DOI Number: 10.37506/v14/i1/2020/ijfmt/193044

Synthesis of Diimidazole Has Pyrazole, Isoxazole and Pyrimidine Derivatives and Evaluation as Antibacterial

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Abstract

New **diimidazole** contains pyrazole , isoxazole and thiopyrimidine were synthesized by using simple methods**.** All compounds were synthesized by using hippuric acid (1) as stating material which was obtained from benzoyl and glycine with. pyrazole derivatives (6a – b) was obtained from reaction (5a – b) with hydrazine hydrate while reaction of (5a – b)with hydroxyl amine isoxazole derivatives (7a – b) were obtained ,finally reaction of thiourea was reacted with 5a – b thiopyrimidine derivatives were get (8a –b) . FTIR and 1HNMR spectra were used to characterized derivatives several bacterial species like *Pseudomonas aeruginosa* , *Staphylococcus aureus,* and *Acinetobacter baumanii* were used to tested antibacterial activity

Keywords: *pyrazole, isoxazole, imidazole, thiopyrimidine*

Introduction

Heterocyclics were found good biological molecules like imidazole [1] molecules with five and six membered rings mostly are high activity [2] . All natural products with heterocyclics are important in biologically active system [3] and medicinal to approved drugs . imidazole derivatives in heterocyclic chemistry considered most important compounds and drugs [4] such as Antioxidant activity [5] anti-microbial (6-7), antiangiogenic [8] , antitumor [9] , analgesic [10] . pyrazoles and isoxoles play important role to synthesis biologically active drugs like Antifungal[11] , antimicrobial [12] anticancer[13] , analgesics[14] , Anthelminthic[15] , Ant pathogenic[16], anti-inflammatory [17]

Mwthod

Synthesis of [(phenyl carbonyl)amino]acetic acid(1)

Glycine (0.1mol) in 15ml of 1N NaOH was cooled to 5 and then benzoyl chloride (0.1 mole) was added to cold drop wise . The reaction mixture was stirring for one hour. The aqueous layer was acidified with 2N HCl and the product was collected and recrystallized from ethanol and product was collected as white powder

Synthesis of(Z)- 2-phenyl -4-benzylidene oxazol-5(4H)-ones (2a - d)

To a mixture of compound (1) (0.01 mole) , acetic anhydride (20 ml) and acetic acid (5 ml), (0.01 mol) of aromatic aldehyde was added. And the mixture was refluxed for 4hr and the temperature was reached to 80C°. The reaction mixture was allowed to cool. , then poured into crushed ice and it was allowed stirred for 30 min. the product was recrystallized from ethanol.

Synthesis of 3-(2-amino)-5-arylidine-2-phenyl-3,5-dihydro-4H-imidazol-4-one (3a – d)

To a mixture of (2a – d) derivatives (0.01 mole) in (20ml) triethyl amine , (0.01 mole) of hydrazine was added. And then it was refluxed 2 h. after that the mixture was cooled to RT. And the desired compound was obtained after recrystallizing from ethanol.

Synthesis of 1-[(4*Z*)-4-(arylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl] thio urea (4a – d)

Potassium thiocyanate was added to a mixture of compounds [3a - d] (0.01 mole) in ethanol (27 ml) and then stirred for 30 min. the mixture was poured in to could water and then filtered, the solid (desired compound) was recrystallized from ethanol.

Synthesis of (5*Z*)-5-(4-chlorobenzylidene)-3-(4-oxo-2-thioxoimidazo lidin-1-yl)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (5a – d)

To solution of (4a – d) (0.01 mole), in 30 ml of dry benzene chloro acetyl chloride was added and the mixture was heated in water bath at (60 0C) for 3 hrs. with stirring after that the solvent was evaporated, and the product desired compound was recrystallized from appropriate solvent.

