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Synthesis and Characterization of Several New Succinimides Linked to Phenyl Azo Benzothiazole or Thiazole Moieties with Expected Biological Activity

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Abstract

In the present work, several new cyclic imides (succinimides) linked to benzothiazole or thiazole moieties through phenyl azo group were synthesized. Synthesis of the new imides was performed via multistep synthesis. The first step involved reaction of equimolar amounts of succinic anhydride and p-toluidine producing N-(4-tolyl) succinamic acid (1) which was dehydrated in the second step via treatment with acetic anhydride and anhydrous sodium acetate affording N-(4-tolyl)succinimide (2).

In the third step, substituted-2-aminobenzothiazoles were introduced in diazotization reaction with nitrous acid producing the corresponding diazonium salts and these inturn were introduced directly in coupling reaction with compound (2) affording the target cyclic imides (3-7). Structures of the new compounds were confirmed by depending on FTIR spectral data and (^{1}HNMR and^{13}CNMR) spectra for some of them which were in good agreement with the proposed ones.

Keywords: N-(4-tolyl)succinamic acid, N-(4-tolyl)succinimide, diazonium salts

تحضير وتشخيص عدد من السكسن ايمايدات الجديدة المرتبطة بمكونة فنيل ازوبنزوثايازول او ثايازول ذات فعالية بايولوجية متوقعة

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الخلاصة

تم في هذا البحث تحضير عدد من الايمايدات الحلقية الجديدة (سكسن ايمايدات) المرتبطة بحلقة البنزوثايازول او الثايازول من خلال مجموعة فنيل ازو. تم انجاز هذا التحضير من خلال عدة خطوات حيث تضمنت الخطوة الاولى تفاعل كميات مولية متساوية من حامض السكسنيك اللامائي مع 4–امينو توليدين لانتاج المركب N–(4–توليل) حامض السكسن اميك (1) والذي بدوره تم سحب الماء منه في الخطوة الثانية من خلال معاملته مع حامض الخليك اللامائي وخلات الصوديوم اللامائية كعامل ساحب للماء وبذلك تم الحصول على المركب N–(4–توليل)سكسن ايمايد (2). في الخطوة الثالثة تم ادخال مركبات 2–امينوبنزوثايازول في تفاعل مع حامض النتروز مما اسفر عن تكوين املاح الدايازونيوم المقابلة والتي تم ادخالها مباشرة في تفاعل ازدواج مع مركب (2) مما اسفر عن تكوين الايمايدات المطلوبة. تم تشخيص تراكيب المركبات المحضرة من خلال الاعتماد على اطياف FTIR اضافة الى اطياف ^{1}HNMR و^{13}CNMR لبعض منها وقد جاءت نتائج التحاليل مطابقة للتراكيب المتوقعة.

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Introduction

Cyclic imides are privileged pharmacophores and important building blocks for the synthesis of natural products, drugs, agrochemicals, advanced materials, and polymers [1-3].

Various drugs, such as lurasidone, phensuximide, lenalidomide [4] and a premilast, contain cyclic imide moieties and possess a wide range of biological properties [5,6]. Besides cyclic imides have found immense applications as herbicides, fungicides and pesticides [7, 8].

On the other hand, benzothiazole derivatives are important class of compounds which is becoming increasingly important due to their broad spectrum of biological activities [9, 10]. Literature survey shows that many benzothiazole derivatives are known to exhibit pharmacological activities such as antitumor, antiviral [11], antiproliferative, anticancer [12], antimicrobial [13] and anti-inflammatory [14] activities.

Thiazoles also have a prominent position among heterocycles and thiazole ring is present in many biologically active compounds and drugs [15].

All these observations encouraged us to synthesize new compounds containing these two active moieties cyclic imide and benzothiazole (or thiazole) present in the same molecule linked together through phenyl azo group with expected biological activity.

Experimental

1. Instruments

Melting points were determined on Thomas Hoover apparatus and were uncorrected. FTIR spectra were recorded as KBr disc using SHIMADZU FTIR-8400 infrared spectrophotometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on NMR spectrometer 400 MHz Avance III 400, Bruker Germany in chemical laboratory of Isfahan University using TMS as internal standard and DMSO-d_6 as a solvent.

2. Chemicals

All employed chemicals were of analytical reagent grade and were used without further purification.

1. Preparation of N-(4-tolyl)succinamic acid (1)

A solution of 4-toluidine (0.01 mol, 1.07g) in (25 mL) of acetone was added dropwise to a solution of (0.01 mol, 1g) of succinic anhydride in (25 mL) of acetone with stirring and cooling [16].

Stirring was continued for 3 h. then the precipitated amic acid was filtered, washed with diethyl ether, dried and recrystallized from ethanol.

2. Preparation of N-(4-tolyl)succinimide (2)

A mixture of (0.01 mol, 2.07g) of N(4-tolyl)succinamic acid in (20 mL) of acetic anhydride and (0.001 mol, 0.082g) of anhydrous sodium acetate was refluxed with stirring for two h. [17]. The resulted homogenous solution was poured into excess cold water with stirring and the obtained precipitate was filtered, washed thoroughly with distilled water, dried then purified by recrystallization from cyclohexane. Physical properties of compounds (1) and (2) are listed in Table-1.

