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Synthesis and schistosomicidal activity of new substituted thioxo-imidazolidine compounds

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Synthesis and physico-chemical properties of 3-benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-ones, 5-benzylidene-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-ones and 4-acridin-9-ylmethylene-1-benzyl-5-thioxo-imidazolidin-2-ones compounds are described. These thioxo-imidazolidine derivatives were prepared by alkylation and condensation with 4-fluoro-benzaldehyde or nucleophilic Michael addition with cyanoacrylates. The schistosomicidal activity of 3-benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one compounds was evaluated.

1. Introduction

Imidazolidine compounds are used for the treatment of schistosomiasis infections. Their efficacy is good but has serious drawbacks (Robinson et al. 1970; Waruiru 1992). This work describes the synthesis and the physicochemical properties of 3-benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-ones, 5-benzyidene-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-ones and 4-acridin-9-ylmethylene-1-benzyl-5-thioxo-imidazolidin-2-one compounds. These derivatives were synthetised using two different general routes. The first process used was condensation with various benzaldehydes while the second was nucleophilic addition with cyanoacrylates. The synthesis of some 5-aryldene-3-benzyl-4-thioxo-imidazolidin-2-ones and 5-aryldene-1-methyl-2-thioxo-imidazolidin-4-ones has been reported in previous papers (Albuquerque et al. 1999; Brandão et al. 2000; Silva et al. 2001; Andrade et al. 2002).

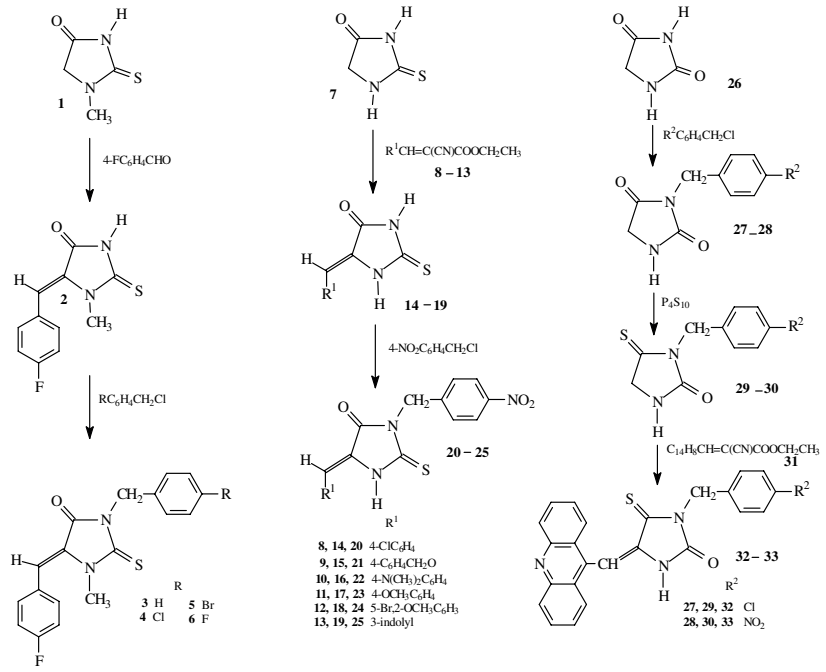
2. Investigations, results and discussion

