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Synthesis and Screening of 3-(4-Oxo-2-Phenyl-1,3-Thiazol-5(4*h*)-Ylidene)-1,3-Dihydro-2*h*-Indol-2-One - *N*-Methylanilines for Antiinflammatory Activity

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Abstract:

A novel 3-(4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline derivatives was synthesized by cyclization of isatins with thiazolidinones. The synthesized compounds were characterized by spectral data (IR, ^{1}HNMR, MASS).The compounds VI(b, c, f, h, i, l) evaluated for in vivo antiinflammatory activity. The Compound VIi(R=5,6-dichloro) showed more in vivo antiinflammatory activity with 72.5% of inhibition among test compounds. The Compound VIf(R=5-F), VIb(R=5=Cl) , VIh(R=5-Br), VIc(R=7-Cl) and VIl(R=5-OH) were next in the order of exhibiting in vivo antiinflammatory activity with 65.75, 63.0, 61.25, 52.5 and 51.25 % respectively, when compared to standard drug Indomethacin with 73.7% of inhibition.

Keywords: Cyclooxygenase, Inflammation, Isatin, Thiazolidinones.

1. INTRODUCTION:

Cyclooxygenases (COX) or prostaglandin endoperoxide synthases are the key enzymes in the synthesis of prostaglandins. The main mediators of inflammation are pain and increased body temperature (hyperpyrexia). The body produces two main isoforms of COX proteins, that is, cyclooxygenases- 1 (COX-1) and cyclooxygenases-2 (COX-2). The COX-1 is responsible for formation of important biological mediators such as prostanoids, including prostaglandins, prostacyclin, and thromboxane, and involved in pain causing, blood clotting, and protecting the stomach [1], whereas COX-2 is involved in the pain by inflammation and plays a major role in prostaglandin biosynthesis in inflammatory cells and central nervous system [2].When COX-1 is inhibited, inflammation is reduced, but the protection of the lining of the stomach is also lost. This can cause stomach upset as well as ulceration and bleeding from the stomach and even the intestines. Whereas COX-2 is usually specific to inflamed tissue, there is much less gastric irritation associated with COX-2 inhibition together with the decreased risk of peptic ulceration [3]. Therefore, selective COX-2 inhibitors such as celecoxib and rofecoxib had been developed for ease of inflammation associated with COX [4].

It is evident from literature that isatin derivatives are known to be associated with broad spectrum of biological activity like anticonvulsant[5], antidepressant [6], antimicrobial[7] , antiviral ,antifungal, antibacterial[8] and antioxidant[9].In view of these facts and as a continuation of our work in the laboratory, prompted us to synthesize some new 3-(4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one-*N*-methylanilines. All the synthesized compounds were screened for their antiinflammatory activity.

It has been reported that the nature of substituents at the 2- or 3-position of the indole nucleus plays an important role in modulating their anti-inflammatory properties [10–14]. Amide-containing compounds have shown to possess a wide range of biological activities, including anti-inflammatory properties. Interestingly, the replacement of the carboxylic groups by amide groups in NSAID drugs indomethacin, meclofenamic acid, and ketoprofen conferred the compounds greater selectivity for COX-2 over the COX-1 enzyme [15].

2. MATERIAL AND METHODS:

All the chemicals used were of analytical grade and obtained from Himedia and SD Fine. Melting points were determined by open capillary tubes using VEEGO VMP-D Digital melting point. FTIR spectra of the powdered compounds were recorded using KBr on a JASCO FTIR 4100 series and are reported in cm-^{1} and ^{1}HNMR spectra were recorded on a Varian Mercury YH300 (300 MHz FT NMR) spectrophotometer using TMS as an internal reference (Chemical shift represented in ppm). Purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapors as the visualizing agent.