3. Synthesis of N-[4-methyl-3-(substituted benzothiazole-2-yl-azo) phenyl] succinimides (3-7)

Solution (A) was prepared by dissolving substituted-2-amino benzothiazole or (2-aminothiazole) (0.01 mol) in concentrated hydrochloric acid (3 mL) and water (3 mL) and cooling at 5°C in an ice bath [18]. Sodium nitrite (0.01 mol, 0.69g) was dissolved in water (10 mL) at 5°C to obtain solution (B). Solution (A) was added dropwise to solution (B) at 5°C with stirring. The resulted mixture was added slowly to the solution of compound (2) N-(4-tolyl)succinimide (0.01 mol, 1.89 g) which was dissolved in (5%) sodium hydroxide solution (20 mL) at 5°C with stirring. The mixture was kept chilled in the ice bath and stirred continuously for 10 minutes. The formed precipitate was filtered, washed with methanol, dried and recrystallized from a suitable solvent. Physical properties of compounds (3-7) are listed in Table-2.

Table 1- Physical Properties of compounds (1, 2)

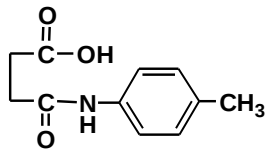
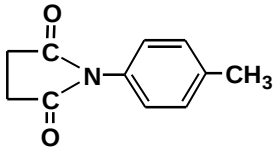
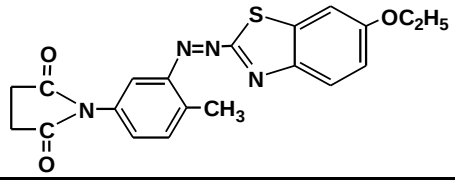
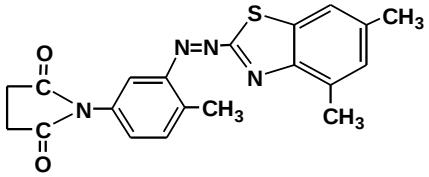
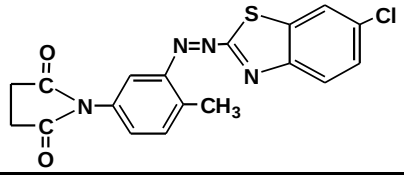
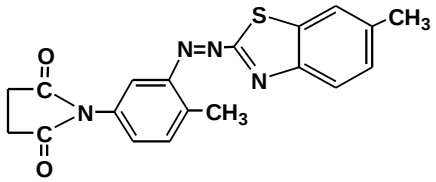
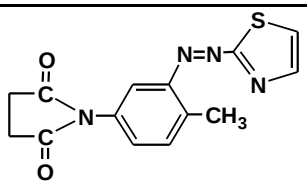
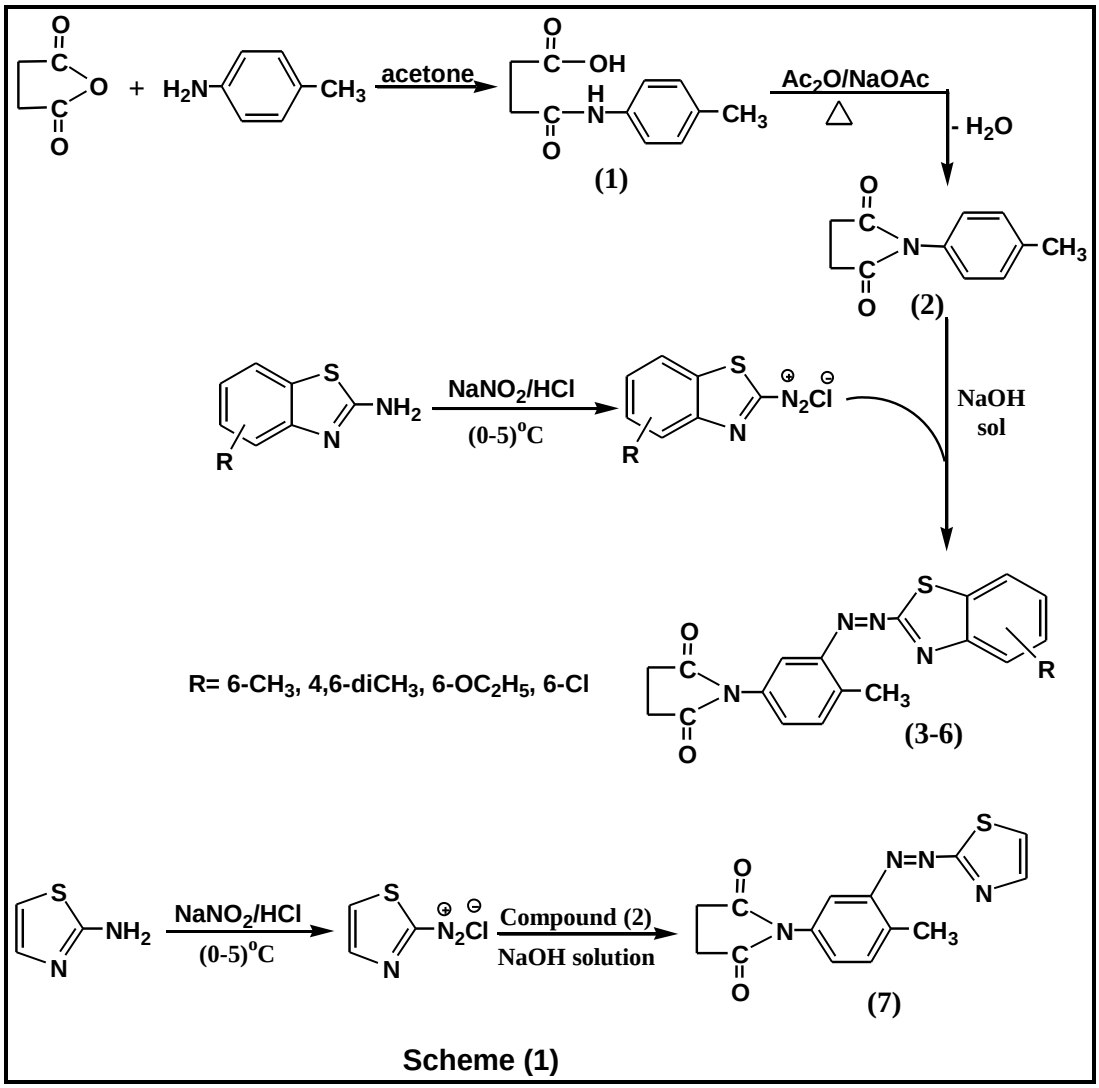
Comp. No.	Compound structure	Colour	Yield, %	Melting Points, °C	Recrystallization Solvent
1		White	84	170-172	Ethanol
2		White	60	146-148	Cyclohexane

