Synthesis of Some New Nucleosides Derived From 2-Mercapto Benzimidazole with Expected Biological Activity.

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ABSTRACT

2-mercaptobenzimidazole derivatives and their acyclic nucleosides were synthesized. The synthesized compounds were tested for their antibacterial activity against Escherichia coli, Staphylococcus aureus and S. epidermidis. Most of tested compounds showed moderate to high antibacterial activity while few compounds were found to show little or no activity against the tested microorganisms.

Keywords: Oxadiazolines, Arylidene derivatives, Nucleosides, Antibacterial activity

INTRODUCTION

The chemistry of heterocyclic compounds was used to prepare 2-mercaptopbenzimidazole and its derivatives for obtaining novel biologically active ingredients such as antihelmintic, anti-HIV, antifungal antimicrobial, CNS depressant, anti-inflammatory, and analgesic activities. In the last years, 2-mercaptopbenzimidazole derivatives play an important role in therapeutic and pharmacological fields. It possesses antimicrobial, analgesic and anti-inflammatory activities. A number of 2-mercaptopbenzimidazole derivatives have been prepared by the general method described by Van Allan and Deacon. The synthesized 2-mercaptopbenzimidazole derivatives exhibit moderate antibacterial and antifungal activities when compared to ampicillin and ketoconazole respectively. 2-mercaptopbenzimidazole derivatives were screened for their anti-inflammatory activity by carrageenan induced paw edema method. The derivatives of 2-mercaptopbenzimidazole were prepared using Mannich reaction showed moderate to high antibacterial activity. The benzimidazole moiety is present in wide antimicrobial, antiprotozoal and analgesic
The pharmacological and biological evaluating of it is clearly concluded that the prepared compounds are promisingly high antimicrobial, anti-inflammatory and analgesic agent. Benzimidazole derivatives play an important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, anti-diabetic and anticancer activity. Benzimidazole derivatives are considered as a promising class of biologically active heterocyclic compounds that show a wide of biological activities like anti-viral, anti-microbial, anticancer, anti-diabetic, anti-parasitic, anti-oxidant, anthelmintics, anti-HIV, anti-proliferative, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-neoplastic, and anti-trichinellosis. Synthesized Schiff base (AMPOHA) showed high activity against Bacillus subtilis, Escherichia coli, Aspergillus and Aspergillus flavus. N-phthalimido and acetomido derivatives has to undergo antimicrobial activity against Klebsiella, Escherichia coli, epidermitis, Staphylococcus, Micrococcus leteus, Bacillus cereus and Staphylococcus aureus.

RESULTS AND DISCUSSION

2-mercaptobenzimidazole (2) was synthesized by manich reaction and allowed to react with ethylchloroacetate in acetone and dry potassium carbonate to afford ethoxycarbonylmethyl-2-mercaptobenzimidazole (3) in 87% yield. Hydrazinolysis of the ethyl ester 3 in ethanol at reflux temperature affording the corresponding hydrazide 4 in 92% yield which was allowed to react with different sugars in ethanol at reflux temperature and in the presence of acetic acid to afford sugar hydrazone derivatives 5a-d in 83-88% yields. Acetylation of 5a-d with acetic anhydride in pyridine at room temperature afforded acetylated sugar hydrazone derivatives 6a-d in 75-92% yields. The acetylation was carried out in acetic anhydride under reflux at 90°C afforded oxadiazoline derivatives 7a-d in 70-78% yields. Treatment of hydrazide 4 with different aldehydes to give arylidene derivatives 8a-d in 88-94% yields. The arylidene derivatives were reacted with acetic anhydride to afford oxadiazoline derivatives 9a-d in 80-88% yields.

EXPERIMENTAL

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer for KBr discs. NMR spectra were recorded on a Varian Gemini 200 NMR Spectrometer at 300 MHz for 1H NMR with TMS as a standard. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F 245. Spectroscopic analyses were performed at the Dr. Ahmed Farag laboratory at Faculty of science, Cairo University, Egypt.
Ethoxycarbonylmethyl-2-mercaptopbenzimidazole (3).

