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المجلة العراقية لبحوث السوق وحماية المستهلك

NEW METHODOLOGY TO SYNTHESIS 3- SECONDARY AMINES OF IMIDAZOBENZOTHIAZOLE DERIVATIVES WITH STUDY THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

In this research, new derivatives of bicyclic fused rings containing bridgehead nitrogen atom imidazo/benzothiazole were prepared from 2-aminobenzothiazole with 2-bromo-1-(4-bromophenyl)ethan-1-one to form compound A1. Then, through the Mannich reaction, compound A2 was prepared from compound A1 with formaldehyde and 4-aminoacetophenone. Schiff bases A3-A6 were prepared from condensation reaction between compound A2 with different amines. Finally, the reduction reaction was accomplished by using $NaBH_4$ to reduce the imine group to forming new compounds A7-A10. These compounds were characterized by FTIR, ^{1}HNMR, and ^{13}CNMR. The prepared compounds showed biological activity against some microorganisms.

Keywords: Fused rings, Imidazo/ benzothiazole, Schiff bases, Anti-bacterial, Anti-fungal.

طريقة جديدة في تحضير مشتقات 3- ثنائي امين من الاميدازوبنزوثايازول مع دراسة فعاليتها الحيوية

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الخلاصة

تم تحضير مشتقات جديدة من الحلقات الملتحمة ثنائية الحلقات المحتوية على ذرة نتروجين جسريه /imidazo benzothiazole من تفاعل 2-أمينوبنزوثيازول مع برومو فنيل فينيسايل بروميد لتشكيل المركب A1. بعد ذلك ، من خلال تفاعل مانخ ، تم تحضير المركب A2 من المركب A1 مع الفورمالديهايد و بارا امينو استو فينون .تم تحضير قواعد شف A3-A6 من تفاعل تكثيف بين المركب A2 بأمينات مختلفة. أخيرًا، تم اجراء تفاعل الاختزال باستعمال $NaBH_4$لاختزال مجموعة الايمين لتشكيل مركبات جديدة A7-A10. شخصت هذه المركبات بـ FT-IR و ^{1}HNMR و ^{13}CNMR. واظهرت المركبات التي تم تحضيرها نشاطاً حيوياً تجاه بعض الاحياء المجهرية.

الكلمات المفتاحية: الحلقات الملتحمة؛ اميدازو/ بنزوثايوزول، قواعد شيف؛، مضاد بكتريا؛ مضاد فطريات.

INTRODUCTION

Heterocyclic compounds that contain in their structure sulfur and nitrogen are important compounds in medicinal chemistry applications. Compounds containing imidazo[2,1-b] benzothiazole fused rings are of remarkable importance, as researchers in the pharmaceutical industry and academics have been keenly interested in the synthesis of these heterocyclic fused rings that contributed to the discovery of modern medicines and which led to the development of pharmaceutical compounds **(Etivand *et al.*, 2019; Sultana *et al.*, 2018; Wu *et al.*, 2019)**. Biological studies of the prepared compounds demonstrated numerous activities against anti-cancer **(Singh *et al.*, 2018)**, anti-bacterial **(Bayanati *et al.*, 2021)**, antimicrobial **(Maddili *et al.*, 2018)**, antioxidant **(Al-Sultani & Al-Lami, 2020; Dincel *et al.*, 2020)**, anti-inflammatory

(Saliyeva *et al.*, 2022). Some of the biological functions of synthesized imidazo/benzothiazole compounds were depicted in (Figure 1)**.** Also, The key physicochemical properties of imidazo[2,1-b]benzothiazole derivatives include those used in other critical technological fields and multiple applications. These compounds were synthesized by several methods, the most important of which are the one-component reactions (MCRs) or the reactions of 2-aminobenzothiazoles with α- halo ketone **(Al-Sultani & Al-Lami, 2020)**. Mannich reaction is made from ancient reactions and has been known for more than a century and is widely used in the fields of organic chemistry. By reacting an aldehyde with a primary or secondary amine and a molecule with a high electronegativity site, secondary and tertiary amines are formed **(Shi *et al.*, 2021)**. An intermediate compound is formed by the reaction of the amine with the carbonyl aldehyde to form an imine group, followed by the reaction imine with active site, to form the Mannich product is a secondary amine **(Chen *et al.*, 2018).**