Table 2- Physical Properties of compounds (3-7)

Comp. No.	Compound structure	Colour	Yield, %	Melting Points, °C	Recrystallization Solvent
3		Dark brown	77	98-100	Acetone
4		Orange	63	135-136	Acetone
5		Light yellow	55	130-132	Acetone
6		Orange	60	110-112	Ethanol
7		Dark brown	68	150-152	Methanol

Results and Discussion

In continuation of our research program directed towards synthesis of new cyclic imides linked to different heterocycles, the target of the present work involved synthesis of several new succinimides linked to benzothiazole (or thiazole) cycles through phenyl azo group. Synthesis of the target compounds was performed by many steps which are summarized in Scheme-1.



Scheme (1)

As indicated in scheme-1 the first step involved preparation of compound (1) N-(4-tolyl) succinamic acid via reaction of 4-toluidine with succinic anhydride. The reaction proceeded through nucleophilic attack of amino group in 4-toluidine on one carbonyl group in succinic anhydride followed by ring opening producing compound (1).

FTIR spectrum of compound (1) showed absorption bands at (3307, 3188 and 3114) cm^{-1} due to ν(OH) carboxyl and ν(N-H) amide. Other absorption bands appeared at 1703 cm^{-1}, 1664, 1598, 3051 and 2925 cm^{-1} which are due to ν(C=O) carboxyl, ν(C=O) amide, ν(C=C) aromatic, ν(C-H) aromatic and ν(C-H) aliphatic respectively[19].

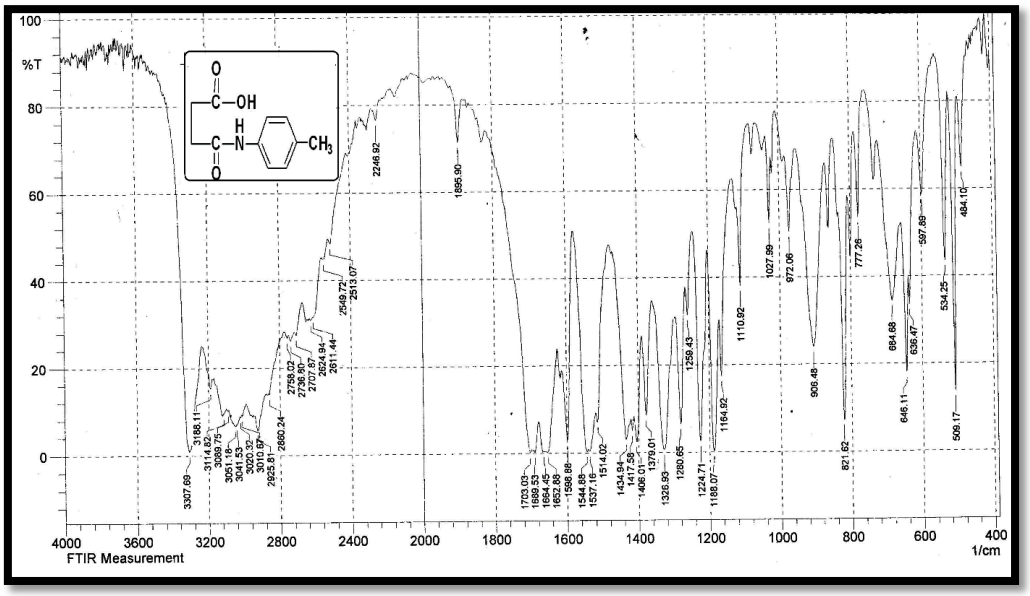
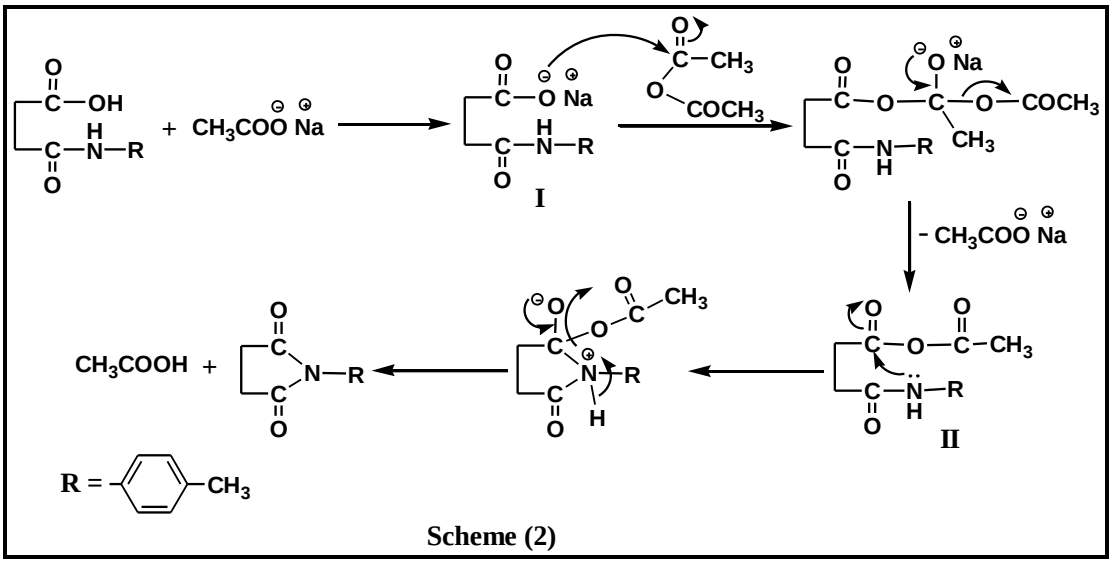