3. CHEMISTRY:

3.1. a) Preparation of 1-Benzylidene-2-Phenylhydrazine(III):

Benzaldehyde (I, 0.01mol) was taken in a beaker and to it phenyl hydrazine hydrate(II,0.01mol) was added drop by drop, precipitate was formed during addition of phenyl hydrazine .It was kept a side for some time. Then crushed ice was added and filtered to get the product. The product obtained was washed with ice cold water and dried. It was purified by recrystallization from suitable solvent.

b) Preparation of 2-Phenyl-3-(phenylamino)-1,3-thiazolidin-4-one(IV):

To the above product (III , 0.01mol) thioglycollic acid (0.01mol) , pinch of $ZnCl_2$ and 10 ml of glacial acetic acid were added and refluxed for 6 hrs. The reaction mixture was poured into crushed ice. To it 10% sodium carbonate solution was added to neutralize the acid. The reaction mixture was filtered and the product obtained was washed

thoroughly with cold water and dried. It was purified by recrystallization from suitable solvent.

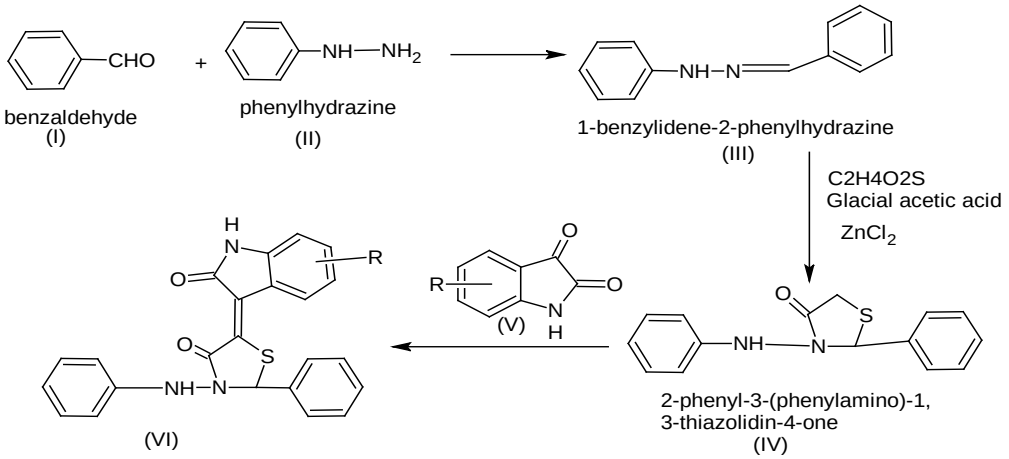
c) Preparation of Indole-2,3-diones(V):

Isonitrosoacetanilides : In a 5 lit RB flask, chloral hydrate (0.54 mol) and 1200mL of water were placed. To this solution, crystallized sodium sulphate (1300 g) was added followed by a solution of an appropriate aromatic amine in 300mL of water and concentrated hydrochloric acid (0.52mol). Finally a solution of hydroxylamine HCl (1.58mol) in 500mL of water was added. The contents of the flask were heated over a wire-gauge of a Mecker burner so that vigorous boiling begins in about 45 minutes. After 1 to 2 minutes of vigorous boiling the reaction was completed. During the heating period itself the crystals of isonitrosoacetanilides were started separating out and leave the reaction mixture for 12 hours. Then it was filtered under suction, air dried, and purified by recrystallization using suitable solvent(s).

To 1 gram of Isonitrosoacetanilide 4ml of concentrated Sulphuric acid was taken in RB flask fitted with an efficient mechanical stirrer and warmed at 50^0C . To this add finely powdered isonitrosoacetanilide (0.46mol) and maintain the temperature between 60°C and 70°C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly. After the addition of isonitroso compound was completed the temperature of the solution was raised to 80°C and maintained at that temperature for 10 minutes, to complete the reaction. Then the reaction mixture was cooled to room temperature and poured on crushed ice (2.5 kg) while stirring. After standing for about half-an-hour, the product separated was filtered, washed several times with small portions of cold water, and dried. Purification of the compound was done by the recrystallization from methanol .

d) Preparation of 3-[4-Oxo-2-phenyl-3-(phenylamino)-1,3-thiazolidin-5-ylidene]-1,3-dihydro-2*H*-indol-2-one (VI) :

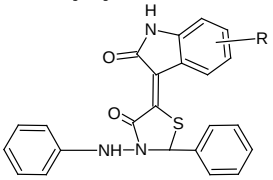
To the compound (IV, 0.01mol), isatin derivative (V, 0.01mol) was dissolved separately in a 10ml of methanol. Glacial acetic acid 2-3 drops was added and refluxed for 10-12hrs.Cool the reaction mixture and poured into crushed ice. Precipitate was filtered and dried. The compound was purified by recrystallization from suitable solvent. Adopting this procedure 12 number of compounds were prepared.



