Synthesis, Characterization and Biological Activity
Evaluation of Some New Azo Derivatives from 2- Amino Benzothiazole and Their Derivatives

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ABSTRACT

This study includes synthesis 2-amino benzothiazole and its substitutes (M1-M14) by the reaction of aniline derivatives with KSCN in presence of Br2 and glacial acetic acid then neutralize by concentrated ammonia solution or (by 50% NaOH). The prepared compounds (M3-M5-M6-M11) were used for preparation diazonium salts through reaction with NaNO2 and HCl, at that point diazonium salts were utilized specifically interaction with 4-amino antipyrine and 4-amino-3-hydroxy-1-naphthalene sulphonic acid (in alkaline medium) to produce azo dyes (M15-M22).

These compounds were characterized by their physical properties, spectroscopic information (FT-IR, 1H-NMR, 13C-NMR and CHNS elemental analysis), and also to systematically defining of a few active functional groups for these prepared compounds. The biological activity evaluated for four of prepared compounds towards four kinds of bacteria.

Keywords: azo dyes, diazonium salts, benzothiazole, 4-amino antipyrine.
تحضير وتشخيص وتقييم الفعالية البيولوجية لبعض أصباغ الأزو الجديدة من 2- أمينو بنزوثايازول ومشتقاته

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الملخص

يتضمن البحث تحضير 2- أمينو بنزوثايازول وموضعاته (M14–M1) عن طريق تفاعل مواد الاتيلين مع KSCN وغيرها من المعوضات، ويتضمن التفاعل مع البروم ومملوءات الأمونيا المركزة (أو 55% عنيدروكسيد الصوديوم). وتم تحضير الأصباغ الأزو (M22–M15) باستخدام أملاح الأزو NaNO2 و HCl، وتم تحضير أملاح الأزو (M11–M6) بواسطة تفاعل أملاح الأزو مع الكواشف العضوية (M22–M15). وتم تحليل هذه المركبات باستخدام الطرق الفيزيائية والطرق المفتيفة مثل طبقة الأشعة تحت الحمراء (IR) والرنين النووي المغناطيسي (1H-NMR, 13C-NMR) وتحليل نسبة العناصر. وتم استخدام الطرق البيولوجية لتشخيص بعض من المجموعات الفعالة للمركبات المحضرة. وتم تقييم الفعالية البيولوجية لأربع من المركبات المحضرة ضد أربعة أنواع من البكتيريا.

الكلمات الدالة: أصباغ الأزو، أملاح الدايزونيوم، بنزوثيازول، 4- أمينو أنثي بايرين.
1- Introduction:

Benzothiazole is un-homogenized a cyclic system due to sulfur atom on position (1) and nitrogen on position (3) on thiazole that attached to benzene ring. It is important because of multi applications, which attracted chemistry and pharmaceutical people because of biological activities [1]. When the benzothiazole discovered, they helped in reducing the death percent due to many diseases that could not cure before or a kind of high cost treatment [2]. From the literatures, the benzothiazole and its derivatives used as virus inhibitors for (1-HIV), and protein activities inhibitors [3]. They contain two un homogenized atoms of (N, S), in which they give anti-inflammable activities [4], anti-tumors [5], anti-convulsant [6], anti-microbial [7], anti-malaria [8], anti-infection bacterial [9], anti-fungi [10], tuber clauses, anti-parasitic worms [11], and anti-diabetes [12]. The benzothiazole derivatives used as painkiller and reduce the muscle spasms and it interact with nerve transfer of glutamate in biochemical and electro-physiological experiments [13].

While the paints Azo, they are organic compounds that were prepared for the first time by scientist (Peter) on 1858. They are prepared by coupling reactions in which Amine group (NH2) is attached to the compound (2-ABT) and its derivatives with organic reagents in acidic environment to give colorful organic compounds that absorbed at UV and visible length [14]. These compounds are characterized by high stability because they contain azo group (-N=N-) with double bond, accordingly it is classified as aliphatic and aromatic homogenized and heterocyclic compounds. It was found that the aliphatic compounds are limited in their distribution compared to aromatic compounds because of their low stability and breaking down to nitrogen and hydrocarbons [15]. While the un-homogenized aromatic azo compounds are distributed widely for their industrial, pharmaceutical, and medicinal importance as they are prepared by the reaction of amine group with different aromatic reagents [16].