Figure 1- FTIR spectrum of compound (1)

In the second step, compound (1) was converted to the corresponding imide N-(4-tolyl) succinimide via dehydration reaction using acetic anhydride and anhydrous sodium acetate as dehydrating agent. The reaction proceeded through nucleophilic attack of carboxylate ion I on carbonyl group in acetic anhydride affording new anhydride II followed by intramolecular nucleophilic attack leading to ring closure and producing of compound (2) as indicated in Scheme-2.



FTIR spectrum of compound (2) showed disappearance of ν(O-H) carboxyl and ν(N-H) amide absorption bands proving success of dehydration reaction. The spectrum showed also appearance of two clear absorption bands at 1780 cm^{-1} and 1704 cm^{-1} due to asym. and sym. ν(C=O) imide and this was the second proof for success of dehydration reaction and imide formation.

Other absorption bands appeared at 1515, 1377, 3068 and 2974 cm^{-1} which are assigned to ν(C=C) aromatic, ν(C-N) imide, ν(C-H) aromatic and ν(C-H) aliphatic respectively [19].

^{1}HNMR spectrum of compound (2) showed singlet signal at (δ= 2.35) ppm belong to CH_3 protons, signal at (δ= 2.77) ppm belong to (-CH_2-CH_2-) protons and doublet signals at (δ=7.12-7.15) and (7.28-7.3) ppm belong to aromatic protons.

^{13}CNMR spectrum of compound (2) showed signal at (δ= 20.68) ppm belong to CH_3 carbon and signals at (δ= 28.39-28.61) ppm belong to (-CH_2-CH_2-) carbons. Signals for aromatic carbons appeared at (δ= 126.47-137.56) ppm and signal for (C=O) imide carbons appeared at δ= 176.99 ppm.

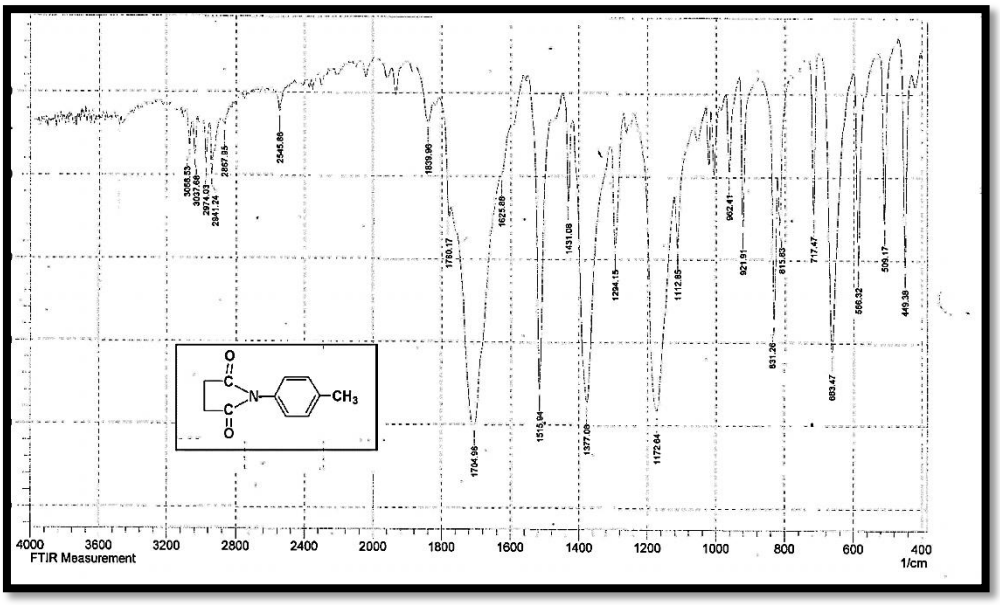


Figure 2- FTIR spectrum of compound (2)