3-(4-Oxo-2-phenyl-1,3-thiazol-5(4H)-ylidene)-1,3-dihydro-2H-indol-2-one-N-methyl aniline

Scheme-1

Table 1: Physical data of the newly synthesized compounds (VIIa–l) Scheme 1:



S. No	Compound	R	M.F	M. Wt.	M.P	%Yield
1	VIa	H	$C_{23}H_{17}N_3O_2S$	413	290-292	53
2	VIb	5-Cl	$C_{23}H_{16}ClN_3O_2S$	433	310-312	78.93
3	VIc	7-Cl	$C_{23}H_{16}ClN_3O_2S$	433	295-297	67
4	VId	5-CH_3	$C_{24}H_{20}N_3O_2S$	429	322-324	62.85
5	VIe	7-CH_3	$C_{24}H_{20}N_3O_2S$	429	348-350	63
6	VIf	5-F	$C_{23}H_{16}FN_3O_2S$	417	288-290	78
7	VIg	7-F	$C_{23}H_{16}FN_3O_2S$	417	330-332	67.32
8	VIh	5-Br	$C_{23}H_{16}BrN_3O_2S$	478	326-328	69.18
9	Vii	5,6-Dichloro	$C_{23}H_{15}Cl_2N_3O_2S$	484	340-342	63
10	VIj	5-NO_2	$C_{23}H_{16}N_4O_4S$	444	300-302	76
11	VIk	7-NO_2	$C_{23}H_{16}N_4O_4S$	444	356-358	76
12	VIl	5-OH	$C_{23}H_{17}N_3O_3S$	415	289-291	62.31

Spectral Data of the Synthesized Compounds

VI(a)3-(4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one-*N*-methylaniline :

IR(KBr) cm^{-1}:3443.59(N-H),3103.33(N-H),1786.69(C=O),1621.53(C=O). ^{1}HNMR (400MHz, CDCl3): δ [ppm],5.6(s,1H,aliphatic),5.8(s,1H,NH),6.8(t,1H,Ar-H)7.0 (d,2H, Ar-H) ,7.18(d,1H, Ar-H),7.25(m,6H, Ar-H),7.4(d,2H, Ar-H),7.6(t,1H,ArH),8.82(d,1H,indoleArH). ^{13}CNMR:29.6,110.2,113.5,113.5,120.8,122.6,123.2,124.2,128.1,128.8,128.8,129.2,129.2,129.5,129.5,131.0,137.2,140.2,141.4,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{17}N_3O_2S$. Calculated Values:C-69.71,H-4.63,N-10.16,S-7.75. Observed values:C-69.68,H-4.61,N-10.11,S-7.73.

MS:m/z:413.12(100.0%),414.12(27.9%),415.12(5.4%),415.13(3.3%),416.12(1.2%).

VI(b) 3-(5-Chloro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3442.49(N-H),3101.31(N-H),1787.29(C=O),1620.33(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.61(s,1H,aliphatic), 5.82(s,1H,NNH),6.81 (t,1H, Ar-H) 7.1(d,2H, Ar-H),7.2(d,1H, Ar-H,7.3(m,5H, Ar-H),7.45(d,2H, Ar-H),7.65(t,1H,ArH),8.83(d,1H,indoleArH).

^{13}CNMR:29.6,113.5,113.5,120.8,124.0,125.0,126.6,128.2,128.8,128.8,129.2,129.2,129.5,129.5,129.8,131.0,137.2,139.5,140.2,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{16}ClN_3O_2S$. Calculated Values:C-64.35,H-4.05,N-9.38,S-7.16 Observed values:C-64.33,H-4.01,N-9.36,S-7.13. MS: m/z:447.08(100.0%),449.08 (37.0%),448.08 (27.9%), 450.08(9.9%),449.09(3.7%),451.08(1.5%),451.07(1.4%).

