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

Mohammed Ali Muayad Hamzah [1], Ihmood K. Jebur [2], Abdullmajeed K. Ahmed [3]

[1,2] Department of Chemistry, College of Science, University of Tikrit, Tikrit, Iraq.
[3] Department of Chemistry, College of Science, Kirkuk University, Kirkuk, Iraq.

[1]mohamadalialnavavi@gmail.com, [2] Ihmood.jebur@yahoo.com,
[3]mohamed2016III@yahoo.com

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 .

Kirkuk University Journal /Scientific Studies (KUJSS)
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تحضير وتشخيص وتقييم الفعالية البايولوجية لبعض أصباغ الازو الجديدة من 2- أمينو بنزوثايازول ومشتقاته

محمد علي مؤيد حمزه[1]، إحمود خلف جبر[2], عبدالمجيد خورشيد احمد [3]

[1,2] قسم الكيمياء، كلية العلوم، جامعة تكريت، تكريت، العراق.

[3] قسم الكيمياء، كلية العلوم، جامعة كركوك، كركوك ، العراق.

[1]mohamadalialnavavi@gmail.com, [2] Ihmood.jebur@yahoo.com,
[3]mohamed2016III@yahoo.com

الملخص

يتضمن البحث تحضير 2- امينو بنزوثايازول ومعوضاته (M14-M1) عن طريق تفاعل معوضات الانيلين مع KSCN وبإضافة حامض خليك الثلجي, و البروم ومعادلته بمحلول الامونيا المركزة (أو 50% هيدروكسيد الصوديوم). وقد استخدمت المركبات المحضرة (M11-M6-M5-M3) لتحضير الأملاح الدايازونيوم، من خلال التفاعل مع NaNO2 و HCl, وتم تحضير أصباغ الآزو (M22-M15) بوساطة تفاعل أملاح الدايازونيوم مع الكواشف العضوية 4- أمينو أنتي بايرين و 4- أمينو -3- هيدروكسي -1- نفثالين حامض سلفونيك (في وسط قاعدي). وتم تشخيص هذه المركبات باستخدام الطرائق الفيزيائية والطرائق الطيفية مثل طيف الأشعة تحت ألحمراء (IR) وطيف الرنين النووي المغناطيسي الكربوني والبروتوني (^{1}H-NMR, ^{13}C-NMR) وتحليل نسبة العناصر للمركبات, (CHNS) وكذلك تم استخدام الكشف التصنيفي لتشخيص بعض من المجاميع الفعالة للمركبات المحضرة. وتم تقييم الفعالية البايولوجية لأربع من المركبات المحضرة ضد أربعة أنواع من البكتيريا.

الكلمات الدالة : أصباغ الآزو, املاح الدايازونيوم, بنزوثايازول, 4- أمينو أنتي بايرين.

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

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

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
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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 $(0\text{-}5)^0$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 $(0\text{-}5)^0$C, then the mixture was stirred for (2 hours) at $(0\text{-}5)^0$C .

The mixture was filtered off and the precipitate dissolved in warm water, then the mixture was heated at $(80)^0$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)

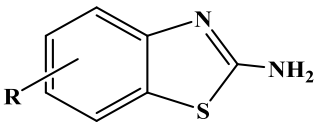

Table (1): physical properties of (M_1-M_{14})

Comp. No.	R	Molecular formula	Colour	M.P(^{0}C)	Yield (%)
M_1	H	$C_7H_6N_2S$	white	126-128	75
M_2	6-OH	$C_7H_6N_2SO$	black	245-248	76
M_3	6-F	$C_7H_5N_2SF$	yellow	186=188	90
M_4	5-Cl	$C_7H_5N_2SCl$	white	187-190	85
M_5	6-Cl	$C_7H_5N_2SCl$	white	200-202	90
M_6	4,6-diCl	$C_7H_4N_2SCl_2$	brown	235-238	78
M_7	4-Me	$C_8H_8N_2S$	brown	137-140	70
M_8	6-OMe	$C_8H_8N_2SO$	brown	166-168	89
M_9	6-COOEt	$C_{10}H_{10}N_2SO_2$	yellow	243-245	87
M_{10}	6-COMe	$C_9H_8N_2SO$	orange	240-243	78
M_{11}	5-NO_2	$C_7H_5N_3SO_2$	red	113-115	81
M_{12}	6-Br	$C_7H_5N_2SBr$	white	215-218	88
M_{13}	4,6-di NO_2	$C_7H_4N_4SO_4$	orange	244-246	80
M_{14}	6-NO_2	$C_7H_5N_3SO_2$	yellow	246-248	86