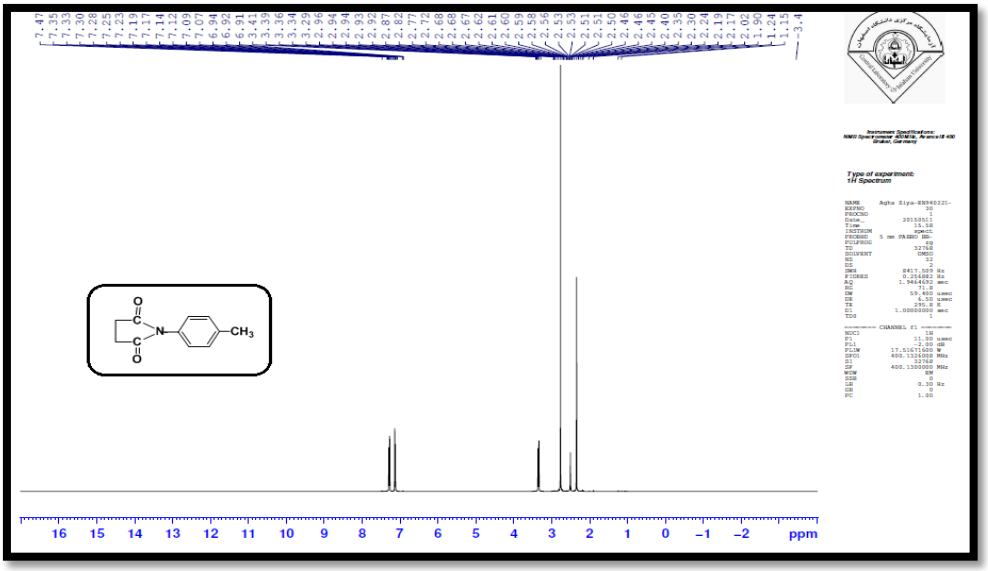


Figure 3- ^{1}HNMR spectrum of compound (2)

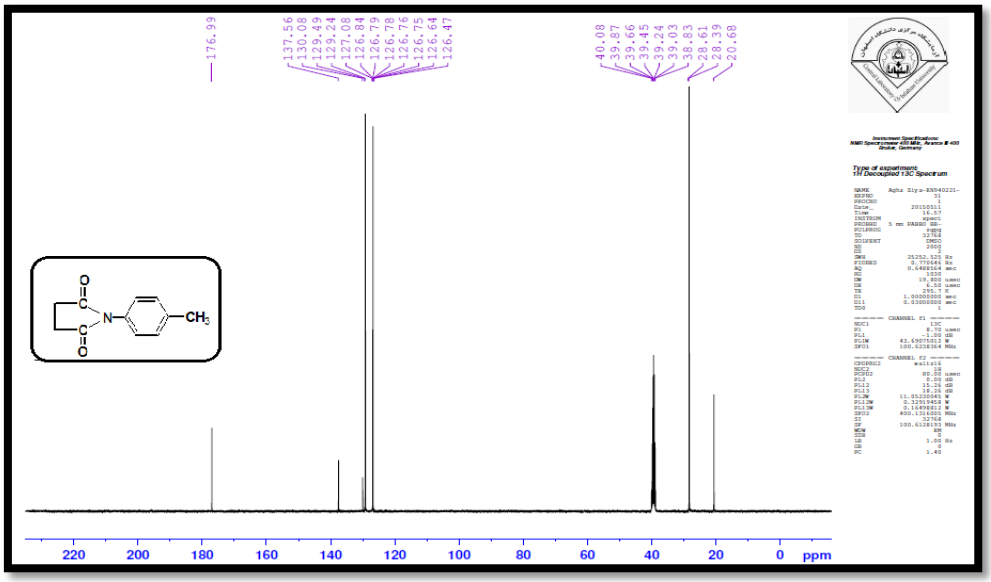


Figure 4- ^{13}CNMR spectrum of compound (2)

In the third step of this work four substituted-2-amino benzothiazoles and 2-amino thiazole were selected as known biologically active heterocyclic amines to introduce in reaction with nitrous acid at (0-5)°C producing the corresponding diazonium salts [18].

The resulted diazonium salts were introduced directly in coupling reaction with compound (2) producing the target new cyclic imides (3-7).

The newly synthesized succinimides are solids with colour range from light yellow, orange to dark brown and other physical properties are listed in Table-2.

FTIR spectra of compounds (3-7) showed absorption bands at (1704-1778) cm^{-1}, (1629-1660) cm^{-1} and (1533-1602) cm^{-1} which are due to asym. and sym. ν(C=O) imide, ν(C=N) and ν(C=C) aromatic respectively.