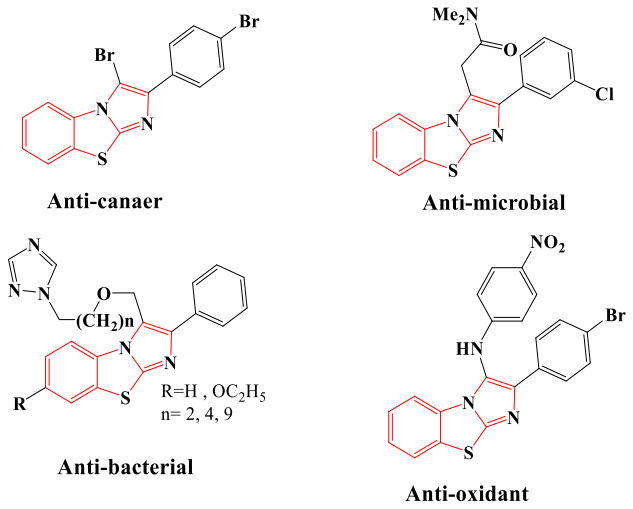


Figure (1): Biological activities of prepared imidazo/benzothiazole derivatives

Schiff's bases are among the compounds that are classed as considered the key to organic chemistry to launch into the synthesis of many other compounds that express therapeutic importance in pharmaceutical chemistry. These compounds contain an imine group or the socalled azomethine, which is synthesized when a primary amine and a carbonyl group from a ketone or aldehyde react together in the presence of G.A.A. as a catalyst **(Dutta *et al.*, 2021; Nief *et al.*, 2017)**. Sodium boro hydrate was used to reduce imine group to corresponding secondary amine.

MATERIALS AND METHODS

Materials and instrumentation

All solvents and chemical materials supplied by the companies Merck, Sigma/Aldrich, and CDH were used. Thin layer chromatography (TLC) was supplied by the Merck Company, and iodine fumes were used to characterize the spots. The melting point was measured using a thermal melting point device. The Shimadzu FT-IR Spectrophotometer (FTIR-8400S) has been utilized in order to record infrared spectral data at the University of Baghdad / College of Sciences. Nuclear magnetic resonance spectroscopy 400 MHz was employed to capture the ^{1}H NMR and ^{13}C NMR data using DMSO-d6 as a solvent. The chemical shifts were measured at Iran, and the University of Basra-Iraq, relative to an internal reference tetramethyl silane TMS in parts per million (ppm).

Synthesis of compounds A1 (Mukku & Maiti, 2019)

2-Aminobenzothiazole (0.002 mol, 0.3 g) with p-Bromo phenacyl bromide (0.002 mol 0.55g) have been dissolved in 50.0 mL of ethanol, after 8 h. of refluxed(with monitoring by TLC; MeOH, Benzene 2:1). The product was re-crystallized from ethanol.

A1:*2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazole*; Beige, 79 % yield, MP 178-180 ^{o}C.

FTIR υmax(cm^{-1}): 3055 (CH $_{aro.}$), 1641 (C=C imidazo ring), 1598 (C=N imidazole), 1558 (C=C$_{aro.}$), 820 (C-Br).

Synthesis of compounds A2

Compound A2 was prepared from the Mannich reaction, where compound A1 (0.001 mol, 0.32 g) was dissolved in ethanol in a small amount and (0.001mol, 0.03g) of formaldehyde has been added with drops of hydrochloric acid. After 5 minutes of stirring, (0.001mol, 0.13g) of 4-aminoacetophenone has been added to reaction and endured two hours of reflux. Precipitate has been filtered then recrystallized from the ethanol.

A2:*1-(4-(((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3-yl)methyl)amino)phenyl)ethan-1-one***;** light orange, 85% yield, MP 220-221 ^{o}C.

