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Note

Synthesis and antimicrobial evaluation of ethoxyphthalimide derivatized spiro [indole-3,5′-(1,3)thiazolo(4,5-*c*)isoxazol]-2(1*H*)-ones *via* ring closure metathesis

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The synthesis of 3′-{(4-substituted phenyl-1-*N*-ethoxyphthalimido-6′-pyridin-2-yl}-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]-thiazolo[4,5-*c*]isoxazol]-2(1*H*)-ones **6a-d** is carried out through a five step pathway starting from acid catalyzed condensation of 2-aminopyridine with isatin yielding 3-(pyridin-2-ylimino)-1,3-dihydro-2*H*-indol-2-one **1** which on reaction with thioacetic acid in the presence of anhydrous $ZnCl_2$ give 3′-pyridin-2-yl-4′*H*-spiro[indole-3,2′-[1,3]thiazolidine]-2,4′(1*H*)-dione **2**. Reaction of **2** with various araldehydes **3a-d** affords the corresponding 5′-[(4-substituted phenyl)methylidene]-3′-pyridin-2-yl-4′*H*-spiro-[indole-3,2′-[1,3]thiazolidine]-2,4′(1*H*)-diones **4a-d**. These chalcones are further cyclised with hydroxylamine hydrochloride to furnish 3′-(4-substituted phenyl)-6′-pyridin-2-yl-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-ones **5a-d** which are subsequently condensed with ω-bromoethoxy-phthalimide to yield the targeted compounds **6a-d**. Structural confirmation of the synthesized compounds has been accomplished by IR, ^{1}H NMR, and mass spectral data. Final compounds have been screened for their antimicrobial activity.

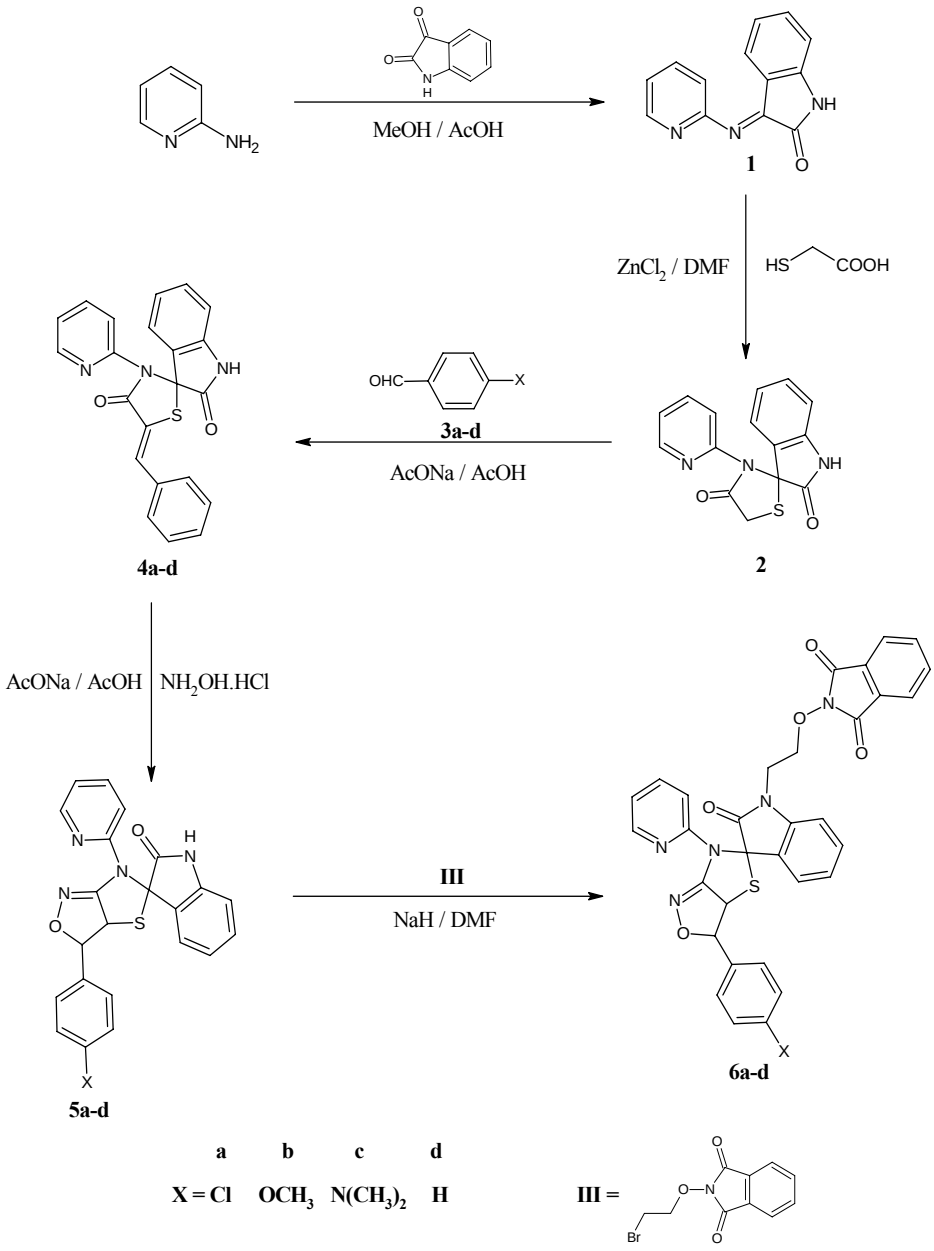
Keywords: Isatin, 2-aminopyridine, thiazolidinone, isoxazole, ω-bromoethoxyphthalimide