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
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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 H_2O with (2 ml) of HCl (37%) and cooled between (0-5^{0}C) in ice-bath for further stirring. In another conical flask dissolved (0.001 mol, 0.0069g) of sodium nitrite in (2 ml) of H_2O was added to first solution slowly with further stirring at temperature between (0-5)^{0}C.

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 H_2O) then cooled to (0-5)^{0}C 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 (M_{15}-M_{18})

Comp. No.	R'	Molecular formula	Colour	M.P(^{o}C)	Yield (%)
M_{15}	6-F	$C_{17}H_{11}N_4S_2O_4F$	white	137-139	65
M_{16}	6-Cl	$C_{17}H_{11}N_4S_2O_4Cl$	white	156-157	67
M_{17}	4,6-diCl	$C_{17}H_{10}N_4S_2O_4Cl_2$	yellow	185-187	70
M_{18}	5-NO_2	$C_{17}H_{11}N_5S_2O_6$	brown	182-185	64

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
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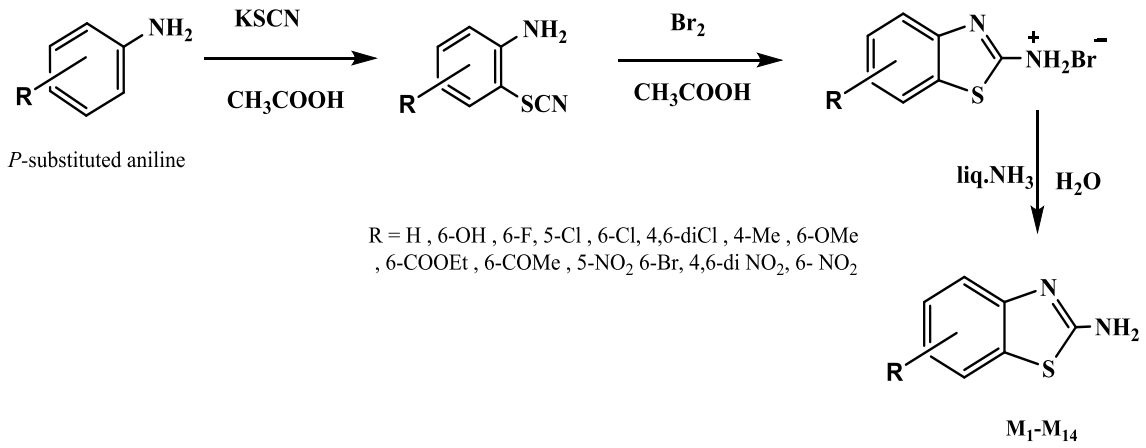
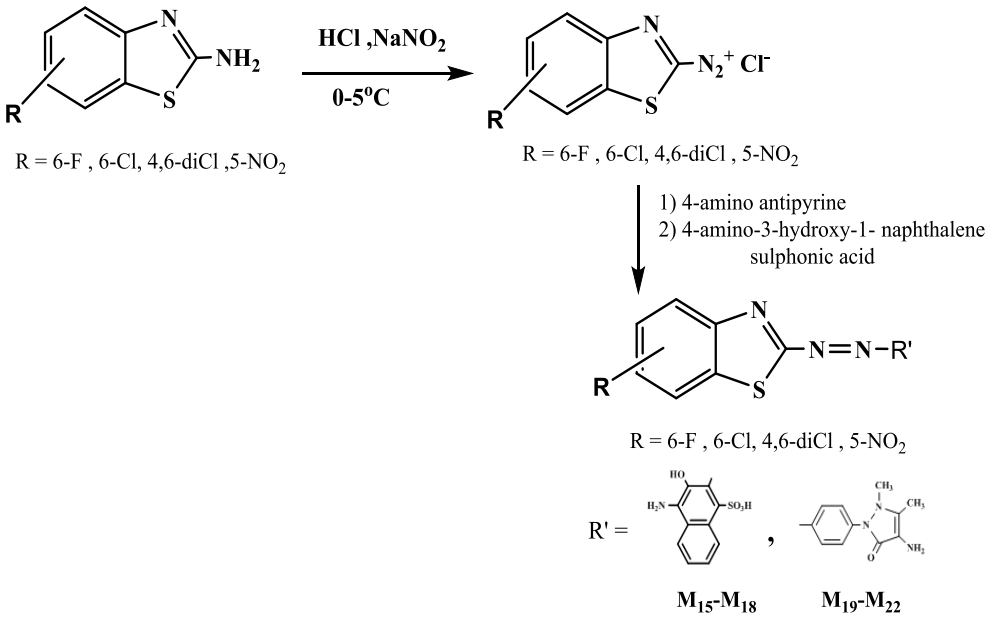
Table (3): physical properties of (M_{19}-M_{22})