2.1. Synthesis of the compounds

The 3-benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-ones were synthesized in three stages. Initially 1-methyl-2-thioxo-imidazolidin-4-one (**1**) was prepared using 1-methyl-glycine and ammonium thiocyanate (Romley et al. 1971). Then, the 1-methyl-2-thioxo-imidazolidin-4-one reacts with 4-fluoro-benzaldehyde in DMF in the presence of sodium methoxyde (Krapcho 1973) to form 5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**2**). The alkylation of this compound was carried out in the presence of potassium hydroxide and benzyl halides in alcoholic medium (Finkbeiner 1965). 3-Benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-ones **3**–**6** were thus obtained. In addition, some other new 5-arylidene or 5-(3-indolylmethylene) 3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-ones **20**–**25** were obtained by nucleophilic Michael addition of 2-thioxo-imidazolidin-4-one **7** to aryl-substituted ethyl-(2-cyano-3-phenyl)-acrylates **8**–**12** or ethyl-[2-cyano-3-(3-indol)]-acrylate **13**. The 5-arylidene or 5-(3-indolylmethylene)-2-thioxo-imidazolidin-4-ones **14**–**19** obtained were alkylated using 4-nitro-benzyl-chloride in the presence of potassium hydroxide. The 4-acridin-9-ylmethylene-1-benzyl-5-thioxo-imidazolidin-2-one derivatives **32**–**33** were only synthesized by nucleophilic addition of substituted 3-benzyl-4-thioxo-imidazolidin-2-ones **29**–**30**, to 9-[ethyl-(2′-cyano)-acrylate]-acridine **31**. In fact, direct condensation of 9-acridinaldehyde with the substituted imidazolidine-2-ones **29**–**30** did not lead to the expected 4-acridin-9-ylmethylene-1-benzyl-5-thioxo-imidazolidin-2-ones **32**–**33**, but to that obtained using 2-thioxo-imidazolidin-4-one. After alkylation of imidazolidin-2-4-dione **26** with benzyl halides, the oxo group in position 4 of substituted 3-benzyl-imidazolidine-2,4-diones **27**–**28** was replaced by thioxo with tetraphosphorous decasulfide. The 9-methyl-acridine starting product for the preparation of 9-acridinaldehyde, was obtained from diphenylamine with zinc dichloride in an acetic acid medium (Silva et al. 2001; Tsuge et al. 1963). Subsequently, oxidation of 9-methyl-acridine with pyridinium chlorochromate gave 9-acridinaldehyde (Silva et al. 2001; Mosher and Natale 1995). The condensation with ethyl cyanoacetate in the presence of piperidine in hot anhydrous benzene leads to the 9-[ethyl-(2′-cyano)-acrylate]-acridine **31** (Scheme).

The thioxoimidazolidines **2**–**6**, **14**–**25** were isolated in single isomer form. X-ray crystallographic studies have demonstrated the preferred *Z* configuration for 5-arylideneimidazolinone (De Simone et al. 1996). The study using coupled spectrometry ^{13}C-^{1}H NMR, determining the $^{3}J_{CH}$

Scheme



coupling constant value between the ethylene proton and the carbon atom located at the α position of the exocyclic bond for 1-methyl-3-(4-chloro-benzyl)-5-(4-chloro-benzylidene)-imidazolidine-2,4-dione also suggests a *Z* configuration (Silva et al. 2001). The molecular mechanics study using the Hyperchem and Mopac programs for 3-benzyl-5-benzylidene-1-methyl-2-thioxo-imidazolidin-4-one compounds confirmed likewise that the Z isomer is also, from the thermodynamic point of view, the most stable (Brandão et al. 2000).

2.2. Biological activity

2.2.1. Schistosomicidal activity

The BH (BH – Belo Horizonte, MG, Brazil) strain of *Schistosoma mansoni* is routinely maintained at LIKA (Keizo Asami Immunopathology Laboratory) by standard passage through *Biomphalaria glabrata* snails provided by the Department of Tropical Medicine (University Federal of Pernambuco). Adult schistosomes, obtained by perfusion using dissecting needles, were recovered from the mesenteric and portal veins of untreated *Swiss* albino mice, weighing 18–22 g, infected 8–12 weeks earlier (Duvall and Dewitt 1967). There are models available which can be used to study the susceptibility of *S. mansoni* adult worms to drugs *in vitro* (Mercer and Chapell 1985). Both males and females were examined in the experiments. The worms were maintained in a RPMI-1640 medium (Sigma) buffered to pH 7.5, supplemented with HEPES (20 mM), 10% foetal bovine serum (Cultilab), penicillin (100 U/mL), and streptomycin (100mg/mL). Incubation was carried out at 37 °C in a humid atmosphere containing 5% CO_2. The effect of 3-benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4- ones compounds **3**–**6** on the viability of on *S. mansoni* was examined by incorporating the drugs into the medium employed for parasite culture. The