A mixture of 2-mercaptopbenzimidazole 2 (15g, 0.1 mole), dry acetone (300 ml), anhydrous K_2CO_3 (13.8 g, 0.1 mole) and ethylchloroacetate (15.92 g, 0.13 mole) was heated under reflux for 6 h (TLC). The reaction mixture was filtered of and the filtrate was evaporated under reduced pressure. The residue was recrystallized from ethanol to yield brown oil in 87% yield. R_f = 0.48 (5% MeOH in CH_2Cl_2). 1H NMR (DMSO-d_6): δ = 1.26 (t, 3H, J = 8.1 Hz, CH_3CH_2), 4.15 (q, 2H, J = 8.1 Hz, CH_3CH_2), 4.55 (s, 2H, CH_2), 5.25 (brs, 1H, NH), 7.32 (d, 2H, J = 5.5 Hz, H-2), 7.57 (d, 2H, J = 5.5 Hz, H-3).

2-((1H-benzo[d]imidazol-2-yl)thio)acetohydrazide (4).

A mixture of 3 (2.36 g, 0.01 mole), hydrazine hydrate (1.5 g, 0.03 mole) and ethanol (40 ml) was heated under reflux for 3 h. (TLC). The product was filtered off, recrystallized from ethanol to yield white powder in 92% yield, m.p. 143-145 °C. R_f = 0.33 (5% MeOH in CH_2Cl_2). 1H NMR (DMSO-d_6): δ = 2.11 (brs, 2H, NH_2), 4.50 (s, 2H, CH_2), 5.35 (brs, 1H, NH), 7.27 (d, 2H, J = 5.5 Hz, Ar-H), 7.55 (d, 2H, J = 5.5 Hz, Ar-H), 8.35 (brs, 1H, NH).

Reaction of (4) with Different sugars to Afford the Corresponding sugar hydrazones 5 (a-d).

To solution of 4 (10 mmol) in absolute ethanol, different sugars (10 mmol) were added and then glacial acetic acid (1 ml) was added to the reaction mixture which was refluxed for 10h (TLC). The solvent was evaporated or concentrated under reduced pressure and the product was filtered off to afford 5(a-d) (83 - 88%) yields.

L-(-)–Arabinose(2-mercaptobenzimidazol-1-yl) acetohydrazide (5a).

Yellow powder (83%), m.p.182-184 °C. R_f = 0.65 (5% MeOH in CH_2Cl_2). 1H NMR (DMSO-d_6): δ = 3.14-3.92 (m, 5H, H-2, H-3, H-4, H-5, H-6), 4.05 (s, 2H, CH_2), 4.95 (brs, 1H, NH), 6.95-7.32 (m, 4H, Ar-H), 7.40 (brs, 1H, NH), 7.55 (s, 1H, CH).

D-(-)–Glucose(2-mercaptobenzimidazol-1-yl) acetohydrazide (5b).

White powder (85%), m.p.202-204 °C. R_f = 0.65 (5% MeOH in CH_2Cl_2). 1H NMR (DMSO-d_6): δ = 3.14-3.92 (m, 5H, H-2, H-3, H-4, H-5, H-6), 4.05 (s, 2H, CH_2), 4.95 (brs, 1H, NH), 6.95-7.32 (m, 4H, Ar-H), 7.55 (s, 1H, CH).


A mixture of the sugar hydrazones 5 (a-d) (10 mmol), was dissolved in 30 ml of pyridine and then (15 mmol) of acetic anhydride was added. The reaction was stirred at room temperature overnight (TLC). The mixture was cooled and poured on crushed ice. The precipitate was filtered off and dried to give 6 (a-d) in 75-92% yields.

L-(-)–Arabinose(2-mercaptobenzimidazol-1-yl)acetylhydrazone (6a).

Yellow gum (75%), m.p. 0.72 (5% MeOH in CH_2Cl_2). 1H NMR (DMSO-d_6): δ = 1.99, 2.01, 2.10, 2.21 (4s, 12H, 4xCH3CO), 4.15 (s, 2H, CH_2), 4.30, 4.41 (2m, 2H, H-5, H-6), 4.60 (m, 1H, H-2), 5.06 (brs, 1H, NH), 5.10 (m, 1H, H-4), 5.12 (m, 1H, H-3), 7.12 (brs, 1H, NH), 7.52 (d, 1H, J=2.5 Hz, H-2), 7.25-7.62 (m, 4H, Ar-H).

D-(-)–Glucose(2-mercaptobenzimidazol-1-yl)acetylhydrazone (6b).

