SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME NEW *N* AND *S*-ALKYLATED ARYLIDENE-THIOXO-IMIDAZOLIDINONES

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Abstract: New arylidene-thioxo-imidazolidinones and *S*-alkylated arylidene-imidazolidinone derivatives were prepared from substituted 2-thioxo-imidazolidin-4-one by nucleophilic addition of cyanoacrylates. *N* and *S*-alkylation was achieved treating 5-arylidene-2-thioxo-imidazolidin-4-ones with benzyl or phenyloxoethyl chlorides under alkaline conditions. The anti-inflammatory activity of the synthesized imidazolidines was evaluated by the air pouch test and the carrageenan-induced paw edema test.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of inflammatory diseases. The main limitations in using NSAIDs consist in their side effects, including gastrointestinal ulceration and renal toxicity. Thiazolidines and bioisosteric imidazolidines are known to carry anti-inflammatory activity as it was demonstrated with some 5-arylidene-4-thioxothiazolidinones and 5-arylidene-thiazolidine-2,4-diones substituted at position 3 by 4-chlorobenzyl group [1]. Synthesis of some 5-arylidene-thioxoimidazolidinones and thioxothiazolidinones substituted at position 3 by a benzyl group or a phenyloxoethyl one, was previously reported [2-4]. Synthesis and physicochemical data of new 3-benzyl-5-benzylidene-2-thioxo-imidazolidin-4-ones, **10-15,** or 5-benzylidene-3-(2-phenyl-2-oxo-ethyl)-2-thioxo-imidazolidin-4-ones, **16-21,** and 5-benzylidene-3-(4-fluorobenzyl)-2-(4-bromobenzylsulfanyl)-3,5-dihydro-imidazol-4-ones, **22-23,** 2-[(4-bromophenyl)-2-oxo-ethylsulfanyl]-3-(4-fluorobenzyl)-5-(4-methoxybenzylidene)-3,5-dihydro-imidazol-4-one, **24,** or 5-benzylidene-3-[2-(4-bromophenyl)-2-oxo-ethyl]-2-[2-(4-bromophenyl)-2-oxo-ethylsulfanyl]-3,5-dihydro-imidazol-4-one, **25,** are now reported (Figure 1). These compounds were obtained from various (2-cyano-3-phenyl)-ethyl acrylates, by a nucleophilic Michael addition on the 2-thioxo-imidazolidin-4-one **1**. The 5-benzylidene-2-thioxo-imidazolidin-4-ones **2-9,** formed were *S*- and *N*-alkylated at position 2 or 3 with benzyl or phenyloxoethyl chlorides under alkaline conditions.

Chemistry and Molecular Structure

Compounds **22-25**, were synthesized in three steps: (*i*), At first, 5-arylidene-2-thioxo-imidazolidin-4-ones **2-9,** were prepared in the presence of piperidine by a 1,4-nucleophilic addition between 2-thioxo-imidazolidin-4-one **1**, and (2-cyano-3-phenyl)-ethyl acrylates. Acrylates were prepared by refluxing equimolar mixture of aldehyde and ethyl cyanoacetate with piperidine in benzene. (*ii*) Then compounds **2-9**, were *N* alkylated at position 3 in the presence of potassium carbonate that leads to the imidazolidine potassium salt. Then, benzyl or phenyloxoethyl chlorides reacted in alcoholic medium [5] to yield the 3-benzyl-5-benzylidene-2-thioxo-imidazolidin-4-ones **10-15,** and the 5-benzylidene-3-(2-phenyl-2-oxo-ethyl)-2-thioxo-imidazolidin-4-ones **16-21**. (*iii*) The 5-benzylidene-3-(4-fluorobenzyl)-2-(4-bromo-benzylsulfanyl)-3,5-dihydro-imidazol-4-ones **22-23,** 2-[(4-bromophenyl)-2-oxo-ethylsulfanyl]-3-(4-fluorobenzyl)-5-(4-methoxybenzylidene)-3,5-dihydro-imidazol-4-one **24,** and 5-benzylidene-3-

[2-(4-bromophenyl)-2-oxo-ethyl]-2-[2-(4-bromophenyl)-2-oxo-ethylsulfanyl]-3,5-dihydro-imidazol-4-one **25,** were prepared in the presence of sodium methoxyde. Finally, one must emphasize that compounds **2-9,** were isolated in a single isomer form which is the Z derivative as shown comparing spectroscopic data with those of imidazolidinones previously investigated [6,7].

