وزارة التعليم العالي والبحث العلمي
جامعـــــة ديـــــــالـى
كليـــــة العلـــــوم
قســـــم الكيميـــاء

تحضير وتشخيص بعض المركبات المشتقة من حامض الميفيناميك واستخدامها في التقدير الطيفي لبعض العناصر

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ياسر جبار مجيد

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بإشراف

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Synthesis, characterization of some compounds derived from mefenamic acid and their use in the spectroscopic estimation of some elements

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By

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Abstract

The new compounds from mefenamic acid were prepared, The chemical structures of the prepared compounds Y_1-Y_4 were determined by some spectroscopy techniques such as FTIR,^{1}HNMR. The reactions were followed by thin layer chromatography (TLC) to ensure that the preparation of these compounds is complete and their purity, some physical properties of prepared compounds were recorded such as melting points and colours.

The current study included some steps:

1. The Compound (Y_1) were synthesized through the reaction of Hydrazine Hydrate with carbon sulfide.
2. The Compound (Y_2) were synthesized through the reaction of mefenamic acid with thiocarbohydrazide.
3. Compound (Y_3) was synthesized through the reaction of 4-amino-5-(2-((2,3-dimethylphenyl)amino)phenyl)-4H-1,2,4-triazole-3-thiol [Y_2] with 3-nitrophenol while the Compound (Y_4) was synthesized through the reaction of 4-amino-5-(2-((2,3-dimethylphenyl)amino)phenyl)-4H-1,2,4-triazole-3-thiol [Y_2] with 4-hydroxy-3-methoxybenzaldehyde.

In addition, the study included the use of Compounds Y_3, Y_4 in the spectral estimation of the following elements, Fe (III), Co (II), Ni (II) and Cd (II).

It included the composition of equipment for each ion with the elements used and the study of the optimal conditions for each complex:

1. Determination of Fe (III) ion with the reagent [Y3] at $\lambda_{max=}$545 nm was found the optimum conditions, the volume of reagent at 2.0 mL, coupling reaction time at 10 min, the temperature at 25 ºC, The stability at 5 min, the calibration curve shows that the (R^2=0.9931), apparent molar absorptivity (ε) was 24963.2 L.mol^{-1}.cm^{-1},

Sandell's sensitivity was 0.0431 µg.cm^{-2}. Also Job's continuous variation methods and molar ratio were determined and it was 1:2.

2. Determination of Co (II) ion with the reagent [Y3] at λ_{max}=532 nm was found optimum reagent volume at 2.0 mL, optimum coupling reaction time at 10 min, optimum temperature at 25 ºC, The optimum stability at 10 min, the calibration curve show that the (R^2=0.9978), apparent molar absorptivity (ε) was 23930.4 L.mol^{-1}.cm^{-1}, Sandell's sensitivity was 0.0423 µg.cm^{-2}. Also Job's continuous variation methods and molar ratio were determine and it was 1:2.
3. Determination of Ni (II) ion with the reagent [Y4] at λ_{max}=664 nm was found optimum reagent volume at 1.0 mL, optimum coupling reaction time at 5 min, optimum temperature at 25 ºC, The optimum stability at 5 min, the calibration curve show that the (R^2=0.9733), apparent molar absorptivity (ε) was 25192 L.mol^{-1}.cm^{-1}, Sandell's sensitivity was 0.0425 µg.cm^{-2}. Also Job's continuous variation methods and molar ratio were determined and it was 1:2.
4. Determination of Cd (II) ion with the reagent [Y4] at λmax=460 nm was found optimum reagent volume at 2.0 mL, optimum sodium hydroxide volume at 1.0 mL, optimum coupling reaction time at 5 min, optimum temperature at 25 ºC, The optimum stability at 5 min, the calibration curve show that the (R^2=0.9948), apparent molar absorptivity (ε) was 9540.8 L.mol^{-1}.cm^{-1}, Sandell's sensitivity was 0.1123 µg.cm^{-2}. Also Job's continuous variation methods and molar ratio were determined and it was 1:2.

It was applied for quantification of of Fe(III), Co(II), Ni(II) and Cd(II) ions in tap water samples (drinking water system in June), river water (Diyala River), industrial wastewater from the Diyala Electrical Industry Company (industrial wastewater from Electrical manufacturing factory) and bottle of juice in the local markets in Baquba, were collected from , Baquba (Diyala, Iraq) and stored in the refrigerator up

Chapter One

Introduction & Previous Studies

1.1 Introduction

Mefenamic acid is a weak organic acid. In particular, it is name as a N-(2,3-xylyl) anthranilic acid and is not a particularly complicated molecule (Figure 1). Interestingly, this acid shares relatedness to 3-hydroxyanthranilic acid, a naturally occurring metabolite of tryptophan. It was initially released as early as 1962 for pharmaceutical purposes and was largely marketed then by Parke, Davis and Company (NJ, USA) in most countries under the names of Ponstan and Ponstel [1]. In the laboratory, it is a derivative of N-phenylanthranilic acid and it is a member of the 'fenamate' family of NSAIDs (one of five broad families of such agents including salicylates, indoleacetic acid analogs, acylpropionic acid congeners, fenamates and coxibs). The drug was known very early to possess anti-inflammatory, analgesic and antipyretic properties.