A perusal of the literature has revealed manifold potential pharmaceutical implications[1-3] of thiazolidin-4-ones *viz.* antibacterial[4,5], antimicrobial[6-8], antiviral[9], and anticonvulsant[10] effects. Spiro [indole-thiazolidines] are endowed with various pharmacological activities e.g. anti-inflammatory[11], fungistatic[12], bacteriostatic[13] and anticonvulsant[14] properties. Consequently, a large number of synthetic protocols leading to these compounds have been reported in the literature[15]. Isatin derivatives have recently received considerable attention owing to their wide application as anti-HIV, antitubercular[16], antiplasmodial[17], anticonvulsant[18], sedative and hypnotic[19] agents. Isoxazole, an another class of azole group is a versatile pharmacophore, possessing diverse pharmacological properties[20,21] such as herbicidal[22], antitumor[23], antipsychotic[24], anticoagulant[25], antimicrobial[26] and antagonist[27]. Many naturally occurring and synthetic compounds containing the pyridine scaffold have been reported to possess various pharmacological properties[28] *viz.* anticonvulsant[29], antimicrobial[30] and has extensively been used in the treatment of cardiovascular[31] disorders. Several derivatives of alkoxyphthalimide have been synthesized[32] and found to be associated with a wide range of pharmacological activities *i.e.* anticancer, antimalarial[33], antiepileptic[34] etc. Prompted by the aforesaid biological and pharmacological, activities, and in sequel to our work we undertake the synthesis of some new combinational molecules, incorporating above moieties with a hope of augmentation in biological activities.