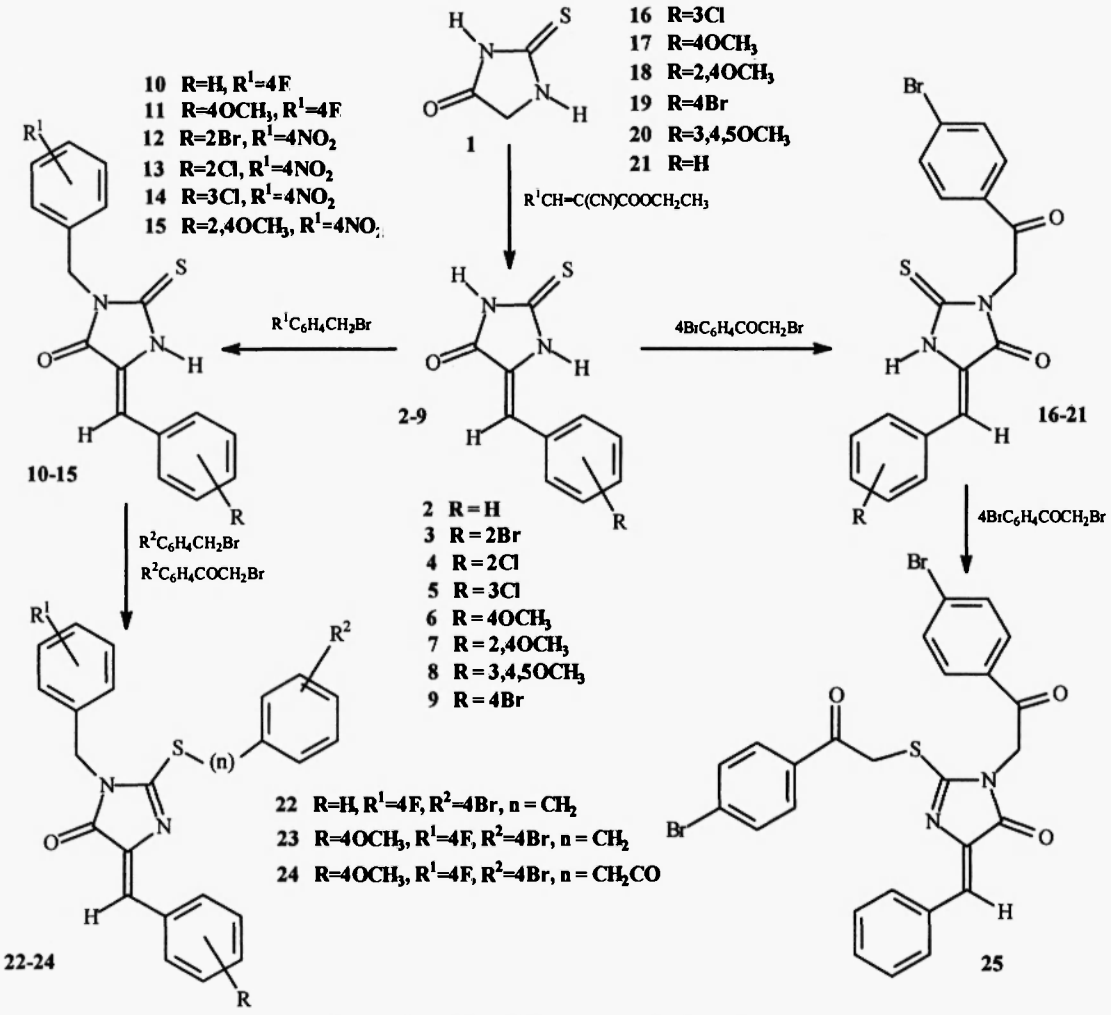

Figure-1: Imidazolidinones: synthetic pathway

Experimental Section

Biological Activity

The synthesized imidazolidines **22** and **24** were assayed for general effects according to the method described by De Luca [8]. These compounds (1000 mg/kg) were dissolved in Tween 80/saline (0.2:10) mixture and were administered orally in female Swiss mice. On the whole, animals were depressed and not stimulated. No lethal effects were observed during the assay. The animals had been observed firstly at 1 h time then each 12 h till 48 h were completed. Neither significant physiological alterations nor behavioral changes were evidenced. Thus, it can be considered that these compounds are only slightly toxic. During the pharmacological assay the maximum dose used was 0.5% of that tested for evaluating the acute toxicity [9].

