compound (2a-e) go to reduction with $SnCl_2$/HCl so far, the resultant compounds (3a-e) were synthesized. These compound used in scheme-2 as an aromatic amine.

The spectral and analytical data of the compounds are as follows

Synthesis of 5-amino-3-fluoro-2-hydroxybenzoic acid(3a)-

mp*- 106^0 C , Yield- 67 % , *IR* (KBr cm^{-1}),3485,3332 cm^{-1}(N-H$_{str.}$) , 3015 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3020 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3330 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2870 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1450,1500,1562 cm^{-1} (Ar. C=C) ,H^1 NMR (400 MHz, CDCl$_3$) δH–6.70(s,1H,Ar-H) , 6.88(s,1H,Ar-H) , 5.30(s,2H,Ar-N-H) , 9.70(s,1H,Ar-OH) , 11.80(s,1H, –COOH)

Synthesis of 5-amino-3-chloro-2-hydroxybenzoic acid(3b)-

mp*- 110^0 C , Yield- 65 %*IR* (KBr cm^{-1}),3480,3330 cm^{-1}(N-H$_{str.}$) , 3012 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3018 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3327 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2868 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1452,1504,1562 cm^{-1} (Ar. C=C) H^1 NMR (400 MHz, CDCl$_3$) δH-6.96(s,1H,Ar-H) , 6.94(s,1H,Ar-H) , 5.30(s,2H,Ar-N-H) , 9.70(s,1H,Ar-OH) , 11.80(s,1H, –COOH)

Synthesis of 5-amino-3-bromo-2-hydroxybenzoic acid(3c)-

mp*- 115^0 C , Yield- 66 % , *IR* (KBr cm^{-1}),3478,3328 cm^{-1}(N-H$_{str.}$) , 3010 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3016 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3325 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2870 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1448,1502,1555 cm^{-1} (Ar. C=C) H^1 NMR (400 MHz, CDCl$_3$) δH-6.88(s,1H,Ar-H) , 7.02(s,1H,Ar-H) , 5.30(s,2H,Ar-N-H) , 9.70(s,1H,Ar-OH) , 11.80(s,1H, –COOH)

Synthesis of 5-amino-3-methyl-2-hydroxybenzoic acid(3d)-

mp*- 132^0 C , Yield- 62 % , *IR* (KBr cm^{-1}),3470,3322 cm^{-1}(N-H$_{str.}$) , 3005 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3010 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3330 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2875 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H) ,2920(sp^3 C-H) ,1450,1500,1560 cm^{-1} (Ar. C=C) , H^1 NMR (400 MHz, CDCl$_3$) δH-6.70(s,1H,Ar-H) , 6.90(s,1H,Ar-H) , 5.30(s,2H,Ar-N-H) , 9.70(s,1H,Ar-OH) , 11.80(s,1H, –COOH) , 2.17(s,3H,-CH$_3$)

Synthesis of 5-amino-3-ethyl-2-hydroxybenzoic acid(3e)-

mp*- 138^0 C , Yield- 60 % , *IR* (KBr cm^{-1}),3468,3320 cm^{-1}(N-H$_{str.}$) , 3007 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3018 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3323 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2873 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H), 2918(sp^3 C-H) , ,1450,1500,1560 cm^{-1} (Ar. C=C) , H^1 NMR (400 MHz, CDCl$_3$) δH-6.76(s,1H,Ar-H) , 6.96(s,1H,Ar-H) , 5.30(s,2H,Ar-N-H) , 9.70(s,1H,Ar-OH) , 11.80(s,1H, –COOH) , 2.47(q,2H,sp^3-CH$_2$) , 1.20(t,3H,sp^3-CH$_3$).

Synthesis of substituted 2-hydroxy-5-(2-oxoindolin-3-ylideneamino)benzoic acid derivative(5a-e).