Synthesis of 1-[3-(Aryl)-5-phenyl-3,3a-dihydroimidazo[4,5-*c*]pyrazol-6(2*H*)-yl]-2-thioxoimidazolidin-4-one (6a – b)

To solution of (5a – b) (0.01 mole), in 20 ml of acetic acid hydrazine hydrate was added and the mixture was heated (refluxed) for 5 hrs. with stirring after that mixture poured to water (200ml) , and the product desired compound was recrystallized from appropriate solvent**.**

Synthesis of 1-[3-(Aryl)-5-phenyl-3,3a-dihydro-6*H*-imidazo [4,5-*c*]isoxazol-6-yl]-2-thioxoimidazolidin-4-one (7a – b)

To solution of (5a – b) (0.01 mole), in 20 ml of acetic acid hydroxyl amine hydrochloride was added and the mixture was heated (refluxed) for 5 hrs. with stirring after that mixture poured to water (200ml) , and the product desired compound was recrystallized from appropriate solvent**.**

Synthesis of 1-[6-(4-chlorophenyl)-8-phenyl-2-thioxo-1,2,5,6-tetra hydro-9*H*-purin-9-yl]-2-thioxoimidazolidin-4-one

To solution of (5a – b) (0.01 mole), in 20 ml of acetic acid thiourea was added and the mixture was heated (refluxed) for 5 hrs. with stirring after that mixture poured to water (200ml) , and the product desired compound was recrystallized from appropriate solvent**.**

Results and Discussion

Scheme (1) shown all compounds were synthesized

Ar = p-NO_2 , p-Cl , p-Br , p-NMe_2

Synthesis of target (1) was done by the reaction of amino acid with benzoyl chloride through nucleophilic mechanism. (93%).m.p (186-188),color (White), The FT-IR spectrum of compound (1) , shows stretching vibration of (OH) of carboxylic acid at (2610-3390) cm^{-1} and appearance of new band at (3350) cm^{-1} for NH .

Compound (1) was treatment with aryl lead to formation of compounds (2a - d)

2a :yield (79%), FT-IR cm^{-1} C=N(1646), C=O(1729), (C=C)ar (1601,1551), (C-H)ar (3083) ,(NO_2),(1534-13), 1H-NMR(ppm) , s,(6.92) for(C=CH) , (7.25-7.76) (m ,aromatic protons .

2b :yield (82%) , FT-IR cm^{-1} C=N(1657) ,C=O(1721), (C=C)ar (1603,1500) , (C-H)ar (3035) ,(C-Cl), (1097) . ,1H-NMR(ppm), s,(6.88) for(C=CH) , (7.44-7.89) (m ,aromatic protons) .

2c :yield (75%) , FT-IR cm^{-1} C=N(1643) ,C=O(1704), (C=C)ar (1604,1509),(C-H)ar (3050) , (C-Br) 975. 1H-NMR(ppm), s,(6.76) for(C=CH) , (7.54-7.91) (m ,aromatic protons .

2d :yield (80%), FT-IR cm^{-1} C=N(1632) ,C=O(1720),(C=C)ar (1603,1508),(C-H)ar (3066) , (C-H)alph (2884-2987). ,1H-NMR(ppm), , s, (3.11) for(NMe_2), s,(6.35) for(C=CH) , (7.47-7.81) (m ,aromatic protons .

Treatment of (2a – d) with hydrazine gives (3a – d)

3a :yield (78%), FT-IR cm^{-1} NH_2 (3345,3213), C=N(1656), C=O(1701), (C=C)ar (1610,1503), (C-H) ar (3079) ,(NO_2),(1545-1351). ,1H-NMR (ppm), s, (5.66) for(NH_2), s,(6.48) for(C =CH) , (7.11-7.69) (m ,aromatic protons .

3b :yield (69%) , FT-IR cm^{-1} NH_2 (3401,3234), C=N(1661) ,C=O(1709), (C=C)ar (1600,1500) , (C-H) ar (3060) ,(C-Cl), (1109). ,1H-NMR (ppm), s, (5.23) for(NH_2), s,(6.31) for(C =CH) , (7.51-7.77) (m ,aromatic protons .