The spectra showed appearance of clear absorption bands at (1446-1490) cm^{-1} due to ν(N=N) and bands at 1377 cm^{-1} and (611-700) cm^{-1} due to ν(C-N) imide and ν(C-S). FTIR spectral data of compounds (3-7) are listed in Table-3.

Table 3- FTIR spectral data (cm^{-1}) of compounds (3-7)

Comp. No.	ν(C-H) Aromatic and Aliphatic	ν(C=O) Imide	ν(C=N) Thiazole	ν(C=C) Aromatic	ν(N=N)	ν(C-N) Imide	ν(C-S)	Others
3	3064 2975	1708	1660	1602	1490	1377	630	ν(C-O-C) 1226
4	3070 2925	1704	1643 1629	1539	1461	1377	620	-
5	3099 2941	1778 1704	1633	1533	1446	1377	700	ν(C-Cl) 1060
6	3070 2941	1706	1639	1539	1465	1377	611	-
7	3040 2974	1778 1706	1635	1590	1470	1377	663	-

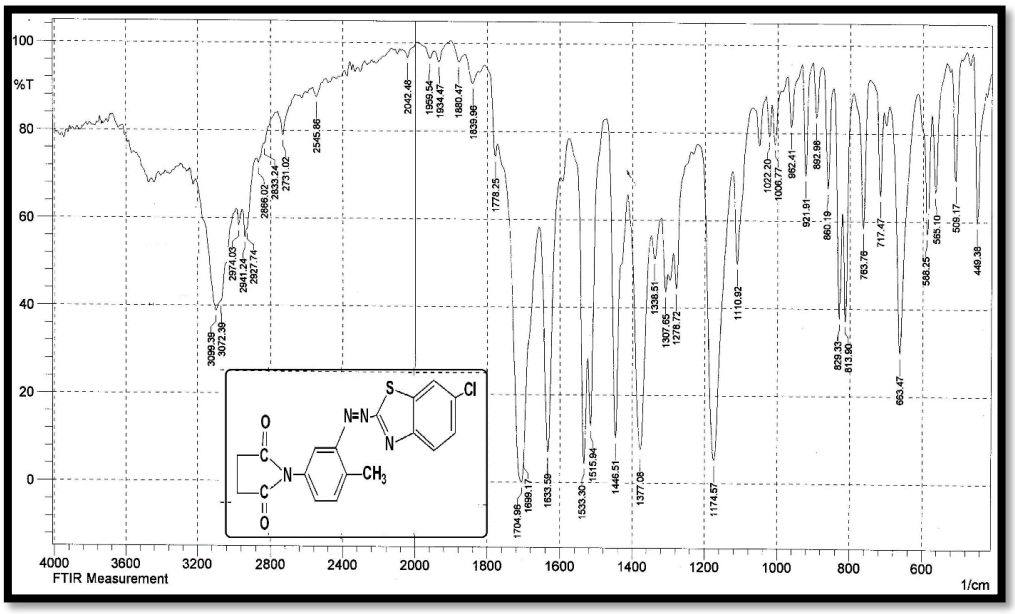


Figure 5- FTIR spectrum of compound (5)

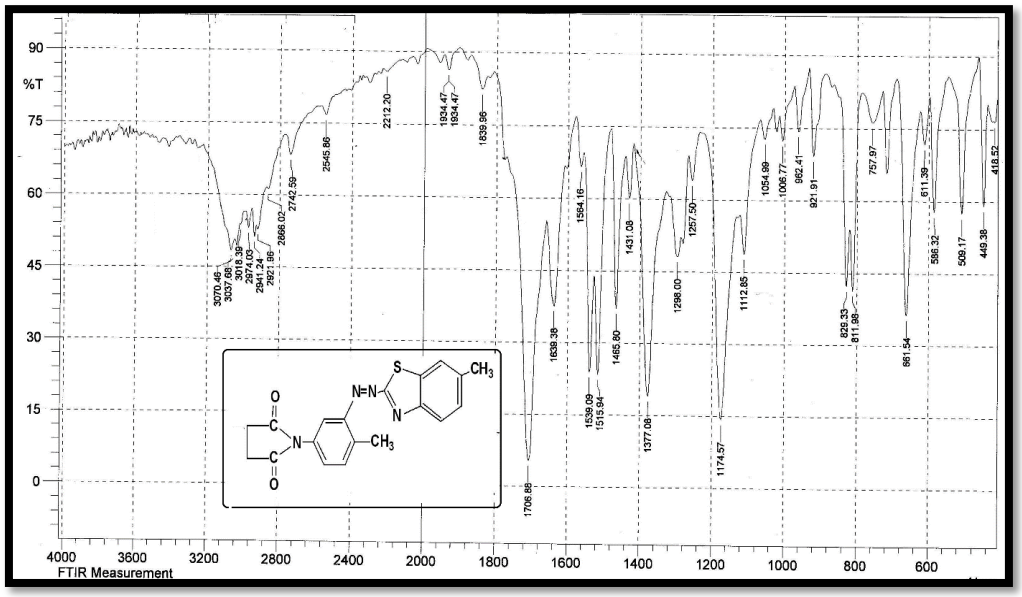


Figure 6- FTIR spectrum of compound (6)

^{1}HNMR spectrum of compound (4) showed three singlet signals at (δ= 2.28, 2.35 and 2.38) ppm belong to protons of three methyl groups. Signal for (-CH_2-CH_2-) protons appeared at (δ= 2.77) ppm and signals for aromatic protons appeared at (δ= 6.86-7.5) ppm [19].