The formally synthesized compound (3a-e) treated with indole 2,3-dione (isatin) took exact amount (0.01) mole presence of dry toluene as a solid support[17-18] under thermal condition comp.(5a-e) have synthesized. These compounds known as Schiff base. The spectral and analytical data of the compounds are as follows-

Synthesis of 3-fluoro-2-hydroxy-5-(2-oxoindolin-3-ylideneamino) benzoic acid (5a)-

mp*- 118^0 C , Yield- 63 % , *IR* (KBr cm^{-1}),3484,3330 cm^{-1}(N-H$_{str.}$) , 3014 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3018 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3328 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2872 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H) ,1722 cm^{-1} (sp^2 carbonyl carbon) ,1450,1500,1562 cm^{-1} (Ar. C=C) , 1646 cm^{-1}(for C=N$_{str.}$) , H^1 NMR (400 MHz, CDCl$_3$) δH-10.00(s,1H,for isatin N-H) , 7.84(s,1H,Ar-H) , 7.46(t,1H,Ar-H) , 7.28(t,1H,Ar-H) , 7.80(d,1H,Ar-H) , 7.13(s,1H,Ar-H) , 7.40(s,1H,Ar-H) , 9.70(s,1H,Ar-OH) , 11.85(s,1H, –COOH).

Synthesis of 3-chloro-2-hydroxy-5-(2-oxoindolin-3-ylideneamino) benzoic acid (5b)-

mp*- 130^0 C , Yield- 62 % , *IR* (KBr cm^{-1}),3478,3326 cm^{-1}(N-H$_{str.}$) , 3006 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3012 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3323 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2868 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1452,1500,1562 cm^{-1} (Ar. C=C) , 1644 cm^{-1}(for C=N$_{str.}$) H^1 NMR (400 MHz, CDCl$_3$) δH-10.00(s,1H,for isatin N-H) ,

7.84(s,1H,Ar-H) , 7.46(t,1H,Ar-H) , 7.28(t,1H,Ar-H) , 7.80(d,1H,Ar-H) , 7.55(s,1H,Ar-H) , 7.53(s,1H,Ar-H) , 9.70(s,1H,Ar-OH) , 11.85(s,1H, –COOH).

Synthesis of 3-bromo-2-hydroxy-5-(2-oxoindolin-3-ylideneamino) benzoic acid(5c)-

mp*- 138^0 C , Yield- 63 % , *IR* (KBr cm^{-1}),3480,3328 cm^{-1}(N-H$_{str.}$) , 3010 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3014 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3325 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2870 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1452,1500,1562 cm^{-1} (Ar. C=C) , 1648 cm^{-1}(for C=N$_{str.}$) H^1 NMR (400 MHz, CDCl$_3$) δH-10.00(s,1H,for isatin N-H) , 7.84(s,1H,Ar-H) , 7.46(t,1H,Ar-H) , 7.28(t,1H,Ar-H) , 7.80(d,1H,Ar-H) , 7.85(s,1H,Ar-H) , 7.54(s,1H,Ar-H) , 9.70(s,1H,Ar-OH) , 11.85(s,1H, –COOH).

Synthesis of 3-methyl-2-hydroxy-5-(2-oxoindolin-3-ylideneamino) benzoic acid(5d)-

mp*- 150^0 C , Yield- 60 % , *IR* (KBr cm^{-1}),3472,3320 cm^{-1}(N-H$_{str.}$) ,3002 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3010 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3323 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2868 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1452,1500,1562 cm^{-1} (Ar. C=C) , 1647 cm^{-1}(for C=N$_{str.}$) H^1 NMR (400 MHz, CDCl$_3$) δH-10.00(s,1H,for isatin N-H) , 7.84(s,1H,Ar-H) , 7.46(t,1H,Ar-H) , 7.28(t,1H,Ar-H) , 7.80(d,1H,Ar-H) , 7.45(2 signal for chemically equalivent two aromatic proton) , 2.13(s,3H,sp^3–CH$_3$) , 12.00(s,1H,Ar-OH), 11.95(s,1H, –COOH).

Synthesis of 3-methyl-2-hydroxy-5-(2-oxoindolin-3-ylideneamino) benzoic acid(5e)-

mp*- 168^0 C , Yield- 58 % , *IR* (KBr cm^{-1}),3470,3318 cm^{-1}(N-H$_{str.}$) ,2996 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3008 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3320 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2864 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1452,1500,1562 cm^{-1} (Ar. C=C) , 1644 cm^{-1}(for C=N$_{str.}$) , H^1 NMR (400 MHz, CDCl$_3$) δH-10.00(s,1H,for isatin N-H) , 7.84(s,1H,Ar-H) , 7.46(t,1H,Ar-H) , 7.28(t,1H,Ar-H) , 7.80(d,1H,Ar-H) , 7.45(s,1H,Ar-H) , 7.44(s,1H,Ar-H) , 12.00(s,1H,Ar-OH) , 2.49(q,2H,sp^3-CH$_2$) , 1.20(t,3H,sp^3-CH$_3$).
11.95(s,1H, –COOH).