Results and Discussion

In the present investigation, we aimed to synthesize ethoxyphthalimide derivatives of 3′-(4-substituted phenyl)-6′-pyridin-2-yl-3,3*a*′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*] isoxazol]-2-(1*H*)-one **5a-d** through a multistep process. For this purpose, schiff base 3-(pyridine-2-ylimino)-1,3-dihydro-2*H*-indol-2-one **1** was prepared from acid catalysed condensation of 2-amino pyridine and isatin. The resonance peak of NH_2 group appearing at δ 6.3 ppm in the ^{1}H NMR of 2-amino pyridine disappeared in the ^{1}H NMR of **1** supporting the participation of this group in the schiff base formation. IR spectra of **1** showed NH group frequency at 3219 cm^{-1} and ^{1}H NMR signals at δ 8.84 (s, 1H, NH of isatin) further confirmed its formation. Compound **1** on refluxing with mercaptoacetic acid in DMF for 10-12 hr in the presence of catalytic amount of anhy. $ZnCl_2$ afforded 3'-pyridin-2-yl-4'*H*-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1*H*)-dione **2**. Its structure was confirmed on the basis of IR spectral peak appearing at 684 cm^{-1} indicating presence of C-S-C stretching and the ^{1}H NMR spectrum displayed a singlet at δ 4.39 (s, 2H, CH_2). Condensation of compound **2** with various araldehydes **3a-d** gave the corresponding arylidene derivatives **4a-d** in quantitative yields. Structure of **4a** was confirmed by

appearance of a peak at 757 cm^{-1} for C-Cl stretching and a new singlet at δ 6.4 (C=CH-Ar) in IR and NMR spectra respectively. Cyclocondensation of **4a-d** with hydroxylamine hydrochloride in presence of sodium acetate yielded **5a-d**. ^{1}H NMR spectrum of **5a** was devoid of a singlet at δ 6.4 (for C=CH-Ar), which was although present in its precursor, confirmed cyclisation. Subsequent condensation of compounds **5a-d** with phthalimidoxyethyl bromide III in NaH and DMF, furnished the target compounds 3′-(4-substituted phenyl)-1-N-ethoxyphthalimido-6′-pyridin-2-yl-3,3*a*′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo-[4,5-*c*]isoxazol]-2-(1*H*)-ones **6a-d** (**Scheme I**). Formation of **6a-d** were supported by the positive chemical test (fluorescence test); characteristic for the phthalimido group. Structure of **6a** was elucidated on the basis of disappearance of N-H stretching band at 3309 cm^{-1} in IR spectra, indicating that NH group of indole has been replaced by imidoxy moiety. Furthermore, appearance of two characteristic triplets for O-CH_2 and N-CH_2 at δ 4.49 and 3.08 confirmed the formation of **6a**. Mass spectrum also supported the



Scheme I

proposed structure by viewing molecular ion peak at *m/z* 623 and M+2 peak at *m/z* 625 corresponding to the molecular formula $C_{32}H_{22}ClN_5O_5S$.

Antimicrobial Screening

Antimicrobial activity i.e. antibacterial and antifungal was screened by Well or Cup method[35] in Nutrient agar and dextrose agar medium. Agar medium was sterilized by autoclaving at 15 psi and 121°C for 20 min. The medium was poured in Petri dishes and left to solidify. These Petri dishes were inoculated with 0.2 mL suspension of organism by spread plate method[36]. Three or four wells of 11 mm diameter were made in the medium with the help of a sterile borer and filled with 500 ppm solution of testing compound in DMF. Similarly other wells were made for standard drugs and filled with standard concentration. These petri plates were incubated at 37°C in an incubator. The petri dishes were examined for zone of inhibition after 48 hr. Bacterial strains used for the present investigation are *P. aureoginosa*, *P. mirabilis, E. coli* and *K. pneumoniae*. Ciprofloxacin was used as a standard drug. *Candida albicans* and *Aspergillus fumigatus* were used as the testing fungal strains and Amphotericin B was used as standard drug. Zone of inhibition was measured in mm. Activity index of all the synthesized compounds was also calculated against the standard drugs. Eight compounds *viz*. **5a-d** and **6a-d** were assayed for antimicrobial activity (**Table I**). Screening results of the compounds **6a-d** established that **6a** showed comparable activity against all the tested micro-organisms as compared to the standard drugs used, while **6b** exhibited good activity and **6c** and **6d** were weakly active against all the four bacterial and two fungal strains. Overall activity profile of compounds **5a-d** was found to be moderate. Thus in the present study, we attempted to increase antimicrobial activities by fusing ethoxyphthalimide moiety with thiazolo [4,5-*c*]isoxazole ring system. As far as the relation between structure and activity are concerned the chloro and methoxy substituted compounds were found to display enhanced activity than the other substituents.