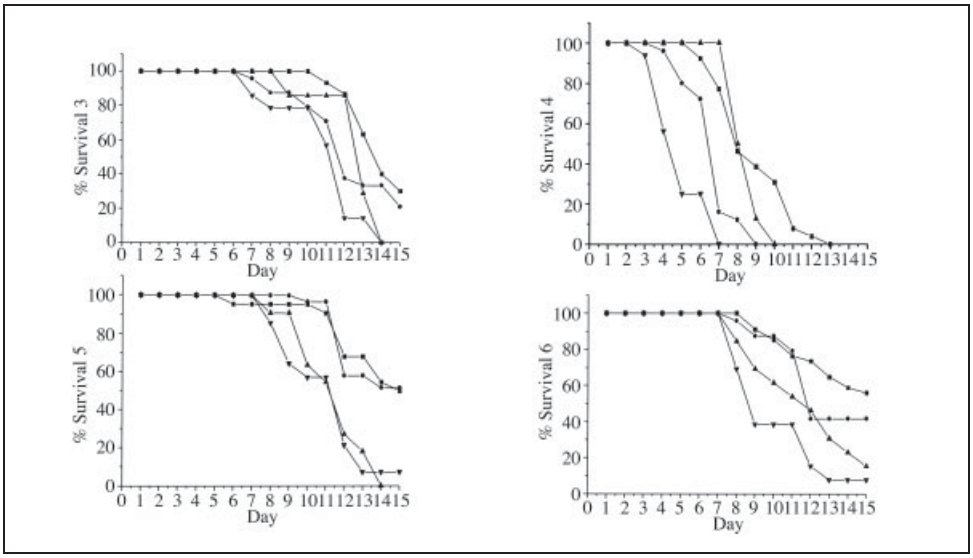


Fig.:
Survival of schistosomes maintained *in vitro* for 15 days in the presence of thioxoimidazolidine compounds **3**–**6** at 120 and 180 μg/mL.
■ Male 120 μg/mL, ● male 180 μg/mL, ▲ female 120 μg/m, ▼ female 180 μg/m

drugs, at appropriate concentrations, were dissolved in DMSO (1.5% v/v). This solvent concentration did not affect the worms' mortality, pairing, or motility. In all experiments two adult worms, unpaired were placed in multiwell plastic tissue culture dishes containing 3 mL of medium. A minimum of 30 worms was used in each treatment and control group. The worms viability was observed using an inverted microscope (60 ×) for 15 days after addition of the drugs. The worms already treated with DMSO were included as a control in every experiment. Praziquantel was chosen as the standard control. Parasites were considered dead when no movement could be detected over a 3-min period. Strict aseptic techniques were used throughout the experiments.

The viability of adult worms was observed *in vitro* during incubation with 120 or 180 μg/mL of thioxoimidazolidine derivatives **3**–**6**. The Fig. shows that up to the 7th day no mortality was observed in the worms, either male or female, at 120 μg/mL of **3**. On the 11th day of the assay all the worms, in the case of both doses, had shown sensitivity to this compound. After 15 days a maximum response had been obtained for the female worms. A relationship was also observed between time- and dose-dependent response.

The *para*-chloro-benzyl compound **4** was the most active of the series. From the 3rd day of contact with this compound onwards the female worms, at a dose of 180 μg/mL, showed sensitivity, and by the end of the period of the assay no parasites had survived. The maximum response was reached on the 7th day with the female worms incubated with 180 μg/mL. This compound also showed a relation between time- and dose-dependent response. The results obtained with the *para*-bromine-benzyl compound **5** were atypical in terms of the dose-response relation. However, by the end of 15th day, the females had proved to be more sensitive than the males, in the case of both doses. With the compound **6** where the fluorine atom is present in the *para* position of two aromatic rings, from the 8th day onwards the male worms showed sensitivity to the dose of 180 μg/mL, and the female worms at both doses. With this compound the maximum response was not achieved, but the females showed greater sensitivity than the males. The action of praziquantel, at a dose of 60 μg/mL showed that females and males began to show signs of sensitivity from the first day and by the end of the 15th day, no parasite had survived.

The motility of the worms was considerably reduced after 24 h of contact with the drugs. By way of microscopic observation, alterations in the worms tegument were observed. With **3**, at a dose of 120 μg/mL, the male worms showed bending and shortening of the body, suggesting a contraction of the longitudinal muscles. With compound **4**, the females showed many bubbles when the 180 μg/mL dose was used. Compound **6** caused degeneration in the internal structure of the worms, leading to a loss of transparency. It should be pointed out that the surviving worms, at the end of the assay period, showed irreversible alterations to the tegument and discrete movements. Control groups were not affected for up to 15 days of observation and all these worms remained paired throughout the observation period and exhibited vigorous activity.

