SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF NEW THIAZOLIDINE-2,4-DIONES, 4-THIOXOTHIAZOLIDINONES AND 2-THIOXOIMIDAZOLIDINONES

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Abstract: New benzylidene imidazolidine and thiazolidine derivatives were prepared by nucleophilic addition on cyanoacrylates from substituted thioxoimidazolidinones, thiazolidinediones and thioxothiazolidinones. Anti-inflammatory activity of the synthesized thiazolidines was evaluated by the carrageenin-induced paw oedema test.

Introduction

Owing to their pharmacological properties [1,2], imidazolidinediones and thiazolidinediones are widely studied compounds. In particular thiazolidines are known to show anti-inflammatory activity. With reference to this, synthesis of some 5-benzylidene-thioxoimidazolidinones and thioxothiazolidinones substituted at the position 3 by a benzyl (or phenacyl) group, were reported in previous papers [3-5]. Synthesis and physicochemical data of new 5-benzylidene-3-(4-chlorobenzyl)-thiazolidine-2,4-diones **8-10** or 5-(1*H*-indol-3-yl-methylene)-3-(4-chlorobenzyl)-4-thioxo-thiazolidin-2-one **11** (Figure 1) are given below. These compounds were obtained from the 3-(4-chlorobenzyl)-thiazolidine-2,4-dione **2** or 3-(4-chlorobenzyl)-4-thioxo-thiazolidin-2-one **3**, by a nucleophilic Michael addition using various [(2-cyano-3-phenyl or 3-(3-indolyl)]-ethyl acrylates **4-7**, as reagents.

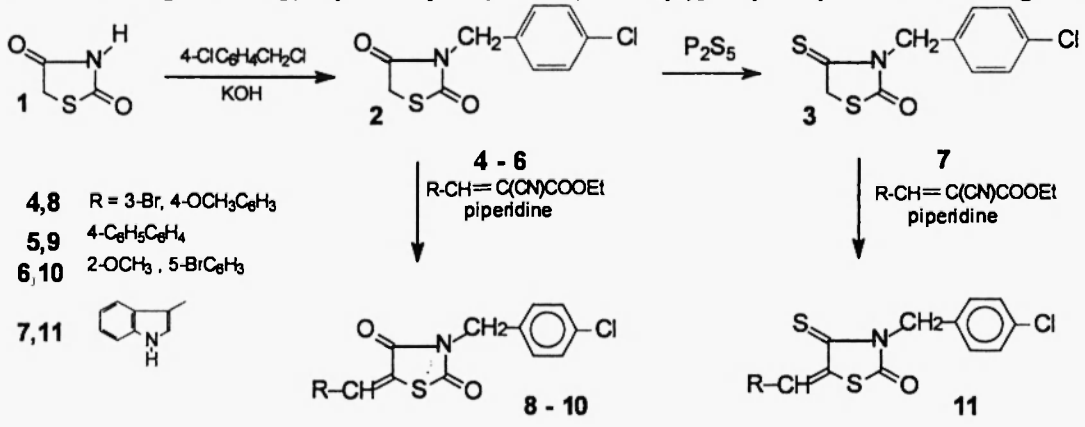

Figure 1. Thiazolidine-2,4-diones and 4-thioxothiazolidinones: synthetic pathway

Moreover 5-benzylidene-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-ones, 27-33, were obtained from the 2-thioxoimidazolidin-4-one 12, by a nucleophilic Michael addition using (2-cyano-3-phenyl)-ethyl acrylates 13-19, as reagents before the intermediates be alkylated at position 3 (Figure 2).

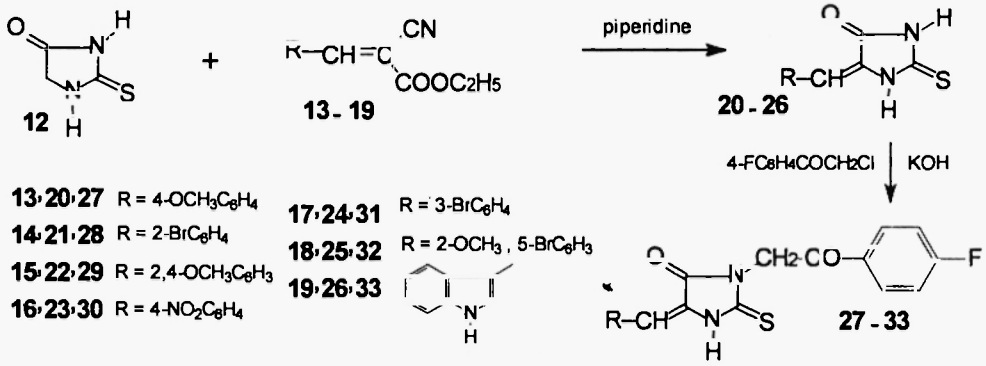

Figure 2. 5-Benzylidene-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-ones: synthetic pathway