Experimental Section

General Procedures: Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra were recorded on Perkin-Elmer spectrometer.

Table I — Antimicrobial activity of the synthesized compounds **5a-d** and **6a-d**. Zone of inhibition (mm) (activity index)[std]

Compd. No.	Antibacterial Activity				Antifungal Activity	
	P. mirabilis	*K. pneumoniae*	*E.coli*	*P. aureoginosa*	*C. albicans*	*A. fumigatus*
5a	10 (0.58)	11 (0.68)	10 (0.62)	12 (0.66)	17 (1.00)	10 (1.0)
5b	10 (0.58)	9 (0.56)	9 (0.56)	11 (0.61)	15 (0.88)	8 (0.8)
5c	8 (0.47)	7 (0.43)	7 (0.43)	6 (0.33)	12 (0.70)	8 (0.8)
5d	9 (0.53)	9 (0.56)	8 (0.50)	8 (0.44)	13 (0.76)	9 (0.9)
6a	11 (0.64)	13 (0.81)	12 (0.75)	13 (0.72)	21 (1.23)	14 (1.4)
6b	9 (0.53)	11 (0.68)	9 (0.56)	8 (0.44)	18 (1.05)	10 (1.0)
6c	7 (0.41)	8 (0.50)	9 (0.56)	7 (0.38)	14 (0.82)	13 (1.3)
6d	8 (0.47)	10 (0.62)	11 (0.68)	9 (0.50)	19 (1.11)	11 (1.1)
C_1	17	16	16	18	17	10

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug
For antibacterial activity: C_1 = Ciprofloxacin
For antifungal activity: C_1 = Amphotericin B

The ^{1}H NMR spectra were scanned on a Bruker DRX-300 MHz. spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer. Phthalimidoxyethyl bromide[37] III was synthesized by literature method.

Synthesis of 3-(pyridin-2-ylimino)-1,3-dihydro-2*H*-indol-2-one 1

An equimolar mixture of 2-amino pyridine and isatin were refluxed in methanol (40 mL) in presence of catalytic amount of glacial acetic acid for 3 hr and allowed for cooling. Schiff base thus obtained was filtered and recrystallised from methanol to give **1,** $C_{13}H_9N_3O$; Mol.Wt. 223; Yield 76%, m.p.179ºC; Anal. Calcd.: N, 18.82; Found: N, 18.78%; IR (KBr): 3219 (N-H str.), 3017 (C-H str., ArH), 1713 (C=Ostr.), 1633 cm^{-1} (C=N str.); ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H, NH), 7.10-6.83 (m, 8H, ArH).

Synthesis of 3′-pyridin-2-yl-4′*H*-spiro[indole-3,2′-[1,3]thiazolodine]-2,4′(1*H*)-dione 2

A well stirred solution of **1** (0.01 mole) in dry DMF containing pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mole) was refluxed for 12 hr. Excess of solvent was distilled off under reduced pressure and the residual reaction-mixture was cooled and poured into ice cold water. The separated solid was filtered washed and recrystalised from ethanol to yield **2**. $C_{15}H_{11}N_3O_2S$; Mol.Wt. 297; Yield 69%, m.p.107ºC; Anal. Calcd.: N, 14.13; S, 10.78; Found: N, 14.07; S, 10.81%; IR (KBr): 3310 (N-H str.), 3029 (C-H str., ArH), 1740 (C=Ostr.), 1642 cm^{-1} (C=N str.), 684 (C-S-C str.); ^{1}H NMR ($CDCl_3$): δ 8.92 (s, 1H, NH), 7.2-7.5 (m, 8H, ArH)), 4.39 (s, 2H, CH_2).

