Contents list available http://www.kinnaird.edu.pk/

Journal of Natural & Applied Sciences Pakistan

Journal homepage: http://journal.kinnaird.edu.pk

ROLE OF OXIDANTS IN THE OXIDATIVE COUPLING REACTIONS AND THEIR EXPLOITATION IN THE SPECTROPHOTOMETRIC DETERMINATION OF PHARMACEUTICAL PREPARATIONS

Mansour S. Abdul Galil[1, 2], Abdulqawi N.[1, 2], Samir Osman M.[*3, 4], Mohyeddine Al-qubati [4, 5], Ahmed A. Alsofi [2], Mufeed M. Omar[2]

[1]Chemistry Department, Faculty of Applied Sciences, Taiz University, Taiz, Yemen
[2]Faculty of Medical Sciences, AlJanad University for Science & Technology, Taiz, Yemen
[3*]Physics Department, Faculty of Science, Ibb University, Ibb, Yemen
[4]Engineering Faculty, AlJanad University for Science & Technology, Taiz, Yemen
[5]Physics Department, Faculty of Applied Sciences, Taiz University, Taiz, Yemen

Article Info

*Corresponding Author
Email Id: Samir.qa@just.edu.ye

Abstract

Oxidative coupling reactions are widely employed in chemical and pharmaceutical analyses due to their ability to form colored products through the interaction of oxidizable substrates with oxidizing agents. This work aims to survey the literature on the application of various oxidizing agents in these reactions for colorimetric analysis, focusing on studies published since 2008. Peer-reviewed articles were selected from major chemical databases. The review highlights recent trends in the selection and effectiveness of oxidants used for the qualitative and quantitative determination of pharmaceutical compounds and oxidative elements. Findings indicate growing research interest in this area, with several oxidants demonstrating high sensitivity and selectivity in routine pharmaceutical analysis. This review highlights the significance of oxidative coupling in streamlining analytical procedures and enhancing the efficiency of drug testing methods.

Keywords

Oxidative coupling; pharmaceutical; chemical analyses; spectrophotometry; chromatography

1. Introduction

Due to the medicinal importance of the drug, several methods have been reported for its determination in various matrices, including spectrophotometry, high-performance liquid chromatography (HPLC), flow injection analysis, electroanalytical methods, capillary electrophoresis, voltammetry, and chemiluminescence. However, these methods often require complex and expensive equipment, hazardous solvents, tedious sample preparation procedures, and advanced instrumental expertise (Sujatha, Swami and Venkateshwarlu, 2016; Afify, Abdelsalam and Hadad, 2018; Manasa *et al.*, 2018; Marcel *et al.*, 2018; Battu, Gandu and Nenavathu, 2020; Serra, 2021; Ibrahem and Rashid, 2022; Onikienko *et al.*, 2022). Spectrophotometry remains a more accessible method due to its simplicity, low cost, and availability in basic laboratories. However, it has limitations, such as a narrow linearity range, the need for heating or extraction, and sometimes the low stability of the colored products formed. Oxidative coupling reactions have gained attention for their utility in determining pharmaceutical compounds and oxidizable metals. Literature reports describe them as simple, green, rapid, and highly sensitive under optimal conditions. The mechanism involves oxidation of a chromogenic ligand to an electrophilic intermediate, which then couples with the analyte to form a measurable colored product. This reaction may occur in acidic or alkaline media and sometimes requires hydrolysis steps, as shown in Figure 1 (M. J. Ahmed and H. H. Abdullah, 2018).

