Synthesis and characterization of some new of thiazolidine ,1,2,4-triazole ,1,3,4-thiadiazole , semicarbazide , oxazoline and a study of their biological activity .

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Key word : **thiazolidine ,triazole ,thiadiazole , semicarbazide , oxazoline.**

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Abstract:

New compounds of oxalic acid dihydrazide [2], bis –[1-phenyl-4-(formyl) thiosemicarbazide [3], bis [5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-4-(hydroxyl) thiazolidine [4] , bis –[5-mercapto-3-yl-4-phenyl-1,2,4-triazole [5] , bis –[5-(phenylamino)-2-yl-1,3,4-thiazole] [6], bis [1-phenyl-4-(formyl) semicarbazide [7], bis –[5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-2-(hydroxyl)oxazoline [8] and bis –[5-hydroxy-4-phenyl-3-yl-1,2,4-triazole [9] have been synthesized. The structures of these compounds were identified by FT-IR spectra and checked by TLC. Some of these compounds were tested against bacteria , Escherchia coli and Staphococcus aureus .

تحضير وتشخيص عدد من المركبات الجديدة من ثايازولدين , 4,2,1-ترايازول و 4,3,1-ثاياديازول و سيميكاربازايد - ودراسة الفعالية البايولوجية لها

ابتسام خليفة جاسم*,ووسام خليفة جاسم* وسلوى عبدالستار**و عبد الله حاتم***

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مفتاح البحث: ثيازوليدين، ترايازول، ثاياديازول، سيميكاربازايد، أوكسازولين

الخلاصة:

تم تحضير عدد من المشتقات الجديدة من حامض الاوكزاليك وهي حامض الاوكزاليك ثنائي الهيدرازيد (2) بس-(1-فنيل-4-(فورميل)ثايوسيميكاربازايد (3) , بس 5-فنيل) 2-(اسدهيدرازيد)-3- ن-فنيل-4-(هيدروكسيل)ثايوزولدين(4), (5-مركبتو-3-يل-4-فنيل-4,2,1-ترايازول(5), بس-(5-فنيل امينو) -2-يل-4,3,1-ثايازول(6) , بس-(1-فنيل-4-(فورميل)سيميكاربازايد(7), بس-(باي فنيل)-2-(اسدهيدرازايد)-3-ن-فنيل-2-(هيدروكسيل)اوكسازولين(8), و بس-(5-هيدروكسي-4-فنيل-3-يل-4,2,1-ترايازول(9), وتم تشخيص التراكيب الكيميائية لهذه المركبات عن طريق اطياف الاشعة تحت الحمراء وكروماتوغرافيا الطبقة الرقيقة والتحليل الدقيق للعناصر كما اختبرت هذه المركبات ضد انواع من البكتريا

Introduction :

Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as ***Schiff*** bases, thiadiazole [(1)],

oxadiazole [2] and triazole[3] derivatives which all were reported to possess biological activities. The structural formula for this type of compounds is (RCONHNH-) . In addition, it was reported that, compounds having triazole moieties, such as vorozole, letrozole and anastrozole, appeared to be very useful for preventing breast cancer [4,5] .

Further more, some reported mercapto triazole derivatives showed potent activity [6] more than Streptomycin against Candida albicans. Thus, among an important type of fungicides, triazole compounds are highly efficient, low poisonous and inward absorbent [7]. Hydrazine-pyridazines continue to be an object of interest for improving medicinal drugs for blood pressure control such as hydralazine, which has been used for many years in the treatment of essential hypertension [8]. It is also known that the presence of an azo moiety in different types of Schiff bases can lead them to exhibit pesticidal activities. Both Schiff bases and azo compounds are important structures in the medicinal and pharmaceutical fields [9] and it has been suggested that the azomethine linkage might be responsible for biological activities displayed by Schiff bases. Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [10,11]. In particular, the ligand combining the oxazoline ring and hydroxy group or an amino group have been reported to show execllent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes[12,13].