The anti-inflammatory activity was prophylactically evaluated according to two different methodologies. The first one was the air-pouch test [10]. Pouches were formed by subcutaneous injections in male and female Swiss mice on the basis of a 2,5 mL air volume on day 0 and day 3. Carrageenan powder was dissolved in saline to a 10 mg/mL concentration and the solution was sterilized and homogenized by storing in oven where temperature is brought at 90°C for about 1 h before to be maintained at 37°C. The carrageenan solution (1 mL) was injected into the pouch six days after the initial injection of air with the aim to induce inflammation. The control group of mice only received the saline. Compounds **22** and **24,** and etoricoxib as reference drug were administered orally 1 h before injection of carrageenan. After 4h, mice were killed by ether exposure and pouches were washed thoroughly with 3 mL of phosphate buffer solution containing 50mUI/mL heparin. The total number of polymorphonuclear leukocytes infiltrated was measured using an improved Newbauer heamocytometer.

Proceeding thus the injection of carrageenan in the air pouch causes a fast influx of leukocytes (4 h after injection), whilst that of the saline solution produces only a non significant leukocyte infiltration (Table-1). The anti-inflammatory effect of the drugs is expressed in terms of percentage of inhibition. Pre-treatment with compounds **22** and **24** at doses from 0.63 to 5 mg/kg, as well as that with etoricoxib at a 20mg/kg dose, produced a strong decrease in the migration of leukocytes when compared to the control group. Moreover, the lesser dose tested (0.63 mg/kg) the better the result.

The second method used was the classical WINTER's one [11]. Each male and female Wistar rat received orally either compounds **22, 24**, or etoricoxib at a 2.5 mg/kg dose. The control group received only the vehicle. One hour after the drug administration, 0.1 mL of a 1% carrageenan aqueous solution as inflammatory agent was injected subcutaneously in the foot arch of the right hind leg. The volume of the leg was measured using a manual pletsmometer. Results are collected in Table-2. Compounds assayed show a significant prophylactic anti-inflammatory activity when compared to the control group.

Table-1: Number of cells found in the pouch 4 hours after the inflammation be produced and inhibitory effects on the leukocyte cellular influx.

Compounds	Doses (mg/kg)	Number of cells/μL	Cellular influx inhibition (%)	Control group
24	0.63	$0.41 \pm 0.05 \times 10^3$	71	Z
24	1.25	$1.49 \pm 0.37 \times 10^3$	65	Y
24	2.5	$1.99 \pm 0.39 \times 10^3$	53	Y
24	5	$2.22 \pm 0.25 \times 10^3$	25	X
22	0.63	$0.46 \pm 0.15 \times 10^3$	67	Z
22	1.25	$1.36 \pm 0.37 \times 10^3$	54	X
22	2.5	$1.92 \pm 0.47 \times 10^3$	35	X
22	5	$1.97 \pm 0.23 \times 10^3$	34	X
Etoricoxib	20	$2.31 \pm 0.41 \times 10^3$	46	Y
Control X		$2.97 \pm 0.45 \times 10^3$	-	
Control Y		$4.26 \pm 0.84 \times 10^3$	-	
Control Z		$1.40 \pm 0.08 \times 10^3$	-	
Control (without lesion)		$0.07 \pm 0.01 \times 10^3$	-	

Table-2: Inhibition of the leg edema [(1)] (%)

Compounds	Time after induction of the edema		
	1 h	2 h	4 h
22	0	59	47
24	32	41	47
Etoricoxib	24	28	42

[(1)] The control group is considered to show 100% of edema.

Compound 24 presents a 32% inhibition at the early stage of the development of edema. This is probably due to the local production of bradykinin. Around 45% inhibition is observed in the second stage (2 and 4 h) where the synthesis of prostaglandins is involved. Compound **22** is only active in the second step, suggesting that this compound is more selective than 24 and perhaps only disrupts the prostaglandin way.

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 infrared spectra be recorded on a IFS 66 Bruker spectrometer, apart from compounds **2,10,11,14,18,21-25** which were studied on a MB 100 M Bomem. ^{1}H NMR spectroscopy was carried out on a Bruker AC 300 P spectrophotometer apart from compounds **2,10,11,21,24-25** which were studied on a Bruker ARX 200MHz spectrometer. 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 **13** which was carried out on a Finnigan GCQ Mat Quadrupole Ion-Trap. Intensity of molecular peaks is given with reference to the most intense peak M^+(%). The already published data of compounds **3,5** [3], **4,9** [12] and **6,7** [1] are not reported here.

Analyses of all the compounds prepared were within ± 0.4% of the theoretical values.