Comp. No.	R'	Molecular formula	Colour	M.P(^{0}C)	Yield (%)
M_{19}	6-F	$C_{18}H_{15}N_6SOF$	yellow	100-103	72
M_{20}	6-Cl	$C_{18}H_{15}N_6SOCl$	milky	78-80	74
M_{21}	4,6-diCl	$C_{18}H_{14}N_6SOCl_2$	yellow	123-125	67
M_{22}	5-NO_2	$C_{18}H_{15}N_7SO_3$	brown	161-163	69





Scheme (1): synthesis of some new 2-amino benzothiazole derivatives and diazonium salts

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

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 Esheriechia 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 $(37)^0$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 (M_{14}) showed characteristic absorption bands at (3421-3326 cm^{-1}) and (1512-1330 cm^{-1}) due to ν(NH_2) in thiazole ring and ν(NO_2) asymmetric and symmetric respectively.

Other bands appeared at (1575 cm^{-1}), (1630,1421cm^{-1}) and (3218,3085cm^{-1})which attributed to ν(C=N)aromatic, ν(C=C)benzene ring and ν(C- H)in aromatic ring respectively. FT-IR spectral data of the prepared compounds (M_1-M_{14}) are listed in Table (4) and Fig. (1) shows the (FT-IR) spectra of (M_{14}).

^{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 ^{13}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.

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

Table (4): FT-IR spectral data of the prepared compounds (M_1-M_{14})

Comp. No.	Characteristic bands of IR. spectra (cm^{-1} , KBr disc)						
	R	υ(NH_2)	υ(C-H) arom.	υ(C=N)	υ(C=C)	υ(C-N)	υ other
M_1	H	3295	3114 3153	1671	1463 1612	1355	——
M_2	6-OH	3275	3125 3164	1680	1471 1583	1359	3200 3600 (OH)
M_3	6-F	3294	3145 3160	1671	1463 1612	1354	1000 1390 (F)
M_4	5-Cl	3270	3156 3180	1684	1471 1583	1344	540 785 (Cl)
M_5	6-Cl	3290	3147 3178	1670	1463 1612	1355	540 785 (Cl)
M_6	4,6-diCl	3270	3133 3145	1680	1471 1583	1350	540 785 (Cl)
M_7	4-Me	3295	3160 3143	1675	1463 1612	1360	2850 (CH_3)
M_8	6-OMe	3330 3384	3076 3095	1676	1598 1554	1357	1307 (C-O) aliph.
M_9	6-COOEt	3291	3135 3165	1675	1463 1612	1355	1735 (C=O)
M_{10}	6-COMe	3275	3135 3168	1680	1471 1583	1352	1715 (C=O)
M_{11}	5-NO_2	3292	3187 3145	1675	1463 1612	1357	1512 1330 (NO_2)
M_{12}	6-Br	3271	3123 3154	1685	1471 1583	1350	510 651 (Br)
M_{13}	4,6-di NO_2	3295	3134 3165	1671	1463 1612	1359	1512 1330 (NO_2)
M_{14}	6-NO_2	3326 3421	3085 3218	1681	1421 1630	1353	1512 1330 (NO_2)