Chemistry and molecular structure

Compounds, **8-11**, were synthesized in three steps: (*i*), At first thiazolidin-2,4-dione **1** was alkylated at the 3 position in the presence of potassium hydroxide. That leads bo the thiazolidine potassium salt, before 4-chloro-benzyl chloride reacts in hot alcoholic medium [6] to yield 3-(4-chloro-benzyl)-thiazolidine-2,4-dione **2**. (*ii*) Then, **2** reacted in anhydre dioxane with tetraphosphorous decasulfide [7] to give 3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one **3**. (*iii*) Finally, 5-benzylidene-3-(4-chlorobenzyl)-thiazolidine-2,4-diones or 5-(1*H*-indol-3-ylmethylene)-3-(4-chlorobenzyl)-4-thioxo-thiazolidin-2-ones were prepared in the presence of piperidine by a 1,4-nucleophilic addition between **2** or **3** and (2-cyano-3-phenyl)-ethyl acrylates **4-7**. The later compounds, **4-7**, were obtained condensing various benzaldehydes with ethyl cyanoacetate [6].

On the other hand, 5-benzylidene-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-ones **27-33**, were obtained in two steps: (*i*), 5-benzylidene-2-thioxo-imidazolidin-4-ones **22-25** or 5-(1*H*-indol-3-ylmethylene)-2-thioxo-imidazolidin-4-one **26**, were prepared in the presence of piperidine by a 1,4-nucleophilic addition between 2-thioxo-imidazolidin-4-one **12**, and (2-cyano-3-phenyl)-ethyl acrylates or 2-cyano-3-(2,3-dihydro-1*H*-indol-3-yl)acrilic acid ethyl ester **13-19**; these compounds were also obtained condensing benzaldehydes with ethyl cyanoacetate [6]. (*ii*) Alkylation of **20-26** by 2-chloro-1-(4-fluoro-phenyl)-ethanone in alkaline medium led to the imidazolidinones **27-33**.

Finally, one must emphasize that compounds 8-11 and 20-26 were isolated in a single isomer form. It has been previously demonstrated [8,9] that the Z isomer is the major one obtained in the case of condensation with arylidene thiazolidinones and imidazolidinones with no substitution at position 1.

EXPERIMENTAL SECTION

Biological activity

Compounds **8-11** were assayed for general pharmacological effects according to the method described by De Luca [10]. These compounds (1000 mg/kg) dissolved in a Tween 80/saline mixture (0,2:10), were delivered intraperitonealy in Swiss male mice. On the whole they act as CNS depressant drugs. No lethal effect was observed during assays. The anti-inflammatory activity was investigated the by carrageenin-induced paw oedema test according to two different methodologies. First, the classical Winter's method [11] was used. It consists in measuring the paw volume of male Wistar rats and then

in inducing oedema by sub plantar injection of carrageenin (1%). In doing that, the drug action is prophylactically evaluated. Compounds dissolved in the Tween 80/ saline (0,2:10) mixture, were delivered intraperitoneally at a 50 mg/kg dose, 1 hour before the carrageenin injection. The oedema evolution was followed by subsequent measures of the paw volume. It was admitted that the control group exhibits 100 % of the inflammatory response (i.e the maximum oedema volume). The percentage of activity was deduced from the differences in the oedema volume shown by the control and the test groups. The standard group was treated in similar conditions with indomethacine (10mg/kg). Results are gathered in table 1.

Table 1: Percentage of paw oedema inhibition by compounds **8-11** at one to six hours after the oedema induction.