1,3,4-thiadiazoles also, are known for their broad-spectrum of biological activity such as antifungal [14, 15], antibacterial [16], herbicidal [17], antiviral [18], and analgesic effect [19, 20].

Experimental:

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and they were uncorrected.

2- Infrared spectra are recorded using Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Chemistry Department, Al-Nahrain University .

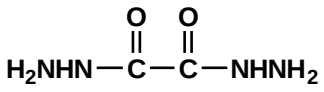
3- Thin layer chromatography (TLC) was carried out, and the plates were developed with iodine vapour.

4- The biological activity was performed by Biotechnology Department, Al-Nahrain University .

1- Synthesis of diethyl oxalate [1][21]

Treating (0.22 mole,20 g) of oxalic acid with (20ml) absolute ethanol, (5ml) conc. Sulphuric acid and refluxed the mixture for 6 hours, yield the expected ester yield 62.27%.

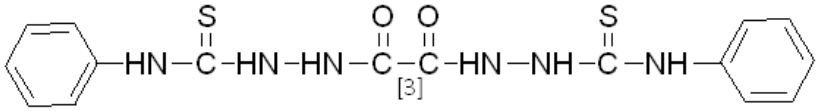
2-Synthesis of Oxalic acid dihydrazide [2][(21)]:



[2]

Compound [2] was synthesized by addition of hydrazine hydrate (0.32 mole, 10 ml) to (0.16 mole, 23 ml) [1] in (25) ml of absolute ethanol then the mixture was refluxed for 2 hours. After cooling, the product was filtered off and recrystallized by using ethanol, m.p. 153-155 ^{0}C ,lit [(22)] 151-153,and yield(85%).

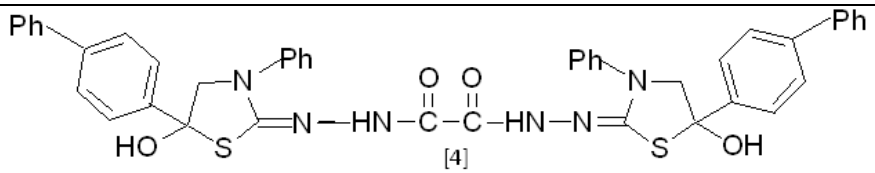
3- Synthesis of bis-[1-phenyl-4- (formyl) thiosemicarbazide] [3][(23)]:



[3]

Compound [2] (1g ,0.008 mole) and phenyl isothiocyanate (2.29ml,0.016 mole) in (15) ml absolute ethanol was refluxed for 7 hours. The solid compound obtained on cooling was filtered off, and then recrystallized from ethanol ,m.p. 215-217 °C, yield 87.92%.

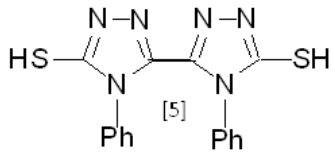
4- Synthesis of bis[5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-4-(hydroxyl)thiazolidine [4] [(21)] :



[4]

Compound [3] (0.00036 mole, 0.14 g) and *p*-phenylphenacyl bromide (0.0007 mole, 0.2g) in absolute ethanol (10 ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water , dried and recrystallized from ethanol, m.p. 240 °C dec., yield 93.24%.

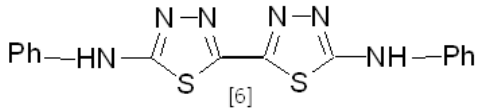
5- Synthesis of bis-[5-mercapto-3-yl-4-phenyl-1,2,4-triazole] [5] [(23)]:



[5]

Compound [3] (0.001 mole, 0.5 g) and (15ml) of 2M sodium hydroxide solution was refluxed with stirring for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered, m.p. 167-170 °C, yield 73.18%.