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

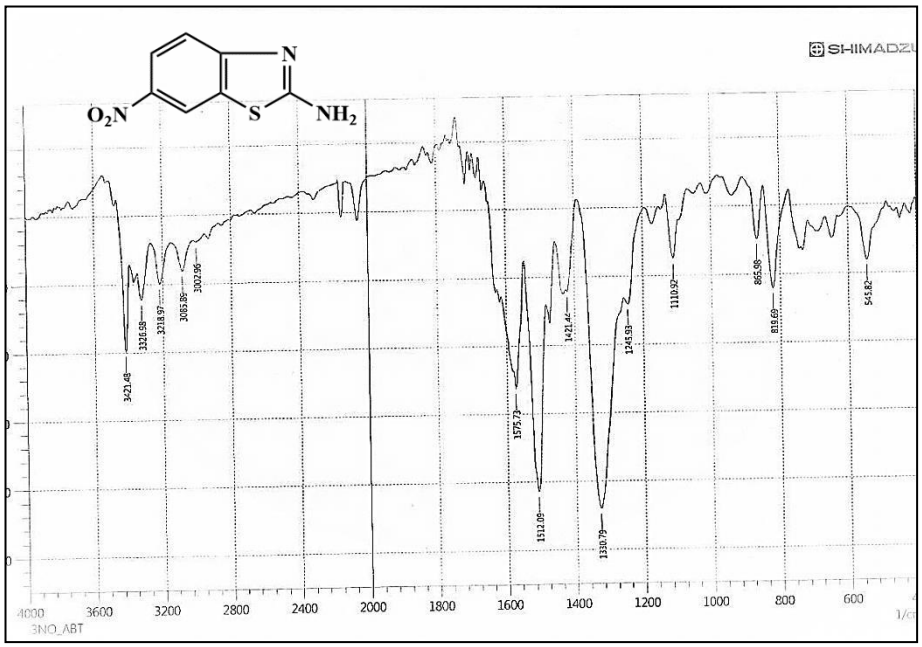


Fig. (1): Infrared spectra (FT-IR) of compound (M_{14})

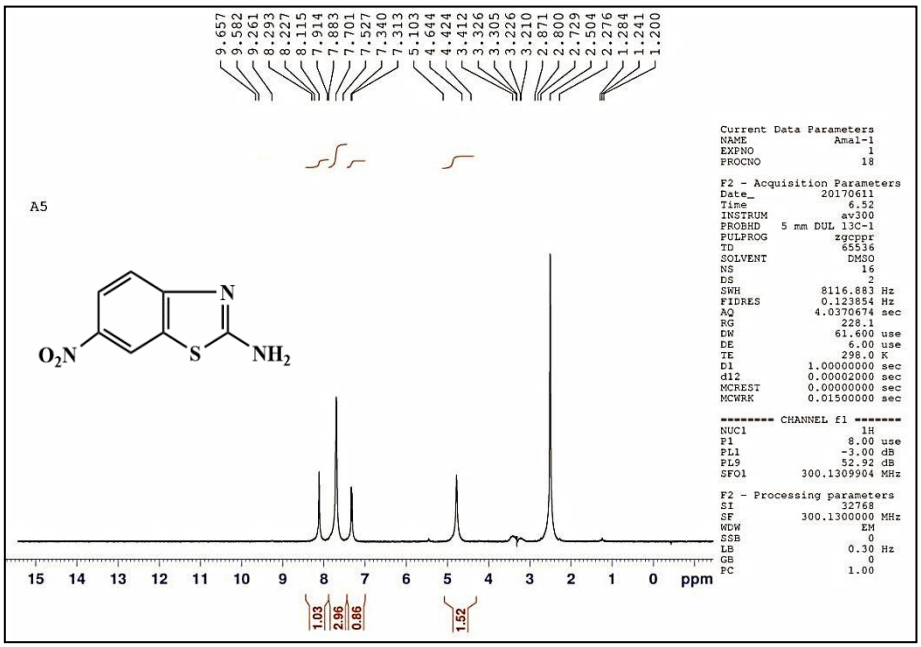


Fig. (2): ^{1}H-NMR spectra of (M_{14})