VI(c) 3-(7-Chloro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3444.69(N-H),3105.13(N-H),1785.29(C=O),1622.33(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.59(s,1H,aliphatic),5.81(s,1H,NNH),6.82 (t,1H, Ar-H)7.15 (d,2H, Ar-H),7.22(d,1H, Ar-H),7.35(m,5H, Ar-H),7.35(d,2H, Ar-H),7.55(t,1H,ArH),8.84(d,1H,indoleArH).^{13}CNMR:29.6,113.5,113.5,120.8,121.3,124.0,125.6,128.8,128.8,129.2,129.2,129.3,129.5,129.5,130.4,131.0,136.3,137.2,140.2,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{16}ClN_3O_2S$. Calculated Values:C-64.35,H-4.05,N-9.38,S-7.16. Observed values::C-64.31,H-4.03,N-9.37,S-7.14. MS :m/z:447.08(100.0%),449.08(37.0%),448.08 (27.9%), 450.08(9.9%), 449.09(3.7%),451.08(1.5%),451.07(1.4%).

VI(d) 3-(5-Methyl-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3441.49(N-H),3100.23(N-H),1784.29(C=O),1623.43(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.58(s,1H,aliphatic),5.8(s,1H,NNH),6.8(t,1H, Ar-H) 7.2(d,2H, Ar-H),7.25(d,1H,aromatic),7.37(m,5H, Ar-H),7.4(d,2H, Ar-H),7.62(t,1H,ArH),8.85(d,1H,indoleArH). ^{13}CNMR:21.7,29.6,113.5,113.5,120.8, 121.4,122.5, 126.8,128.4,128.8,128.8,129.2,129.2,129.5,129.5,131.0,133.9,137.2,138.4,140.2,149.4,150.0,163.7,167.2,170.3.

Elemental analysis: $C_{24}H_{20}N_3O_2S$ Calculated Values:C-70.24,H-4.95,N-9.83,S-7.50. Observed values::C-70.21,H-4.92,N-9.81,S-7.47. MS: m/z:427.14(100.0%),428.14(27.4%),429.13 (4.5%), 429.14(4.5%), 428.13(1.9%),430.13(1.3%).

VI(e) 3-(7-Methyl-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3440.29(N-H),3105.13(N-H),1782.29(C=O),1624.23(C=O) . ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.57(s,1H,aliphatic),5.82(s,1H,NNH),6.81(t,1H, Ar-H) 7.25 (d,2H, Ar-H),7.27(d,1H, Ar-H),7.4(m,5H, Ar-H),7.45(d,2H, Ar-H),7.63(t,1H,ArH),8.82 (d,1H,indoleArH). ^{13}CNMR: 9.1(s,1H,amide)^{13}CNMR:17.7,29.6,113.5,113.5,120.2, 120.8 ,122.5,124.1,127.0,128.8,128.8,129.2,129.2,129.5,129.5,129.9,131.0,137.2,140.2,141.9,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{24}H_{20}N_3O_2S$. Calculated Values:C70.24-,H-4.95,N-9.83,S-7.50. Observed values::C-70.21,H-4.92,N-9.80,S-7.48. MS: m/z: 427.14(100.0%), 428.14(27.4%),429.13(4.5%),429.14(4.5%),428.13(1.9%),430.13(1.3%).

VI(f) 3-(5-Fluoro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3441.20(N-H),3105.22(N-H),1784.23(C=O),1623.43(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.55(s,1H,aliphatic),5.8(s,1H,NNH),6.82(t,1H,aromatic) 7.24 (d,2H,aromatic),7.26(d,1H,aromatic),7.45(m,5H,aromatic), 7.5(d,2H,aromatic),7.64(t,1H,ArH),8.84(d,1H,indoleArH).^{13}CNMR:29.6,111.4,112.5,113.5,113.5,114.9,120.8,124.2,128.8,128.8,129.2,129.2,129.5,129.5,131.0,137.0,137.2,140.2,149.4,150.0,158.4,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{16}FN_3O_2S$. Calculated Values:C-66.81,H-4.20,N-9.74,S-7.43. Observed values: C66.79, H4.17, N9.71, S7.42; MS:m/z:431.11(100.0%), 432.11(27.9%),433.11(5.4%),433.12(3.3%),434.11(1.2%)