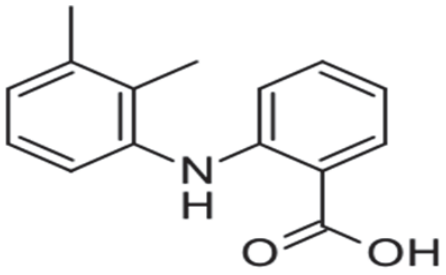


Figure (1.1): Mefenamic acid.

Mefenamic acid is highly cited in the existing scientific and medical literature, and the mefenates are among the most highly studied existing pharmacological agents. Soon after mefenamic acid became available for public use (1963), it was one of the most highly prescribed medications. In the (1990), it was ranked by some as being among the top three NSAIDs prescribed [1]. Several investigators have found that mefenamic acid is detectable in waste and ground water [2,3]. The finding of this drug in bovine milk is also cited [4].

Diazonium salt are useful synthetic building blocks in organic synthesis because these compounds can be linked to methine or aromatic sp^2 hybridized C-atoms. The

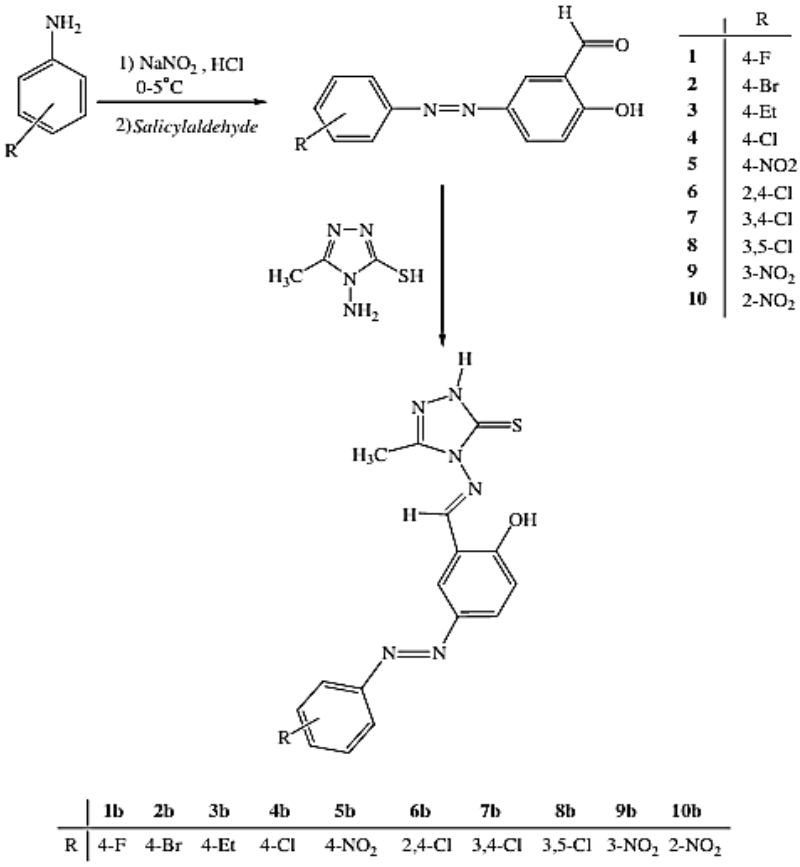
diazotization and diazo coupling reactions are usually carried out with protonation of nitrous acid under strongly acidic conditions, and azo coupling is carried out at low temperatures in the presence of nucleophilic coupling components, the reactivity of a nucleophilic substrate increases with increasing basicity [5,6]. Arene diazonium salts are common, easily prepared and highly useful intermediates in organic synthesis due to their rich reactivity and diverse transformations [7].

Dyes have a long history and constitute an important component in our daily lives. The dye industry began by using natural plant and insect sources, and then rapidly turned to synthetic manufacturing processes. Unfortunately, several synthetic dyes, especially azo dyes, have been found to be toxic and mutagenic, and are banned throughout the world. However, because of their low cost and other desirable properties, the use and manufacture of azo dyes continues even today [8]. Synthetic azo dyes are widely used in industries. Gerhardt Domagk discovered that the antimicrobial effect of red azo dye Prontosil was caused by the reductively cleaved (azo reduction) product sulfanilamide. The significance of azo reduction is thus revealed [9].

1.2 Previous Studies

Jawad, S.K. et al (2012). 2-[(Benzo thiazolyl)azo]-4-benzyl phenol is used as complexing agent spectrophotometric determination Pb and 2-[(3-Bromophenyl)azo]-4,5-diphenylimidazole used as complexing agent for spectrophotometric determination Cd ions are quantitatively extracted in TritonX-100 after separation ,5ml of 1,2 Dichloroethane was added to Cloud point layer of Pb and 5ml ethanol added for cloud point layer of Cd before to its analysis by UV-Visible Spectrometry. The study showed several parameter effect on complex such as pH, concentration of TritonX-100, effect of temperature, time of heating, organic solvent effect, stoichiometry, synergism, when rated in the suggest method were applied for the determination of Pb(II) and Cd(II) in various samples [10].