Synthesis of 2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid derivative(7a-e).

The synthesis of 2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid derivative(7a-e) by two methods (1) conventional method[19] (2) Non conventional , but by conventional method higher yield were obtained so it is easy way to synthesized compound (7a-e).

Conventional[19]	***Nonconventional***
A equimolar mixture of compound (5) and thia glyco acid(0.01 mole) and anhydrous sodium acetate in glac acetic acid(10-15ml).After this ethanol(20-15ml) added this mixture and reflux it for 3-4 h. Cooling into ice cc water. The obtained solid was filtered and wash with benzene. Yield-60%	The equimolar mixture of compound(3) & (4) treated with thia glycolic acid(synthesized in situ) were adsorbed on mont.KSF(3.5g).Washed this mixture and irradiated for an appropriate time until the completion of reaction Monitored it by TLC technique for separation[20] . Yield-48%

The spectral and analytical data of the compounds are as follows-

Synthesis of 3-fluoro-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid (7a)-

mp*- 125^0 C , Yield- 60 % ,*IR* (KBr cm^{-1}),3482,3332 cm^{-1}(N-H$_{str.}$) , 3016 cm^{-1}(C-H$_{str.}$, Ar-H for C$_4$) , 3024 cm^{-1}(C-H$_{str.}$, Ar-H for C$_6$) , 3324 cm^{-1} (O-H$_{str.}$ due to H-bonding proton) , 2790 cm^{-1} (–COOH$_{str.}$ i.e. acidic O-H) ,1722 cm^{-1} (sp^2 carbonyl carbon) ,1450,1500,1562 cm^{-1} (Ar. C=C) , 2940 cm^{-1}(sp^3 C-H for N-CH$_2$) , 2935 cm^{-1} sp^3 C-H for S-CH$_2$) , H^1 NMR (400 MHz, CDCl$_3$) δH- 10.58(s,1H,for isatin N-H) , 7.36(d,1H,Ar-H for isatin ring) ,

7.20(t,1H, Ar-H for isatin ring) , 7.02(t,1H, Ar-H for isatin ring) , 7.14(d,1H,Ar-H) , 3.72,3.70(dd,2H , sp^3 C-H) , 2.62,2.60(dd,2H , sp^3 C-H) , 6.84(s,1H,Ar-H) , 7.02(s,1H,ar-H) , 9.80(s,1H,O-H) , 11.82(s,1H, –COOH).

Synthesis of 3-chloro-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid(7b)-

mp*- 136^0 C , Yield- 58 % , *IR* (KBr cm^{-1}),3480,3328 cm^{-1}(N-$H_{str.}$) , 3008 cm^{-1}(C-$H_{str.}$, Ar-H for C_4) , 3014 cm^{-1}(C-$H_{str.}$, , Ar-H for C_6) , 3325 cm^{-1} (O-$H_{str.}$ due to H-bonding proton) , 2870 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H) ,1452,1500,1562 cm^{-1} (Ar. C=C) , 2942 cm^{-1}(sp^3 C-H for N-CH_2) , 2937 cm^{-1} sp^3 C-H for S-CH_2) , H^1 NMR (400 MHz, $CDCl_3$) δH- 10.60(s,1H,for isatin N-H) , 7.37(d,1H,Ar-H for isatin ring) , 7.22(t,1H, Ar-H for isatin ring) , 7.03(t,1H, Ar-H for isatin ring) , 7.16(d,1H,Ar-H) , 3.72,3.70(dd,2H , sp^3 C-H) , 2.62,2.61(dd,2H , sp^3 C-H) , 6.86(s,1H,Ar-H) , 7.05(s,1H,ar-H) , 9.82(s,1H,O-H) , 11.84(s,1H, –COOH).

