International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-3, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Synthesis and Antiulcer, Anti-secretory Activity of Some New substituted 2-(Pyrimidinylsulfinyl) Benzimidazoles Derivatives

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Manuscript No: IJPRS/V3/I3/00324, Received On: 01/07/2014, Accepted On: 08/07/2014

ABSTRACT

A series of all new substituted 2-(pyrimidinylsulfinyl) benzimidazoles derivatives synthesized from different starting material and evaluation against antiulcer and antisecretory activity as a inhibition of gastric H+/K+- ATPase by induction of gastric ulcerations experimentally in male Wister rats according to the method. The newly synthesized compounds were characterized by IR and elemental analysis. All compounds were tested for antiulcer and antisecretory activities. The antiulcer activities of the compounds were assessed by Acetylsalicylic acid (ASA) method-induced gastric ulcer.

KEYWORDS

Antiulcer and Antisecretory Activity, 2-Pyrimidinylsulfinyl, Benzamidazoles.

INTRODUCTION

In our research program to develop antiulcer and antisecretory agents from benzimidazole derivatives[1]. Benzimidazoles structures are classified under several classes of drugs[1,2], based on the possible substitution at different positions of the benzimidazoles nucleus. Introduction of a small substitution on 2nd and 5th position of benzimidazoles is characteristic for antihelmentic activity; whereas, bulky substitution on 2nd position showed proton pump inhibitory and antihistaminic activity. Thus, benzimidazoles skeleton is therapeutically important moiety Benzimidazoles are in general high melting compounds. The parent compound melts at 170ºC.[3] However, substitution of iminohydrogen lowers down the melting or boiling point of benzimidazoles.

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The benzimidazoles are soluble in polar solvents and sparingly soluble in nonpolar solvents and sparingly soluble in nonpolar solvents. Introduction of nonpolar substituents in different position of benzimidazoles ring increases their solubility in nonpolar solvents e.g.. 2 methyl benzimidazoles is soluble in ether. On the contrary introduction of polar groups in ring increases solubility in polar solvents e.g. 2 amino benzimidazoles is soluble in water.[4] The ring system in which the benzene ring is fused at the 4, 5 position of imidazole ring[5] (1) is designed as benzimidazole. (2) The various positions in benzimidazole ring are numbered with imino function as number one. Benzimidazoles and its derivatives have been found to possess divergent biological activities.[6] They have been found to be active often with high potency. Benzimidazoles are relatively nontoxic.[7] The interest in Benzimidazole chemistry revived by the discovery, that 5,6-dimethyl Benzimidazoles is a part of vitamin B12 Chemical structure[8-9]. This shows the possibility of an anticancer activity exhibited by

benzimidazole derivatives. Some benzimidazoles do have vitamin B12 like activity and some are reported to be antisarnetious anemia factor[13-18]. Most of the benzimidazoles are antimetabolites to purine and folic acid also.

MATERIALS AND METHOD

Generals

All chemicals used in this work were of Hi-Media, E-Merck, Loba chemicals etc. grade. The percentage yield was based upon the products obtained after purification and recrystallisation. The solvents used for recrystallisation has been mentioned within brackets after melting points. The melting points of the compounds were determined in open capillary. Porous silica gel plates activated atm 110°C for 30 min. were used for thin layer chromatography (TLC) and were developed with iodine vapours. Though the different solvent system which gives better Rf values were selected and reported in preceding text.IR spectra of compounds were recorded using KBr pellets on FTIR 8400s from Shimadzu at Sharad Pawar College of pharmacy, Nagpur.

Synthesis of Compounds

The synthesis of compounds is illustrated in Scheme 1, 2 and 3. Details are described as follows.

Scheme 1

Preparation of Benzimidazole 2- Thiolate

A mixture of 32.4 g(0.1 mol) of Ortho phenyldiamine (OPD), 19.5g (0.1 mol) of Potasium hydroxide (KOH) and 26 g (0.1 mol) of carbon disulphide (CS_2), 300 ml of 95% ethanol and 45 ml of water in round bottom flask and reflux for 3 hour. Norit was then added cautiously & after mixture has been heated for 10 minutes. Norit was removed by filtration. A yellowish filtrate of benzimidazole 2- thiolate was collected in conical flask.