Khanmohammadi, H., et al (2012). A new series of monoiminated 1,2,4-triazole-based azo–azomethine dyes have been synthesized via condensation reaction of 4-amino-3-methyl-5-mercapto-1,2,4-triazole with various substituted azo-coupled salicylaldehyde. The dyes have been characterized by using FT-IR, UV–Vis and ^{1}H NMR spectroscopic methods as well as elemental analysis. The electrochemical behavior of the dyes has been investigated by cyclic voltammetry in DMSO at five different scan rates. Solvatochromic behavior of the dyes has been also investigated in four organic solvents with different polarities. Furthermore, the ^{1}H chemical shielding of the dyes were studied by the gauge independent atomic orbital (GIAO) method at the level of density functional theory (DFT) [11].

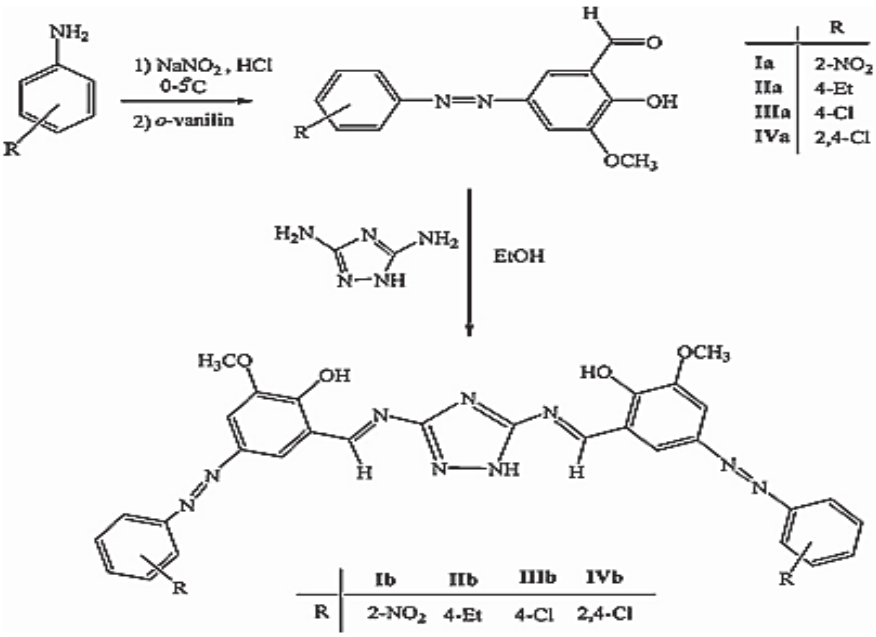


	R
1	4-F
2	4-Br
3	4-Et
4	4-Cl
5	4-NO2
6	2,4-Cl
7	3,4-Cl
8	3,5-Cl
9	3-NO_2
10	2-NO_2

	1b	2b	3b	4b	5b	6b	7b	8b	9b	10b
R	4-F	4-Br	4-Et	4-Cl	4-NO_2	2,4-Cl	3,4-Cl	3,5-Cl	3-NO_2	2-NO_2

Scheme1.1: General synthesis of1,2,4-triazole-basedazo–azomethinedyes.

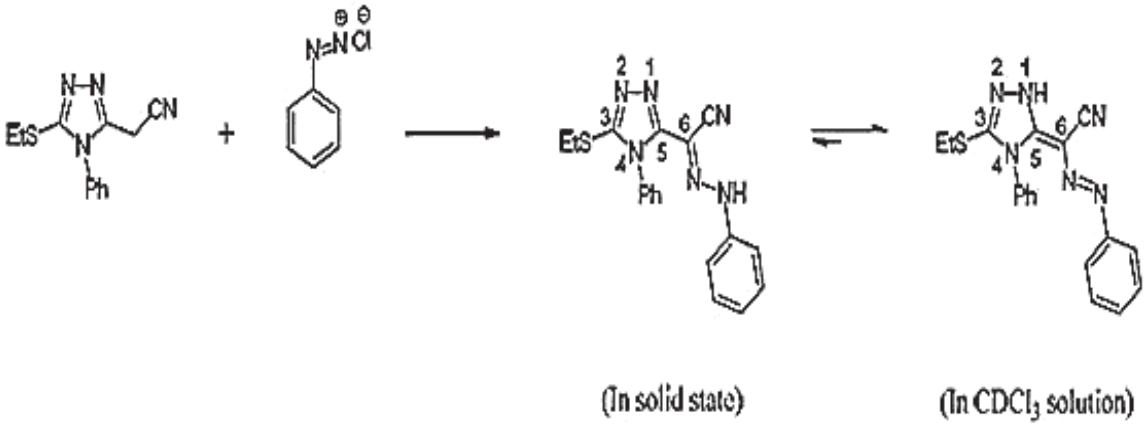
Khanmohammadi, H., et al (2012). Four new 1,2,4-triazole-based azo-azomethine dyes were synthesized via condensation of 3,5-diamino-1,2,4-triazole with azo-coupled o-vanillin precursors. The prepared dyes were characterized by IR, UV–vis and ^{1}H NMR spectroscopic methods as well as elemental analyses. Thermal properties of the prepared dyes were examined by thermogravimetric analysis. Results indicated that the framework of the dyes was stable up to 225 °C. Also, the influence of various factors including time and mixed DMSO/EtOH solution on UV–vis spectra of the dyes were investigated [12]