^{13}CNMR spectrum of compound (4) showed signals at (δ= 18.16-20.7) ppm belong to carbons of three methyl groups. Other signals appeared at δ= 28.39, (118.21-149.46), 164.85 and 176.99 ppm which belong to (-CH_2-CH_2-) carbons, aromatic cabons, (C=N) and (C=O) imide carbons respectively.

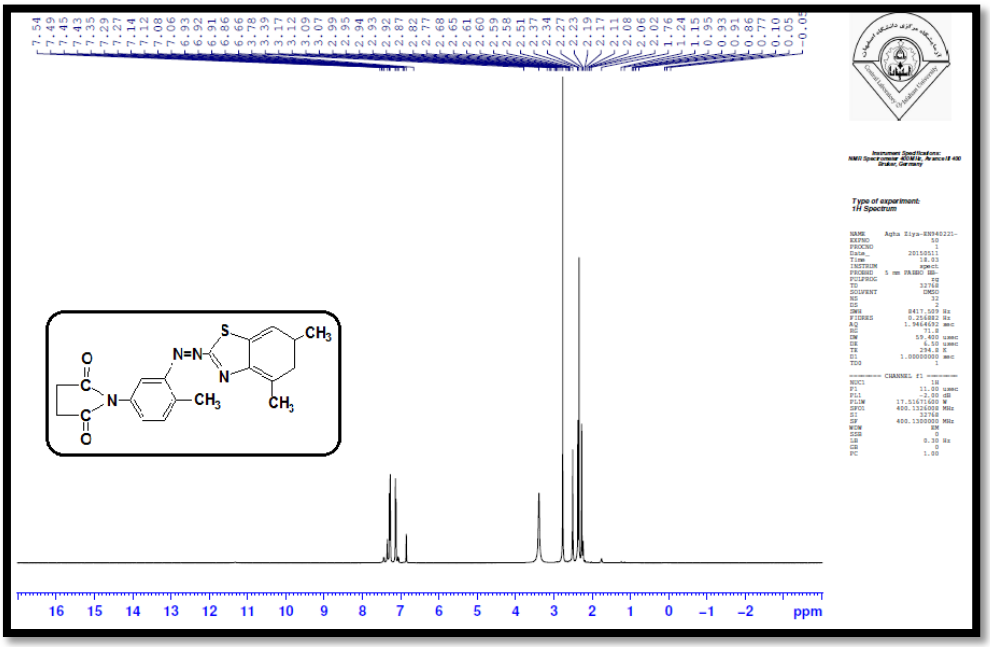


Figure 7- ^{1}HNMR spectrum of compound (4)

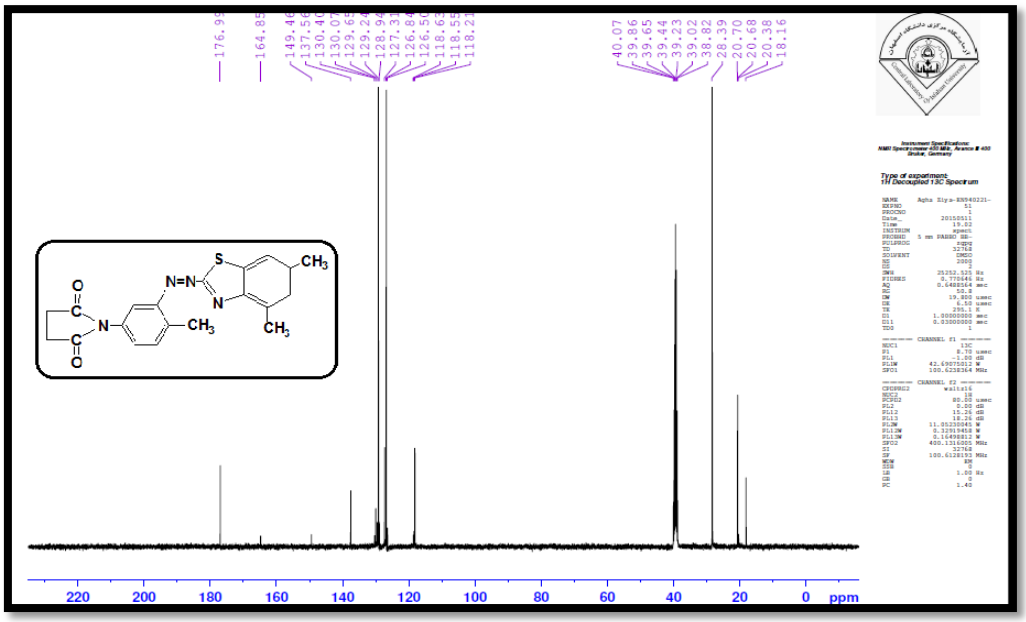


Figure 8- ^{13}CNMR spectrum of compound (4)

^{1}HNMR spectrum of compound (6) showed two singlet signals at (δ= 2.31 and 2.35) ppm belong to protons of two methyl groups. Signal for (-CH_2-CH_2-) protons appeared at (δ= 2.72) ppm while multiplet signal for aromatic protons appeared at (δ= 7.1-7.47) ppm [20].