2- Experimental Section

Melting point was determined by electro thermal, Melting Point Apparatus (uncorrected). The IR absorption spectra were recorded via Shimadzu Transform FT-IR 8400S infrared Spectrophotometer Fourier as KBr disc. The $^1$H-NMR spectrum were recorded by $^1$H-NMR-Spectrophotometer Bruker 500 MHz – Avance (III). The percentage of the CHNS elements
were calculated for a group of compounds. Biological activity was evaluated against four different types of bacterial was performed for the produced derivatives.

**Synthesis of 2-amino Benzothiazole Substitutes (M1-M14) [17]:**

(0.2 mol) of p-fluoro aniline or substituted aniline and (0.2 mol, 19.4 g) of potassium thiocyanate were added to (350 ml) of (97%) glacial acetic acid, the mixture was cooled between (0-5)°C then (0.1 mol, 5.1 ml) of bromine dissolved in (50 ml) glacial acetic acid, which was added slowly with stirring, temperature was kept between (0-5)°C, then the mixture was stirred for (2 hours) at (0-5)°C.

The mixture was filtered off and the precipitate dissolved in warm water, then the mixture was heated at (80)°C for (15 min). The produced solution neutralized with (50%) NaOH. The precipitate was filtered off and collected on a filter paper and dried, recrystallization from ethanol. The physical properties of the synthesized compounds are given in Table (1).

![Chemical structure of benzothiazole substitute](image)

**Table (1): physical properties of (M1-M14)**

| Comp. No. | R     | Molecular formula | Colour | M.P(°C) | Yield (%) |
|-----------|-------|-------------------|--------|---------|-----------|
| M1        | H     | C7H6N2S           | white  | 126-128 | 75        |
| M2        | 6-OH  | C7H5N2SO          | black  | 245-248 | 76        |
| M3        | 6-F   | C7H5N2SF          | yellow | 186-188 | 90        |
| M4        | 5-Cl  | C7H5N2Cl          | white  | 187-190 | 85        |
| M5        | 6-Cl  | C7H5N2Cl          | white  | 200-202 | 90        |
| M6        | 4,6-diCl | C7H4N2Cl2       | brown  | 235-238 | 78        |
| M7        | 4-Me  | C8H8N2S          | brown  | 137-140 | 70        |
| M8        | 6-OMe | C8H8N2SO         | brown  | 166-168 | 89        |
| M9        | 6-COOEt | C10H10N2SO2      | yellow | 243-245 | 87        |
| M10       | 6-COMe | C9H9N2SO         | orange | 240-243 | 78        |
| M11       | 5-NO2 | C7H5N2SO2        | red    | 113-115 | 81        |
| M12       | 6-Br  | C7H5N2SBr        | white  | 215-218 | 88        |
| M13       | 4,6-di NO2 | C7H4N4SO4     | orange | 244-246 | 80        |
| M14       | 6-NO2 | C7H5N3SO2        | yellow | 246-248 | 86        |
Synthesis of the Reagent Diazonium Salt With Coupling Solution (M15-M22) [18]:

a. Synthesis of Diazonium Salt:
(0.001 mol) of 2-amino benzothiazole derivative was dissolved in acidic solution (5 ml) of H₂O with (2 ml) of HCl (37%) and cooled between (0-5)⁰C in ice-bath for further stirring. In another conical flask dissolved (0.001 mol, 0.0069 g) of sodium nitrite in (2 ml) of H₂O was added to first solution slowly with further stirring at temperature between (0-5)⁰C.

b. Synthesis of Coupling Solution:
Reagents 4-amino antipyrine, 4-amino -3- hydroxy-1- naphthalene sulphonic acid (0.001 mol) were dissolved in (10 ml) of sodium hydroxide (10%) ((1 gm) of sodium hydroxide dissolved in (10 ml) of H₂O) then cooled to (0-5)⁰C with stirring for 10 min. The diazonium salt solution that prepared in step (a) was added to the solution prepared in step (b) with further stirring for (2 hour) and cooled by ice, then filtered color precipitation then washed with diethyl ether then recrystallized with absolute ethanol. The physical properties of the syntheses compounds are given in Tables (2) and (3) and scheme (1) shows the synthesis of some new 2-amino benzothiazole derivatives with diazonium salt.