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

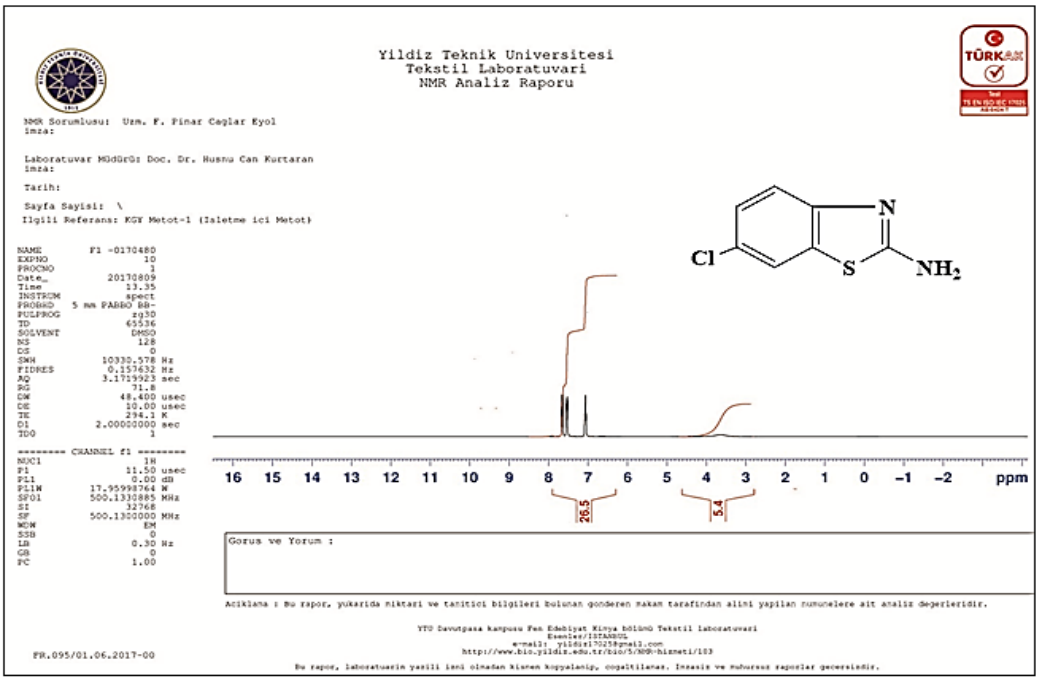


Fig. (3): ^{1}H-NMR spectra of (M_5)