Compounds	time					
	1 h*	2 h	3 h	4 h	5 h	6 h
8	7	33	43	42	65	43
9	16	30	33	47	45	72
10	35	**48**	56	79	78	72
11	23	55	68	78	70	60
Indomethacine	18	45	47	49	59	57

Statistically significant difference in relation to the control is expressed by $p < 0,05$ (Student's *t* test)
* $p > 0,05$

Activity shown by **8** and **9** is slightly lower than that of indomethacine. In contrast anti-inflammatory activities of **10** and **11** are respectively, about 15 % and 13 % (mean), higher than that of indomethacine, indicating that these compounds have high anti-inflammatory potential.
Derivatives **8-11** showed an oedema inhibition profile similar to that of indomethacine, without inhibiting the early phase of the oedema development, probably resulting in a local production of bradikinin which is insensitive to the NSAIDs action. However, the oedema development is quantitatively blocked in the second phase (from one to five hours). That suggests a great similarity in the mechanism of action of the tested thiazolidines to that of indomethacine.
Biochemical data - mainly resulting from the dosage of prostaglandin E_2 (PGE_2) and tromboxane A_2 (TXA_2) - prove that the mechanism of action of indomethacine is related to both COX-1 and COX-2 enzyme inhibition [12]. By analogy the tested drugs probably act via the COX enzyme inhibition.
It is not possible to infer uniquely by the EPC which of the two isoform is preferentially inhibited. However according to Smith and co-workers [12], the COX-1 specific drugs are not capable to inhibit prophylactically the oedema formation, while the COX-1 and COX-2 drugs, and the selective COX-2 drugs are. Thus, it is possible to presume that the thiazolidines **8-11** would be not specific COX-1 inhibitors.
The Winter's modified assay [13] is similar to the classical one, but the drug tested is delivered therapeutically one hour after induction of inflammation. In this case, the percentage of oedema inhibition by a 100mg/kg dose was significant only at one and six hours after the carrageenin injection (table 2).
The tested substances act in the same way that indomethacine. This is in agreement with previous results from Zhang and co-workers [13], where the therapeutic administration of ketorolac, an unspecific COX inhibitor that inhibits both isoforms, reduced oedema in a first step before the group under evaluation and the control one behave similarly.
One must emphasize the fact that results obtained by Smith and co-workers [12] revealed that the therapeutic administration of SC-560 and celecoxib, which are respectively COX-1 and COX-2

selective inhibitors, did not revert the established oedema during the time course of the experiment, although they induced the reduction of PGE_2 levels. This result indicates that a COX inhibition occured.

Table 2: Percentage of paw oedema inhibition by compounds **8-11** (100 mg/kg) at one and six hours after the oedema induction

T (h)	**8**	**9**	**10**	**11**
1	**41**	**34**	**35**	**48**
6	**47**	**49**	**79**	**77**

Smith and co-workers [12] also verified that despite the celecoxib administration does not lead to the decrease of the volume oedema where as this drug was capable to reduce the paw oedema in the prophylactic is winter classical test, analgesic features were observed. That confirms the COX inhibition which is in this case, a COX-2 inhibition.
The differences displayed by the two methods used for measuring the anti-inflammatory activity suggest that the paw oedema evaluation based on the therapeutic administration of the drug, six hours after the induction of inflammation, is not adequate, probably because the time course is not enough to allow reversion of the established oedema. In addition, it can be suggested that to revert an established oedema situation involves others still unknown mechanisms which are not related to the COX enzyme inhibition but more probably to the exudate draining mechanism.

Chemistry
Melting points were measured on a Buchi apparatus. Thin layer chromatography was performed on Merck 60 F254 silica gel plates with a 0.2 mm thickness. Compounds were powdered, mixed with KBr at 1% concentration and pressed into pellets before the infrared spectra be recorded on a IFS 66 Bruker spectrometer, apart from compounds 22 and 23 which were studied on a Perkin-Elmer 1310 spectrometer.
^{1}H NMR spectroscopy was carried out on a Bruker AC 300 P spectrophotometer. DMSO-d_6 was used as solvent and TMS as reference. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in hertz (Hz).
70eV Electronic impact mass spectra were recorded on a Delsi-Nermag R-1010c spectrometer. apart from compound 35 which was studied by chemical ionization, in ammonia and isobutane. Intensities of molecular peaks are given with reference to the most intense peak M^+(%). Fragmentations and peak intensities observed in electronic impact MS allowed to propose molecular structures of compounds isolated.
Synthesis and usual data of compounds 2,3 [14] and 14,18,19,21,25,26 [15] are given in literature.

[(2-cyano-3-phenyl or 3-(3-indolyl)]-ethyl acrylates 4-7,13-19 : general procedure
Equimolar (23mM) mixture of aldehyde and ethyl cyanacetate, added with piperidine (3 drops) and benzene (20mL) was heated at 110-120°C for **8**-10h. After cooling, the mixture is caught in mass. The solid phase was recrystallized from an ethanol-water mixture.