Preparation of Benzimidazole 2-Thiol

Filtrate of benzimidazole 2-thiolate was heated at 60-70 0C, mix 300ml of water followed by 25 ml of glacial acetic acid with efficient stirring. The product benzimidazole 2- thiol was separated as glisten white crystal. Then it was placed in refrigerator for 3 hours to complete crystallization.

Scheme 2

Preparation of Substituted Pyrimidine

Preparation of Ethanimide

Acetonitrile, hydrochloric acid and methanol was taken in double necked conical flask in ratio 1:3:1 followed by the ammonia solution, the pressure was maintained less than 26.6kPa by using null vacuum, cooling was maintained up to 30 ° C with the help of water which flowed continually, the reaction has been carried out for 3 hour, ethanimide crystals were collected on upper surface of solution. The yield of 85% Nature: a white long-prism-like crystal. 177-178°C melting point. Soluble in water, soluble in acetone, ethyl ether. Extreme moisture absorption.

Preparation of 2-Methyl, 6-Alkylpyrimidine-4-Ol

In 250 ml round bottom flask 5.8 g(0.1 mol) of ethanimide and 10.80 ml (0.1 mol) alkyl acetoacetate were placed then sodium ethoxide was added and refluxed for 2-3 hours Reaction mixture filtered and 2-Methyl 6-pyrimidine-4-ol was collected the solid.

Preparation of 4-Chloro 2 Methyl, 6-Alkylpyrimidine- 4-Ol

In 250 ml round bottom flask 2.5gm (0.1 mol) of 2,6 alkylprimidine-4-ol and 10 ml (0.1 mol) thionyl Chloride was placed followed by few pieces of porcelain and refluxed for 2-3 hours, the reaction mixture was filtered and solid product of 4-Chloro 2 methyl,6 Alkyl pyrimidine- 4-ol was collected **.**

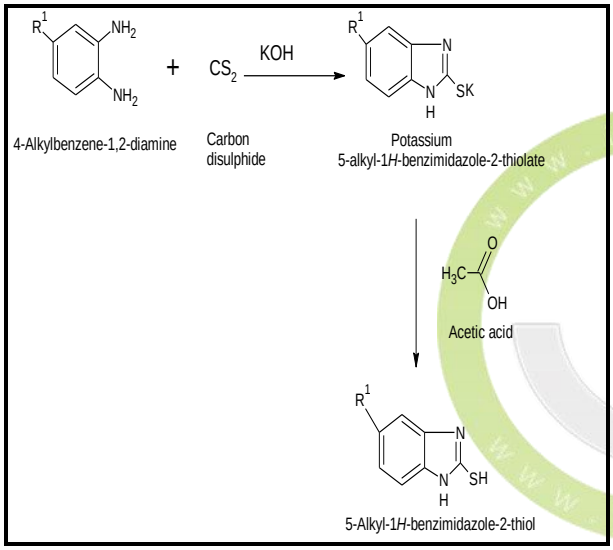
Scheme 3

Preparation of 2- (Pyrimidinylsulfinyl) Benzimidazol Derivatives

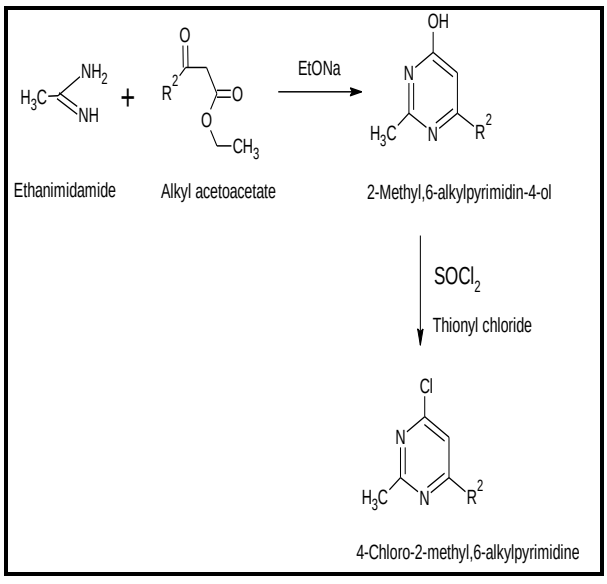
Preparation of 2-[(2,6- Alkylpyrimidin-4-Yl) Sulfanyl] 5- Alkyl-1h-Benzimidazole