FTIR υmax(cm^{-1}): 3431 (NH), 3062 (CH $_{aro.}$), 2860 (CH $_{ali.}$), 1720 (C=O), 1639 (C=C imidazo ring), 1598 (C=N imidazole), 1562 and 1527 (C=C $_{aro.}$), 825 (C-Br).

^{1}H NMR (400MHz, DMSO-d_6) δ_H; 8.08-6.76 (m, Ar-H), 4.76 (s, NH), 3.33 (s, 2 H, CH_2), 2.45 (s, 3 H, CH_3)**.**

Synthesis of compounds A3-A6 (Mahal *et al.*, 2019; Gumrukcuoglu & Bilgin Sokmen, 2020; Ermiş & Durmuş, 2020; Iman *et al.*, 2019)

Schiff bases A3-A6 were synthesized from dissolving compound A2 (0.001 mol, 0.47 g) in benzene with a few drops of glacial acetic acid, after 15 minutes of stirring were added (0.001 mol) of different amines were added to the previous solution and heated under reflux for 8-10 hrs. with monitoring by TLC (Methanol, Benzene 3:1). The separated solid was filtered and recrystallized from ethanol.

A3:*N-((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)-4-(1-((2-nitrophenyl)imino)ethyl)aniline*; Bright yellow, 82% yield, M.P. 241-243 °C.

FT-IR υmax(cm^{-1}): 3429 (NH), 3060 (CH$_{aro.}$), 2970 (CH $_{ali.}$), 1647 (C=C imidazo ring), 1622 (C=N imine), 1571 and overlap (C=C $_{aro.}$), 825 (C-Br).

A4:*N-((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)-4-(1-((4-methoxyphenyl)imino) ethyl)aniline*; Yellow, 76% yield, MP 263-264 ^{o}C.

FT-IR υmax(cm^{-1}): 3433 (NH), 3002 (CH $_{aro.}$), 2977 (CH $_{ali.}$), 1637 (C=C imidazo ring), 1615 (C=N imine), 1593 (C=N imidazo ring), 1560 and 1527 overlap (C=C $_{aro.}$), 825 (C-Br)**.**

A5:*2-((1-(4-(((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)amino)phenyl)ethylidene)amino)-1-methyl-1,5dihydro-4H-imidazol-4-one*; Maronite, 70% yield, MP 227-229 ^{o}C.

FTIR υmax(cm^{-1}): 3431 (NH), 3004 (CH$_{aro.}$), 2891 (CH $_{ali.}$), 1699 (C=O), 1646 (C=N imine), 1639 (C=C imidazo ring), 1593 (C=N imidazo ring), 1577 and 1527 (C=C $_{aro.}$), 827 (C-Br)**.**

A6:*4-((1-(4-(((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)amino)phenyl)ethylidene)amino)-1,5dimethyl-2phenyl-1,2-dihydro-3H-pyrazol-3one*; Bright yellow, 81% yield, MP 275-277 ^{o}C.

FT-IR υmax(cm^{-1}): 3431 (NH), overlap (CH $_{aro.}$), 2977 (CH $_{ali.}$), 1685 (C=O), 1644 (C=N imine), 1639 (C=C imidazo ring), 1598 (C=N imidazo ring), 1558 and overlap (C=C $_{aro.}$), 823 (C-Br).

^{1}H NMR (400MHz, DMSO-d_6) δ_H; 8.93-6.63 (m, Ar-H), 5 (s, NH), 3.18 (d, 2 H, CH_2), 2.71

(s, 3 H, N-CH_3), 2.27 (s,3H,C=C-CH_3), 1.86 (s, 3 H, N=C-CH_3).

Synthesis of compounds A7-A10 (Ermiş & Durmuş, 2020)

The products of Schiff bases A3-A6 were reduced by dissolving them in MeOH (0.001) mol with the addition of (0.001) mol of sodium boronhydrate, and after 6 h. refluxed (monitored the reactions by TLC Methanol, Benzene 3:1), the solution has been left to cool and solution was neutralized by (acid-base treatment). By using 10% HCl and NH_4OH. The precipitates were washed with cold water and recrystallized with abs. ethanol.