Synthesis of 5′-[(4-chloro phenyl)methylidene]-3′-pyridin-2-yl-4′*H*-spiro[indole-3,2′-[1,3]thiazolidine]-2,4′(1*H*)-dione 4a

To a refluxing mixture of **2** (0.01 mole) and sodium acetate (0.01 mole) as a base in glacial acetic acid, 4-chlorobenzaldehyde **3a** (0.01 mole) was added and refluxing was continued for 16 hr. After completion of reaction, ice cold water was added to the reaction-mixture to get crude product which was filtered, washed and recrystallised from ethanol to give **4a**. $C_{22}H_{14}ClN_3O_2S$; Mol.Wt. 419; Yield 64%, m.p.194ºC; Anal. Calcd.: N, 10.01; S, 7.64; Found: N, 10.09; S, 7.56%; IR (KBr): 3326 (N-H str.), 3043 (C-H str., ArH), 1726 (C=Ostr.), 1633 cm^{-1} (C=N str.), 692 (C-S-C str.), 757 cm^{-1} (C-Cl str.), 1259 (C-N str.); ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H, NH), 7.01-7.84 (m, 12H, ArH)), 6.4 (s, 1H, C=CH-Ar).

Compounds **4b-d** were prepared by similar method with minor change in reaction conditions. Their spectral data are given below.

5′-[(4-Methoxy phenyl)methylidene]-3′-pyridin-2-yl-4′*H*-spiro[indole-3,2′-[1,3]thiazolidine]-2,4′(1*H*)-dione 4b. $C_{23}H_{17}N_3O_3S$; Mol.Wt. 415; Yield 59%, m.p.204ºC; Anal. Calcd.: N, 10.11; S, 7.72. Found: N, 10.05; S, 7.66%; IR (KBr): 3318 (N-H str.), 3024 (C-H str., ArH), 1707 (C=Ostr.), 1614 (C=N str.), 681 (C-S-C str.), 1034 (C-O str.), 1251 cm^{-1} (C-N str.); ^{1}H NMR ($CDCl_3$): δ 8.94 (s, 1H, NH), 7.2-7.6 (m, 12H, ArH), 6.1 (s, 1H, C=CH-Ar), 3.1 (s, 3H, OCH_3).

5′-[(4-Dimethylamino phenyl)methylidene]-3′-pyridin-2-yl-4′*H*-spiro[indole-3,2′-[1,3]thiazolidine]-2,4′-(1*H*)-dione 4c. $C_{24}H_{20}N_4O_2S$; Mol.Wt. 428; Yield 66%, m.p.271ºC; Anal. Calcd.: N, 13.07; S, 7.48; Found: N, 13.16; S, 7.46%; IR (KBr): 3312 (N-H str.), 3039 (C-H str., ArH), 1724 (C=Ostr.), 1602 (C=N str.), 672 (C-S-C str.), 1234 cm^{-1} (C-N str.); ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H, NH), 7.48-7.86 (m, 12H, ArH), 6.3 (s, 1H, C=CH-Ar), 3.72 (s, 6H, CH_3).

5′-(Phenyl)methylidene-3′-pyridin-2-yl-4′*H*-spiro-[indole-3,2′-[1,3]thiazolidine]-2,4′(1*H*)-dione 4d. $C_{22}H_{15}N_3O_2S$; Mol.Wt. 385; Yield 68%, m.p.158ºC; Anal. Calcd.: N, 10.90; S, 8.32. Found: N, 10.79; S, 8.29%; IR (KBr): 3323 (N-H str.), 3024 (C-H str., ArH), 1732 (C=Ostr.), 1624 (C=N str.), 686 (C-S-C str.), 1242 cm^{-1} (C-N str.); ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H, NH), 7.4-7.6 (m, 13H, ArH), 5.9 (s, 1H, C=CH-Ar).