Sodium hydroxide 0.13 g (3.3mol) was slowly added over 5 min to a stirred solution of 2-mercaptobenzimidazole 0.29 g (1.4 mol) in ethanol 20 ml. 4-chloro 2 methyl, 6 alkylpyrimidine- 4-ol was slowly added to the 2- mercaptobenzimdazole solution at 0^0C, and stirred for 12 hours at room temperature. After the solvent was removed under reduced pressure, the residue was poured into 10% $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. The desired coupling product 0.35 g, (74%) was obtained as a semi-solid.

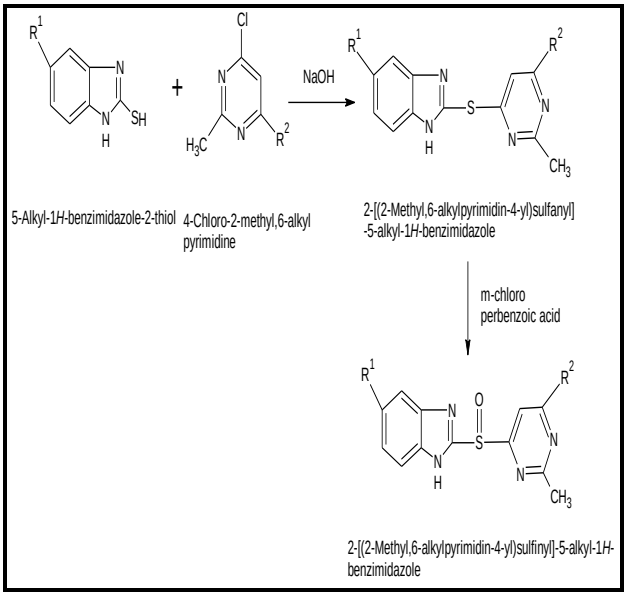
Scheme 1



Scheme 2



Scheme 3



Preparation of 2-[(2,6- alkylpyrimidin-4-yl) sulfinyl] 5- alkyl-1h benzimidazole

A solution of *m*-chloroperbenzoic acid 0.30 g (1.75 mol) was added drop wise to solution of 2-[(2 methyl,6-alkylpyrimidin-4-yl) sulfanyl]-5-alkyl- 1*H*-benzimidazole in 35 ml of CH_2Cl_2 at 0^0C. The reaction mixture was stirred at the same temperature for an hour. The solution was washed with 10% Na_2CO_3 solution and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography. 2-[(2 alkyl,6- alkylpyrimidin-4-yl) sulfinyl]-5-alkyl-1*H*benzimidazole was obtained in 89% yield. The structure of final compounds were characterized by, IR, NMR techniques.

2- [(2, 6-dimethylpyrimidin-4-yl)sulfinyl]-1*H*benzimidazole (1)

This compound was obtained as yellowish white solid in 92% yield, IR (KBr, v, cm^{-1}):3450 (O-H), 3050 (C-H), 1600 (N-H), 1483 (C-H), 825 (C-H); H-NMR(200 MHz, CDCl3):δ 3.65 (d, J=15.46, 1H, CH_2-Fu), 3.81 (d, J=15.28, 1H, HA), 3.85 (dd, J=1.86 & 15.28, 1H, HB), 4.91 (d, J=15.47, 1H, CH_2-Fu), 6.09 (d, J=3.08, 1H, H3-Fu), 6.26 (t, 1H, H4-Fu), 6.54 (d, J=2.08, 1H, H-2), 7.10-7.39 (m, 4H, H3, H4, & H5-Ph and H5-Fu).

2-[(6-ethyl-2-methylpyrimidin-4-yl)sulfinyl]-1*H*benzimidazole (2)

This compound was obtained as yellow semisolid in 84% yield, IR (KBr, v, cm^{-1}): Vmax C=O 1683 cm^{-1}; H-NMR(200 MHz, $CDCl_3$):δ 3.65 (d, J=15.29, 1H, CH_2-Fu), 6.09 (d, J=3.11, 1H, H3- Fu), 6.23 (m, 1H, H4-Fu), 6.99 (m, 1H, H4-Ph), 7.19 (d, J=1.17, 1H, H-2), 7.23-7.29 (m, 3H, H3, & H5-Ph and H5-Fu).