(5*Z*)-5-Benzylidene-3-(4-chlorobenzyl)-thiazolidine-2,4-diones 8-10 and (5*Z*)-5-(1*H*-indol-3-ylmethylene)-3-(4-chlorobenzyl)-4-thioxo-thiazolidin-2-one 11: general procedure.
An equimolar (0.83mM) mixture of 3-chlorobenzyl-thiazolidine-2,4-dione 2 or 3-chlorobenzyl-4-tioxo-thiazolidin-2-one 3 and (2-cyano-3-phenyl)-ethyl acrylates 4-6 or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)acrilic acid ethyl ester 7 dissolved in ethanol (10mL) with piperidine (250µL) was heated at 50°C for 2-3h. After cooling, the precipitated product was recrystallized from an ethanol-water mixture.

(5*Z*)-5-(3-Bromo-4-methoxy-benzylidene)-3-(4-chlorobenzyl)-thiazolidine-2,4-dione 8
$C_{18}H_{13}BrClNO_3S$. Yield 83%. M.p. 190-191°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,75. IR cm^{-1} (KBr): υ 3030, 1740, 1676, 1592, 1498, 1292, 1144, 797 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.93 (s, 3H OCH_3), 4.83 (s, 2H CH_2), 7.93 (s, CH ethylenic), 7.34 (d, 2H benzyl, J=8.7Hz), 7.42 (d, 2H benzyl, J=8.7Hz), 7.3 (d, 1H benzylidene, J=8.7Hz) 7.64 (dd, 1H benzylidene, J=8.7, 2.1Hz), 7.91 (d, 1H benzylidene, J=2.1Hz). MS m/z(%): 437(M^+ 9.57%), 439(7.75), 242(36.1), 244(42.8), 227(16.6), 229(11.5), 125(100), 127(44.8), 120(23.2), 89(15.1).

(5*Z*)-5-(Biphenyl-4-yl-methylene)-3-(4-chlorobenzyl)-thiazolidine-2,4-dione 9
$C_{23}H_{16}ClNO_2S$. Yield 81%. M.p. 190-195°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,95. IR cm^{-1} (KBr): υ 3030, 1752, 1689, 1614, 1600, 1485, 1418, 1386, 1153, 764 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 4.85 (s, 2H CH_2), 8.03 (s, CH ethylenic), 7.36 (d, 2H benzyl, J=8.4Hz), 7.43 (d, 2H benzyl, J=8.4Hz), 7.74 (d, 2H benzylidene, J=8.1Hz) 7.88 (d, 2H benzylidene, J=8.7Hz), 7.49-7.53 (m, 2H C_6H_5), 7.42-7.45 (m, 1H C_6H_5), 7.76 (dd, 2H C_6H_5,' J=6,9 1,8). MS m/z(%): 405(M^+ 42.1%), 407(16.8), 210(100), 167(29.5), 125(18.2), 89(9.6).

(5*Z*)-5-(5-Bromo-2-methoxy-benzylidene)-3-(4-chlorobenzyl)-thiazolidine-2,4-dione 10
$C_{18}H_{13}BrClNO_3S$. Yield 77%. M.p. 164-165°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,82. IR cm^{-1} (KBr): υ 2933, 1735, 1685, 1594, 1481, 1380, 1337, 1254, 812 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.9 (s, 3H OCH_3), 4.82 (s, 2H CH_2), 7.97 (s, CH ethylenic), 7.34 (d, 2H benzyl, J=8.4Hz), 7.42 (d, 2H benzyl, J=8.4Hz), 7.15 (d, 1H benzylidene, J=8.7Hz) 7.55 (d, 1H benzylidene, J=2.4Hz), 7.67 (dd, 1H benzylidene, J=8.7 2.4Hz). MS m/z(%): 437(M^+ 12.3%), 439(11.7), 242(14.4), 244(14.5), 153(17.1), 125(100), 127(35), 107(12.1), 89(12.7), 77(18).