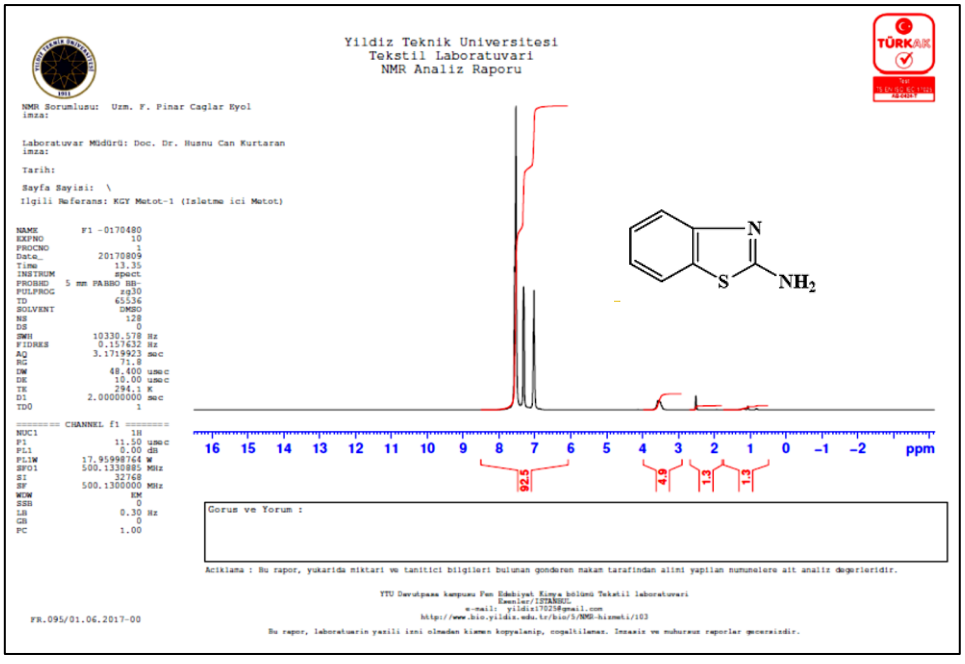


Fig. (4): ^{1}H-NMR spectra of (M_1)

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

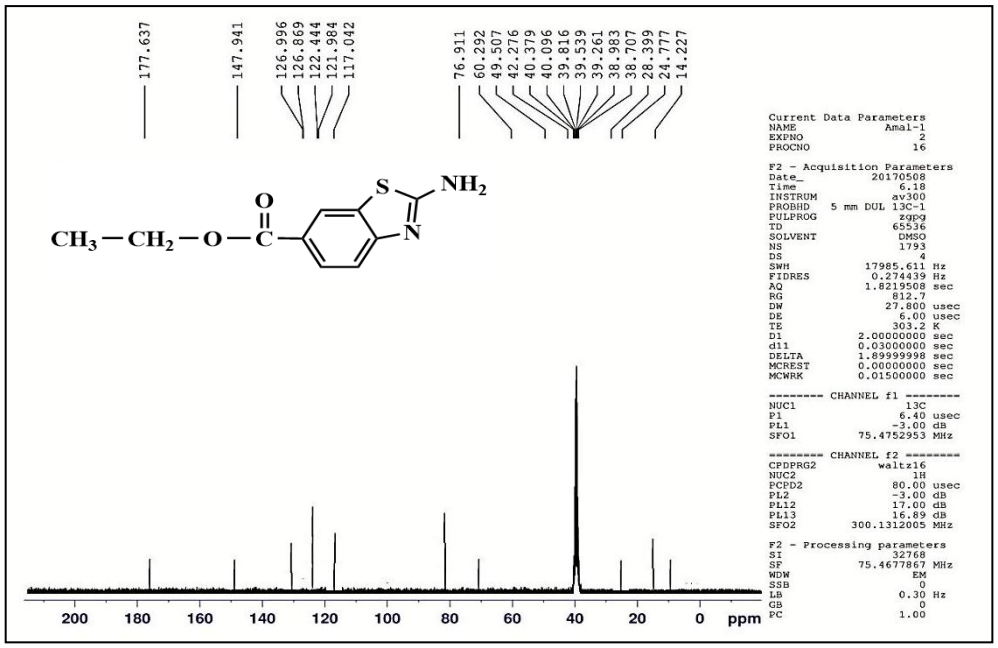


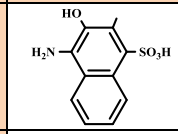
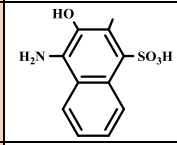
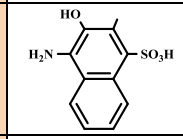
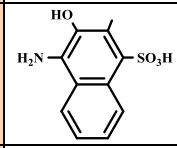
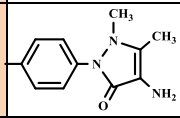
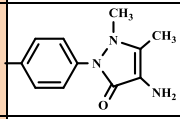
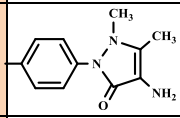
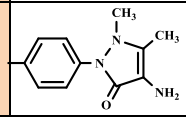
Fig. (5): ^{13}C-NMR spectra of (M_9)