2-[(2-methyl-6-propylpyrimidin-4-yl)sulfinyl]- 1*H*-benzimidazole (3)

This compound was obtained as yellowish white solid in 82% yield, m.p. 79-81^{0}C; IR (KBr, v,cm-1): Vmax C=O 1688cm^{-1}; 1H-NMR (200 MHz, $CDCl_3$):δ 3.65 (d, J=15.15, 1H, HA), 3.82(d, J=15.48, 1H, CH_2-Fu), 3.90 (d, J=15.15, 1H, HB), 4.87 (d, J=15.47, 1H, CH_2-Fu), 6.00 (s, 1H, H-2), 6.15 (d, J=3.04, 1H, H3-Fu), 6.25 (t, 1H, H4-Fu), 6.85 (t, 2H, H3, & H5-Ph), 7.22-7.37 (m, 2H, H4-Ph and H5-Fu).

2-[(2,6-dimethylpyrimidin-4-yl)sulfinyl]-5-nitro- 1*H*-benzimidazole (4)

This compound was obtained as brown solid in 60% yield, m.p. 94-96^{0}C; IR (KBr, v, cm^{-1}) Vmax C=O 1677cm-1; 1H-NMR (200 MHz, $CDCl_3$):δ d 1.58 (d, J=7.0, 3H, CH_3), 3.78 (d, J=15.57, 1H, CH_2-Fu), 4.01 (q, J=7.00, 1H, $CHCH_3$), 4.85 (d, J=15.48, 1H, CH_2-Fu), 5.92 (s, 1H,CH), 6.14 (d, J=15.48 1H,CH_2-Fu), 5.92 (s, 1H, CH), 6.14(d, J=3.09, 1H, H3-Fu), 6.23 (t, 1H, H4-Fu), 7.23- 7.31 (m, 2H, H4-Ph and H5-Fu).

2-[(6-ethyl-2-methylpyrimidin-4-yl)sulfinyl]-5- nitro-1*H*-benzimidazole (5)

This compound was obtained as yellowish white solid in 67% yield, m.p. 86-89^{0}C; IR (KBr, v, cm-1): Vmax C=O 1688cm^{-1}; 1H-NMR (200 MHz, $CDCl_3$):δ 2.65 (s, 3H, CH_3), 3.88(d, J=15.48, 1H, HA), 4.11 (dd, J=2.05 & 15.84, 1H, HB), 7.03-7.18 (m, 2H, H3 & H5-Ph), 7.25 (m, 1H, H4-Ph), 7.31 (d, 1H, J=1.61 H2), 7.71 (d, J=8.74, 1H, H3-Py), 7.93 (d, J=8.73, 1H, H4-Py),

2-[(2-methyl-6-propylpyrimidin-4-yl)sulfinyl]-5- nitro-1*H*-benzimidazole (6)

This compound was obtained as yellow solid in 70% yield, m.p. 90-92^{0}C; IR (KBr, v, cm^{-1}) Vmax C=O 1672cm^{-1}; 1H-NMR (200 MHz, $CDCl_3$):δ 1.61-2.35 (m, 10H), 3.66 (d, J=14.48, 1H, HA), 3.91 (d, J=14.94, 1H,HB), 6.66 (s, 1H, H-2), 7.16-7.36 (m, 3H, H3, H4 & H5-Ph).

RESULTS AND DISCUSSION

The 2-(pyrimidinylsulfinyl) benzimidazole compound was successfully prepared by developed process and further purified using different solvents the compound were recrystalized by using ethanol and checked the purity by thin layer chromatographic techniques. The title compound was further characterized by physicochemical method and spectral analysis. Melting Point was recorded 155^{O}C by two different method capillary tube method and visible melting point apparatus methods and were uncorrected. Though the different solvent system which gives better Rf values were selected and reported in preceding text. The synthesized compound was characterized by physicochemical method, IR and NMR spectroscopy.