(5*Z*)-5-Arylidene-2-thioxo-imidazolidin-4-ones, **2,8**: general procedure.

An equimolar (4.3mmol) mixture of 2-thioxoimidazolidin-4-one, **1** (0.5g) and (2-cyano-3-phenyl)-ethyl acrylate dissolved in ethanol (10mL) with piperidine (250μL) added 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-Benzylidene-2-thioxo-imidazolidin-4-one, **2**

$C_{10}H_8N_2OS$. Yield 72%. M.p. 268-270°C. TLC, (*n*-hex:AcOEt, 70:30) R_f 0,53. IR (KBr; υ, cm^{-1}) 3237, 1724, 1643, 1499, 1478, 1187, 768. H^1 NMR (δ ppm, DMSO-d_6): 6.47 (s, CH ethylenic), 7.38-7.41 (m, 3H benzylidene), 7.71-7.75 (dd, 2H benzylidene, J=7.8-1.6 Hz), 12.17 (s, NH), 12.37 (s, NH). MS EI m/z(%): 204 (M^+ 100%), 205 (M^{+1} 21%), 117(70), 90(72), 89(58), 59(65).

(5*Z*)-2-Thioxo-5-(3,4,5-trimethoxybenzylidene)-imidazolidin-4-one, **8**

$C_{13}H_{14}N_2O_4S$. Yield 48%. M.p. 218-220°C. ,TLC, (n-hex.:AcOEt, 50:50) R_f 0,58. IR (KBr; υ, cm^{-1}) 3117, 1725, 1653, 1577, 1502, 1333, 1127, 961, 638. H^1 NMR (δ ppm, DMSO-d_6): 3.69 (s, 3H OCH_3), 3.85 (s, 6H OCH_3), 6.45 (s, CH ethylenic), 6.97 (s, 2H benzylidene), 12.26 (s, NH), 12.39 (s, NH). MS EI m/z(%): 294 (M^+ 100%), 295 (M^{+1} 16%), 279(35), 192(17), 91(9), 78(18), 77(18).

(5*Z*)-3-Benzyl-5-benzylidene-2-thioxo-imidazolidin-4-ones, **10-15**, and (5*Z*)-5-benzylidene-3-(2-phenyl-2-oxo-ethyl)-2-thioxo-imidazolidin-4-ones, **16-21**: general procedure.

A solution of 5-substituted 2-thioxo-imidazolidin-4-one **2-9**, (3.8mmol), potassium carbonate (5.5mmol) in methanol (10mL) was stirred at room temperature for 1h. Then 1-bromomethyl-4-fluoro-benzene or 1-bromomethyl-4-nitro-benzene and 2-bromo-1-(4-fluoro-phenyl)-ethanone or 1-(4-bromo-phenyl)-ethanone (4.2mmol) was added and the mixture was stirred 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*)- 5-Benzylidene-3-(4-fluorobenzyl)- 2-thioxo-imidazolidin-4-one, **10**

$C_{17}H_{13}FN_2OS$. Yield 97%. M.p. 185-187°C. TLC, (*n*-hex:AcOEt, 70:30) R_f 0,53. IR (KBr; υ, cm^{-1}) 3067, 1708, 1633, 1509, 1410, 1159. H^1 NMR (δ ppm, DMSO-d_6): 4.55 (s, CH_2), 6.74 (s, CH ethylenic), 7.16 (t, 2H benzyl, J=8.6 Hz), 7.55 (dd, 2H benzyl J=8.6 5.6 Hz), 7.43 (t, 3H benzylidene J=8.2 Hz), 8.18 (d, 2H benzylidene J=8.2 Hz), 11.84 (s, NH). MS EI m/z(%): 312 (M^+ 26%), 313 (M^{+1} 4%), 116(8), 109(100), 89(11), 83(17).

(5*Z*)-3-(4-Fluorobenzyl)-5-(4-methoxybenzylidene)-2-thioxo-imidazolidin-4-one, **11**

$C_{18}H_{15}FN_2O_2S$. Yield 92%. M.p. 213-215°C. TLC, (*n*-hex:AcOEt, 60:40) R_f 0,59. IR (KBr; υ, cm^{-1}) 3073, 1704, 1630, 1597, 1511, 1264, 1170. H^1 NMR (δ ppm, DMSO-d_6): 3.8 (s, OCH_3), 4.53 (s, CH_2), 6.72 (s, CH ethylenic), 7.01 (d, 2H benzylidene, J=9.1 Hz), 7.16 (t, 2H benzyl, J=8.8 Hz), 7.54 (dd, 2H benzyl J=8.8 5.8 Hz), 8.16 (d, 2H benzylidene, J=9.1 Hz), 11.71 (s, 1H NH). MS EI m/z(%): 342 (M^+ 43%), 343 (M^{+1} 14%), 309(15), 174(34), 146(13), 109(100), 83(40).