3c :yield (73%) , FT-IR cm^{-1} NH_2 (3389,3143), C=N(1666) ,C=O(1712), (C=C)ar (1599,1501),(C-H)ar (3069) , (C-Br) 977. ,1H-NMR (ppm), s, (5. 46) for(NH_2), s,(6.76) for(C =CH) , (7.55-7.92) (m ,aromatic protons

3d :yield (61%), FT-IR cm^{-1} NH_2 (3345,3207), C=N(1643) ,C=O(1718),(C=C)ar (1607,1500),(C-H)ar (3070) , (C-H) alph (2879-2980) . ,1H-NMR (ppm), s, (3.61) for(NMe_2) , s, (5.66) for(NH_2), s,(6.48) for(C =CH) , (7.11-7.69) (m ,aromatic protons .Reaction of compounds (3a – d) with KSCN in ethanol , compounds (4a – d) was formed

4a :yield (71%), FT-IR cm^{-1} , NH_2 (3311,3225), NH (3112), C=N (1646), C=O(1731), (C=C)ar (1601,1551), (C-H)ar (3083) ,(NO_2), (1534-1330). ,1H-NMR (ppm), s, (9.21) for (NH) , s, (8.47) for (NH_2) , s,(6.43) for(C =CH) , (7.19-7.68) (m ,aromatic protons

4b :yield (56%) , FT-IR cm^{-1} NH_2 (3432,3267), NH (3152), C=N(1657) ,C=O(1723), (C=C)ar (1603,1500) , (C-H)ar (3035) ,(C-Cl), (1097). 1H-NMR (ppm), s, (9.71) for (NH) , s, (8.62) for (NH_2) , s,(6.53) for(C =CH) , (7.33-7.78) , m ,aromatic protons

4c :yield (60%) , FT-IR cm^{-1}, NH_2 (3415,3270), NH (3165), C=N(1643) ,C=O(1715), (C=C)ar (1604,1509),(C-H)ar (3089) , (C-Br) 975. 1H-NMR (ppm), s, (9.22) for (NH) , s, (8.41) for (NH_2) , s,(6.69) for (C =CH) , (7.69-7.94) , m ,aromatic protons

4d :yield (58%), FT-IR cm^{-1} NH_2 (3411,3272) NH (3149),C=N(1632) ,C=O(1708),(C=C)ar (1603,1508),(C-H)ar (3066) , (C-H) alph. (2884-2987) . 1H-NMR (ppm), s, (3. 54) for (NMe_2) , s, (9.49) for (NH) , s, (8. 61) for (NH_2) , s,(6.59) for(C =CH) , (7.67-7.85) (m ,aromatic protons

Cyclization of compounds (4a – d) with chloro acetyl chloride gives compounds (5a – d)

5a :yield (75%), FT-IR cm^{-1} , NH (3110), C=N (1638), C=O(1721), C=O thio imidazole (1751) , 1H-NMR (ppm), s, (4. 21) for (CH_2 , thio imidazole) , s, (9.23) for (NH) , s,(6.62) for(C =CH) , (7.71-7.90) (m ,aromatic protons

5b :yield (68%) , FT-IR cm^{-1}, NH (3176), C=N(1650) ,C=O(1702), C=O thio imidazole (1757) (C=C)ar (1612,1509) , (C-H)ar (3067) ,(C-Cl), (1019) . 1H-NMR (ppm), s, (4. 25) for (CH_2 , thio imidazole) , s, (9.11) for (NH) , s,(6.59) for(C =CH) , (7.18-7.73) (m ,aromatic protons

5c :yield (60%) , FT-IR cm^{-1}, NH (3134), C=N(1657) ,C=O(1728), C=O thio imidazole (1749) (C=C)ar (1600,1501),(C-H)ar (3070) , (C-Br) 912. 1H-NMR (ppm), s, (4. 42) for (CH_2 , thio imidazole) , s, (9.68) for (NH) , s,(6.68) for(C =CH) , (7.26-7.53) (m ,aromatic protons

5d :yield (58%), FT-IR cm^{-1} NH (3190),C=N(1648) ,C=O (1716), C=O thio imidazole (1746) (C=C)ar (1615,1529),(C-H)ar (3079) , (C-H) alph. (2879-2956) . 1H-NMR (ppm), s, (3. 29) for (NMe_2), s, (4. 22) for (CH_2 , thio imidazole) , s, (9.39) for (NH) , s,(6.14) for(C =CH) , (7.17-7.65) (m ,aromatic protons).