Scheme 1.2: 1,2,4-Triazole-based azo-azomethine dyes.

Karamat Mahmood, et al.(2012). Karamat Mahmood and et al developed a simple, selective and cheap method to determine cobalt metal based on the metal reacts with ninhydrin at pH 8.2, using sodium acetate buffer solution. Absorbance of the complex was measured at 395 nm. Various factors, such as volume of the ligand used, solution pH, stability of the complex with time and interference of other metals, which effect the complex formation have been studied in detail. Present developed method can be used for the spectrophotometric estimation of cobalt with ninhydrin complex [13].

Al-Sheikh, M., et al (2014). New 1,2,4-triazole colorants were obtained, in high yields, by coupling 3-ethylthio-5-cyanomethyl-4-phenyl-1,2,4-triazole with diazotized aniline derivatives . The azo dyes prepared in this work may exist in three tautomeric forms. We found that the tautomerism is influenced mainly by the nature of substituent at the para position of the aniline coupling component. This tautomerisation was observed in the NMR spectra of the dyes. The dyes were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS spectroscopic techniques [14].

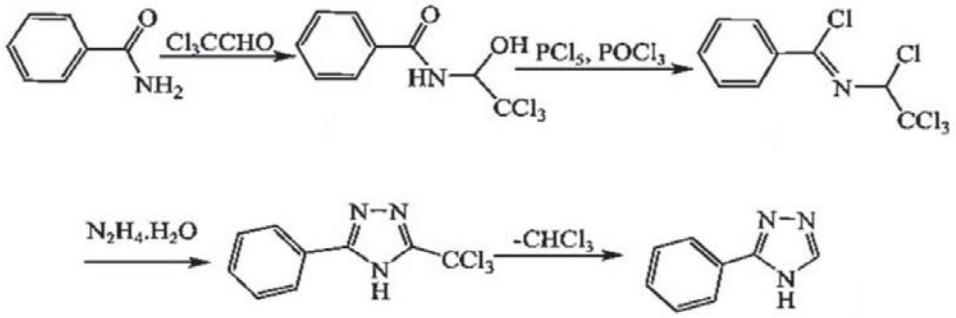


Equation 1.1: Synthesis of azo dyes compounds

Erfantalab, Malihe; et al (2014). A new 1,2,4-triazole-based azo–azomethine compound, H_2L, has been prepared by condensation reaction of 1-(3-formyl-4-hydroxyphenylazo)-4-ethylbenzene with prepared triazole-based diamine. The structure of H_2L was characterized by using FT-IR, UV–Vis and ^1H NMR spectroscopic methods as well as elemental analysis. Hard model chemometrics method has been used to determine the formation constants of zinc(II), copper(II), nickel(II) and cobalt(II) complexes of H_2L in DMSO by UV–Vis spectrophotometric method. Solvatochromic behavior of the dye has been also investigated in some organic solvents with different polarities. Thermal properties of the prepared dye was examined by thermogravimetric analysis. Results indicated that the framework of the dye was stable up to 245 °C. Furthermore,^1H chemical shifts and UV–Vis of H_2L were studied by the gauge independent atomic orbital (GIAO), continuous set of gauge transformations (CSGT) and time-dependent density functional theory (TD-DFT) methods respectively at the level of density functional theory using B3LYP/6-311+G(d) basis sets in DMSO. The computational data are in reasonably good agreement with the experimental data [15].

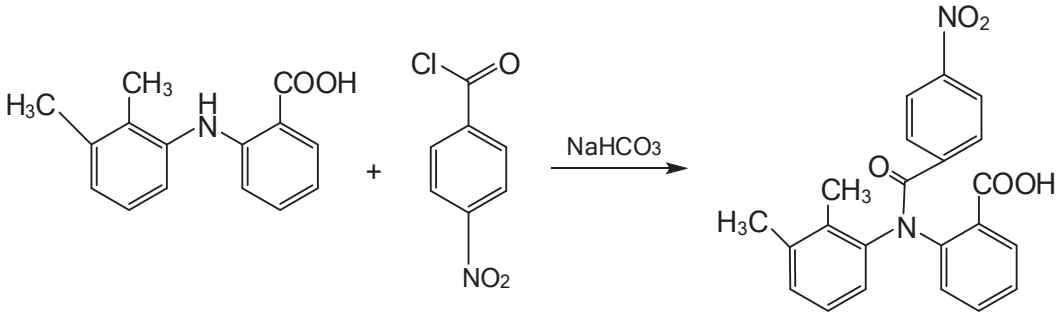
Guirado, A., et al (2016). A new, high-yield synthesis of 3-aryl-1, 2,4- triazoles. Tetrahedron, 72(49), 8055-8060.3-Aryl-1,2,4-triazole derivatives can be synthesized by a multistep synthetic route. The reaction of benzamides 30 with chloral hydrate gives