Synthesis of the reagent diazonium salt with coupling solution (M15-M22) :

FT-IR spectra of compound (M_{18}) showed characteristic absorption bands at (3544 cm^{-1}) and (1469 cm^{-1}) due to ν(O-H) phenol and ν(N=N) azo group. Other bands appeared at (1672 cm^{-1}) and (1168 cm^{-1}) which attributed to ν(C=N) in thiazole ring and ν(C-F) in aromatic ring respectively. FT-IR spectral data of the prepared compounds (M_{15}-M_{22}) are listed in Table (5) and Fig. (6) shows the (FT-IR) spectra of (M_{18}). ^{1}HNMR spectrum [22]. of compounds (M_{15}-M_{22}) 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.

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
ISSN 1992 – 0849

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	$\bar{R}$	υ(OH)	υ(C-H) arom.	υ(C=C)	υ(C=N)	υ(C-N)	υ others
M_{15}		6 – F	3544	2927 3060	1463 1612	1672	1359	1168 1380 (C-F)
M_{16}		6 – Cl	3342	3104 3165	1471 1583	1687	1355	540 785 (Cl)
M_{17}		4.6 – diCl	3354	3114 3150	1463 1612	1678	1366	540 785 (Cl)
M_{18}		5 – NO_2	3544	2927 3060	1433 1596	1672	1315	1512 1330 (NO_2)
M_{19}		6 – F	3350	3114 3153	1463 1612	1675	1365	1168 1380 (C-F)
M_{20}		6 – Cl	3340	3150 3160	1471 1583	1682	1353	540 785 (Cl)
M_{21}		4.6 – diCl	3358	3155 3150	1463 1612	1668	1377	540 785 (Cl)
M_{22}		5 – NO_2	3359	3155 3178	1471 1583	1679	1356	1512 1330 (NO_2)

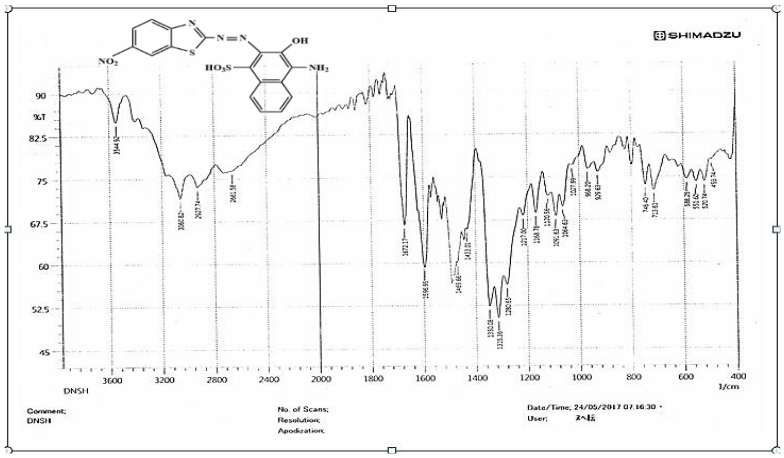


Fig. (6): Infrared spectra (FT-IR) of compound (M_{18})

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 1, March 2018, pp. (212- 227)
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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, Esheriechia 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,Esheriechia coli, and Eterobactern.

a. The compounds (M_{11}, M_3 and M_{17}) 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 (M_3) showed high effect against (Eterobactern), while compounds (M_{11} and M_{17}) showed moderate to good activity against .
c. The compound (M_{11}) showed highly effect against (Staphylococcus aureus coli) while compounds (M_{14} and M_{17}) showed good
d. effect against. While non existing effect for compound (M_3).
e. The compounds (M_{14} and M_{11}) showed moderate effect against (Esheriechia coli), while compounds (M_3 and M_{17}) 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).

Table (6): antibacterial activity

Comp. No.	Code of Compounds	Bacillus subtilis	Eterobactern	Staphylococcus aurea	Esheriechia coli
1-	M_{11}	23	14	19	12
2-	M_3	26	35	_	_
3-	M_{17}	24	15	13	_
4-	M_{14}			17	13

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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 sulphonic 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^{o}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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