Table 2: physical properties of (M15-M18)

| Comp. No. | R' | Molecular formula | Colour  | M.P(⁰C) | Yield (%) |
|-----------|----|-------------------|---------|---------|-----------|
| M15       | 6-F | C₁₇H₁₁N₅S₂O₄F     | white   | 137-139 | 65        |
| M16       | 6-Cl| C₁₇H₁₁N₅S₂O₄Cl    | white   | 156-157 | 67        |
| M17       | 4,6-diCl | C₁₇H₁₀N₅S₂O₄Cl₂ | yellow  | 185-187 | 70        |
| M18       | 5-NO₂| C₁₇H₁₁N₅S₂O₆      | brown   | 182-185 | 64        |
Table (3): physical properties of (M_{19}-M_{22})

| Comp. No. | R'  | Molecular formula | Colour    | M.P(°C) | Yield (%) |
|-----------|-----|-------------------|-----------|---------|-----------|
| M_{19}   | 6-F | C_{18}H_{15}N_{6}SOF | yellow   | 100-103 | 72        |
| M_{20}   | 6-Cl| C_{18}H_{15}N_{6}SOCl | milky    | 78-80   | 74        |
| M_{21}   | 4,6-diCl | C_{18}H_{14}N_{6}SOCl_{2} | yellow | 123-125 | 67        |
| M_{22}   | 5-NO_{2} | C_{18}H_{15}N_{7}SO_{3} | brown   | 161-163 | 69        |

Scheme (1): synthesis of some new 2-amino benzothiazole derivatives and diazonium salts
3. Evaluation Biological [19]:

The biological evaluation was carried out on four different types of bacteria for a number of compounds prepared (4 compounds) against four types of pathogenic bacteria were used in this study one of them (gram positive) is Staphylococcus aurea, and the rest (gram negative) is Escheriechia Coli, Enterobacter Cloaca's and Bacillus subtilis. All these species are very important in the medical field because of their resistance to antibiotics then incubated at (37°C) for (24 hours).

The test solutions were prepared for some synthesized compounds and used dimethyl sulfoxide (DMSO) as a solvent to concentrations (150, 100, 50) mg / ml were obtained for each of these derivatives by dissolved (150 mg) in (1ml) of (DMSO) obtained to (150 mg / ml) of concentrated solution, then took (1ml) of the (150mg / ml) concentrated solution and added (0.5ml) of solvent (DMSO) obtained to (100 mg / ml) of concentrated solution. Also took (1ml) of the (150mg / ml) concentrated solution and add (2.0ml) of solvent (DMSO) to obtained to (50 mg / ml) concentrated of solution.

4. Results and Discussion

Synthesis 2-aminobenzothiazole substitutes (M1-M14) :

FT-IR spectra [20] of (M14) showed characteristic absorption bands at (3421-3326 cm\(^{-1}\)) and (1512-1330 cm\(^{-1}\)) due to \(\nu(\text{NH}_2)\) in thiazole ring and \(\nu(\text{NO}_2)\) asymmetric and symmetric respectively.

Other bands appeared at (1575 cm\(^{-1}\)), (1630,1421cm\(^{-1}\)) and (3218,3085cm\(^{-1}\))which attributed to \(\nu(\text{C=K})\)aromatic, \(\nu(\text{C=C})\)benzene ring and \(\nu(\text{C- H})\)in aromatic ring respectively. FT-IR spectral data of the prepared compounds (M1-M14) are listed in Table (4) and Fig. (1) shows the (FT-IR) spectra of (M14).

\(^1\)HNMR spectrum of compound (M\(_{14}\), M\(_{5}\), M\(_{1}\)) Figure (2,3 and 4), showed clear signals at (4.64) ppm and (8.2-7.15) ppm belong to (NH\(_2\)) and aromatic protons respectively .While \(^1\)CNMR spectrum [21] of the compound (M\(_{9}\)) Fig. (5), showed signals at (17.5) ppm, (22 ppm), (112 – 131) ppm and (161) ppm due to CH\(_3\) carbons, O-CH\(_3\) carbons, aromatic carbons and C=O carbon respectively.
### Table (4): FT-IR spectral data of the prepared compounds (M<sub>1</sub>-M<sub>14</sub>)