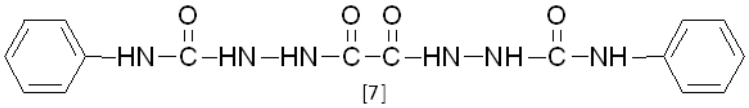
6- Synthesis of bis-[5-(phenyl amino)-2-yl-1,3,4-thiadiazole][6] [(23)]:



[6]

Compound [3] (0.0008 mole, 0.3 g) was added portion wise to (5) ml of concentrated sulfuric acid at 0°C with continuous stirring. The reaction mixture was stirred further for 3 hours at room temperature and then allowed to stand overnight. Neutralization with dilute sodium bicarbonate prepcipitated acrude solid, which was filtered and recrystallized from ethanol, m.p. 235-237 °C, yield 77.17%.

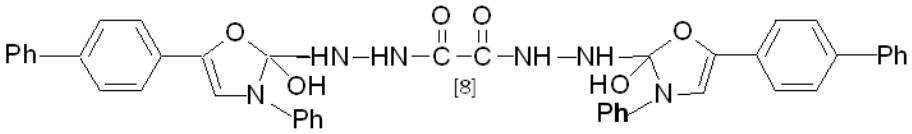
7- Synthesis of bis-[1-phenyl-4-(formyl) semicarbazide] [7] [(23)]



[7]

A mixture of compound [2] (0.008 mole, 1 g) and phenyl isocyanate (0,016 mole, 2 ml) in (10) ml absolute ethanol was refluxed for 7 hours. The solid compound obtained on cooling, then filtered off to give final compound, m.p. 250-252 °C, yield 89%.

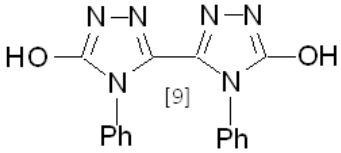
8- Synthesis of bis-[5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-2-(hydroxy)oxazoline] [8] [(21)]:



[8]

A mixture of compound [7] (0.0004 mole, 0.13 g) and *p*-phenylphenacyl bromide (0.0008 mole, 0.2 g) in absolute ethanol (10ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, and recrystallized from ethanol to give the final product, m.p. > 300 °C, yield 69.41%.

9- Synthesis of bis-[5-hydroxy-4-phenyl-3-yl-1,2,4-triazole[9] [(23)].



[9]

A mixture of compound [7] (0.002 mole, 0.5 g) and 2M sodium hydroxide solution was refluxed with stirring for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the

precipitate was filtered to give the final product, m.p. > 300 °C, yield 74.29%. table (1) showed the physical properties of the synthesized compounds.

Table (1): physical properties of the synthesized compounds.

Comp .No.	Molecular formula	Molecular weight (g/mol)	Yield (%)	M.P (^{0}C)	Colour	cal/found C.	H.	N
2	$C_2H_6N_4O_2$	118	85	153-155	White	20.33 19.90	5.08 4.96	47.45 47.00
3	$C_{16}O_2N_6S_2H_{16}$	388	87.92	215-217	White	49.48 49.06	4.12 4.20	21.64 21.20
4	$C_{42}O_4N_6S_2H_{36}$	779	93.2	240dec	Yellow	64.6 64.10	4.60 4.20	10.78 10.31
5	$C_{16}N_6S_2H_{12}$	352	73.18	167-170	White	54.50 54.00	3.40 3.10	23.80 23.00
6	$C_{16}N_6S_2H_{12}$	352	89	235-237	pale yellow	54.50 54.10	3.40 3.00	23.80 23.00
7	$C_{16}H_{16}O_4N_6$	356	89	250-252	Green	53.90 53.20	53.90 53.20	23.50 23.00
8	$C_{42}H_{34}N_6O_6$	718	69.41	>300	yellow	70.19 70.10	4.70 4.20	11.69 11.30
9	$C_{16}H_{12}O_2N_6$	320	74.29	>300	White	60.00 59.40	3.75 3.30	26.25 26.00

Results and Discussion :

1-Synthesis of oxalic acid dihydrazide [2]:

The acid hydrazide was synthesized by the reaction of ester [1] with hydrazine hydrate in absolute ethanol.