(5*Z*)-3-(4-Chlorobenzyl)-5-(1*H*-indol-3-yl-methylene)-4-thioxo-thiazolidin-2-one 11
$C_{19}H_{13}ClN_2OS_2$. Yield 70%. M.p. 145-147°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,57. IR cm^{-1} (KBr): υ 3260, 2931, 1725, 1666, 1598, 1383, 1330, 1146, 741 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 4.84 (s, 2H CH_2), 8.23 (s, CH ethylenic), 7.34 (d, 2H benzyl, J=8.4Hz), 7.43 (d, 2H benzyl, J=8.4Hz), 7.21-7.29 (m, 2H indolidene), 7.51 (d, 1H indolidene, J=8.7Hz), 7.84 (s, 1H indolidene), 7.91-7.93 (m, 1H indolidene). MS m/z(%): 384(M^+ 0.39%), 240(70.1), 212(34.3), 195(32.3), 168(51.7), 166(55.2), 140(77.9), 127(49.9), 125(100), 89(46.9), 75(23.1).

(5*Z*)-5-Benzylidene-2-thioxo-imidazolidin-4-ones 20,22-25: general procedure.
An equimolar (4.3mM) mixture of 2-thioxoimidazolidin-4-one, 12 (0.5g,) and (2-cyano-3-phenyl)-ethyl acrylates 13,15-18 or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)acrilic acid ethyl ester 19 dissolved in ethanol (10mL) with piperidine (250µL) was heated at 80-90°C for 4-8h. After cooling, the precipitate was collected and washed with water or recrystallized from ethanol or methanol.

(5*Z*)-5-(4-Methoxy-benzylidene)-2-thioxo-imidazolidin-4-one 20
$C_{11}H_{10}N_2O_2S$. Yield 72%. M.p. 260-262°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,57. IR cm-1 (KBr): υ 3140, 1715, 1640, 1590, 1510, 1475, 1365, 1255, 1170, 820 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.81 (s, 3H OCH_3), 6.47 (s, CH ethylenic), 6.99 (d, 2H benzylidene, J=8.7Hz), 7.75 (d, 2H benzylidene, J=8.7Hz), 12.25 (s, 2H NH). MS m/z(%): 234(M^+ 100%), 147(33.4), 132(23.2), 117(6.4), 103(7.4).

(5*Z*)-5-(2,4-Dimethoxy-benzylidene)-2-thioxo-imidazolidin-4-one 22
$C_{12}H_{12}N_2O_3S$. Yield 66%. M.p. 218-219°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,26. IR cm-1 (KBr): υ 3210, 1725, 1713, 1600, 1504, 1310, 1270, 1025, 830 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.84 (s, 3H OCH_3), 3.88 (s, 3H OCH_3), 6.7 (s, CH ethylenic), 6.59 (dd, 1H benzylidene, J=2.4 8.7Hz), 6.62 (d, 1H benzylidene, J=2.4Hz), 7.77 (d, 1H benzylidene, J=8.7Hz), 12.25 (s, 2H NH). MS m/z(%): 264(M^+ 100%), 265(17.5), 266(5.1), 233(1), 107(1), 86(2.8).

(5*Z*)-5-(4-Nitro-benzylidene)-2-thioxo-imidazolidin-4-one 23
$C_{10}H_7N_3O_3S$. Yield 40%. M.p. 294°C decomp. TLC, (*n*-hex.:AcOEt 60:40) R_f 0,64. IR cm^{-1} (KBr): υ 3350, 1765, 1750, 1660, 1595, 1530, 1485, 1345, 1190, 975, 875 cm^{-1}. H1 NMR (δ ppm DMSO d_6): 6.57 (s, CH ethylenic), 7.97 (d, 2H benzylidene, J=9Hz), 8.23 (d, 2H benzylidene, J=8.7Hz), 12.43 (s, 1H NH), 12.58 (s, 1H NH). MS m/z(%): 249(M^+ 23%), 162(25.7), 132(31.5), 116(26.8), 104(36.2), 93(100), 92(50.1), 91(75.9), 77(64.8), 67(81.6).

(5*Z*)-5-(3-Bromo-benzylidene)-2-thioxo-imidazolidin-4-one 24
$C_{10}H_7BrN_2OS$. Yield 86%. M.p. 169-170°C. TLC, (*n*-hex.:AcOEt 70:30) R_f 0,56. IR cm^{-1} (KBr): υ 3175, 1737, 1720, 1651, 1499, 1371, 1194, 893, 780 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 6.44 (s, CH ethylenic), 7.34 (t, 1H benzylidene, J=7.8Hz), 7.56 (d, 1H benzylidene, J=7.8Hz), 7.7 (d, 1H benzylidene, J=7.8Hz), 7.96 (s, 1H benzylidene), 12.29 (s, 1H NH), 12.39 (s, 1H NH). MS m/z(%): 282(M^+ 93.4%), 284(100), 195(26.6), 197(25.9), 116(30), 89(49.2).