The results presented demonstrate that **4**, at a dose of 180 μg/mL, is the most active of the series, achieving a maximum response by the 9th day of contact with the worms.

Except for compound **5**, the effectiveness of the derivatives studied was observed to be dose-dependent. At the end of the experiment the worms in the control groups remained viable. A great difference in the biological response was observed between the four composites of the series due to the different substitutes in the benzyl ring. The impossibility of determining a dose-response relation in the case of **5** is, perhaps, due to the presence of the voluminous bromine atom. The mechanism through which the antiparasitic effect is mediated still remains unknown. The potency of these derivatives might be taken as a basis for the development of new antischistosomal compounds.

2.2.2. Toxicological data

Adult Swiss albino mice of both sexes weighing between 25 and 35 g, were acquired from the Bioterium of the Department of Physiology and Pharmacology at the Federal University of Pernambuco. The animals received as much water and food (Labina®) as requested and were kept under controlled lighting conditions (12 h light/dark cycle) and temperature (23–26 °C).

Seventy mice, deprived of food for 12 h, were divided randomly into 14 groups (n = 5/group). Subsequently, the compounds **3**–**6** were diluted in DMSO (1.5%, v/v) and administered orally in doses of 40, 200 and 1000 mg/kg with a volume of 0.1 mL/10 g. The control groups received saline solution (NaCl 0.9%) and DMSO in the same volume. After oral administration, the animals were carefully observed for 6 h on a flat surface and then transferred to their respective cages and observed at regular intervals for 96 h. Effects seen were as follows: excitement or depression of the central nervous system, stereotyped movements, piloerection, spontaneous movement, diarrhoea. These observations were noted using the table designed by Malone (1977).

The administration of compounds **3**–**6** did not produce any alteration in the behaviour pattern of the animals in comparison to the control groups. No mouse from any group died. These data show that, in principle, compounds **3**–**6** exhibit low levels of toxicity, even when administered in high doses.

3. Experimental

Melting points were measured in a capillary tube on Büchi (or Quimis) apparatus. TLC was performed on silicagel plates Merck 60 F_{254}. IR of 1% KBr pellets were recorded on a Bruker IFS66 spectrometer or Perkin Elmer 1310 for **2**–**6, 17**. ^{1}H NMR spectra were recorded on a Bruker AC 300 P spectrophotometer or Bruker AC 200 FT for **2**–**6** in DMSO-d_6

MS, by electronic impact 70eV, were recorded on Delsi-Nermag R 1010 C spectrometer or HP G1019A for **3**–**6, 32, 33**. The intensity of the molecular peaks is given compared to the most intense peak M^+(%). The fragmentations observed were in accordance with the structures suggested.

The published chemical data for **1** (Brandão et al. 2000), **8** (Le Moal et al. 1966), **9**, **12**–**15**, **18**, **19** (Brandão et al. in press), **27** (Lima et al. 1992), **28** (Finkbeiner 1965), **29** (Albuquerque et al. 1995), **30** (Valls et al. 1985) and **31** (Silva et al. 2001) were not reported.

3.1. 5-(4-Fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**2**)

A mixture of 1-methyl-2-thioxo-imidazolidin-4-one (**1**) (1.3 g, 10 mmol), 4-fluoro-benzaldehyde (1.86 g, 15mmol) and sodium acetate (2.5 g) in 10 mL of acetic acid was refluxed for 3 h. After cooling, the precipitated product was washed with water and acetic acid. Yield 57%. M.p. 222–224 °C. R_f ($CHCl_3$: CH_3OH 96 : 4) 0.7. IR cm^{-1} (KBr): ν 3100, 1730, 1630, 1490, 1160, 840 cm^{-1}. RMN ^{1}H (δ ppm DMSO d_6): 3.45 (s, 3 H NCH_3), 6.74 (s, CH ethylenic), 7.56 (t, 2H benzylidene, J = 8,9 Hz), 8.13 (dd, 2 H benzylidene, J = 5.7 Hz); 12.37 (s, 1 H NH).