(5*Z*)- 5-(2-Bromobenzylidene)-3-(4-nitrobenzyl)-2-thioxo-imidazolidin-4-one, **12**

$C_{17}H_{12}BrN_3O_3S$. Yield 47%. M.p. 194-196°C. TLC, (*n*-hex.:AcOEt, 60:40) R_f 0,5. IR (KBr; υ, cm^{-1}) 3120, 3058, 1706, 1630, 1514, 1492, 1407, 1342, 1186, 763. H^1 NMR (δ ppm, DMSO-d_6): 4.68 (s, CH_2), 6.96 (s, CH ethylenic), 7.33 (dt, 1H benzylidene, J=7.5 1,5 Hz), 7.54 (t, 1H benzylidene, J=7.5 Hz), 7.73 (d, 1H benzylidene, J=8.1 Hz), 7.8 (d, 2H benzyl, J=8.7 Hz), 8.22 (d, 2H benzyl, J=8.7 Hz), 8.73 (d, 1H benzylidene, J=8.1 Hz), 12.05 (s, NH). MS EI m/z(%): 417 (M^+ 4%), 419 (M^{+2} 6%), 338(60), 203(84), 116(38), 115(52), 90(51), 89(100).

(5*Z*)- 5-(2-Chlorobenzylidene)-3-(4-nitrobenzyl)-2-thioxo-imidazolidin-4-one, **13**

$C_{17}H_{12}ClN_3O_3S$. Yield 67%. M.p. 224-226°C. TLC, (benzene:AcOEt, 80:20) R_f 0,5. IR (KBr; υ, cm^{-1}) 3122, 3057, 1706, 1631, 1599, 1512, 1410, 1340, 1186, 759. H^1 NMR (δ ppm, DMSO-d_6): 4.68 (s, CH_2), 7 (s, CH ethylenic), 7.41 (dt, 1H benzylidene, J=7.5 1,8 Hz), 7.48 (dt, 1H benzylidene, J=7.5 1.5 Hz), 7.54 (dd, 1H benzylidene, J=7.8 1.5 Hz), 7.78 (d, 2H benzyl, J=8.4 Hz), 8.21 (d, 2H benzyl, J=8.7 Hz), 8.73 (d, 1H benzylidene, J=8.1 Hz), 11.98 (s, NH). MS m/z(%): 373 (M^+ 2%), 372(6), 337(100), 304(13), 292(11), 202(13), 150(10), 89(8).

(5*Z*)- 5-(3-Chlorobenzylidene)-3-(4-nitrobenzyl)-2-thioxo-imidazolidin-4-one, **14**

$C_{17}H_{12}ClN_3O_3S$. Yield 72%. M.p. 200-201°C. TLC, (benzene:AcOEt, 70:30) R_f 0,6. IR (KBr; υ, cm^{-1}) 3142, 3074, 1714, 1609, 1520, 1348, 1184. H^1 NMR (δ ppm, DMSO-d_6): 4.69 (s, CH_2), 6.75 (s, CH ethylenic), 7.44-7.51 (m, 2H benzylidene), 7.83 (d, 2H benzyl, J=8.4 Hz), 8.02 (d, 1H benzylidene, J=6.6 Hz), 8.21 (d 2H, benzyl, J=8.4 Hz), 8.34 (s, 1H benzylidene), 12.01 (s, NH). MS EI m/z(%): 373 (M^+ 7%), 375 (M^{+2} 4%), 150(26), 106(17), 90(58), 89(100), 78(86), 63(41).

(5*Z*)- 5-(2,4-Dimethoxybenzylidene)-3-(4-nitrobenzyl)-2-thioxo-imidazolidin-4-one, **15**

$C_{19}H_{17}N_3O_5S$. Yield 79%. M.p. 212-214°C. TLC, (benzene:AcOEt, 70:30) R_f 0,52. IR (KBr; υ, cm^{-1}) 3058, 2820, 1721, 1604, 1509, 1348, 1289, 1258, 1186, 951. H^1 NMR (δ ppm, DMSO-d_6): 3.85 (s, OCH_3), 3.87 (s, OCH_3), 4.65 (s, CH_2), 6.6 (d, 1H benzylidene, J=2.4 Hz), 6.68 (dd, 1H benzylidene, J=8.7; 2.4 Hz), 7.05 (s, CH ethylenic), 7.78 (d, 2H benzyl, J=8.7 Hz), 8.21 (d, 2H benzyl, J=8.7 Hz), 8.61 (d, 1H benzylidene, J=9 Hz), 11.68 (s, NH). MS EI m/z(%): 399 (M^+ 24%), 400 (M^{+1} 4%), 264(91), 204(100), 169(32), 136(47), 106(25), 89(57), 78(51).