VI(g) 3-(7-Fluoro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline:

IR(KBr) cm^{-1}: 3443.59(N-H),3103.33(N-H),1786.69(C=O),1621.53 (C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.56(s,1H,aliphatic), 5.82(s,1H,NNH), 6.84 (t,1H,aromatic) 7.25(d,2H,aromatic),7.28(d,1H,aromatic),7.5(m,5H,aromatic),7.55(d,2H,aromatic),7.65(t,1H,ArH),8.81(d,1H,indoleArH).

^{13}CNMR:29.6,113.5,113.5,114.9,118.8,120.8,122.9,124.2,125.8, 128.8,128.8,129.2,129.2,129.5,129.5,131.0,137.2,140.2,149.4,150.0,162.7,163.7,167.2, 170.3 . Elemental analysis: $C_{23}H_{16}FN_3O_2S$. Calculated Values:C-66.81,H-4.20,N-

9.74,S-7.43 Observed values::C-66.78,H-4.18,N-9.72,S-7.41. MS:m/z: 431.11(100.0%), 432.11(27.9%), 433.11(5.4%), 433.12(3.3%),434.11(1.2%).

VI(h) 3-(5-Bromo-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline: IR(KBr) cm^{-1}: 3441.59(N-H),3100.33(N-H),1784.69(C=O),1624.53(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.5(s,1H,aliphatic),5.81(s,1H,NNH),6.85(t,1H,aromatic) 7.3(d,2H,aromatic),7.35(d,1H,aromatic),7.55(m,5H,aromatic),7.6(d,2H,aromatic),7.7(t,1H,ArH),8.82(d,1H,indoleArH) . ^{13}CNMR: 29.6,113.5,113.5,117.8,118.6,120.8,124.8,128.8,128.8,129.2,129.2,129.5,129.5,130.1,131.0,133.8,137.2,140.2,140.4,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{16}BrN_3O_2S$ Calculated Values:C-58.54,H-3.68,N-8.53,S-6.51. Observed values::C-58.52,H-3.67,N-8.52,S-6.49. MS:m/z:493.03(100.0%),491.03(97.4%),494.03(27.9%),492.03(27.2%),495.02(4.3%),495.03(4.1%),493.04(3.2%),496.03(1.2%).

VI(i) 3-(5,6-Dichloro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline: IR(KBr) cm−1: 3442.21(N-H),3105.23(N-H),1784.69(C=O),1624.23 (C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.55(s,1H,aliphatic), 5.83(s,1H,NNH),6.88(t,1H,aromatic) 7.4(d,2H,aromatic),7.45(d,1H,aromatic), 7.6(m,4H,aromatic), 7.65(d,2H,aromatic) ,7.75(t,1H,ArH),8.83(d,1H,indoleArH). ^{13}CNMR: 29.6,113.5,113.5,120.8,122.1,123.3,128.0 ,128.8,128.8,128.9,129.2,129.2,129.5,129.5,130.4,131.0,137.2,140.2,143.5,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{15}Cl_2N_3O_2S$. Calculated Values:C-59.76,H-3.55,N-8.71,S-6.65 Observed values::C-59.74,H-3.53,N-8.69,S-6.63. MS :m/z:481.04(100.0%),483.04(69.0%), 482.05(26.2%),484.04(19.1%),485.04(11.0%),483.05(3.7%),486.04(3.6%),485.03(2.9%),485.05(2.1%),482.04(1.9%).

VI(j) 3-(5-Nitro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline: IR(KBr) cm^{-1}: 3440.67(N-H),3101.45(N-H),1782.45(C=O),1625.32 (C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm], 5.57(s,1H,aliphatic), 5.84(s,1H,NNH) ,6.9(t,1H,aromatic)7.45(d,2H,aromatic),7.5(d,1H,aromatic), 7.65(m,5H,aromatic),7.7(d,2H,aromatic),7.8(t,1H,ArH),8.84(d,1H,indoleArH). ^{13}CNMR: 29.6,113.5,113.5, 120.2,120.8,122.4 ,123.3,123.5,128.8,128.8,129.2,129.2,129.5,129.5,131.0,137.2,140.2,143.4,147.5,149.4,150.0,163.7,167.2,170.3. Elemental analysis: $C_{23}H_{16}N_4O_4S$. Calculated Values:C-62.87,H-3.96,N-12.22,S-6.99 .Observed values::C-62.85,H-3.94,N-12.20,S-6.98 MS: m/z:458.10(100.0%),459.11(26.3%),460.11(4.7%),460.10(4.5%),459.10(2.3%),461.10(1.3%).