$C_{11}H_9FN_2OS$

3.2. 3-Benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-ones: general procedure

A solution of sodium hydroxide (0.12 g, 2.2 mmol) in methanol (3 mL) was added drop-wise to a stirred suspension of 5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (0.47 g, 2 mmol) in methanol (2 mL). After 10 min of contact, the benzyl halide (2.5 mmol) was added and left at room temperature for 24 h. After cooling, the precipitate was filtered

and washed with water and diethyl ether. The benzylidene imidazolidines resulting from this reaction showed a degree of purity sufficient for the analyses and antishistosomal assays.

3.2.1. 3-Benzyl-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**3**)

Yield 50%. M.p. 220–222 °C. TLC, ($CHCl_3$: CH_3OH 99 : 1) R_f 0,91. IR cm^{-1} (KBr): ν 1674, 1610, 1595, 1458, 1389, 1153, 831 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.3 (s, 3 H NCH_3), 4.57 (s, 2 H NCH_2), 6.83 (s, CH ethylenic), 7.31–7.49 (m, 5 H benzyl), 7.25 (t, 2 H benzylidene, J = 8.8 Hz), 8.33 (dd, 2 H benzylidene). MS m/z (%): 326 (M^+ 19.5), 293 (100), 235 (6.2), 148 (6.5), 134 (9.1).
$C_{18}H_{15}FN_2OS$

3.2.2. 3-(4-Chloro-benzyl)-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**4**)

Yield 33%. M.p. 218–220 °C. TLC, ($CHCl_3$: CH_3OH 98 : 2) R_f 0,91. IR cm^{-1} (KBr): ν 1684, 1594, 1453, 1373, 1152, 826 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.29 (s, 3 H NCH_3), 4.57 (s, 2 H NCH_2), 6.84 (s, CH ethylenic), 7.25 (t, 2 H benzylidene, J = 8.9 Hz), 7.4 (d, 2 H benzyl, J = 8.4 Hz), 7.5 (d, 2 H benzyl, J = 8.4 Hz), 8.33 (dd, 2 H benzylidene). MS m/z (%): 360 (M^+ 100), 327 (92.7), 292 (41.8), 235 (64), 148 (40.5), 134 (50.2).
$C_{18}H_{14}ClFN_2OS$

3.2.3. 3-(4-Bromo-benzyl)-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**5**)

Yield 69%. M.p. 215–217 °C. TLC, ($CHCl_3$: CH_3OH 98 : 2) R_f 0,76. IR cm^{-1} (KBr): ν 1689, 1612, 1595, 1453, 1374, 1158, 837 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.29 (s, 3 H NCH_3), 4.55 (s, 2 H NCH_2), 6.83 (s, CH ethylenic), 7.25 (t, 2 H benzylidene, J = 8.8 Hz), 7.43 (d, 2 H benzyl, J = 8.3 Hz), 7.54 (d, 2 H benzyl, J = 8.2 Hz), 8.33 (dd, 2 H benzylidene). MS m/z (%): 404 (M^+ 100), 406 (100), 373 (65.7), 371 (59), 292 (74.3), 235 (58.5), 148 (36.3), 134 (35.1).
$C_{18}H_{14}BrFN_2OS$

3.2.4. 3-(4-Fluoro-benzyl)-5-(4-fluoro-benzylidene)-1-methyl-2-thioxo-imidazolidin-4-one (**6**)

Yield 54%. M.p. 220–222 °C. TLC, ($CHCl_3$: CH_3OH 98 : 2) R_f 0,85. IR cm^{-1} (KBr): ν 1674, 1616, 1600, 1510, 1463, 1242, 1160, 837 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.29 (s, 3 H NCH_3), 4.57 (s, 2 H NCH_2), 6.84 (s, CH ethylenic), 7.17 (t, 2 H benzyl, J = 8.8 Hz), 7.25 (t, 2 H benzylidene, J = 8.8 Hz), 7.54 (dd, 2 H benzyl), 8.33 (dd, 2 H benzylidene). MS m/z (%): 344 (M^+ 100), 311 (66.5), 235 (25.1), 148 (25.8), 134 (26.2).
$C_{18}H_{14}F_2N_2OS$

3.3. 3-Aryl-2-cyano-ethyl acrylates: general procedure

An equimolar (23 mMol) mixture of aldehyde and ethyl cyanoacetate dissolved in benzene (20 mL) with piperidine (3 drops) was heated at 110–120 °C for 4–7 h. Upon cooling the precipitated product was recrystallized from ethanol.