Yellow gum (80%), m.p. 0.72 (5% MeOH in

CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 1.97, 2.03, 2.04, 2.06, 2.25 (5s, 15H, 5xCH₃CO), 4.13(s, 2H, CH₂), 4.25, 4.47 (2m, H, H-H₂, H₂2), 4.60 (m, 1H, H-H₂, H₂2), 5.00 (m, 1H, H-H₂), 5.05 (brs, 1H, NH), 5.10 (m, 1H, H-H₂), 5.12 (m, 1H, H-H₂), 7.12 (brs, 1H, NH), 7.25-7.58 (m, 4H, Ar-H), 7.60 (d, 1H, J=2.5 Hz, H₁2).

2,3,4,5-Tetra-O-acetyl-D-(+)-Mannose(2-mercaptobenzimidazol-1-yl)acetylhydrazone (6c)

Yellow gum (85%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 2.11, 2.18, 2.20, 2.22, 2.26 (5s, 15H, 5xCH₃CO), 4.11(s, 2H, CH₂), 4.29, 4.47 (2m, 2H, H₁₂, H₁₂₂), 4.57 (m, 1H, H-₂₂), 5.04 (m, 1H, H-₃₂), 5.09 (brs, 1H, NH), 5.13 (m, 1H, H-₄₂), 5.19 (m, 1H, H-₅₂), 7.19 (brs, 1H, NH), 7.29-7.59 (m, 4H, Ar-H), 7.65 (d, 1H, J=2.5 Hz, H₁₂).

2,3,4,5-Tetra-O-acetyl-D-(+)-Galactose(2-mercaptobenzimidazol-1-yl)acetylhydrazone (6d)

Brown gum (92%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 2.16, 2.21, 2.24, 2.26, 2.29 (5s, 15H, 5xCH₃CO), 4.11(s, 2H, CH₂), 4.27, 4.49 (2m, 2H, H₁₂, H₁₂₂), 4.58 (m, 1H, H-H₂), 5.03 (m, 1H, H-H₂), 5.07 (brs, 1H, NH), 5.12 (m, 1H, H-H₂), 5.16 (m, 1H, H-H₂), 7.17 (brs, 1H, NH), 7.27-7.57 (m, 4H, Ar-H), 7.63 (d, 1H, J=2.5 Hz, H₁₂).

General procedure for the synthesis of 4-acetyl-5-(tetra-and penta-O-acetylalditolyl)-2-(2-mercaptobenzimidazol-1-yl)-1,3,4-oxadiazoline 7 (a-d)

A solution of sugar hydrazones 5(a-d) (0.01 mol) in acetic anhydride (10 ml) was heated at 90 °C for 3 h. The resulting solution was poured onto crushed-ice and the product that separated out was filtered off, washed with water, and then dried. The products were recrystallized from methanol to give 7(a-d) in 70-78% yields.

4-Acetyl-5-(1,2,3,4-tetra-O-acetyl-L-arabinotetritolyl)-2-(2-mercaptobenzimidazol-1-yl)-1,3,4-oxadiazoline (7a)

Brown oil (70%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 2.03, 2.05, 2.07, 2.10, 2.21 (5s, 15H, 5xCH₃CO), 4.40 (s, 2H, CH₂), 4.12, 4.45 (2m, 2H, H-₄₂, H₄₂₂), 5.05 (brs, 1H, NH), 5.14 (m, 1H, H-H₂), 5.19 (m, 1H, H-H₂), 5.89 (dd, 1H, J=3.2, 6.2 Hz, H₁₂), 5.89 (d, 1H, J=8.8 Hz, oxadiazoline H₅), 7.24-7.59 (m, 4H, Ar-H).

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)-2-(2-methylbenzimidazol-1-yl)-1,3,4-oxadiazoline (7b)

Brown oil (72%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 2.04, 2.07, 2.09, 2.12, 2.22, 2.34 (6s, 18H, 6xCH₃CO), 4.60 (s, 2H, CH₂), 4.27, 4.48 (2m, 2H, H-₅₂, H₅₂₂), 5.10 (brs, 1H, NH), 5.15 (m, 1H, H-H₂), 5.21 (m, 1H, H-H₂), 5.28 (m, 1H, H-H₂), 5.32 (dd, 1H, J=3.2, 6.2 Hz, H₁₂), 5.93 (d, 1H, J=8.8 Hz, oxadiazoline H₆), 7.25-7.60 (m, 4H, Ar-H).