chloralamides 31 which react with a mixture of phosphorus pentachloride and phosphorus oxychloride to give N-(1,2,2,2-tetrachloroethyl) benzimidoyl chlorides 32, treatment of the later with hydrazine hydrate produces 3-aryl-1,2,4-triazoles 33 in high to quantitative yields, Scheme 1.3 [16].



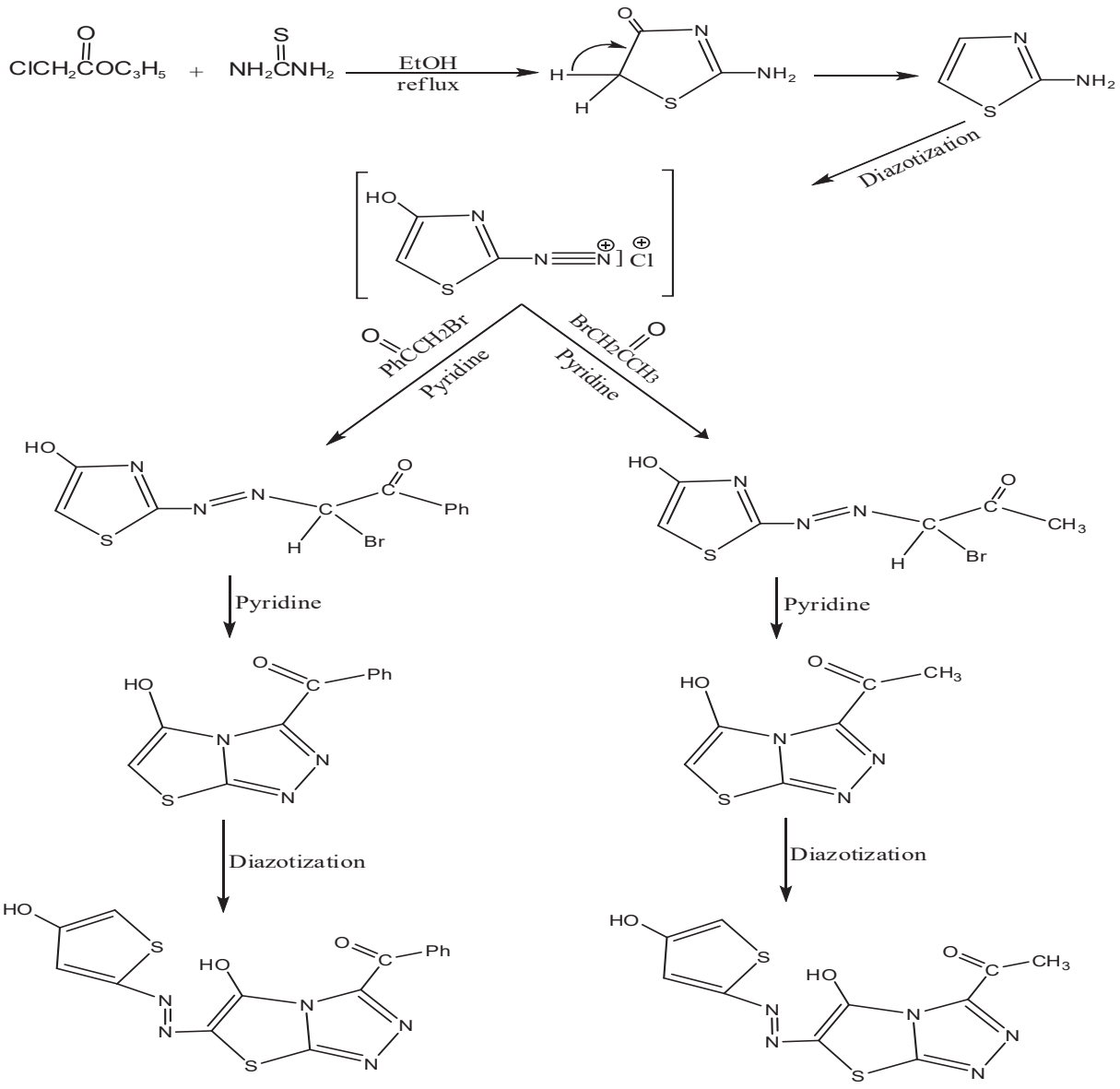
Scheme 1.3: synthesis 3-aryl-1,2,4-triazole

Puspaningtyas, A. R. (2017). A new compound of Mefenamic Acid derivate, 4-nitrobenzoyl-mefenamic acid has been synthesized by benzoylation reaction between mefenamic acid and 4-nitrobenzoyl chloride after prediction by in silico study/molecular approach. A derivative of mefenamic acid (4-NO2-benzoyl-mefenamic acid) has been synthesized for increase its activity as candidate of analgesic drug/inhibitor COX-2 (Cyclooxigenase-2). This compound has been identified this structure using H-NMR 400 MHz and FTIR-KBr, 4NBMA was tested analgetic activity by hot plate method and it showed that 4-nitrobenzoyl-mefenamic acid has been higher activity than mefenamic acid [17].