(5*Z*)-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-5-(3-chlorobenzylidene)-2-thioxo-imidazolidin-4-one, **16**

$C_{18}H_{12}BrClN_2O_2S$. Yield 78%. M.p. 139-140°C. TLC, (*n*-benzene:AcOEt, 80:20) R_f 0,5. IR (KBr; υ, cm^{-1}) 3132, 3074, 1704, 1633, 1503, 1415, 1183, 779. H^1 NMR (δ ppm, DMSO-d_6): 4.98 (s, CH_2), 6.63 (s, CH ethylenic), 7.1 (t, 1H benzylidene, J=7.8 Hz), 7.29-7.32 (m, 1H benzylidene), 7.77-7.82 (m, 1H benzylidene), 7.81 (d, 2H phenacyl, J=8.4 Hz), 8.03-8.06 (m, 1H benzylidene), 8.04 (d, 2H phenacyl, J=8.7 Hz), 11.97 (s, NH). MS m/z(%): 434 (M^+ 2%), 436(M^{+2} 2%), 402(4), 238(59), 240(30), 183(100), 185(84), 151(51), 116(27), 89(56).

(5*Z*)-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-5-(4-methoxyibenzylidene)-2-thioxo-imidazolidin-4-one, **17**

$C_{19}H_{15}BrN_2O_3S$. Yield 94%. M.p. 176-177°C. TLC, (*n*-hex.:AcOEt, 60:40) R_f 0,46. IR (KBr; υ, cm^{-1}) 3140, 3069, 1711, 1633, 1597, 1509, 1255, 1181, 1168, 830. H^1 NMR (δ ppm, DMSO-d_6): 3.76 (s, OCH_3), 4.9 (s, CH_2), 6.54 (d, 2H benzylidene, J=9 Hz), 6.63 (s, CH ethylenic), 7.75 (d, 2H benzylidene, J=9 Hz), 7.88 (d, 2H phenacyl, J=8.7 Hz), 8.09 (d, 2H phenacyl, J=8.7 Hz), 11.78 (s, NH). MS EI m/z(%): 430 (M^+ 23%), 432 (M^{+2} 29%), 247(74), 234(27), 183(100), 185(89), 155(63), 157(43), 146(82), 132(39), 78(48).

(5*Z*)-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-5-(2,4-dimethoxybenzylidene)-2-thioxo-imidazolidin-4-one, **18**

$C_{20}H_{17}BrN_2O_4S$. Yield 88%. M.p. 187°C. TLC, (*n*-hex.:AcOEt, 55:45) R_f 0,44. IR (KBr; υ, cm^{-1}) 3063, 3129, 1708, 1604, 1493, 1284, 1183, 948, 830. H^1 NMR (δ ppm, DMSO-d_6): 3.78 (s, OCH_3), 3.82 (s, OCH_3), 4.88 (s, CH_2), 5.8 (dd, 1H benzylidene, J=9 2.4 Hz), 6.51 (d, 1H benzylidene, J=2.4 Hz), 6.95 (s, CH ethylenic), 7.87 (d, 2H phenacyl, J=8.4 Hz), 8.04 (d, 1H benzylidene, J=9 Hz), 8.08 (d, 2H phenacyl, J=8.4 Hz), 11.73 (s, NH). MS EI m/z(%): 460 (M^+ 1%), 462 (M^{+2} 1%), 428(1), 430(1), 264(18), 183(54), 185(75), 155(20), 157(23), 76(62), 64(100).

(5*Z*)-5-(4-Bromobenzylidene)-3-[2-(4-bromophenyl)-2-oxo-ethyl]-2-thioxo-imidazolidin-4-one, **19**

$C_{18}H_{12}Br_2N_2O_2S$. Yield 64 M.p. >270°C. TLC, (*n*-hex.:AcOEt, 60:40) R_f 0,5. IR (KBr; υ, cm^{-1}) 3063, 1713, 1689, 1633, 1583, 1505, 1179 1072, 819. H^1 NMR (δ ppm, DMSO-d_6): 4.93 (s, CH_2), 6.65 (s, CH ethylenic), 7.16 (d, 2H benzylidene, J=8.7 Hz), 7.73 (d, 2H benzylidene, J=8.7 Hz), 7.87 (d, 2H phenacyl, J=8.4 Hz), 8.08 (d, 2H phenacyl, J=8.4 Hz), 11.95 (s, NH). MS EI m/z(%): 478 (M^+ 12%), 480 (M^{+2} 20%), 183(52), 185(69), 157(32), 155(35), 137(100), 116(22), 115(21), 89(20), 76(27).