Synthesis of 3′-[(4-chloro phenyl)]-6′-pyridin-2-yl-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo-[4,5-c]isoxazol]-2(1*H*)-one 5a

Anhydrous sodium acetate (0.01 mole) was dissolved in hot acetic acid. Compound **4a** (0.01 mole) was taken in absolute alcohol (10 mL) and to it hydroxylamine hydrochloride (0.01 mole) in absolute alcohol (10 mL) was added. The solution of sodium acetate in acetic acid was transferred to this reaction-mixture and refluxed for 10 hr. It was poured into ice cold water, the product obtained was filtered and recrystallised from DMF to yield **5a**. $C_{22}H_{15}ClN_4O_2S$; Mol.Wt. 434; Yield 65%, m.p.218ºC; Anal. Calcd.: N, 12.88; S, 7.37. Found: N, 12.82; S, 7.43%; IR (KBr):

3309 (N-H str.), 3054 (C-H str., ArH), 1696 (C=Ostr.), 1620 (C=N str.), 687 (C-S-C str.), 755 cm^{-1} (C-Cl str.), 1246 (C-N str.), 1352 (N-O str.), 1072 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 8.16 (s, 1H, NH), 7.56-7.34 (m, 12H, ArH), 3.86 (d, 1H, CH-S), 4.47 (d, 1H, CH-O).

Similarly, **5b-d** were also synthesized by similar method using with minor modifications in reflux time. Their spectral data are given below:

3′-[(4-Methoxy phenyl)]-6′-pyridin-2-yl-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 5b. $C_{23}H_{18}N_4O_3S$; Mol.Wt. 430; Yield 61%, m.p. 190ºC; Anal. Calcd.: N, 13.01; S, 7.45; Found: N, 13.04; S, 7.41%; IR (KBr): 3301 (N-H str.), 3037 (C-H str., ArH), 1702 (C=Ostr.), 1621 (C=N str.), 673 (C-S-C str.), 1242 (C-N str.), 1372 (N-O str.), 1072 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 8.56 (s, 1H, NH), 7.41-7.84 (m, 12H, ArH), 3.73 (d, 1H, CH-S), 4.51 (d, 1H, CH-O), 3.3 (s, 3H, OCH_3).

3′-[(4-Dimethylamino phenyl)]-6′-pyridin-2-yl-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo-[4,5-*c*]isoxazol]-2(1*H*)-one 5c. $C_{24}H_{21}N_5O_2S$; Mol.Wt. 443; Yield 67%, m.p.229ºC; Anal. Calcd. N, 15.79; S, 7.23; Found: N, 15.88; S, 7.15%. IR (KBr): 3307 (N-H str.), 3022 (C-H str., ArH), 1712 (C=Ostr.), 1645 (C=N str.), 659 (C-S-C str.), 1249 (C-N str.), 1367 (N-O str.), 1063 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 8.51 (s, 1H, NH), 7.01-7.84 (m, 12H, ArH), 3.73 (d, 1H, CH-S), 4.51 (d, 1H, CH-O), 3.78 (s, 6H, CH_3).

3′-Phenyl-6′-pyridin-2-yl-3,3a′-dihydro-6′*H*-spiro-[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 5d. $C_{22}H_{16}N_4O_2S$; Mol.Wt. 400; Yield 63%, m.p. 201ºC; Anal. Calcd.: N, 13.99; S, 8.01; Found: N, 13.92; S, 8.06%; IR (KBr): 3319 (N-H str.), 3031 (C-H str., ArH), 1724 (C=Ostr.), 1637 (C=N str.), 676 (C-S-C str.), 1233 (C-N str.), 1354 (N-O str.), 1037 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 8.31 (s, 1H, NH), 7.23-7.56 (m, 13H, ArH), 3.71 (d, 1H, CH-S), 4.46 (d, 1H, CH-O).

Synthesis of 3′-{[(4-chloro phenyl)-1-N-ethoxy-phthalimido]-6′-pyridin-2-yl}-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 6a.