Synthesis of 3-bromo-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid(7c)-

mp*- 150^0 C , Yield- 56 % ,*IR* (KBr cm^{-1}),3482,3330 cm^{-1}(N-$H_{str.}$) , 3014 cm^{-1}(C-$H_{str.}$, Ar-H for C_4) , 3016 cm^{-1}(C-$H_{str.}$, , Ar-H for C_6) , 3330 cm^{-1} (O-$H_{str.}$ due to H-bonding proton) , 2876 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H) ,1452,1504,1564 cm^{-1} (Ar. C=C) , 2946cm^{-1}(sp^3 C-H for N-CH_2) , 2940 cm^{-1} sp^3 C-H for S-CH_2) , H^1 NMR (400 MHz, $CDCl_3$) δH- 10.62(s,1H,for isatin N-H) , 7.39(d,1H,Ar-H for isatin ring) , 7.25(t,1H, Ar-H for isatin ring) , 7.05(t,1H, Ar-H for isatin ring) , 7.18(d,1H,Ar-H) , 3.70,3.68(dd,2H , sp^3 C-H) , 2.62,2.60(dd,2H , sp^3 C-H) , 7.00(s,1H,Ar-H) , 7.20(s,1H,ar-H) , 15.50(s,1H,O-H) , 11.84(s,1H,
–COOH).

Synthesis of 2-hydroxy-3-methyl-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid (7d) –

mp*- 175^0 C , Yield- 54 % , *IR* (KBr cm^{-1}),3468,3318 cm^{-1}(N-$H_{str.}$) ,2996 cm^{-1}(C-$H_{str.}$, Ar-H for C_4) , 3006 cm^{-1}(C-$H_{str.}$, , Ar-H for C_6) , 3320 cm^{-1} (O-$H_{str.}$ due to H-bonding proton) , 2864 cm^{-1} (–$COOH_{str.}$ i.e. acidic O-H) ,1450,1506,1560 cm^{-1} (Ar. C=C) , 2944cm^{-1}(sp^3 C-H for N-CH_2) , 2938cm^{-1} sp^3 C-H for S-CH_2) , H^1 NMR (400 MHz, $CDCl_3$) δH- 10.56(s,1H,for isatin N-H) , 7.34(d,1H,Ar-H for isatin ring) , 7.18(t,1H, Ar-H for isatin ring) , 7.01(t,1H, Ar-H for isatin ring) , 7.12(d,1H,Ar-H) , 3.72,3.70(dd,2H , sp^3 C-H) , 2.60,2.58(dd,2H , sp^3 C-H) , 6.81(s,1H,Ar-H) ,2.13(s,3H,sp^3 methyl group) 6.98(s,1H,Ar-H) , 12.02(s,1H,O-H) , 11.80(s,1H, –COOH).

Synthesis of 3-ethyl-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid (7e) –

mp*- 180^0 C , Yield- 53 % *IR* (KBr cm^{-1}),3464,3316 cm^{-1}(N-$H_{str.}$) ,2992 cm^{-1}(C-$H_{str.}$, Ar-H for C_4) , 3002 cm^{-1}(C-$H_{str.}$, , Ar-H for C_6) , 3316 cm^{-1} (O-$H_{str.}$ due to H-bonding proton) , 2860 cm^{-1} (–COOH $_{str.}$ i.e. acidic O-H) ,1446,1502,1556 cm^{-1} (Ar. C=C) , 2940cm^{-1}(sp^3 C-H for N-CH_2) , 2934cm^{-1} (sp^3 C-H for S-CH_2) , H^1 NMR (400 MHz, $CDCl_3$) δH- 10.57(s,1H,for isatin N-H) , 7.35(d,1H,Ar-H for isatin ring) , 7.19(t,1H, Ar-H for isatin ring) , 7.03(t,1H, Ar-H for isatin ring) , 7.14(d,1H,Ar-H) , 3.72,3.71(dd,2H , sp^3 C-H) , 2.60,2.59(dd,2H , sp^3 C-H) , 6.81(s,1H,Ar-H) ,2.52(q,2H , for sp^3 –CH_2 for ethyl) , 1.27(t,3H, for sp^3 methyl group) 6.98(s,1H,Ar-H) , 12.06(s,1H,O-H) , 11.80(s,1H, –COOH

RESULT AND DISCUSSION

The most favorable conditioning compound, 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid**(7)** were synthesized from the reaction of indole 2,3 –dione **(4)** and substituted 4-amino salicylic acid (3) by the solvent free multi component condensation reaction[7-9]. Before the synthesis of the above compound **(7)** compound **(5)** is form as a mediator, this mediator compound is known as Schiff base. The relative reactivity of the Schiff base depends on the substituent. The Schiff bases are synthesized from the reaction of indole 2, 3 –dione (**4)** andsubstituted 4-amino salicylic acid (3) presence of dry toluene under thermal condition. As we know that this reaction is solvent free till synthesizing compound **(5)**. Schiff base (**5)** of isatin can be synthesized by the condensation reaction between isatin **4** and substituted 4-amino salicylic acid **3** (scheme-2) [10]. This Schiff base also synthesized in the presence of glacial acetic acid in the solvent ethanol in the reflux condition or MW[11-12].