| Comp. No. | Characteristic bands of IR. spectra ( cm<sup>-1</sup>, KBr disc ) |
|-----------|---------------------------------------------------------------|
|           | R                              | v(NH<sub>2</sub>) | v(C-H) | v(C=N) | v(C=C) | v(C-N) | v other |
| M<sub>1</sub> | H                        | 3295        | 3114-3153 | 1671  | 1463-1612 | 1355 | —       |
| M<sub>2</sub> | 6-OH                        | 3275        | 3125-3164 | 1680  | 1471-1583 | 1359 | 3200-3600 (OH) |
| M<sub>3</sub> | 6-F                          | 3294        | 3145-3160 | 1671  | 1463-1612 | 1354 | 1000-1390 (F) |
| M<sub>4</sub> | 5-Cl                          | 3270        | 3156-3180 | 1684  | 1471-1583 | 1344 | 540-785 (Cl) |
| M<sub>5</sub> | 6-Cl                          | 3290        | 3147-3178 | 1670  | 1463-1612 | 1355 | 540-785 (Cl) |
| M<sub>6</sub> | 4,6-diCl                       | 3270        | 3133-3145 | 1680  | 1471-1583 | 1350 | 540-785 (Cl) |
| M<sub>7</sub> | 4-Me                          | 3295        | 3160-3143 | 1675  | 1463-1612 | 1360 | 2850 (CH<sub>3</sub>) |
| M<sub>8</sub> | 6-OMe                        | 3330 3384   | 3076 3095 | 1676  | 1598-1554 | 1357 | 1307 (C-O) aliph. |
| M<sub>9</sub> | 6-COOEt                     | 3291        | 3135 3165 | 1675  | 1463-1612 | 1355 | 1735 (C=O) |
| M<sub>10</sub> | 6-COMe                 | 3275        | 3135 3168 | 1680  | 1471-1583 | 1352 | 1715 (C=O) |
| M<sub>11</sub> | 5-NO<sub>2</sub>          | 3292        | 3187 3145 | 1675  | 1463-1612 | 1357 | 1512 1330 (NO<sub>2</sub>) |
| M<sub>12</sub> | 6-Br                      | 3271        | 3123-3154 | 1685  | 1471-1583 | 1350 | 510 651 (Br) |
| M<sub>13</sub> | 4,6-diNO<sub>2</sub>      | 3295        | 3134-3165 | 1671  | 1463-1612 | 1359 | 1512 1330 (NO<sub>2</sub>) |
| M<sub>14</sub> | 6-NO<sub>2</sub>        | 3326 3421   | 3085 3218 | 1681  | 1421-1630 | 1353 | 1512 1330 (NO<sub>2</sub>) |
Fig. (1): Infrared spectra (FT-IR) of compound (M₁₄)

Fig. (2): ¹H-NMR spectra of (M₁₄)
Fig. (3): $^1$H-NMR spectra of (M₈)

Fig. (4): $^1$H-NMR spectra of (M₁)
**Synthesis of the reagent diazonium salt with coupling solution (M15-M22):**

FT-IR spectra of compound (M18) showed characteristic absorption bands at (3544 cm\(^{-1}\)) and (1469 cm\(^{-1}\)) due to \(\nu(\text{O-H})\) phenol and \(\nu(\text{N=N})\) azo group. Other bands appeared at (1672 cm\(^{-1}\)) and (1168 cm\(^{-1}\)) which attributed to \(\nu(\text{C=N})\) in thiazole ring and \(\nu(\text{C-F})\) in aromatic ring respectively. FT-IR spectral data of the prepared compounds (M15-M22) are listed in Table (5) and Fig. (6) shows the (FT-IR) spectra of (M18). \(^1\)HNMR spectrum [22]. of compounds (M15-M22) showed clear signals at (8.2-7.25) ppm, (3.4) ppm and (6.7) ppm belong to aromatic protons, (NH\(_2\)) and (O-H) proton respectively.
Table (5): FT-IR spectral data of the prepared compounds (M_{15}-M_{22})