3.3.1. 2-Cyano-3-(4-dimethylamino-phenyl)-ethyl acrylate (**10**)

Yield, 50%. R_f, C_6H_6 : AcOEt (95 : 5), 0.61. F, 122–123 °C. IR (cm^{-1}): 3775, 2993, 2209, 1705, 1612, 1569, 1527, 1383. 1274, 1184, 1086, 838. ^1H NMR (δ ppm DMSO d_6): 1.28 (t, 3 H CH_3, J = 6.9 Hz), 3.83 (s, 6 H NCH_3), 4.26 (q, CH_2, J = 6.9 Hz), 6.84 (d, 2 H Ar, J = 9 Hz), 7.96 (d, 2 H Ar, J = 9.3 Hz), 8.11 (s, CH ethylenic).
$C_{14}H_{16}N_2O_2$

3.3.2. 2-Cyano-3-(4-methoxy-phenyl)-ethyl acrylate (**11**)

Yield, 36%. R_f, C_6H_6 : AcOEt (95 : 5), 0.75. F, 81–83 °C. IR (cm^{-1}): 2993, 2216, 1717, 1586, 1561, 1261, 1185, 1019, 838. ^1H NMR (δ ppm DMSO d_6): 1.29 (t, 3 H CH_3, J = 7.2 Hz), 3.83 (s, 3 H OCH_3), 4.29 (q, CH_2, J = 6.9 Hz), 7.14 (d, 2 H Ar, J = 9 Hz), 8.07 (d, 2 H Ar, J = 9 Hz), 8.29 (s, CH ethylenic).
$C_{13}H_{13}NO_3$

3.4. 5-Arylidene-2-thioxo-imidazolidin-4-ones: general procedure

An equimolar (4.3 mMol) mixture of 2-thioxoimidazolidin-4-one, **7** (0.5 g) and 3-aryl-2-cyanoethyl acrylate **10**, **11** dissolved in ethanol (10mL) with piperidine (250 µL) was heated at 80–90 °C for 6–8 h. After cooling, the precipitated product was recrystallized from ethanol (**16**) or acetic acid (**17**).

3.4.1. 5-(4-Dimethylamino-benzylidene)-2-thioxo-imidazolidin-4-one (**16**)

Yield 50%. M.p. 251–253 °C. TLC, (n-hex. : AcOEt 60 : 40) R_f 0,61. IR cm^{-1} (KBr): ν 3811, 3087, 1732, 1713, 1640, 1589, 1482, 1374, 1320, 1185, 1164, 809 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3 (s, 6 H NCH_3), 6.43 (s, CH ethylenic), 6.72 (d, 2 H benzylidene, J = 9 Hz), 7.64 (d, 2 H benzylidene, J = 8.7 Hz), 12.02 (s, 2 H NH). MS m/z (%): 247 (M^+ 100), 159 (5.1), 89 (9.5).
$C_{12}H_{13}N_3OS$

3.4.2. 5-(4-methoxi-benzylidene)-2-thioxo-imidazolidin-4-one (**17**)

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

3.5. 5-Arylidene or 5-(1H-Indol-3-ylmethylene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-ones: general procedure

A solution of 5-substituted 2-thioxo-imidazolidin-4-one **14**–**19**, (0.4 mMol), potassium carbonate (0.48 mMol) in ethanol (2 mL) was stirred at room temperature for 1 h. Then 4-nitro-benzyl chloride (0.4 mMol) was added and the mixture was agitated for 18–24 h. Upon cooling in an ice bath, the product precipitated and was collected and washed with *n*-hexane, methanol and water.