The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide derivatives; it is a tetrahedral nucleophilic substitution reaction [(24)]. The FTIR spectrum shows the appearance of the characteristic absorption bands in the region (3292.3-3190) cm^{-1} due to asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, a new band appeared at (1662.5) cm^{-1} due to the stretching vibration of amide I and appearance of amide II bending vibration band at for (NH) group at (1502) cm^{-1}.

2-Synthesis of bis-[1-phenyl-4- (formyl) thiosemicarbazide] [3]:

The FTIR spectrum , for bis –[1-phenyl-4-formylthiosemicarbazide] [3] show disappearance of the two absorption bands at (3292.3) cm^{-1} , (3190) cm^{-1}due to asymmetric and symmetric stretching vibration of $NH–NH_2$ group of acid hydrazide [2] , appearance of the two absorption bands at (3213.19) cm^{-1} , (3114.82) cm^{-1} due to the three groups of N-H and appearance band of C=S at (1332.72) cm^{-1} ,aromatic (-CH) appeared at (3000) cm^{-1} ,and amide C=O appeared at (1687.60) cm^{-1}.

3- Synthesis of bis-[5-biphenyl-2-(acid hydrazide)-3-N-phenyl-5-(hydroxyl)thiazolidine] [4]:

Thiazolidine derivative [4] was synthesized from the reaction of thiosemicarbazide [3] with *p*-phenyl phenacyl bromide which was used for cyclization of the previous compound.

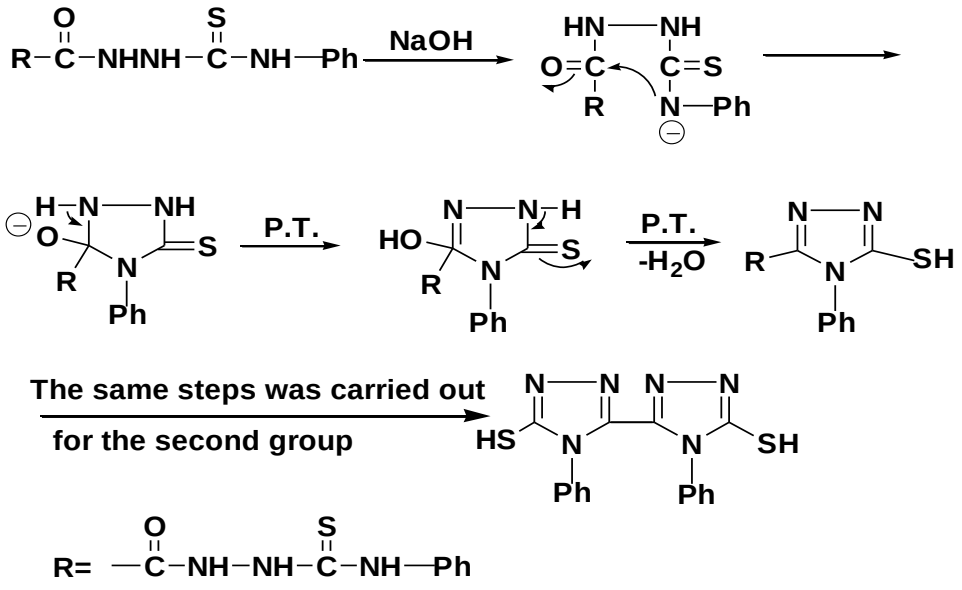
The FTIR spectrum , shows the disappearance of thione group of the thiosemicarbazide [3] at (1332.72) cm^{-1} , appearance of band at (3527.56) cm^{-1} assinable to (OH) group, band due to (NH-) group appeared at (3406.05) cm^{-1}, C=N band appears at (1604.66) cm^{-1} and band at (694.33) cm^{-1} belongs to (C-S-C) group.

4-Synthesis of bis-[5-mercapto-3-yl-4-phenyl-1,2,4-triazole] [5] :

Thiol-triazole prepared through the reaction of thiosemicarbazide derivative with 2N NaOH under refluxing condition by interamolecular cyclization through the loss of H_2O.