A7:*N-((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)-4-(1-((2-nitrophenyl)amino)eth-yl)aniline*; Dark orange, 66% yield, MP 191^{o}C-193^{o}C.

FTIR υmax(cm^{-1}): 3436 and 33423 (NH), 3002 (CH $_{aro.}$), 2902 (CH $_{ali.}$), 1639 (C=C imidazo ring), 1593 (C=N imidazo ring), 1573 and overlap (C=C $_{aro.}$), 825 (C-Br)**.**

A8:*N-((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)-4-(1-((4-methoxyphenyl)amino)ethyl)aniline*; Red, 67% yield, MP 198^{o}C-200^{o}C.

FT-IR υmax(cm^{-1}): 3433 and 3430 (NH), 3049 (CH $_{aro.}$), 2975 (CH $_{ali.}$), 1639 (C=C imidazo ring), 1597 (C=N imidazo ring), 1560 and overlap (C=C $_{aro.}$), 810 (C-Br)**.**

A9:*2-((1-(4-(((2-(4-bromophenyl)benzo[d]imidazo[2,1-b]thiazol-3yl)methyl)amino)phenyl)ethyl)amino)-1-methyl-1,5-dihydro-4H-imidazol-4one*; Light red, 64% yield, MP 181-183^{o}C.

FTIR υmax(cm^{-1}): 3452 and 3367 (NH), 3049 ($CH_{aro.}$), 2906 ($CH_{ali.}$), 1701 (C=O), 1659 (C=C Creatinine ring), 1632 (C=C imidazo ring), 1596 (C=N imidazo ring), overlap and 1525 (C=C $_{aro.}$), 829 (C-Br)**.**

^{1}H NMR (400MHz, DMSO-d_6) δ_H; 8.11-6.57 (m,Ar-H), 4.77 and 4.01 (s,2NH), 3.93 (q, 1H, CH), 3.59 (s,2H,CH_2 imidazo), 3.41 (s,2H,CH_2) 3.06 (s,3H,N-CH_3), 2.38 (d, 3H,N-C-CH_3).

^{13}C NMR (100 MHz, DMSO-d_6) δ_c; 168.2, 147.5, 133.4, 132.7-111.8, δ55.3, 53.5, 38.0, 31.7 and 26.5.

A10:*4-((1-(4-(((2-(4-bromophenyl)benzo[d]imidazo[2,1b]thiazol-3yl)methyl)amino)phenyl)ethyl)amino)-1-methyl-2-phenyl-1,2dihydro-3H-pyrazol-3one*; Light maroon, 60% yield, MP 185^o-187 ^{o}C.

FTIR υmax(cm^{-1}): 3436 and 3421 (NH), 3047 (CH $_{aro.}$), 2877 (CH $_{ali.}$), 1689 (C=O), 1659 (C=C 4-AAP ring), 1639 (C=C imidazo ring), 1590 (C=N imidazo ring), 1575 and overlap (C=C $_{aro.}$), 829 (C-Br)**.**