3.5.1. 5-(4-Chloro-benzylidene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**20**)

Yield 68%. M.p. 219–220 °C. TLC, (n-hex : AcOEt 60 : 40) R_f 0,52. IR cm^{-1} (KBr): ν 3081, 2809, 1717, 1683, 1633, 1518, 1349, 1184, 712 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 4.69 (s, 2 H NCH_2), 6.75 (s, CH ethylenic), 7.52 (d, 2 H benzyl, J = 8.4 Hz), 8.15 (d, 2 H benzyl, J = 8.4 Hz), 7.8 (d, 2 H benzylidene, J = 8.7 Hz), 8.23 (d, 2 H benzylidene, J = 8.7 Hz), 11.89 (s, 1 H NH). MS m/z (%): 373 (M^+ 58), 294 (12.3), 106 (22.1), 89 (100), 77 (22.8).
$C_{17}H_{12}ClN_3O_3S$

3.5.2. 5-(4-Benzyloxy-benzylidene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**21**)

Yield 71%. M.p. 209–211 °C. TLC, (n-hex : AcOEt 50 : 50) R_f 0,6. IR cm^{-1} (KBr): ν 3071, 2833, 1711, 1634, 1599, 1511, 1344, 1253, 1167, 734 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 4.67 (s, 2 H NCH_2), 5.19 (s, 2 H OCH_2), 6.72 (s, CH ethylenic), 7.1 (d, 2 H benzyl, J = 9 Hz), 7.8 (d, 2 H benzyl, J = 9 Hz), 8.1 (d, 2H benzylidene, J = 8.7 Hz), 8.21 (dd, 2H benzylidene, J = 6.9, 2,1 Hz), 11.73 (s, 1 H NH). MS m/z (%): 445 (M^+ 7.3), 106 (12.1), 91 (100), 77 (21.7).
$C_{24}H_{19}N_3O_4S$

3.5.3. 5-(4-Dimethylamino-benzylidene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**22**)

Yield 87%. M.p. 215–216 °C. TLC, (n-hex : AcOEt 50 : 50) R_f 0,75. IR cm^{-1} (KBr): ν 3067, 2807, 1695, 1586, 1530, 1372, 1345, 1167, 944, 819 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.02 (s, 6 H $N(CH_3)_2$), 4.66 (s, 2 H NCH_2), 6.67 (s, CH ethylenic), 6.76 (d, 2 H benzyl, J = 9.3 Hz), 7.8 (d, 2 H benzyl, J = 9 Hz), 7.98 (d, 2 H benzylidene, J = 8.7 Hz), 8.23 (d, 2H benzylidene, J = 8.7 Hz), 11.63 (s, 1 H NH). MS m/z (%): 382 (M^+ 5.4), 246 (16.9), 169 (15.7), 106 (9.1), 89 (51.6), 78 (100), 63 (68.4).
$C_{19}H_{18}N_4O_3S$

3.5.4. 5-(4-Methoxy-benzylidene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**23**)

Yield 79%. M.p. 186–187 °C. TLC, (n-hex : AcOEt 50 : 50) R_f 0,48. IR cm^{-1} (KBr): ν 2992, 2832, 1701, 1634, 1597, 1510, 1345, 1255, 1172, 889 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.83 (s, 3 H OCH_3), 4.68 (s, 2 H NCH_2), 6.74 (s, CH ethylenic), 7.04 (d, 2 H benzyl, J = 8.7 Hz), 7.81 (d, 2 H benzyl, J = 8.7 Hz), 8.12 (d, 2 H benzylidene, J = 8.7 Hz), 8.23 (dd, 2 H benzylidene, J = 8.7 Hz), 11.77 (s, 1 H NH). MS m/z (%): 369 (M^+ 100), 233 (15.8), 174 (22.3), 146 (18.8), 106 (12.2), 89 (37.1), 77 (20.8).
$C_{18}H_{15}N_3O_4S$

3.5.5. 5-(5-Bromo-2-methoxy-benzylidene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**24**)

Yield 76%. M.p. 236–237 °C. TLC, (n-hex:AcOEt 50 : 50) R_f 0,74. IR cm^{-1} (KBr): ν 3070, 2832, 1717, 1633, 1520, 1508, 1350, 1254, 1188, 1027, 807 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 3.87 (s, 3 H OCH_3), 4.66 (s, 2 H NCH_2), 6.98 (s, CH ethylenic), 7.06 (d, 1 H benzylidene, J = 9 Hz), 7.56 (dd, 1 H benzylidene, J = 8.7, 2, 4 Hz), 7.84 (d, 2 H benzyl, J = 8.4 Hz), 8.21 (d, 2 H benzylidene, J = 8.4 Hz), 8.85 (d, 1 H benzylidene, J = 2.1 Hz), 12 (s, H NH). MS m/z (%): 447 (M^+ 20), 449 (30.3), 312 (7.7), 254 (9), 102 (14.2), 89 (52.2), 78 (100), 63 (44.5).
$C_{18}H_{14}BrN_3O_4S$