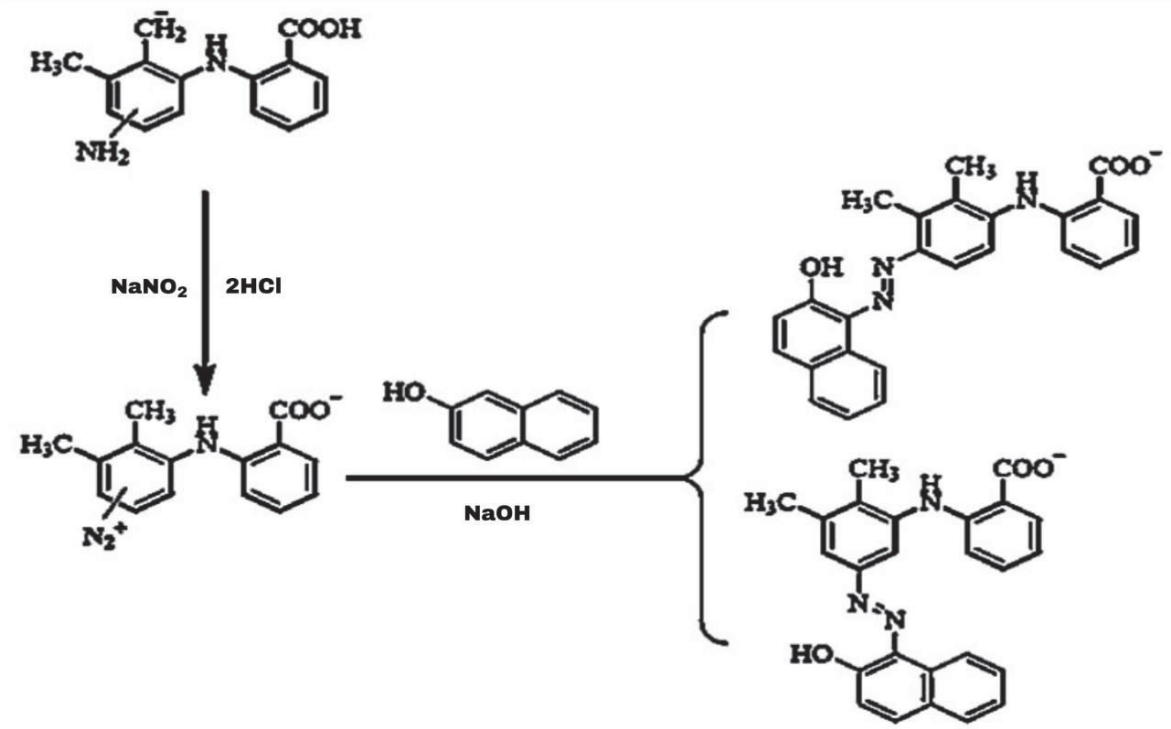
Equation 1.2: Reaction of Mefenamic acid derivative.

Aftan, M. M., et al (2021). The aim of this work synthesis of disperse dyes which can be used as dyes for polyester fabrics with orange and red color, these dyes were obtainedby preparing, (2-amino-4- hydroxy- thiazole), Where the diazotization and coupling process was performed to produced (compound III and IV), Which were introduced by another coupling with diazonium salt of compound I diazotization to synthesize disperse dyes (VII,VIII). The synthesized heterocyclic and synthesized dyes were studied by UV Spectroscopy, FT-IR, ^{1}H-NMR and ^{13}C-NMR. The antibacterial activities were studied against different kinds of bacteria, namely Eschershia coli and Klebsiella Pneumonia Gram (-) ve, Staphylococcus aureus and Staphylococcus epidermidis Gram (+) ve. In addition, evaluation of laser efficacy was showed for the compounds (I,III,IV,VII,VIII) were radiated by laser for (10, 20, 30) seconds, It was observed that the prepared compounds were not affected and did not polymerize or degradation when measuring melting point and color [18].