The FTIR spectrum , shows disappearance of the bands at (3213.19) cm^{-1} ,(3114.82) cm^{-1} due to (NH-NH) group with appearance of a weak band due to (–SH) group at (2400) cm^{-1}, also show the disappearance of the band at (1687.60) cm^{-1} due to C=O of amide I and appearance of a band at (1595) cm^{-1} assignable to C=N of triazole ring.

The suggested mechanism for the reaction is



Scheme (1)

The reaction of acid hydrazide with phenyl isothiocyanate in absolute ethanol gave the thiosemicarbazide [3].

4-Synthesis of bis-[5-(phenylamino)-2-yl-1,3,4-thiadiazole [6] :

1,3,4-Thiadiazole derivative [6] was synthesized from the reaction of thiosemicarbazide derivative with concentrated sulfuric acid at (0) ^{0}C.

The FTIR spectrum shows band at (3300) cm^{-1} due to (N-H) group, band at (1650) cm^{-1} for (C=N) and band at (611.39) cm^{-1} attributed to C-S-C band is a good evidence for thiadiazole formulation.

5- Synthesis of bis-[1-phenyl-4-(formyl) semicarbazide] [7] :

The reaction of acid hydrazide with phenyl isocyanate in absolute ethanol gave the substituted semicarbazide [7].

The FTIR , for bis–[1-phenyl-4-(formyl)semicarbazide] shows disappearance of the two absorption bands at (3292.3) cm^{-1} , (3190) cm^{-1}due to asymmetric and symmetric stretching vibration of $NH–NH_2$ group of acid hydrazide [2] and the appearance of the two absorption bands at (3396.41) cm^{-1} , (3182.33) cm^{-1} due to the two groups of N-H ,aromatic (-CH) appeared at (3041.53) cm^{-1} , and two (C=O) groups appeared at range (1622.02-1733.09) cm^{-1}.

6- Synthesis of bis-[5-biphenyl-2-acid hydrazide-3-N- phenyl-2-(hydroxyl) oxazoline [8] :

N-subsituted-oxazoline derivative was synthesized through the reaction of semicarbazide [7] with *p*-phenyl phenacyl bromide under refluxing condition affected by intermolecular cyclization through S_N2 mechanism and tetrahedral nuclephilic substitution [25].

The FTIR spectrum of compound [8] shows band of O-H group at (3460) cm^{-1}, (C=O) of amide appeared at (1675) cm^{-1},(C=C) band appeared at (1560) cm^{-1},aromatic (C-H) appeared at (3050) cm^{-1} and (C-O-C) asymmetric and symmetric bands appeared at (1125- 1380) cm^{-1} .

Synthesis of bis-[5-hydroxy-4-phenyl-3-yl-1,2,4-triazole] [9] :

1,2,4-Triazole derivative prepared through the reaction of semicarabazide derivatives with NaOH and reflux for (4) hours effected interamolecular cyclization through the loss of H_2O.

The FTIR spectrum of compound [9] shows band at (3425.3) cm^{-1} due to O-H group, the (C=N) band appeared at (1631.7) cm^{-1}, (C=C) band appeared at (1575) cm^{-1} and aromatic (C-H) appeared at (3069.8) cm^{-1}.

Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds (3-8) were assayed for their antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia*

coli) and Gram-positive bacteria (*staphylococcus aurous*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 100µl of the prepared compounds (0.03g of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (2).

The biological activity test showed that compounds with free (-SH) groups and free ($-NH_2$) groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also considered biologically active on *bacteria* while when free ($-NH_2$) and (-SH) groups disappeared the existence of Pyridine lead to increase of the biological activity .