Compounds (6a – b) , (7a – b) and (8a – b) were obtained by cyclizing compounds (5a – b) with hydrazine , hydroxyl amine and thiourea respectively.

6a :yield (65%), FT-IR cm^{-1} , NH (3213), NH of pyrazole, (3171) , C=N (1645), C=O thio imidazole (1735) , (C=C)ar (1611,1500), (C-H)ar (3060) ,(NO_2), (1555-1353). 1H-NMR (ppm), s, (4. 29) for (CH_2 , thio imidazole) , s, (9.22) for (NH) , s,(8.27) for(NH , pyrazole) , (7.53-7.98) (m ,aromatic protons).

6b :yield (61%) , FT-IR cm^{-1}, NH (3269), NH of pyrazole, (3199) C=N(1661) , C=O thio imidazole (1739) (C=C)ar (1600,1501) , (C-H)ar (3071) ,(C-Cl), (1021),). 1H-NMR (ppm), s, (4.19) for (CH_2 , thio imidazole) , s, (9.82) for (NH) , s,(8. 79) for(NH , pyrazole) , (6.89-7.24) (m ,aromatic protons).

7a :yield (71%), FT-IR cm^{-1} , NH (3245), C=N (1651), C=O thio imidazole (1743) , (C=C)ar (1605,1516), (C-H)ar (3079) ,(NO_2), (1532-1350) . 1H-NMR (ppm), s, (4.02) for (CH_2 , thio imidazole) , s, (9.46) for (NH) , (6.92-7.48) (m ,aromatic protons).

7b :yield (77%) , FT-IR cm^{-1}, NH (3211), C=N(1670), C=O thio imidazole (1728) (C=C)ar (1609,1511) , (C-H)ar (3079) ,(C-Cl), (1011), 1H-NMR (ppm), s, (4.10) for (CH_2 , thio imidazole) , s, (9.32) for (NH) , (6.89-7.24) (m ,aromatic protons).

8a :yield (57%), FT-IR cm^{-1} , NH (3311), NH of pyrimidine , (3165) C=N (1649), C=O thio imidazole (1741) , (C=C)ar (1601,1511), (C-H)ar (3092) ,(NO_2), (1539-1355). 1H-NMR (ppm), s, (4.20) for (CH_2 , thio imidazole) , s, (9.71) for (NH) , s,(8.16) for(NH , pyrimidine) , (6.72-7.30) (m ,aromatic protons).

8b :yield (54%) , FT-IR cm^{-1}, NH (3302), NH of pyrimidine, (3190) C=N(1644) , C=O thio imidazole (1733) (C=C)ar (1600,1500) , (C-H)ar (3085) ,(C-Cl), (1077). , 1H-NMR (ppm), s, (4.51) for (CH_2 , thio imidazole) , s, (9.76) for (NH) , s,(8.36) for(NH , pyrimidine) , (6.99-7.59) (m ,aromatic protons).

Table 1. Antibacterial Activity of derivatives (4a – d, 5a – d, 6a – b, 7a – b and 8a – b) .

Compound No.	Staph. aureus	E. coli	Proteus mirabilis
4a	++++	++	++
4b	+++	+++	+++
4c	+++	++	+++
4d	+++	++	+
5a	+	+++	+
5b	++	+++	+++
5c	++	++	++
5d	+	+	++
6a	+++	+++	+++
6b	++	+++	++
7a	+	++	+++
7b	++	+++	++
8a	+++	++++	++++
8b	++++	+++	++++

Antibacterial activity of derivatives

It might be observed that derivatives which that tested were active but 8a , 8b , 4b and 6a have high activity toward all types of tested bacterial while compound 5a and 5d have weak activity toward all types of tested bacteria compound 8a was showed high inhibition with E. coli and Proteus mirabilis

Conclusion

Financial disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Faculty of Dentistry, University of Babylon, Hillah city, Iraq and all experiments were carried out in accordance with approved guidelines.

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