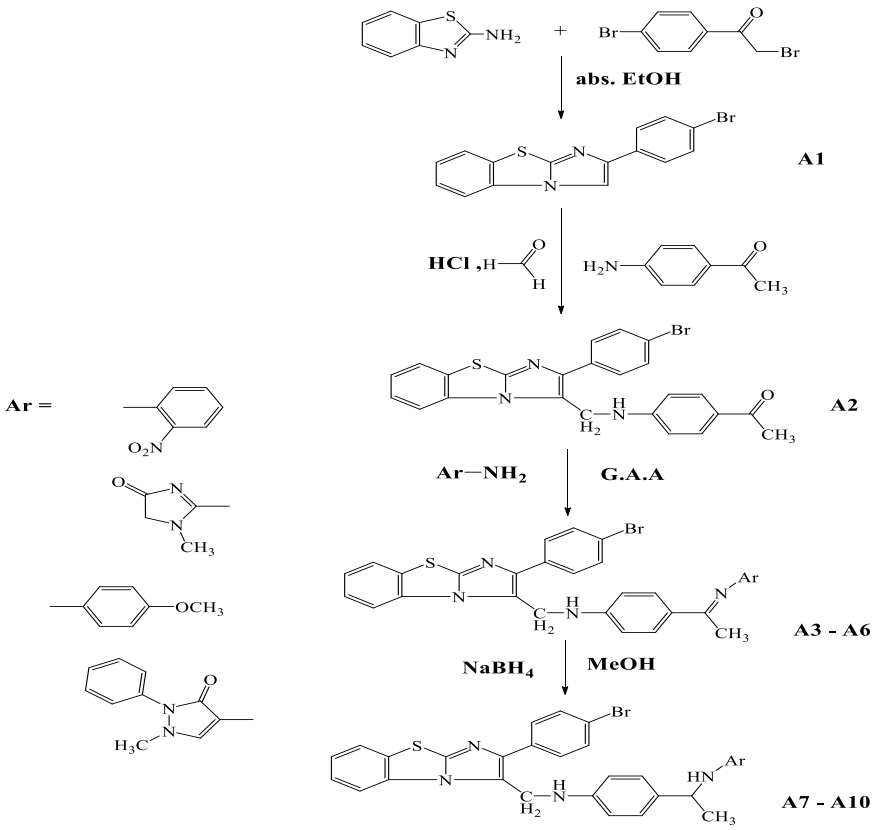
Biological evaluation (Khorsheed *et al.*, 2020)

In an agar diffusion method, certain substances were tested for their antibacterial and antifungal activity against 4 different bacteria types (which include: *Staphylococcus aureus*, *Bacillus cereus*), gram (+) and gram (-) bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and 1 kind of fungus (*Candida albicans*). These sterile agar mediums were added to Petri dishes and allowed to be set, and then microbe suspensions were distributed over the surface using the clean triangular loop. [A pre-sterilized stainless steel cylinder used for boredom-inducing activities]. Using a micropipette, the synthesized compounds (10^{-2}M) were added serially and left to diffuse for an hour. These plates had a 37 °C incubation period (24 h). The cup's zone of inhibition was observed, and it was measured in mm unit.