(5*Z*)-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-5-(3,4,5-trimethoxybenzylidene)-2-thioxo-imidazolidin-4-one, **20**

$C_{21}H_{19}BrN_2O_5S$. Yield 52%. M.p. 174°C. TLC, (*n*-hex.:AcOEt, 50:50) R_f 0,57. IR (KBr; υ, cm^{-1}) 3063, 1708, 1633, 1576, 1503, 1461, 1245, 1130, 993, 809. H^1 NMR (δ ppm, DMSO-d_6): 3.6 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3), 5.11 (s, CH_2), 6.69 (s, CH ethylenic), 7.48 (s, 2H benzylidene), 7.8 (d, 2H phenacyl J=8.7 Hz), 7.97 (d, 2H phenacyl, J=8.7 Hz), 11.89 (s, NH). MS EI m/z(%): 490 (M^+ 1%), 492 (M^{+2} 1%), 294(17), 183(89), 185(100), 157(30), 155(42), 128(11), 76(63).

(5*Z*)-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-5-benzylidene-2-thioxo-imidazolidin-4-one, **21**

$C_{18}H_{13}BrN_2O_2S$. Yield 46%. M.p. 199-200°C. TLC, (*n*-hex.:AcOEt, 50:50) R_f 0,79. IR (KBr; υ, cm^{-1}) 3064, 1717, 1633, 1584, 1509, 1176, 989. H^1 NMR (δ ppm, DMSO-d_6): 4.92 (s, CH_2), 6.65 (s, CH ethylenic), 7.02 (t, 2H benzylidene J=7.4 Hz), 7.24 (t, 1H benzylidene J=7.4 Hz), 7.8 (d, 2H benzylidene J=7.4 Hz), 7.83 (d, 2H phenacyl, J=8.6Hz), 8.06 (d, 2H phenacyl, J=8.6Hz), 11.9 (s, 1H NH). MS EI m/z(%): 400 (M^+ 17%), 402 (M^{+2} 10%), 217(17), 183(100), 185(98), 155(22), 76(35), 64(14).

(5*Z*)-5-Benzylidene-2-(4-bromobenzylsulfanyl)-3-(4-fluorobenzyl)-3,5-dihydro-imidazol-4-ones, **22-23**, and 2-[(4-bromophenyl)-2-oxo-ethylsulfanyl]-3-(4-fluorobenzyl)-5-(4-methoxybenzylidene)-3,5-dihydro-imidazol-4-one, **24**: general procedure.

A mixture of **10** or **11** (0.45 mmol), 1-bromomethyl-4-bromo-benzene or 2-bromo-1-(4-bromophenyl)-ethanone (0.67 mmol) and sodium methoxide (0.54 mmol) in acetonitrile (10 ml) was stirred at room temperature for 3 at 12 h. After cooling, the fluffy product was collected by filtration and washed with water.

(5*Z*)-5-Benzylidene-2-(4-bromobenzylsulfanyl)-3-(4-fluorobenzyl)-3,5-dihydro-imidazol-4-one, **22**

$C_{24}H_{18}BrFN_2OS$. Yield 72%. M.p. 132-133°C. TLC, (*n*-hex.:AcOEt, 80:20) R_f 0,64. IR (KBr; υ, cm^{-1}) 3411, 3067, 1716, 1635, 1509, 1493, 1361, 1220, 1188, 1071, 972. H^1 NMR (δ ppm, DMSO-d_6): 4.6 (s, CH_2), 4.74 (s, CH_2), 6.97 (s, CH ethylenic), 7.17 (t, 2H benzyl, J=9 Hz), 7.21(d, 2H benzylsulfanyl, J=8,4 Hz), 7.42-7.52 (m, 3H benzylidene), 7.52-7.56 (m, 2H benzyl), 7.55 (d, 2H benzylsulfanyl, J=8.4 Hz), 8.23-8.25 (m, 2H benzylidene). MS EI m/z(%): 480 (M^+ 1%), 482 (M^{+2} 1%), 447(1), 449(1), 371(2), 373(2.5), 311(5), 280(2), 169(8.4), 171(8), 109(100), 89(21).