| Comp. No. | Characteristic bands of IR. spectra (cm\(^{-1}\), KBr disc) |
|-----------|---------------------------------------------------------|
|           | R | \(\bar{R}\) | \(\nu\) (OH) | \(\nu\)(C-H) | \(\nu\)(C=C) | \(\nu\)(C=N) | \(\nu\) others |
| M_{15}    | 6 – F | 3544 | 2927 | 3060 | 1463 | 1612 | 1672 | 1359 | 1168 \(\text{C-F}\) 1380 |
| M_{16}    | 6 – Cl | 3342 | 3104 | 3165 | 1471 | 1583 | 1687 | 1355 | 540 \(\text{Cl}\) 785 |
| M_{17}    | 4.6 – diCl | 3354 | 3114 | 3150 | 1463 | 1612 | 1678 | 1366 | 540 \(\text{Cl}\) 785 |
| M_{18}    | 5 – NO\(_2\) | 3544 | 2927 | 3060 | 1433 | 1596 | 1672 | 1315 | 1512 \(\text{NO}\(_2\)\) 1330 |
| M_{19}    | 6 – F | 3350 | 3114 | 3153 | 1463 | 1612 | 1675 | 1365 | 1168 \(\text{C-F}\) 1380 |
| M_{20}    | 6 – Cl | 3340 | 3150 | 3160 | 1471 | 1583 | 1682 | 1353 | 540 \(\text{Cl}\) 785 |
| M_{21}    | 4.6 – diCl | 3358 | 3155 | 3150 | 1463 | 1612 | 1668 | 1377 | 540 \(\text{Cl}\) 785 |
| M_{22}    | 5 – NO\(_2\) | 3359 | 3155 | 3178 | 1471 | 1583 | 1679 | 1356 | 1512 \(\text{NO}\(_2\)\) 1330 |

Fig. (6): Infrared spectra (FT-IR) of compound (M_{18})
5. Biological Activity:

The Preliminary study of antimicrobial activity for the most of prepared compounds showed that compound (M11,M3,M17 and M14) has activity against Staphylococcus aureus, Bacillus subtilis, Escheriechia coli and Eterobactern in comparable to ofloxacin. The 2-amino benzothiazoles and its derivatives have biological activity against type of bacterial [23], therefore we tried to study evaluation of biological activity for derivatives prepared from 2-amino benzothiazoles, and choose four types of bacterial, and they were; Staphylococcus aureus, Bacillus subtilis, Escheriechia coli, and Eterobactern.

a. The compounds (M11, M3 and M17) showed highly significant activity against (Bacillus subtilis), The compounds highly affected electronegative groups compared to compounds with halogen groups against (Bacillus subtilis).

b. The compound (M3) showed high effect against (Eterobactern), while compounds (M11 and M17) showed moderate to good activity against .

c. The compound (M11) showed highly effect against (Staphylococcus aureus coli) while compounds (M14 and M17) showed good
d. effect against. While non existing effect for compound (M3).

e. The compounds (M14 and M11) showed moderate effect against (Escheriechia coli), while compounds (M3 and M17) non existing effect show against this bacteria.

The results showed that most of the tested compounds possessed good antibacterial activity as shown in Table (6).

| Comp. No. | Code of Compounds | Bacillus subtilis | Eterobacter | Staphylococcus aureus | Escheriechia coli |
|-----------|-------------------|------------------|-------------|----------------------|------------------|
| 1-        | M11              | 23               | 14          | 19                   | 12               |
| 2-        | M3               | 26               | 35          |                     |                  |
| 3-        | M17              | 24               | 15          | 13                   |                  |
| 4-        | M14              |                  | 17          | 13                   |                  |

Table (6): antibacterial activity
6. Conclusion

In this study used substituted 2-Amino benzothiazoles have different groups to prepare a substituted diazonium salt and coupling new reagents, 4-amino antipyrine and 4-amino -3-hydroxy-1-naphthalene sulphonlic acid and prepare derivatives sulphonamide.

One step process for synthesis of 2-aminobenzothiazole by using substituted aniline, potassium thiocyanate and bromine in acidic condition at low temperature (0-5°C). For the acidic media, acetic acid as solvent. Based on previous results, the study concluded the followings:

1- Purity and characterization of the synthesized compounds were confirmed by determination of physical properties (melting points, FT IR spectroscopy, elemental microanalysis, $^1$H NMR spectra and $^{13}$C-NMR).

2- From the antimicrobial and cytotoxic activity studies, compound (M$_{11}$) showed the best activity that may be a potential candidate for a new drug discovery.

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