VI(k) 3-(7-Nitro-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline: IR(KBr) cm^{-1}:3441.24(N-H),3105.12(N-H),1782.24(C=O),1624.21 (C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.5(s,1H,aliphatic), 5.7(s,1H,NNH), 6.85 (t,1H,aromatic 7.5(d,2H,aromatic),7.55(d,1H,aromatic),7.7(m,5H,aromatic),7.75(d,2H,aromatic),7.85(t,1H,ArH),8.85(d,1H,indoleArH). ^{13}CNMR: 29.6,113.5,113.5,120.8,123.5,124.5,125.1, 128.8,128.8,129.2, 129.2,129.3,129.5,129.5,131.0,131.0,137.2,140.2,142.3,149.4,150.0,163.7,167.2,170.3 . Elemental analysis: $C_{23}H_{16}N_4O_4S$. Calculated Values:C-62.87,H-3.96,N-12.22,S-6.99. Observed values:C-62.85,H-3.94,N-12.20,S-6.98. MS: m/z:458.10(100.0%),459.11(26.3%), 460.11(4.7%),460.10(4.5%),459.10(2.3%),461.10(1.3%).

VI(l) 3-(7-Hydroxy-4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline: IR(KBr) cm^{-1}: 3443.59(N-H),3103.33(N-H),1786.69(C=O), 1621.53(C=O). ^{1}HNMR (400MHz,CDCl3): δ [ppm],5.55(s,1H,aliphatic) ,5.72(s,1H,NNH),6.8(t,1H,aromatic) 7.55(d,2H,aromatic),7.65(d,1H,aromatic),7.75(m,5H,aromatic),7.8(d,2H,aromatic),7.85(t,1H,ArH),8.82(d,1H,indoleArH). ^{13}CNMR: 29.6,112.3,113.5,113.5,115.3,120.8, 122.9,124.0 ,128.8 ,128.8, 129.2,129.2,129.5,129.5,131.0,134.0,137.2,140.2,149.4,150.0,154.0,163.7, 167.2,170.3. Elemental analysis: $C_{23}H_{17}N_3O_3S$. Calculated Values:C-67.12,H-4.46,N-9.78,S-7.47. Observed values:C-67.10,H-4.45,N-9.77,S-7.45. MS: m/z:429.11(100.0%),430.12(26.3%),431.11(4.5%), 431.12(4.4%),430.11(1.9%),432.11(1.2%).

4. BIOLOGICAL ACTIVITY:

4.1 Acute Toxicity Studies: The study was conducted in accordance with OECD guidelines (Testing of Chemical Number 1757). Healthy and adult male albino Swiss mice were used in this investigation. Animals were fasted for 24 hours and divided into groups of six animals. The test compounds, suspended in normal saline, were administered intraperitoneally, in doses of 10mg to 1000mg per kg (b.w.). The control groups of animals received only the vehicle (normal saline). The animals were observed for 48 hours from the time of administration of test compound, in a dose of 1000mg/kg produce mortality (LD50). Soon, tenth of the LD50, that is, 100mg/kg (ED50), was selected as a dose for an antiinflammatory.