Antiulcer activity

Statistical analysis all the data from in vivo experiments are expressed as mean 7 standard error (SE). The statistical significance of difference between groups was evaluated by using Student's t-test through Graph pad Instat tm v 2.04a 941245s. $p<0.05$ was considered as significant.

Discussion

The antiulcer activity of test compounds was performed in the Albino rats of Wistar strain. The antiulcer activity of compounds was done by using induction of ulcer by acetylsalicylic acid as control dose. The above result shows that the test compounds showed significant antiulcer activity compared with the standard drug pentaprozole. The Compound BD1, BD2 and BD6 possess good antiulcer activity.

Antisecretory activity

This study reports the antisecretory gastric acid activities of the benzimidazole derivative were

assayed on gastric acid secretion of animals Wistar rats, on acute models of gastric mucosal lesions, and on gastric H+, K+-ATPase preparations. Intraduodenal injection of BD (0.5–2.0 g/kg), i.d produced a dose-related decrease of the basal gastric acid secretion in 4-h animals Wistar rats. At 1.0 g/kg, BD decreased the volume (28%) and total acidity (33%) of the basal acid secretion, and reversed the histamine (2.5 mg/kg, s.c.)- indicating inhibition of the gastric proton pump. Pretreatment of wistar rats with the BD (0.5–1.5 g/kg) protected against gastric mucosal lesions induced by 75% ethanol, indomethacin (30 mg/kg,). BD also decreased the gastric H+, K+-ATPase activity in vitro proportionately to the concentration (IC50 ¼ 58.8 mg/ml).

Discussion

The antisecretory activity of test compounds was performed in the Albino rats of Wistar strain. The antisecretory activity of compounds was done by using the collection of gastric secretion and its final volume and pH were determined. Total acidity of the gastric juice was titrated with 0.1N NaOH, using 2% phenolphthalein as indicator. The above result shows that the test compounds showed significant antiulcer activity compared with the standard drug pentaprozole. The compound BD3 and BD6 possess good antisecretory activity.

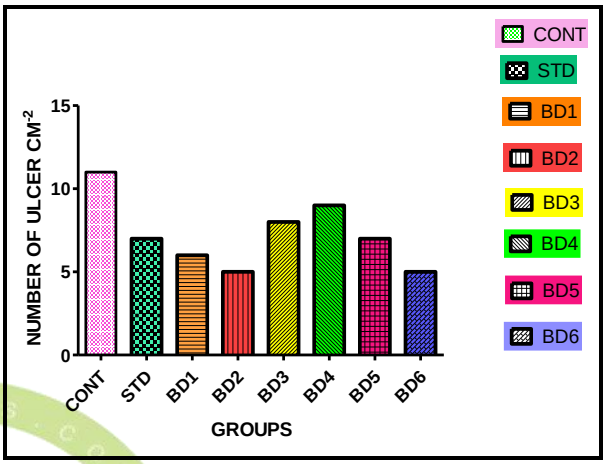


Figure 1: Antiulcer activity of 2(pyrimidinylsufinyl) benzimidazole

Table 1: Anti-ulcer effect of 2-(pyrimidinylsulfinyl) benzimidazole derivatives against ulcerogenic agent Acetylsalicylic acid (ASA)

Group No.	Group specification	Total ulcer index after Dosing %w/v Number of ulcer cm^{-2}
I	Control (Tween 80)	11 ± 3.75
II	Standard (Pentaprozole)	7 ± 0.25
III	BD 1	6 ± 2.25
IV	BD 2	5 ± 2.25
V	BD 3	8 ± 1.75
VI	BD 4	9 ± 2.75
VII	BD 5	7 ± 0.25
VIII	BD 6	5 ± 2.25

Results are means ± SE of the numbers of animals in parenthesis. Different from control group (ANOVA, and Dunnett's test $p < 0.05$; $p < 0.01$).