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)-2-(2-methylbenzimidazol-1-yl)-1,3,4-oxadiazoline (7c)

Brown oil (73%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 1.97, 1.99, 2.03, 2.06, 2.10, 2.32 (6s, 18H, 6xCH₃CO), 4.60 (s, 2H, CH₂), 4.24, 4.46 (2m, 2H, H-₅₂, H₅₂₂), 5.12 (brs, 1H, NH), 5.15 (m, 1H, H-H₂), 5.22 (m, 1H, H-H₂), 5.26 (m, 1H, H-H₂), 5.34 (dd, 1H, J=3.2, 6.2 Hz, H₁₂), 5.94 (d, 1H, J=8.8 Hz, oxadiazoline H₆), 7.22-7.52 (m, 4H, Ar-H).

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)-2-(2-methylbenzimidazol-1-yl)-1,3,4-oxadiazoline (7d)

Brown oil (78%), Rf = 0.72 (5% MeOH in CH₂Cl₂). 1H NMR (DMSO-d₆): δ = 1.95, 1.97, 1.99, 2.04, 2.07, 2.34 (6s, 18H, 6xCH₃CO), 4.58 (s, 2H, CH₂), 4.25, 4.47 (2m, 2H, H-₅₂, H₅₂₂), 5.11 (brs, 1H, NH), 5.17 (m, 1H, H-H₂), 5.21 (m, 1H, H-H₂), 5.26 (m, 1H, H-H₂), 5.32 (dd, 1H, J=3.2, 6.2 Hz, H₁₂), 5.90 (d, 1H, J=8.8 Hz, oxadiazoline H₆), 7.20-7.560 (m, 4H, Ar-H).

General procedures for the reaction of (4) with aromatic aldehydes to afford Schiff2s bases 8(a-d)

A solution of 4 (0.01 mol), an aromatic aldehyde (0.01 mol) in abs. ethanol (30 ml) and glacial acetic acid (1 ml) was refluxed for 6-8 h (TLC). The solvent was evaporated under reduced pressure and the residue was filtered off and recrystallized from ethanol to afford 8(a-d) in 88-94% yields.
2-((1H-benzo[d]imidazol-2-yl)thio)-N’-benzylideneacetohydrazide (8a)
Yellow gum (88%), Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 4.18 (s, 2H, CH₂), 5.55 (brs, 1H, NH), 7.23-7.85 (m, 9H, Ar-H), 8.13 (s, 1H, CH), 8.45 (brs, 1H, NH).

2-((1H-benzo[d]imidazol-2-yl)thio)-N’-(2-hydroxybenzylidene)acetohydrazide (8b).
Yellow gum (90%), Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 4.15 (s, 2H, CH₂), 5.10 (brs, 1H, NH), 5.34 (s, 1H, OH), 7.05-7.65 (m, 8H, Ar-H), 8.00 (brs, 1H, NH), 8.95 (s, 1H, CH).

2-((1H-benzo[d]imidazol-2-yl)thio)-N’-(furan-2-ylmethylene)acetohydrazide (8c).
White crystals (92%), m.p. 160-164 °C. Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 4.20 (s, 2H, CH₂), 5.15 (brs, 1H, NH), 6.50-7.80 (m, 7H, Ar-H), 7.95 (brs, 1H, NH), 8.42 (s, 1H, CH).

2-((1H-benzo[d]imidazol-2-yl)thio)-N’-(4-(dimethylamino)benzylidene)acetohydrazide (8d).
White crystals (94%), m.p. 158-160 °C. Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 3.10 (s, 6H, 2CH₃), 4.18 (s, 2H, CH₂), 5.11 (brs, 1H, NH), 6.58-7.64 (m, 9H, Ar-H), 8.05 (brs, 1H, NH), 8.37 (s, 1H, CH).

General procedure for preparation of oxadiazoline derivatives 9 (a–d).
A mixture of the shiff bases 8(a–d) (10 mmol), were dissolved in acetic anhydride (10 ml) and the reaction mixture was refluxed at 100 °C 5-7h (TLC). The mixture was onto crushed-ice and the product that separated out was filtered off, washed with water, and then dried. The products were recrystallized from methanol to give 9(a–d) in 80-88 yields.