RESULTS AND DISCUSSION

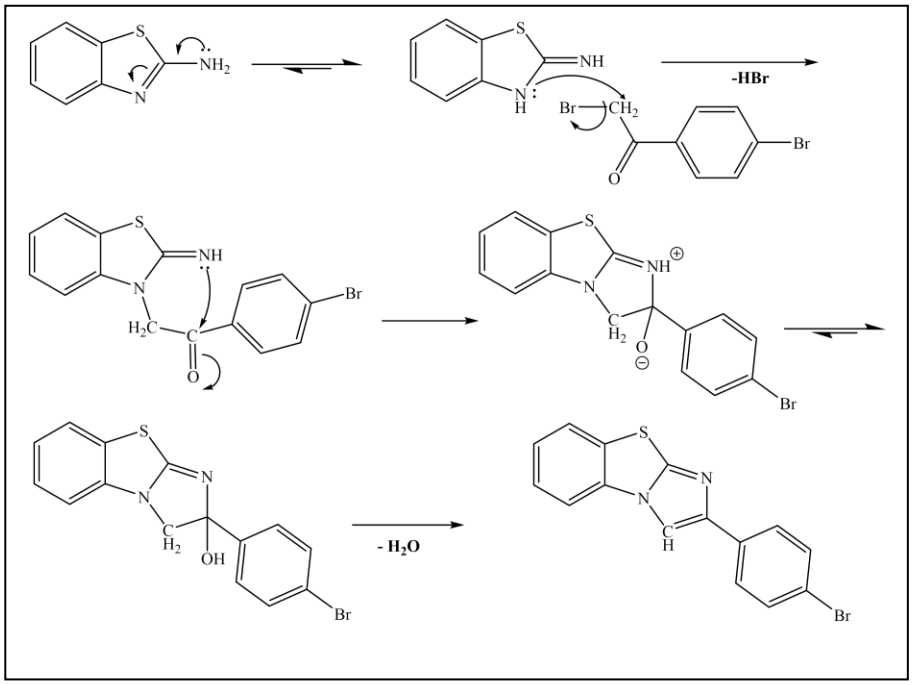
Synthesis

The synthesized new compounds gave good results by characterizing them spectroscopically FT-IR, some of them by ^{13}CNMR and ^{1}H-NMR. (Scheme 1) showed all synthesized compounds.



Scheme (1): Total synthesis of compounds

The compound imidazo[2,1b]benzothiazol has been prepared through a condensation reaction in the presence of the tautomeric state of the compound 2- amino- benzothiazol to obtain a more basic nitrogen atom, which in turn attacks the compound p-Bromophenacylbromide, suggested mechanism of this reaction as can be seen in (Scheme 2).



Scheme (2): Suggested mechanism to the synthesis compound A1.

The FT-IR spectra of the compound A1 had shown appearance of new peaks at 1641 cm-1 indicating (C=C) and another peak at 1598 cm-1 belonging to (C=N) which belong to the imidazo fused ring and the disappearance of the carbonyl and amine groups in the reactants. The FT-IR spectrum of the compound A2 showed presence of stretching bands in 3431 cm-1 referring to (NH) and new bands to the carbonyl group in the region 1720 cm-1 (C=O) (Aldujaili & Ezzat, 2021). In addition to that appearing new bands belong to (C=C) in 1639 and (C=N) in 1598cm-1. 1H NMR spectrum of A2 had shown many signals owing to the aromatic proton at δ8.08-6.76 ppm and showed a singlet signal in δ4.76 ppm due to (NH) and showed signals at δ3.33 and 2.45 refers to CH2 and CH3 respectively. Schiff's bases for compounds A3-A6 were characterized through the FT-IR spectrum, where the imine bonds were found from 1646 to 1615 with the carbonyl group at 1720 cm-1 for the compound A2. The 1H NMR spectrum of A6 showed many signals in 8.93-6.63 ppm due to the aromatic protons and had shown a singlet signal at 5.00ppm owing to NH and showed signals at 3.18 referring to CH2 and three signals in 2.71, 2.17 and 1.23 ppm due to the methyl groups in compounds. In the last step, the synthesized compounds showed the disappearance of the imine group at 1646-1615 cm-1in addition the results of the 1H NMR for compound A9 showed the presence of two signals at 4.77 and 4.01 back to NH and in the 13C NMR spectrum the disappearance of the group C=N.

3.2 Biological activity assay

Four different bacterial species (*S. aureus, B. cereus, E. coli, and P. aeruginosa*) and one kind of fungal species (*C. albicans*) were tested using compounds produced in concentrations of (10^{-2} M) for their antibacterial and antifungal activities. For all the substances, DMSO was used as a solvent and a control. Different biological activities were displayed by these synthesized chemicals (Table1).

Table(1): The zones of inhibition of some of the synthesized compounds**.**

No. of the Compound	Inhibition Zone (mm.)				
	Gram Positive (+)		Gram Negative (-)		*C. albicans*
	B. cereus	*S. aureus*	*E. coli*	*P. aerug.*	
A 1	-	-	8	11	10
A 2	11	10	9	13	14
A3	13	17	15	16	14
A4	14	-	16	12	13
A7	-	10	14	-	9
A9	13	18	14	19	17
A10	19	20	17	16	13
DMSO	--	--	--	--	--

CONCLUSION

A new methodology was applied in this contribution, by using the Mannich base as a key intermediate for further reactions. This intermediate was condensed with different amino drags to give new Shiff bases, which were then subjected to a reduction reaction. Some al new prepared compounds were evaluated as antimicrobial agents. The final results of biological studies showed high to moderate inhibition zone.

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