(5*Z*)-5-Benzylidene-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-ones 27-32 and (5*Z*)-5-(1*H*-indol-3-ylmethylene)-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one 33: general procedure.
A solution of 5-substituted 2-thioxo-imidazolidin-4-one 20-26, (3.8mMol) and potassium carbonate (5.5mM) in methanol (10mL) was stirred at room temperature for 1h. Then 2-chloro-1-(4-fluorophenyl)-ethanone (4.2mM) was added and the mixture was stirred again for 12-18h. Upon cooling in an ice bath, the product precipitated was collected and washed with water or recrystallized from ethanol or methanol.

(5*Z*)-3-[2-(4-Fluorophenyl)-2-oxo-ethyl]-5-(4-methoxy-benzylidene)-2-thioxo-imidazolidin-4-one 27
$C_{19}H_{15}FN_2O_3S$. Yield 89%. M.p. 183°C. TLC, (n-hex.:AcOEt 70:30) R_f 0,39. IR cm^{-1} (KBr): υ 3071, 1711, 1633, 1597, 1508, 1255, 1174, 832 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.74 (s, 3H OCH_3), 4.91 (s, CH_2), 6.63 (s, CH ethylenic), 6.57 (d, 2H benzylidene, J=9Hz), 7.79 (d, 2H benzylidene, J=8.7Hz), 7.48 (t, 2H phenacyl, J=9Hz), 8.21-8.26 (m, 2H phenacyl), 11.75 (s, 1H NH). MS m/z(%): 370 (M^+ 38.5%), 273(65.2), 271(51.6), 247(34.6), 146(40.9), 137(100), 123(94.3), 83(18.6), 57(98.5).

(5Z)-5-(2-Bromo-benzylidene)-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one 28
$C_{19}H_{12}BrFN_2O_2S$. Yield 77%. M.p. 180-182°C. TLC, (n-hex.:AcOEt 50:50) R_f 0,63. IR cm^{-1} (KBr): υ 3072, 1704, 1626, 1596, 1503, 1412, 1185, 832, 770 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 4.96 (s, CH_2), 6.9 (s, CH ethylenic), 6.79 (t, 1H benzylidene, J=7.5Hz), 7.18 (dt, 1H benzylidene, J=7.5 1.8Hz), 7.63 (dd, 1H benzylidene, J=8.1 1.2Hz), 8.31 (dd, 1H benzylidene, J=8.1 1.8Hz), 7.44 (t, 2H phenacyl, J=9Hz), 8.18-8.23 (m, 2H phenacyl), 12.04 (s, 1H NH). MS m/z(%): 418 (M^+ 0.397%), 420(0.739), 339(9.2), 271(6.8), 273(7.5), 136(27.2), 137(26.7), 123(100), 93(70.5), 77(56.4).

(5Z)-5-(2,4-Dimethoxy-benzylidene)-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one 29
$C_{20}H_{17}FN_2O_4S$. Yield 84%. M.p. 203-205°C. TLC, (n-hex.:AcOEt 50:50) R_f 0,57. IR cm^{-1} (KBr): υ 3068, 1701, 1687, 1605, 1499, 1291 1257, 1186, 835 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 3.75 (s, 3H OCH_3), 3.82 (s, 3H OCH_3), 4.89 (s, CH_2), 6.92 (s, CH ethylenic), 5.84 (d, 1H benzylidene, J=9Hz), 6.51 (d, 1H benzylidene, J=2.4Hz), 8.1 (d, 1H benzylidene, J=8.7Hz), 7.48 (t, 2H phenacyl, J=8.7Hz), 8.21-8.25 (m, 2H phenacyl), 11.73 (s, 1H NH). MS m/z(%): 400 (M^+ 1.69%), 368(1.6), 277(4.6), 264(16.7), 256(14.4), 162(15.7), 123(100), 95(52), 77(20.9), 64(65.4).