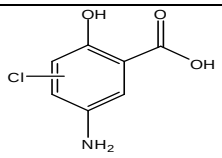
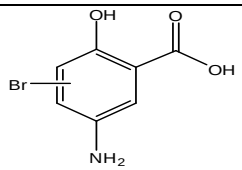
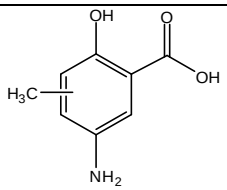
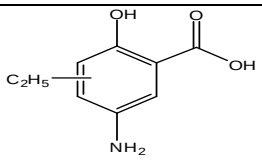
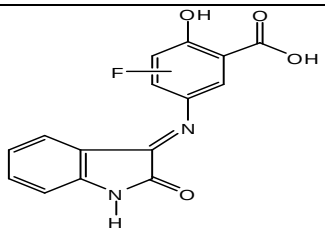
The Spiro[indole-thiazadinone] system(7a-e) has been synthesized earlier time with two steps procedure with obtain yield 55%-65% using substituted aromatic amine(synthesized in scheme-1) as a key intermediate. In this compound the mixed alcohol was removal by azeotropic method[13].These reactions

were proceed presence of dehydrogenating agent and using large amount of volatile and toxic solvents at elevated temperature for several hours of heating were of some utility. Further the product is generally purified by stream distillation methods or column chromatography with further need of solvent.

Now we took spectral and analytical study of the synthesized compound. The IR spectrum of the 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid derivative compounds displaced characteristic absorption band in region 1690-1720 cm^{-1} due to C=O vibration. The appearance of C=N band at 1650 cm^{-1} and no absorption in the region 1670 cm^{-1} show that –CO-C=N- moiety of Schiff base use in cyclization , and a sharp characteristic absorption band due to –CO-OH i.e. acidic in the region 2500-3000 cm^{-1} but it actually obtained 2868 cm^{-1} .

The H^1 NMR spectra for resultant compound **(7a-e)** are- exhibit four separate peaks appear in the region δH 6.64, 7.05, 6.72 and 7.04 respectively for Ar-H attached with the isatin benzene ring. Another peak exhibit three peaks appear in the region δH 6.70, 7.21, 7.26 respectively for Ar-H attached with the salicylic acid ring.

CONCLUSION

product	X	Mol. Formula & Mol. Weight	Mol. Structure	m.p.	Time(min)	Yield %
3b	Cl	$C_7H_6NO_3Cl$ 187		110	25-30	65
3c	Br	$C_7H_6NO_3Br$ 222		115	30-35	66
3d	CH_3	$C_8H_9NO_3$ 167		132	31-36	62
3e	C_2H_5	$C_9H_{11}NO_3$ 181		138	30-35	60
5a	F	$C_{15}H_9N_2O_4F$ 299		118	18-24	63

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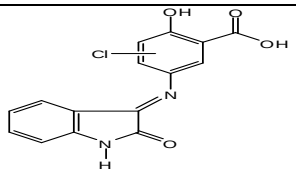
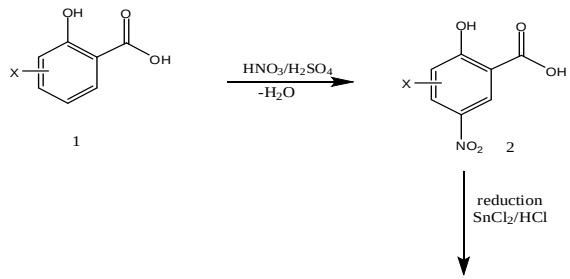
5b	Cl	$C_{15}H_9N_2O_4Cl$ 316		130	18-24	62