(Table 2):Antibacterial activities of some of the synthesized compounds

Comp. No.	*E*scherichia coli	*S*taphococcus aureus
3	-	-
4	+	-
5	-	++
6	++	-
7	+	+

- = No inhibition = inactive

\+ = (5-10) mm = slightly active

++ = (11-20) mm = moderately active

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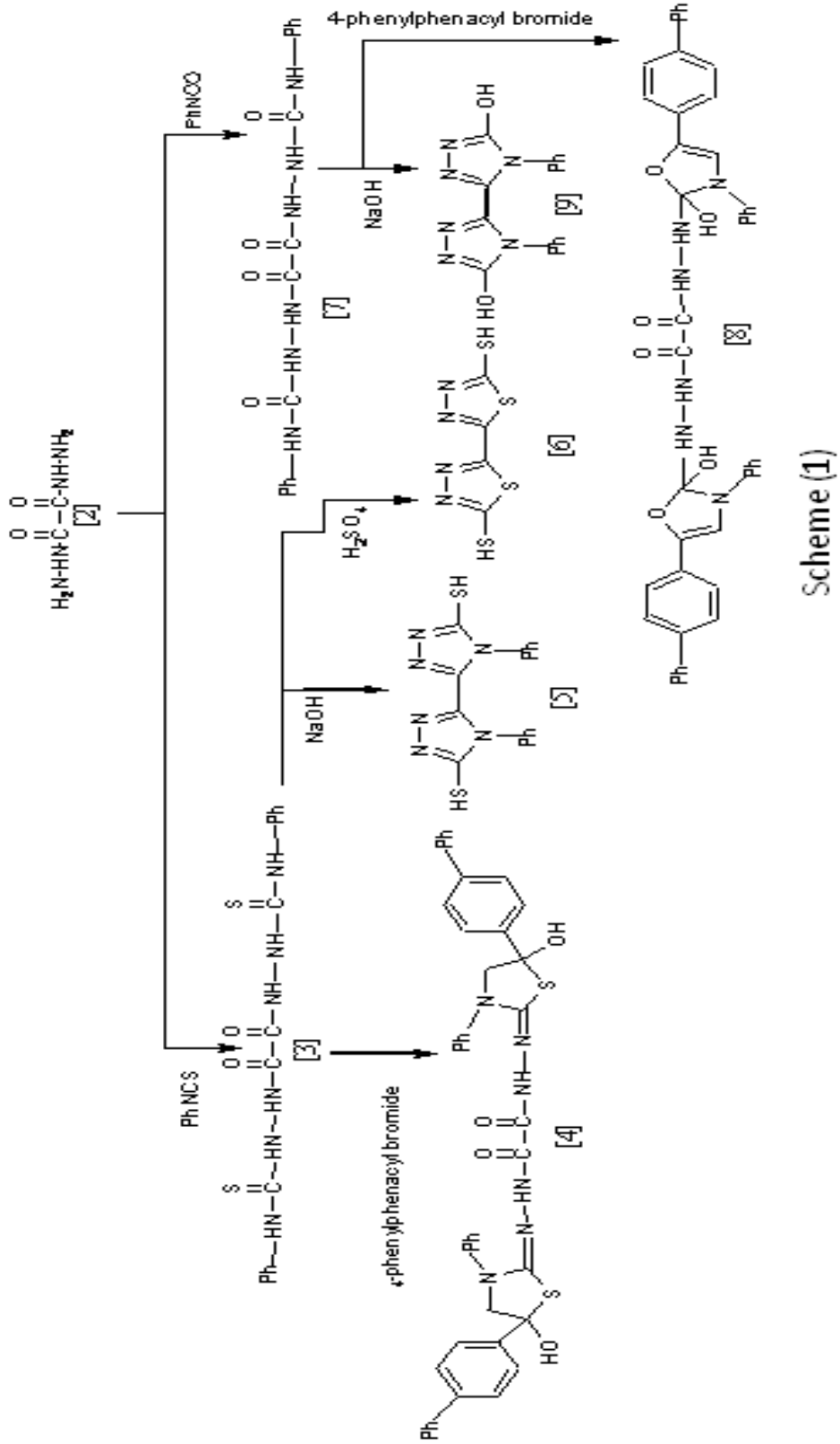
4-phenylphenacyl bromide
PhNCO
NaOH
H_2SO_4
NaOH
PhNCS
4-phenylphenacyl bromide
[2]
[3]
[4]
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[6]
[7]
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Scheme (1)