(5Z)-3-[2-(4-Fluorophenyl)-2-oxo-ethyl]-5-(4-nitro-benzylidene)-2-thioxo-imidazolidin-4-one 30
$C_{18}H_{12}FN_3O_4S$. Yield 91%. M.p. 193-195°C. TLC, (n-hex.:AcOEt 60:40) R_f 0,57. IR cm^{-1} (KBr): υ 3553, 3479, 3414, 3070, 1715, 1691, 1507, 1343, 1160, 835 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): *Z* ~70% 5 (s, CH_2), 6.78 (s, CH ethylenic), 7.82 (d, 2H benzylidene, J=8.4Hz), 8.09 (d, 2H benzylidene, J=9Hz), 7.49 (t, 2H phenacyl, J=9Hz), 8.2-8.27 (m, 2H phenacyl), 12.12 (s, 1H NH). *E* ~30% 4.98 (s, CH_2), 6.48 (s, CH ethylenic), 8.22 (d, 2H benzylidene, J=8.7Hz), 8.35 (d, 2H benzylidene, J=9Hz), 7.42 (t, 2H phenacyl, J=9Hz), 8.13-8.18 (m, 2H phenacyl), 12.49 (s, 1H NH). MS m/z(%): 385 (M^+ 2.79%), 264(0.25), 170(0.83), 123(100), 95(11.8), 75(12.5).

(5Z)-5-(3-Bromo-benzylidene)-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one 31
$C_{19}H_{12}BrFN_2O_2S$. Yield 67%. M.p. 199-202°C. TLC, (*n*-hex.:AcOEt 60:40) R_f 0,71. IR cm^{-1} (KBr): υ 3472, 1716, 1693, 1506, 1202, 668 cm^{-1}. H^1 NMR (δ ppm DMSO d_6): 5.02 (s, CH_2), 6.68 (s, CH ethylenic), 7.03 (t, 1H benzylidene, J=8.1Hz), 7.46 (d, 1H benzylidene, J=7.8Hz), 7.87 (d, 1H benzylidene, J=7.8Hz), 8.24 (s, 1H benzylidene), 7.44(t, 2H phenacyl, J=8.7Hz), 8.18-8.23 (m, 2H phenacyl), 11.99 (s, 1H NH). MS m/z(%): 418 (M^+ 2.37%), 420(2.07), 123(77.7), 93(42.3), 77(33), 51(51.9), 39(100).

(5Z)-5-(5-Bromo-2-methoxy-benzylidene)-3-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one 32
$C_{19}H_{14}BrFN_2O_3S$. Yield 78%. M.p. 220-221°C. TLC, ($CHCl_3$:MeOH 90:10) R_f 0,5. IR cm^{-1} (KBr): υ 2915, 1719, 1685, 1628, 1599, 1504, 1246, 1183, 825. (δ ppm DMSO d_6): 3.85 (s, OCH_3), .5.06 (s, CH_2), 6.95 (s, CH ethylenic), 6.99 (d, 1H benzylidene, J=9Hz), 7.42(d, 1H benzylidene, J=9Hz), 8.62(d, 1H benzylidene, J=2.4Hz), 7.42 (t, phenacyl, J=9Hz), 8.15-8.19 (m, 2H phenacyl), 11.97 (s, 1H NH). MS m/z(%): 449 (M^+ + 1 100%), 451(94.32), 417(7.5), 313(14), 315(19.6), 171(34.7), 139(59.2), 123(84.4).

(5*Z*)-3-[2-(4-Fluorophenyl)-2-oxo-ethyl]-5-(1*H*-indol-3-yl-methylene)-2-thioxo-imidazolidin-4-one 33 $C_{20}H_{14}FN_3O_2S$. Yield 88%. M.p. 235°C. TLC, ($CHCl_3$:MeOH 85:15) R_f 0,45. IR cm^{-1} (KBr): υ 3329, 3097, 1710, 1688, 1625, 1505, 1426, 1244, 949, 752. (δ ppm DMSO d_6): 5.02 (s, CH_2), 7.06 (s, CH ethylenic), 6.89-6.94 (m, 1H indolidene), 7.1-7.16 (m, 1H indolidene), 7.45 (d, 1H indolidene J=8.7Hz), 8.06 (d, 1H indolidene J=9.2Hz), 8.05 (s, 1H indolidene), (t, phenacyl, J=6.9Hz), 8.19-8.24 (m, 2H phenacyl), 11.58 (s, 1H NH), 11.74 (s, 1H NH). MS m/z(%): 379 (M^+ 3.6%), 347(7.2), 155(28.6), 123(100), 95(49.2), 75(25.9), 64(71.5).

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