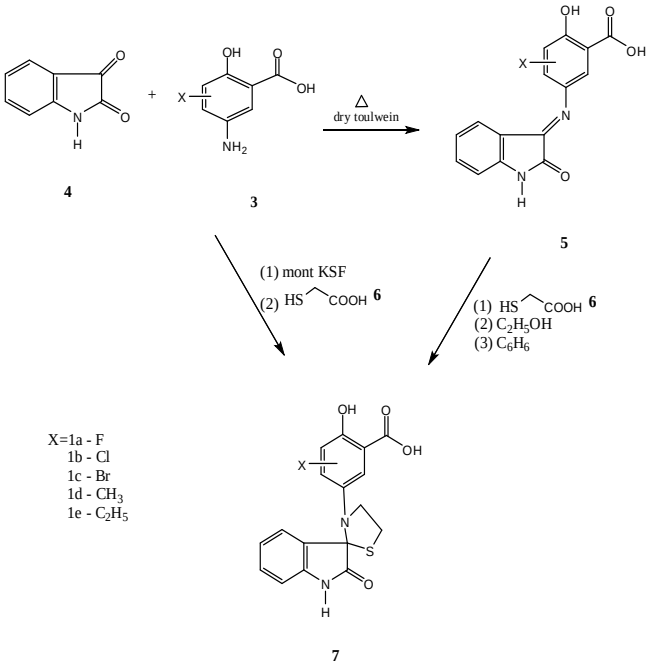
From the above detail study we can advocate this route such as- facile, efficient and environmental or economical for the one-pot synthesis of a series of 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid **(7a-e)** with few drops of DMF using montmorillonite KSF and silica mesh 120-160 as a inorganic solid support. The advantages are –

(i) Obtained good yields.
(ii) These reactions are solid support so no need of any solvent.
(iii) Non inflammable and nontoxic reaction medium,
(iv) No requirement for additional reagent/catalyst
(v) Virtually no waste generation and
(vi) Ease of product isolation and further purification.

SCHEME-1



SCHEME-2



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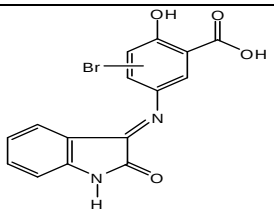
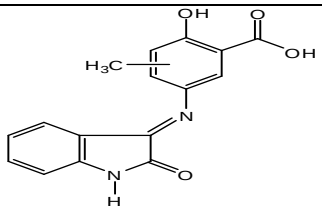
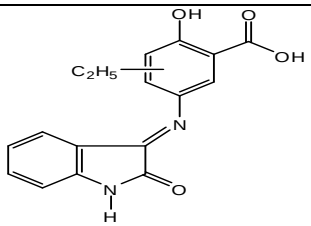
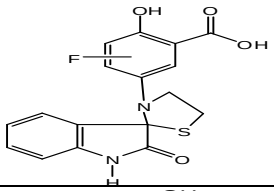
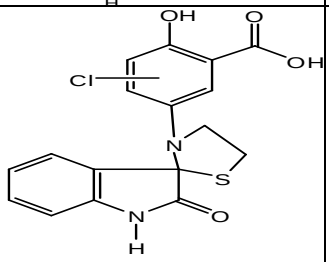
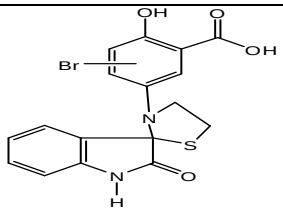
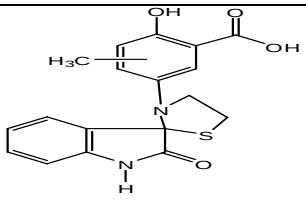
5c	Br	$C_{15}H_9N_2O_4Br$ 351		138	20-25	63
5d	CH_3	$C_{16}H_{12}N_2O_4$ 296		150	25-30	60
5e	C_2H_5	$C_{17}H_{14}N_2O_4$ 310		168	30-35	58
7a	F	$C_{17}H_{13}N_2SO_4F$ 359		125	35-40	60
7b	Cl	$C_{17}H_{13}N_2SO_4Cl$ 376		136	35-40	58
7c	Br	$C_{17}H_{13}N_2SO_4Br$ 411		150	38-44	56
7d	CH_3	$C_{18}H_{16}N_2SO_4$ 356		175	30-35	54

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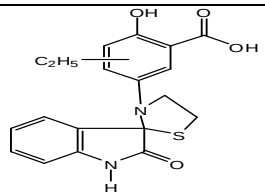
7e	C_2H_5	$C_{19}H_{18}N_2SO_4$ 370		180	35-40	53

Biological evolution of synthesized 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acidderivative.