(5*Z*)-2-(4-Bromobenzylsulfanyl)-3-(4-fluorobenzyl)-5-(4-methoxybenzylidene)-3,5-dihydro-imidazol-4-one, **23**

$C_{25}H_{20}BrFN_2O_2S$. Yield 74%. M.p. 141-142°C. TLC, (*n*-hex.:AcOEt, 80:20) R_f 0,53. IR (KBr; υ, cm^{-1}) 3440, 2837, 1702, 1635, 1599, 1509, 1499, 1257, 1171, 1029. H^1 NMR (δ ppm, DMSO-d_6): 3.82 (s, OCH_3), 4.58 (s, CH_2), 4.72 (s, CH_2), 6.95 (s, CH ethylenic), 7.05 (d, 2H benzylidene, J=9 Hz), 7.17 (t, 2H benzyl, J=9 Hz), 7.19 (d, 2H benzylsulfanyl, J=8.4 Hz), 7.51-7.55 (m, 2H benzyl), 7.54 (d, 2H benzylsulfanyl, J=8.1 Hz), 8.23 (d, 2H benzylidene, J=9 Hz). MS m/z(%): 510 (M^+ 10%), 512 (M^{+2} 9%), 402(6), 404(7), 341(6), 169(20), 171(18), 146(22), 109(100), 89(24).

2-[(4-Bromophenyl)-2-oxo-ethylsulfanyl]-3-(4-fluorobenzyl)-5-(4-methoxybenzylidene)-3,5-dihydro-imidazol-4-one, **24**

$C_{26}H_{20}BrFN_2O_3S$. Yield 79%. M.p. 201-202°C. TLC, (*n*-hex.:AcOEt, 70:30) R_f 0,6. IR (KBr; υ, cm^{-1}) 3433, 1702, 1634, 1597, 1511, 1260, 1173. H^1 NMR (δ ppm, DMSO-d_6): 3.82 (s, OCH_3), 4.60 (s, CH_2), 5.22 (s, CH_2), 6.93 (s,

CH ethylenic), 7.05 (d, 2H benzylidene, J=8.8 Hz), 7.17 (t, 2H benzyl, J=8.7 Hz), 7.79 (d, 2H benzylsulfanyl, J=8.5 Hz), 7.54 (dd, 2H benzyl, J=8.7 5.6 Hz), 7.98 (d, 2H benzylsulfanyl, J=8.5 Hz), 8.24 (d, 2H benzylidene, J=8.8 Hz). MS m/z(%): 538 (M^+ 7%), 540 (M^{+2} 8%), 341(38), 183(100), 174(48), 146(61), 109(66), 83(18).

(5*Z*)-5-Benzylidene-3-[2-(4-bromophenyl)-2-oxo-ethyl]-2-[2-(4-bromophenyl)-2-oxo-ethylsulfanyl]-3,5-dihydro-imidazol-4-ones, **25**

A mixture of 21 (0.05 g, 0.13 mmol), 1-bromomethyl-4-bromo-benzene (0.05 g, 0.19 mmol) and sodium hydride (0.013 g, 0.58 mmol) in acetonitrile (5 mL) was stirred at room temperature for 24 h. After cooling, the fluffy product was collected by filtration and washed with water. $C_{26}H_{18}Br_2N_2O_3S$. Yield 30%. M.p. 136-138°C. TLC, (n-hex:AcOEt, 70:30) R_f 0,6. IR (KBr; υ, cm^{-1}) 3426, 2920, 1710, 1697, 1635, 1584, 1498, 1362, 1229, 1191, 1070, 994. H^1 NMR (δ ppm, DMSO-d_6): 5 (s, CH_2), 5.34 (s, CH_2), 6.85 (s, CH ethylenic), 6.98-7.07 (m, 2H benzylidene), 7.28 (t, 1H benzylidene, J=7.3 Hz), 7.42-7.61 (m, 2H benzylidene), 7.83 (d, 2H phenacyl, J=8.4 Hz), 7.85 (d, 2H phenacyl, J=8.6 Hz), 8.04 (d, 2H phenacyl, J=8.8 Hz), 8.08 (d, 2H phenacyl, J=8.8 Hz). MS EI m/z(%): 596 (M^+ 1%), 598(M^{+2} 1%), 22 4(9), 183(100), 185(94), 160(41), 155(29), 157(25), 128(26), 76(13), 64(37).

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