Compound **5a** (0.01 mole) was dissolved in 15 mL DMF and sodium hydride (0.01 mole) was added portionwise with constant stirring at 0-10ºC for 4 hr. Phthalimidoxyethyl bromide (0.01 mole) was added to above mixture with continuous stirring on a magnetic stirrer. Further the reaction-mixture was refluxed for 6 hr. Excess of solvent was distilled off and the residual reaction-mixture was cooled and poured into ice cold water. Solid obtained was recrystallised from ethanol to give **6a**. $C_{32}H_{22}ClN_5O_5S$; Mol.Wt. 623; Yield 62%, m.p.164ºC; Anal. Calcd.: N, 11.22; S, 5.14. Found: N, 11.19; S, 5.11%; IR (KBr): 3054 (C-H str., ArH), 1689, 1713 (C=Ostr.), 1627 (C=N str.), 684 (C-S-C str.), 1249 (C-N str.), 1332 (N-O str.), 1037 (C-O str.), 753 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 7.31-8.29 (m, 16H, ArH), 3.9 (d, 1H, CH-S), 4.19 (d, 1H, CH-O), 4.49 (t, 2H, OCH_2), 3.08 (t, 2H, NCH_2); MS: *m/z* 625 $[M+2]^{+\cdot}$, 623 $[M]^{+\cdot}$, 547 $[M\text{-}C_6H_4]^{+\cdot}$, 491 $[M\text{-}C_8H_4O_2]^{+\cdot}$, 461 $[M\text{-}C_8H_4NO_3]^{+\cdot}$, 433 $[M\text{-}C_{10}H_8NO_3]^{+\cdot}$, 391 $[M\text{-}C_{11}H_8N_2O_4]^{+\cdot}$, 315 $[M\text{-}C_{17}H_{12}N_2O_4]^{+\cdot}$, 271 $[M\text{-}C_{18}H_{12}N_2O_4S]^{+\cdot}$,179 $[M\text{-}C_{23}H_{16}N_4O_4S]^{+\cdot}$, 153 $[M\text{-}C_{25}H_{18}N_4O_4S]^{+\cdot}$, 124 $[M\text{-}C_{25}H_{17}N_5O_5S]^{+\cdot}$, 111 $[M\text{-}C_{26}H_{18}N_5O_5S]^{+\cdot}$

Similarly, compounds **6b-d** were also prepared with some change in reflux time and reaction work up. Their characteristic spectral and analytical data are given below:

3′-{[(4-Methoxy phenyl)-1-N-ethoxyphthalimido]-6′-pyridin-2-yl}-3,3a′-dihydro-6′*H*-spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 6b. $C_{33}H_{25}N_5O_6S$; Mol. Wt. 619; Yield 58%, m.p. 254ºC; Anal. Calcd.: N, 11.30; S, 5.17; Found: N, 11.23; S, 5.04%; IR (KBr): 3049 (C-H str., ArH), 1672, 1729 (C=Ostr.), 1634 (C=N str.), 673 (C-S-C str.), 1219 (C-N str.), 1313 (N-O str.), 1042 (C-O str.), 761 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 7.43-8.16 (m, 16H, ArH), 3.5 (d, 1H, CH-S), 4.09 (d, 1H, CH-O), 4.03 (t, 2H, OCH_2), 3.2 (t, 2H, NCH_2), 3.1 (s, 3H, OCH_3); MS: *m/z* 619 $[M]^{+\cdot}$, 588 $[M\text{-}CH_3O]^{+\cdot}$, 512 $[M\text{-}C_7H_7O]^{+\cdot}$, 486 $[M\text{-}C_9H_9O]^{+\cdot}$, 444 $[M\text{-}C_{10}H_9NO_2]^{+\cdot}$, 412 $[M\text{-}C_{10}H_9NO_2S]^{+\cdot}$, 334 $[M\text{-}C_{15}H_{13}N_2O_2S]^{+\cdot}$, 308 $[M\text{-}C_{16}H_{13}N_3O_2S]^{+\cdot}$, 255 $[M\text{-}C_{19}H_{14}N_3O_3S]^{+\cdot}$, 148 $[M\text{-}C_{25}H_{19}N_4O_4S]^{+\cdot}$, 106 $[M\text{-}C_{26}H_{19}N_5O_5S]^{+\cdot}$, 94 $[M\text{-}C_{27}H_{19}N_5O_5S]^{+\cdot}$