Before we go to the study of some biological importance of 2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acidderivative **,** study of biological importance of salicylic acid take place.

Salicylic acid (SA) (2-hydroxy benzoic acid), a phenolic compound, has been studied for its medicinal use in humans and plant. It contain –OH and –COOH group in nearby carbon atom at benzene ring so it goes to hydrogen bonding. Salicylic acid plays an important role for the growth and development of the plant response to abiotic stress such as-chilling, heavy metal toxicity,osmotic stress and heat[21-22] etc. Some of the Salicylic acid derivative play important role in plant immune system[23].

Antimicrobial activity

The previous report reveals that Schiff base of isatin with substituted aromatic amine of salicylic acid show good antimicrobial activity, specially halogenated aromatic amine**(7a-c)**. Suspension of each micro organism was prepared and applied with cup plate method using DMF, after incubated(approx 15-18 h) at elevated temperature 35-40^{o} C. All the synthesis compounds were tested for vitro antimicrobial activity contained MIC value against pathogenic (*S.aureus* and *S.Pyogenes* , *clostridium*) and non-pathogenic bacteria.

Antifungal activity

The antifungal activity of these compounds generally methyl and ethyl **(7d-e)** were studies with pathogenic fungi such as- *Mucor, Penisellium, Aspergillus fumigatus* and *fugerium* etc. using cup plate method too.Suspension of each fungus were prepared separately and applied to agar plates with sequentially diluted compounds to be tested. The plates were incubated at 25-28 ^{o}C for 75-80 h and MIC's were determined.

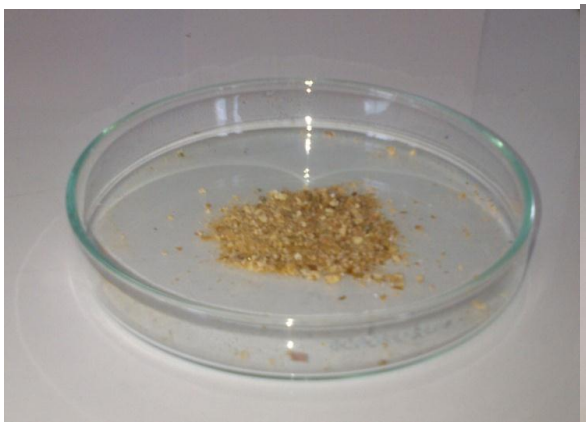


Fig.1. 3-bromo-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid

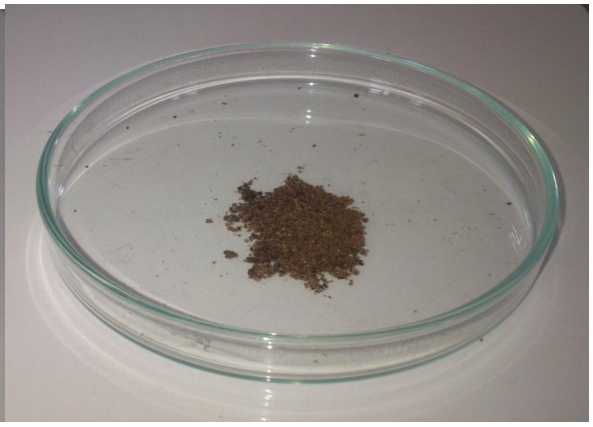


Fig.2. 3-chlaro-2-hydroxy-5-(2-oxospiro[indoline3,2'-thiazolidine]-3'-yl)benzoic acid

The above both two compounds shown in fig.1 &2 having antibacterial properties against S.aureus and S.Pyogenes and clostridium. This compound has antibacterial activity against gram negative rather than gram positive so far. The antibacterial properties checked by disc diffusion technique.

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Fig.2. 3-methyl-2-hydroxy-5-(2-oxospiro[indoline-3,2'-thiazolidine]-3'-yl)benzoic acid

The above compound show in fig.2. has antifungal activity against aspergillus Niger, aspergillus fumigatus, aspergillus flavus , Penisellium and fugerium etc. The antifungal properties also checked by disc diffusion technique.

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