1-(5-(((1H-benzo[d]imidazol-2-yl)thio)methyl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone (9a).
Yellow powder (80%) m.p. 152-154 °C. Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 2.10 (s, 3H, COCH₃), 4.50 (s, 2H, CH₂), 5.13 (brs, 1H, NH), 6.55 (s, 1H, CH) 7.24-7.57 (m, 9H, Ar-H).

1-(5-(((1H-benzo[d]imidazol-2-yl)thio)methyl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (9b).
Yellow powder (84%) m.p. 136-138 °C. Rf = 0.72 (5% MeOH in CH₂Cl₂). ¹H NMR (DMSO-d₆): δ = 5.37 (s, 1H, OH), 6.95 (s, 1H, CH) 6.85-7.56 (m, 8H, Ar-H).

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Table 1: Antibacterial activity of different synthesized compounds.
1-(5-(((1H-benzo[d]imidazol-2-yl)thio)methyl)-2-(furan-2-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (9c).

Yellow powder (85%) m.p. 142-144 °C. Rf = 0.72 (5% MeOH in CH2Cl2). 1H NMR (DMSO-d6): δ = 2.09 (s, 3H, COCH3), 4.40 (s, 2H, CH2), 5.14 (brs, 1H, NH), 6.87 (s, 1H, CH), 6.35-7.69 (m, 7H, Ar-H).

1-(5-(((1H-benzo[d]imidazol-2-yl)thio)methyl)-2-(4-(dimethylamino)phenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (9d).

White crystals (88%), m.p. 170-172 °C. Rf = 0.72 (5% MeOH in CH2Cl2). 1H NMR (DMSO-d6): δ = 3.12 (s, 6H, 2CH3), 2.10 (s, 3H, COCH3), 4.50 (s, 2H, CH2), 5.14 (brs, 1H, NH), 6.65 (s, 1H, CH), 6.27-7.66 (m, 8H, Ar-H).

MATERIALS AND METHODS

Antibacterial sensitivity test:

Microbiological investigation hole well method the investigated isolates of bacteria were seeded in tubes with nutrient broth (NB) two different bacteria species were used Escherichia coli (E.coli), Staphylococcus epidermidis (S. epidermidis) and Staphylococcus aureus (S.aureus). antimicrobial activity of chemical compounds was evaluated by Hole well method, Briefly inoculum containing approx. cell density (1.5 * 10^8 CFU/ml) was spread on Mueller-Hinton agar (MHA) plates the holes diameter (0.5 cm) were done in the cool medium after that 50µ from different concentration of compounds 10,20 and 30 was applied using a micropipette. After incubation for 24h in an incubator at 37 °C for bacteria the inhibition zone diameters were measured and expressed in cm. The previous procedure was repeated with 30 µg/disc of tetracycline and with ampicillin at 10 µg/disc.

Microbiological investigation of compounds.

Antibacterial of compounds are carried out against the (Gram –ve) as E.coli and ( Gram +ve) as S.aureus and (S. epidermidis) , the antimicrobial activity was estimated based on size of inhibition zone around dishes against Gram+v the 7a fig. 1 5a , 5c, 9a fig. 2, 3, 4 and 9b are varied degree of inhibitory effect against S.aureus and 8a,bc and 8a varied degree of inhibitory effect against S.epidermidis, also in Gram-v the 8b, 6a, 8a, 7a fig. 5, 5c and 9b are varied degree of inhibitory effect against E.coli. The antibacterial activities of compounds against E. coli, S. aureus and S.epidermidis tested and compared to known antibiotics Tables. The results showed that increasing the zone of inhibition in compared with known antibiotic Amoxicillin and tetracycline, the data showed in Table1.
Fig. 5. influence of the synthesized compound 7a on E.coli.

CONCLUSION

In this research the 2-mercaptobenzimidazole derivatives were synthesized and then were coupled with different sugars (arabinose, glucose, mannose and arabinose) and aromatic aldehydes to give the corresponding sugar hydrazones and arylidene derivatives respectively. The synthesized compounds were showed high to moderate activity against the (Gram –ve) as E.coli and (Gram +ve) as S.aureus and (S. epidermidis).

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