3′-{[(4-Dimethylamino phenyl)-1-N-ethoxyphthalimido]-6′-pyridin-2-yl}-3,3a′-dihydro-6′*H*-spiro-[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 6c. $C_{34}H_{28}N_6O_5S$; Mol.Wt. 632; Yield 64%, m.p. 289ºC; Anal. Calcd.: N, 13.28; S, 5.07. Found: N, 13.23; S, 5.05%. IR (KBr): 3036 (C-H str., ArH), 1664, 1721 (C=Ostr.), 1614 (C=N str.), 664 (C-S-C str.), 1217 (C-N str.), 1318 (N-O str.), 1037 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.49-8.25 (m, 16H, ArH), 3.6 (d, 1H, CH-S), 4.2 (d, 1H, CH-O), 4.08 (t, 2H, OCH_2), 3.4 (t, 2H, NCH_2), 3.64 (s, 6H, $N(CH_3)_2$); MS: *m/z* 632 $[M]^{+\cdot}$, 499 $[M\text{-}C_9H_{11}N]^{+\cdot}$, 483 $[M\text{-}C_9H_{11}NO]^{+\cdot}$,

444 [M- $C_{11}H_{12}N_2O$]$^{+\cdot}$, 366 [M-$C_{16}H_{16}N_3O$]$^{+\cdot}$, 308 [M-$C_{17}H_{16}N_4OS$]$^{+\cdot}$, 280 [M-$C_{18}H_{16}N_4O_2S$]$^{+\cdot}$, 204 [M-$C_{24}H_{20}N_4O_2S$]$^{+\cdot}$, 162 [M-$C_{26}H_{24}N_5O_2S$] $^{+\cdot}$, 76 [M-$C_{28}H_{24}N_6O_5S$] $^{+\cdot}$.

3′-{(Phenyl-1-N-ethoxyphthalimido)-6′-pyridin-2-yl}-3,3a′-dihydro-6′*H* spiro[indole-3,5′-[1,3]thiazolo[4,5-*c*]isoxazol]-2(1*H*)-one 6d. $C_{32}H_{23}N_5O_5S$; Mol.Wt. 589; Yield 67%, m.p. 241ºC; Anal. Calcd.: N, 11.88; S, 5.44. Found: N, 11.80; S, 5.49%. IR (KBr): 3056 (C-H str., ArH), 1681, 1732 (C=Ostr.), 1638 cm^{-1} (C=N str.), 671 (C-S-C str.), 1229 (C-N str.), 1319 (N-O str.), 1054 (C-O str.); ^{1}H NMR ($CDCl_3$): δ 7.32-8.08 (m, 17H, ArH), 3.4 (d, 1H, CH-S), 4.1 (d, 1H, CH-O), 4.09 (t, 2H, OCH_2), 3.3 (t, 2H, NCH_2); MS: *m/z* 589 [M]$^{+\cdot}$, 512 [M-C_6H_5]$^{+\cdot}$, 486 [M-C_8H_7]$^{+\cdot}$, 456 [M-C_8H_7NO]$^{+\cdot}$, 352 [M-$C_{14}H_{11}N_3O$]$^{+\cdot}$, 308 [M-$C_{15}H_{11}N_3OS$]$^{+\cdot}$, 280 [M-$C_{16}H_{11}N_3O_2S$]$^{+\cdot}$, 148 [M-$C_{24}H_{15}N_3O_4S$]$^{+\cdot}$, 118 [M-$C_{24}H_{15}N_4O_5S$] $^{+\cdot}$, 90 [M-$C_{26}H_{19}N_4O_5S$] $^{+\cdot}$, 76 [M-$C_{26}H_{19}N_5O_5S$] $^{+\cdot}$.

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