3.5.6. 5-(1H-Indol-3-ylmethylene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (**25**)

Yield 68%. M.p. 228–230 °C. TLC, (n-hex : AcOEt 50 : 50) R_f 0,85. IR cm^{-1} (KBr): ν 3393, 3061, 1697, 1621, 1512, 1346, 1232, 949, 742 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 4.73 (s, 2 H NCH_2), 7.13 (s, CH ethylenic), 7.12 (dt, 1 H indolyl, J = 7.8 1.5 Hz), 7.2 (dt, 1 H indolyl, J = 7.8, 1.5 Hz), 7.47 (d, 1 H indolyl, J = 8.1 Hz), 7.83 (d, 2 H benzyl, J = 9 Hz), 8.08 (d, 1 H indolyl, J = 7.8 Hz), 8.24 (d, 2 H benzyl, J = 8.7 Hz), 8.37 (s, 1 H indolyl), 11.88 (s, 1 H NH). MS m/z (%): 378 (M^+ 16.8), 242 (12.9), 169 (30.3), 155 (30.3), 136 (16.1), 106 (32.9), 90 (39), 89 (63.9), 78 (100), 63 (57.4).
$C_{19}H_{14}N_4O_3S$

3.6. 4-Acridin-9-ylmethylene-1-benzyl-5-thioxo-imidazolidin-2-ones: general procedure

3-Benzyl-4-thioxo-imidazolidin-2-one **29**–**30** (0.5 mmol) and 9-[ethyl-(2′-cyano)-acrylate]-acridine, **31**, (0.5 mmol) were dissolved in abs. ethanol (12 ml). The solution was refluxed for 2 h in the presence of a small amount of piperidine as a catalyst. The precipitate obtained was filtered and washed with water. The compounds isolated were of acceptable purity and were analysed without further recrystallization.

3.6.1. 4-Acridin-9-ylmethylene-1-(4-chloro-benzyl)-5-thioxo-imidazolidin-2-one (**32**)

Yield 89%. M.p. 265 dec.°C. TLC, (C_6H_6:AcOEt 70 : 30) R_f 0,62. IR cm^{-1} (KBr): ν 2939, 2706, 1754, 1651, 1437, 1340, 1222, 1149, 737 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 5.08 (s, 2 H NCH_2), 7.44 (s, 4 H benzyl), 7.69 (s, CH ethylenic), 7.65 (dt, 2 H acridinyl, J = 7.2 Hz), 7.88 (dt, 2 H acridinyl, J = 7.5 Hz), 8.05 (d, 2 H acridinyl, J = 8.7 Hz), 8.21 (d, 2 H acridinyl, J = 8.7 Hz), 10.84 (s, 1 H NH). MS m/z (%): 429 (M^+ 47.4), 428 (100), 397 (19.1), 304 (58.4), 229 (22.8), 218 (21.3), 125 (23.9).
$C_{24}H_{16}ClN_3OS$

3.6.2. 4-Acridin-9-ylmethylene-1-(4-nitro-benzyl)-5-thioxo-imidazolidin-2-one (**33**)

Yield 75%. M.p. 286–288 °C. TLC, (C_6H_6:AcOEt 70 : 30) R_f 0,52. IR cm^{-1} (KBr): ν 2938, 2711, 1758, 1656, 1605, 1521, 1342, 1225, 1152, 757 cm^{-1}. ^1H NMR (δ ppm DMSO d_6): 5.23 (s, 2 H NCH_2), 7.67 (d, 2 H benzyl, J = 9 Hz), 8.24 (d, 2H benzyl, J = 9 Hz), 7.71 (s, CH ethylenic), 7.66 (dt, 2 H acridinyl), 7.88 (dt, 2 H acridinyl, J = 7.5, 1,2 Hz), 8.08 (d, 2 H acridinyl, J = 8.4 Hz), 8.21 (d, 2 H acridinyl, J = 8.1 Hz), 10.9 (s, 1 H NH). MS m/z (%): 440 (M^+ 1.3), 353 (9.25), 301 (27.8), 229 (100), 203 (20.6), 192 (16.9).
$C_{24}H_{16}N_4O_3S$

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