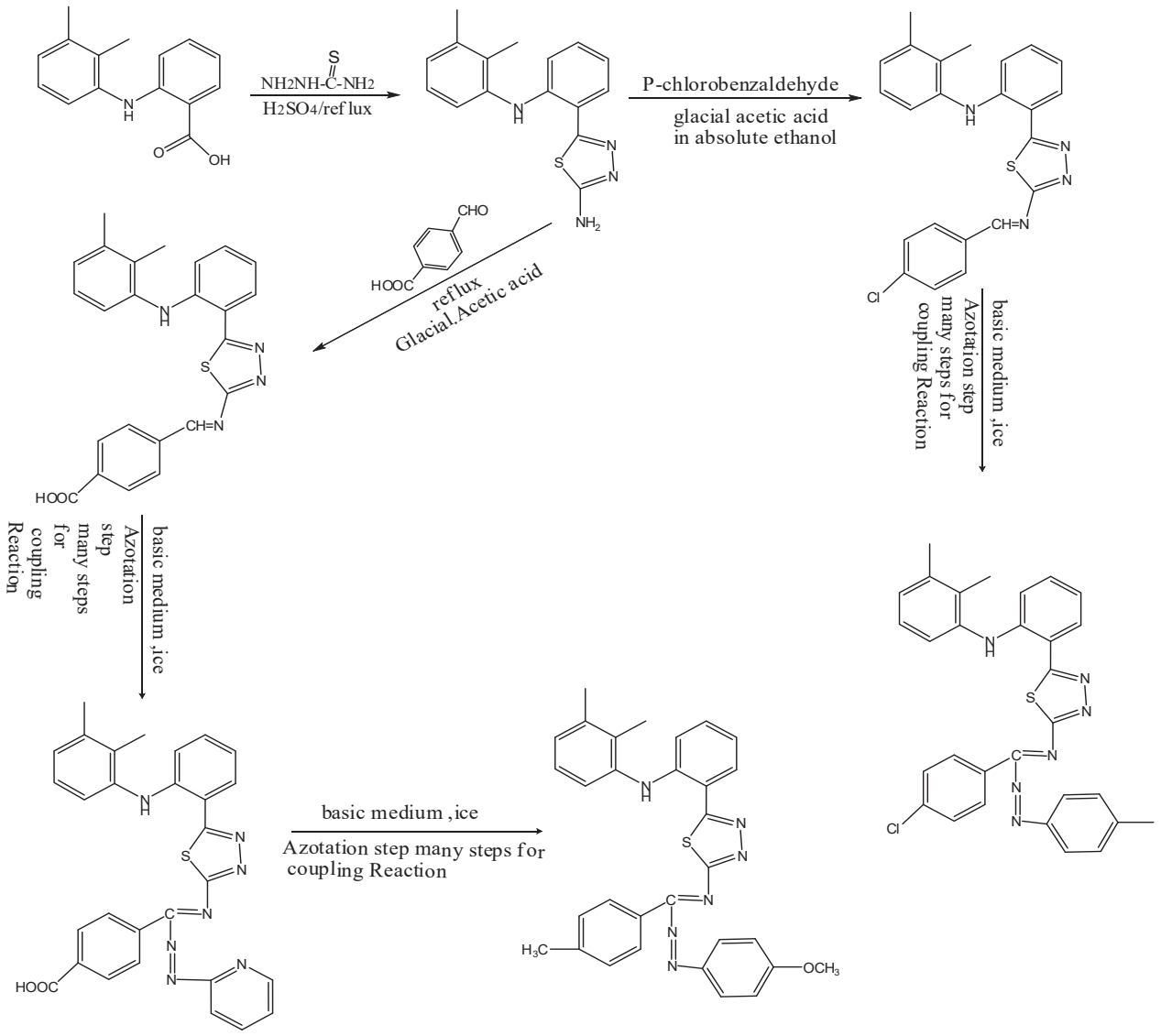
Scheme 1.4: Route of prepared compounds (I - VIII)

Amooshahi, Parvaneh, et al. (2022), were are using electrochemical reduction of produced nitromefenamic acids cyclic voltammetry and controlled-potential coulometry techniques. Eventually, two new azo derivatives have been generated via electroreduction of produced nitromefenamic acids and conduction of diazotization reaction, respectively. Both nitro and azo products are approved as paints [19].