4.2. Antiinflammatory activity by Carrageenan Induced Rat Hind Paw Edema Method: In carrageenan model [27] albino rats of all groups were treated with subcutaneous injection of 0.1mL of 1% w/v solution of carrageenan into the subplantar region of the right hind paw. The paw was marked with permanent marker at the planter region where the paw volume was to be measured. The indomethacin 10 mg/kg and test compounds 100mg/kg were suspended in 0.3% sodium carboxymethyl cellulose. The test compounds and vehicle (control)were administered i.p. one hour after the injection of carrageenan in subplantar region of right paw. Mean

normal paw volume was measured 30 min prior to carrageenan injection by using plethysmometer. Mean increase in the paw volume for control group (after carrageenan injection) and test group was measured at 1 hr, 2 hr, 3 hr, and 4 hr. The percent inhibition of inflammation after test/standard was calculated using the formula. The mean percent inhibition of indomethacin and tested compounds at 10mg /kg concentrations was compared with control using repeated measures

The 6 compounds were selected and evaluated for in vivo antiinflammatory activity at a dose range of 100mg/kg body weight by carragenan induced rat paw edema method, from the data it was reveals that all the tested compounds significantly reduced carrageenan induced edema and the results were presented in Table 2 and 3.

Table 2: In vivio antiinflammatory activity

S. No	Compound(100mg/kg body weight)	R	Mean Paw Edema Volume in ml ± SD			
			1h	2h	3h	4h
1	Vib	5-Cl	0.51±0.043	0.46±0.040	0.38±0.031	0.28±0.052
2	Vic	7-Cl	0.53±0.050	0.49±0.021	0.42±0.075	0.38±0.32
3	Vif	5-F	0.43±0.030	0.38±0.083	0.32±0.032	0.29±0.045
4	Vih	5-Br	0.46±0.080	0.39±0.038	0.36±0.043	0.31±0.020
5	Vii	5,6-Dichloro	0.32±0.042	0.29±0.052	0.25±0.084	0.21±0.031
6	VIl	5-OH	0.49±0.076	0.43±0.031	0.41±0.056	0.39±0.054
7	**Control Group (carrageenan induced)**		0.56±0.090	0.63±0.064	0.71±0.034	0.80±0.090
	Indomethacin(10mg/kg body wt)		0.35± 0.070	0.33±0.120	0.28 ± 0.080	0.21 ± 0.062

Table 3: In vivo antiinflammatory activity

S. No	Compound(100mg/kg body weight)	R	% Inhibition of Paw Edema			
			1h	2h	3h	4h
1	VIb	5-Cl	8.92	26.98	46.48	63.0
2	VIc	7-Cl	5.35	22.22	40.85	52.5
3	VIf	5-F	23.21	39.68	54.93	65.75
4	VIh	5-Br	17.86	38.1	49.3	61.25
5	VIi	5,6-Dichloro	42.86	53.97	64.79	72.5
6	VIl	5-OH	12.5	31.75	42.25	51.25
7	**Indomethacin(10mg/kg body wt)**		37.5	47.6	60.5	73.7

5. RESULTS AND DISCUSSION:

Some of the new isatin derivatives were obtained by cyclization of isatins with 2-Phenyl-3-(phenylamino)-1,3-thiazolidin-4-one in presence of methanol with glacial acetic acid depicted in scheme 1. Physical data of all the synthesized compounds are shown in Table1.

5.1 IN VIVO ANTIINFLAMMATORY ACTIVITY:

From scheme-1 , we were selected six compounds and evaluated for in vivo antiinflammatory activity at a dose range of 100mg/kg body weight by carrageenan induced rat paw edema method, From the data it was revealed that all the tested compounds significantly reduced carrageenan induced edema and the results were presented in Table 2 and 3. Among the tested compounds VIi(R=5,6-dichloro),VIf(R=5-F),VIb(R=5=Cl) and VIh(R=5-Br) are considered to possess potent anti-inflammatory activity when compared to standard drug indomethacin. From the obtained results it is clear that di halo substituted derivative (VIi(R=5,6-dichloro)) is found to be more potent compared to other synthesized compounds.

6. CONCLUSION:

The present study involves synthesis and evaluation of 3-**(4-Oxo-2-phenyl-1,3-thiazol-5(4*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one - *N*-methylaniline** for In vivo antiinflammatory activity. The title compounds have shown potent antiinflammatory activity.

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REFERENCES:

1. S. S. Chhajed, P. B. Hiwanj, V. A. Bastikar et al., "Structure based design and in-silico molecular docking analysis of some novel benzimidazoles," *International Journal of ChemTech Research*, vol. 2, no. 2, pp. 1135–1140, 2010.
2. P. McGettigan and D. Henry, "Cardiovascular risk and inhibi-tion of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxyge-nase 2," *The Journal of the American Medical Association*, vol. 296, no. 13, pp. 1633–1644, 2006.