^{13}CNMR spectrum of compound (6) showed signals at (δ= 20.68 and 20.71) ppm belong to carbons of two methyl groups and signal at δ= 28.39 ppm belong to (-CH_2-CH_2-) carbons. Other signals appeared at (δ= 117.37-130), 137.56 and 176.99) ppm belong to aromatic carbons, (C=N) and (C=O) imide carbons respectively [20].

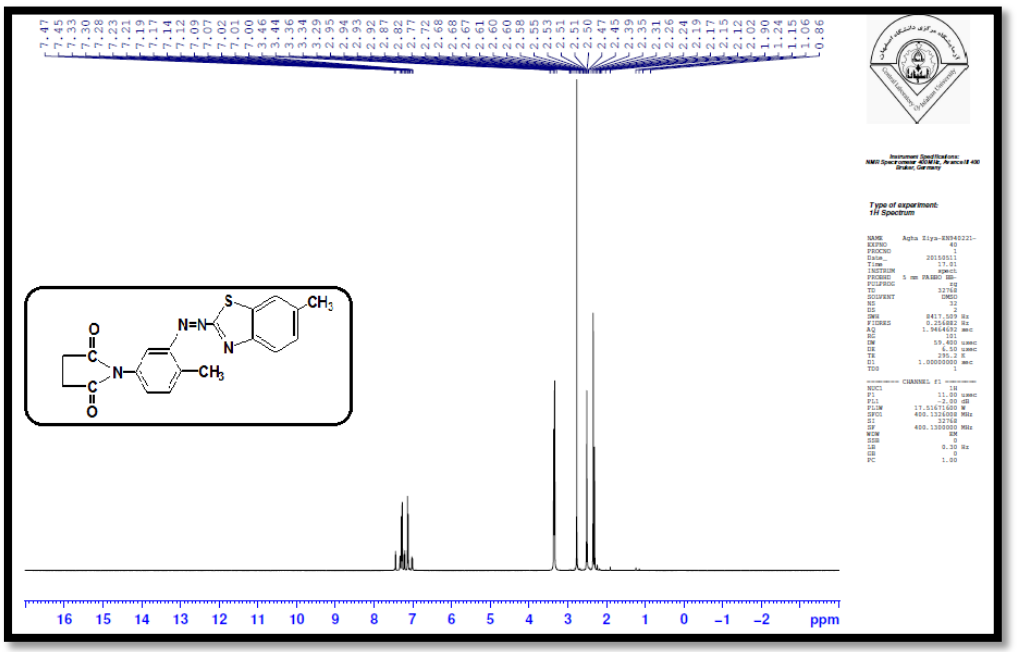


Figure 9- ^{1}HNMR spectrum of compound (6)

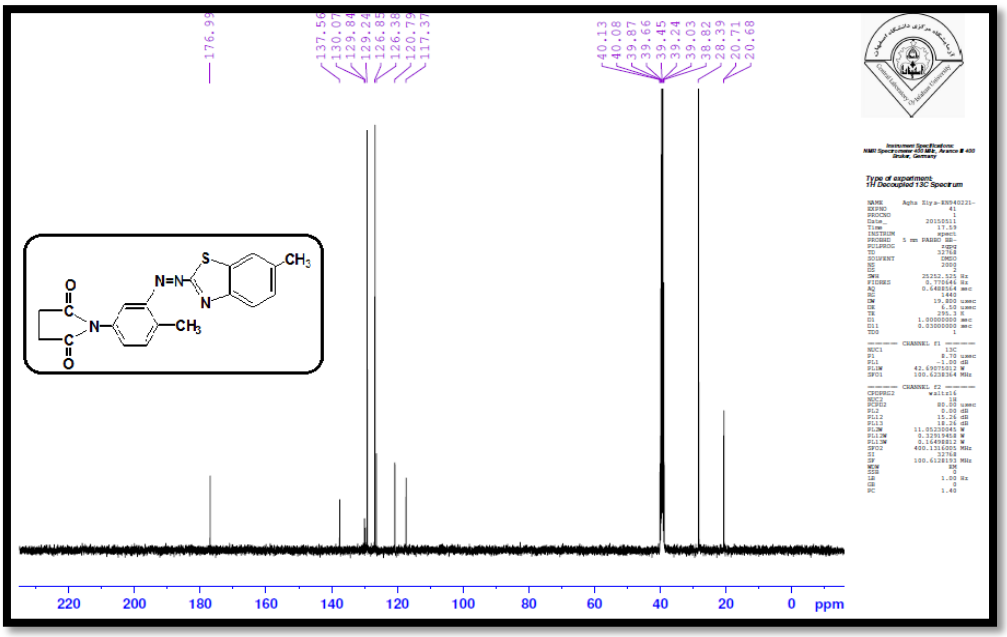


Figure 10- ^{13}CNMR spectrum of compound (6)

Conclusion

In this work two known biologically active components namely succinimide and benzothiazole (or thiazole) are incorporated together in the same molecule with phenyl azo group linking between them via multistep synthesis producing new cyclic imides.

The newly synthesized succinimides are expected to possess biological activity since they are basically built from biologically active components.

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