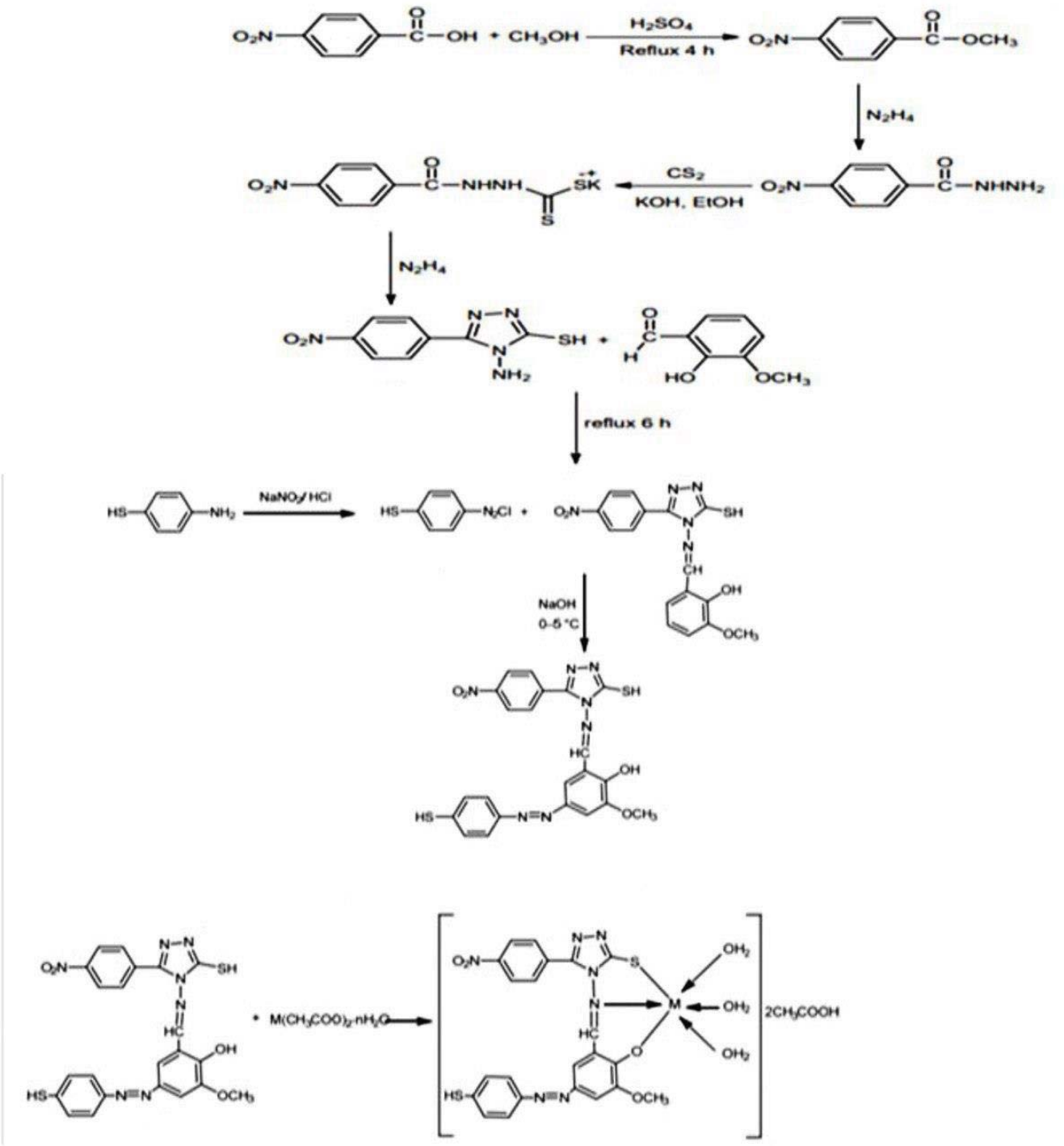
Scheme 1.5: Diazotization and azo coupling

Aljamali, D. et al. (2022), in this work Postane Fort was linked with formazan to increase its pharmacological effectiveness as an antifungal – microbial via various reactions like condensation of anil compounds ,then coupling steps with imine group in other donating compounds, then linking two active groups to formation new drugs represented by Mefenamic-Formazan or Postan-Formazan. Numerus of Postane Fort (drug) derivatives were prepared as a new organic compounds via several chemical reactions . All organic reactions and all formatted compounds had been monitored through (FT IR-Spectra , ^{1}H.NMR-Spectra, Mass-Spectra)., Melting points, other studies represented by (Thermal investigation, antifungal Evaluation)., all created ponstan derivatives appeared good antifungi activity because their strctures that involved formazan group (N=N-C=N-) linked with some heterocyclic ring like thiadiazole and other types of cycles [20].



Scheme 1.6: Preparation of Mefenamic acid derivatives.

Al-qasii, N. et al (2023), the study focused on producing and examining the properties of the 2-(((3-mercapto-5-(4-nitrophenyl)-4H-1,2,4-triazol-4-yl)imino)methyl)-4-(((4-mercaptophenyl) diazenyl)phenol) ligand (L) and its complexes with three transition metal ions, namely Ni(II), Co(II), and Cu(II). The ligand was formed through diazotization and coupling reactions between 4-aminobenzenethiol and a coupling Schiff base derived from 1,2,4-triazole. The characterization of the ligand and its metal ion complexes was carried out using analytical techniques such as FTIR, ^{1}H- and ^{13}C-NMR, UV-visible spectroscopy, and thermal analysis (TGA and DTG) [21].



Scheme 1.7: Novel Azo-Dye Schiff Base.

1.3 Aims of the study

1. Synthesized two organic compounds which is utilized for spectrophotometric determination Fe(III) ,Co (II), Ni(II) and Cd(II) as cations.

2. This Study involves limitation of optimum conditions for azo dye complex formation as, metal ions concentration, shaking time and stoichiometry.

3. Apply the developed method in this thesis in tap water, industrial wastewater, diyala river water and a sample of local juice .