3. C. J. Hawkey, "COX-2 inhibitors," *The Lancet*, vol. 353, no. 9149, pp. 307–314, 1999.
4. R. P. Mason, M. F. Walter, H. P. McNulty et al., "Rofecoxib increases susceptibility of human LDL and membrane lipids to oxidative damage: a mechanism of cardiotoxicity," *Journal of Cardiovascular Pharmacology*, vol. 47, no. 1, pp. S7–S14, 2006.
5. G. Saravanan, V. Alagarsamy, and P. Dineshkumar, "Anticonvulsant activity of novel 1-(morpholinomethyl)-3-substituted isatin derivatives," *Bulletin of Faculty of Pharmacy, Cairo University*, vol. 52, no. 1, pp. 115–124, 2014.
6. C. Radhika, A. Venkatesham, and M. Sarangapani, "Synthesis and antidepressant activity of di substituted-5-aryl-1,2,4-tria-zoles," *Medicinal Chemistry Research*, vol. 21, no. 11, pp. 3509– 3513, 2012.
7. A. M. Naglah, H. M. Awad, M. A. Bhat, M. A. Al-Omar, and A. E. Amr, "Microwave-assisted synthesis and antimicrobial activity of some novel isatin schiff bases linked to nicotinic acid via certain amino acid bridge," *Journal of Chemistry*, vol. 2015, Article ID 364841, 8 pages, 2015.
8. A. Jarrahpour, J. Sheikh, I. E. Mounsi, H. Juneja, and T. B. Hadda, "Computational evaluation and experimental in vitro antibacterial, antifungal and antiviral activity of bis-Schiff bases of isatin and its derivatives," *Medicinal Chemistry Research*, vol. 22, no. 3, pp. 1203–1211, 2013.
9. R. Anisetti and M. S. Reddy, "Synthesis, antimicrobial, anti-inflammatory and antioxidant activity of novel Spiro (imida-zo[4 ,5 :4,5]benzo[1,2-e][1, 4] thiazepine)-9,3 -indolines," *Jour-nal of Sulfur Chemistry*, vol. 33, no. 3, pp. 363–372, 2012.
10. D. Galanakis, A. P. Kourounakis, K. C. Tsiakitzis et al., "Syn-thesis and pharmacological evaluation of amide conjugates of NSAIDs with L-cysteine ethyl ester, combining potent antiinflammatory and antioxidant properties with signifi-cantly reduced gastrointestinal toxicity," *Bioorganic & Medicinal Chemistry Letters*, vol. 14, no. 14, pp. 3639–3643, 2004.
11. C. Papadopoulou, A. Geronikaki, and D. Hadjipavlou-Litina, "Synthesis and biological evaluation of new thiazolyl/benzo-thiazolyl-amides, derivatives of 4-phenyl-piperazine," *II Far-maco*, vol. 60, no. 11-12, pp. 969–973, 2005.
12. T. Onkol, E. Banoglu, Y. Dundar,¨ E. Kupeli,¨ and M. F. S¸ahin, "Amide derivatives of [6-acyl-2-benzothiazolinon-3-yl] acetic acids as potential analgesic and anti-inflammatory compounds," *Medicinal Chemistry Research*, vol. 19, no. 1, pp. 11–24, 2010.
13. N. M. Raghavendra, A. Jyothsna, A. Venkateswara Rao, and C.
14. V. S. Subrahmanyam, "Synthesis, pharmacological evaluation and docking studies of N-(benzo[d]thiazol-2-yl)-2-(piperazin-1-yl)acetamide analogs as COX-2 inhibitors," *Bioorganic and Medicinal Chemistry Letters*, vol. 22, no. 2, pp. 820–823, 2012.
15. T. Takahashi and M. Miyazawa, "N-Caffeoyl serotonin as selective COX-2 inhibitor," *Bioorganic and Medicinal Chemistry Letters*, vol. 22, no. 7, pp. 2494–2496, 2012.