Table 2: Anti-Secretory effect of 2-(pyrimidinylsulfinyl) benzimidazole derivatives against Standard drug pentaprozole

Treatment	Volume (ml)	pH	Total acidity (mEq[H+]/l/4h)
Test Drug BD (n = 6)			
BD1	1.04 ± 0.09	3.0 ± 0.4	7.76 ± 1.47
BD2	0.87 ± 0.18	3.4 ± 0.6	5.80 ± 1.72
BD3	0.49 ± 0.14	3.6 ± 0.4	2.70 ± 0.69
BD4	0.58 ± 0.11	3.2 ± 0.8	4.25 ± 0.70
BD5	0.65 ± 0.04	4.8 ± 0.5	4.35 ±0.68
BD6	0.55 ± 0.16	4.5 ± 0.2	3.08 ± 0.80
Std drug SD (n = 1)			
PNTZ	0.65 ± 0.04	4.4 ± 0.3	3.18 ± 0.90

Results are means ± SE of the numbers of animals in parenthesis. Different from control group (ANOVA, and Dunnett's test $p < 0.05$; $p < 0.01$).

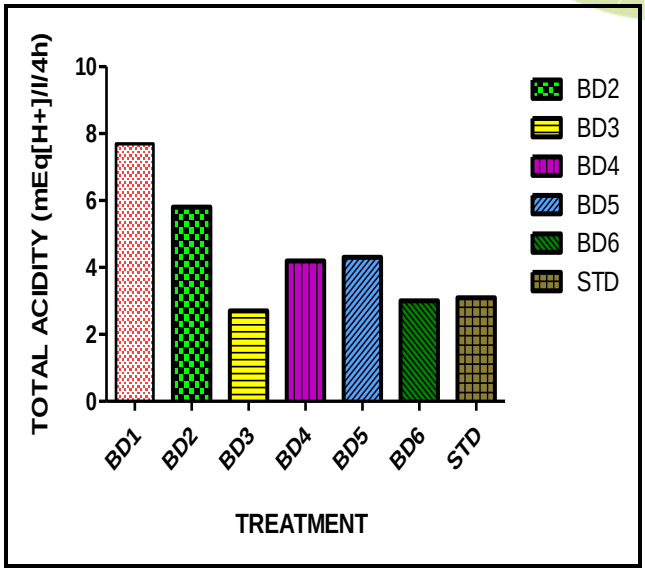


Figure: 2- Antisecretory activity 2-(pyrimidinylsulfinyl) benzimidazole

CONCLUSION

Ulceration evidence of many diseases is major concern for physicians throughout the world. In the literature, it has been proved that the 2-(pyridinylsulfinyl) benzimidazole derivatives has promising antiulcer and antisecretory activity. Hence, it was planned to synthesize the 2- (pyrimidinylsulfinyl) benzimidazole derivatives to get good antiulcer activity. A series of 2-(pyrimidinylsulfinyl) benzimidazole derivatives, were synthesized using appropriate synthetic route and screened for antiulcer and antisecretory activity. Preliminary pharmacological screening was performed, which includes approximate toxicity testing (LD50) and antiulcer activity. The LD50 of the test compounds performed on the rats as per the OECD guidelines for selecting the dose. The LD50 of all the derivatives was found >75mg/kg.

The antiulcer and antisecretory activity of test compounds was performed in the Albino rats of Wister strain. The antiulcer and antisecretory activity of compounds was done by using induction of ulcer by acetylsalicylic acid as control dose. The test compounds showed significant antiulcer activity compared with the standard drug pentaprozole. The Compound BD1, BD2 and BD6 possess good antiulcer activity with reduced toxicity. While the compound BD3 and BD6 shows good antisecretory activity. Thus research work was undertaken for substitution at 2-(pyrimidinylsulfinyl) benzimidazole ring. This research work provokes further to work on the different benzimidazole derivatives which may have lesser side effect and better antiulcer activity than the marketed drugs. Hence the above result shows that 2- (pyrimidinylsulfinyl) benzimidazole derivative gives good antiulcer and antisecretory drugs with lesser side effect. The encouraging results showed may lead to the development of novel antiulcer and antisecretory drugs if explored further.

ACKNOWLEDGEMENTS

It's my privileged to take this opportunity with pride and immense thanks in my deep sense of gratitude to **Ibrahim maliki, Dr. Sultan**, i, My All Family members & Friends.

I can't forget to express my heartfelt gratitude to the **Jaffar Ibrahim, Kadhar Nivass & Dr. Ram** I wish him grand successes for a future & I will remain thankful to them forever.

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