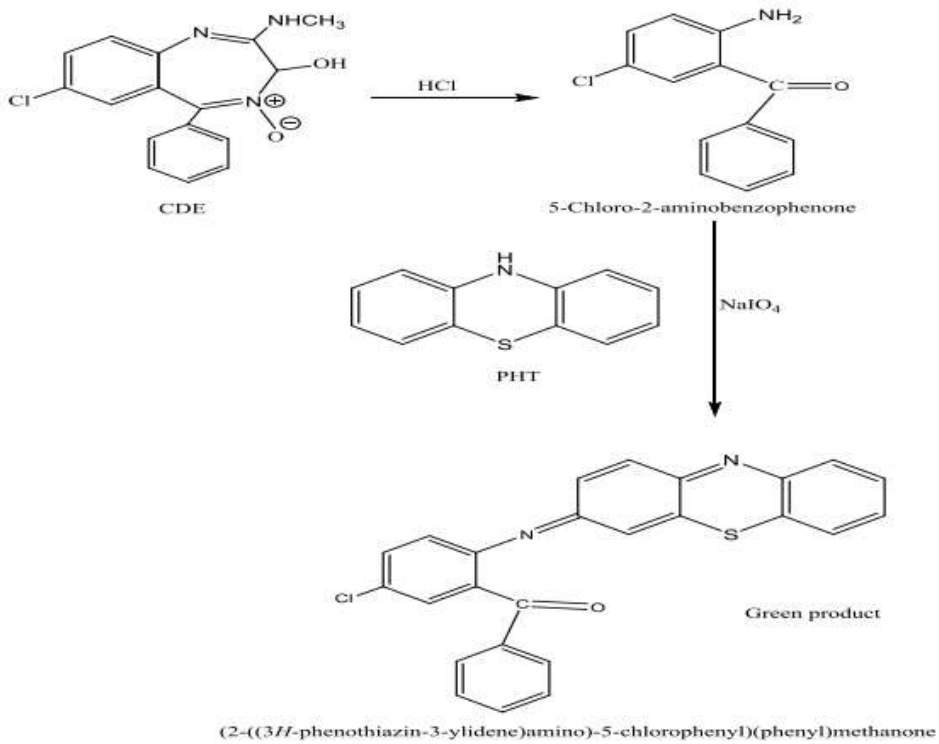


Figure: 1 Example(M. J. Ahmed and H. H. Abdullah, 2018)

To the best of our knowledge, no comprehensive review has been published since 2008 focusing on the role of oxidizing agents in oxidative coupling reactions within spectrophotometric analysis of

pharmaceuticals. Therefore, this review aims to address this gap by exploring the types, functions, and applications of oxidants in such reactions. These approaches offer fast, efficient, and environmentally friendly alternatives for drug analysis, particularly important in today's evolving scientific and regulatory landscape.

2. Review Methodology

2.1. Inclusion Criteria

Studies were included in this review if they met the following criteria:

- Study Design: Experimental studies, observational studies, and systematic reviews involving oxidative coupling reactions in pharmaceutical analyses.
- Pharmaceutical Focus: Research involving pharmaceutical preparations analyzed using spectrophotometric methods or oxidative coupling reactions.
- Oxidizing Agents: Studies that examined oxidants such as ferric chloride, potassium periodate, and ammonium ceric sulfate in analytical procedures.
- Time Frame: Publications from 2008 to 2025.
- Language: Articles published in English or Arabic.
- Accessibility: Only studies with full-text availability were considered to ensure comprehensive evaluation.

2.2. Exclusion Criteria

The following types of studies were excluded:

- Irrelevant Scope: Studies not specifically addressing oxidative coupling reactions or spectrophotometric pharmaceutical analysis.
- Narrative Reviews: General review articles lacking original data or analysis.
- Animal Studies: Studies involving animal models unless directly relevant to pharmaceutical assay techniques.
- Obsolete Techniques: Research using outdated oxidizing agents or non-current methodologies.

2.3. Databases and Sources

The literature search was conducted using the following databases:

- PubMed: Articles focused on pharmaceutical analysis and oxidative reactions.
- Scopus: Systematic reviews and experimental studies in chemical and pharmaceutical sciences.
- ScienceDirect: Research on spectrophotometric techniques and drug analysis.
- Google Scholar: Additional resources from broader and non-traditional academic outlets.

2.4. Searching Keywords:

Oxidative Coupling Reactions, Spectrophotometric Pharmaceutical Analysis, Oxidizing Agents in Pharmaceutical Analysis, Pharmaceutical Preparations Determination, Ferric Chloride in Pharmaceutical Analysis, Chromogenic Compounds in Pharmaceutical Tests, Oxidative Reactions in Drug Determination, MBTH Coupling Reagents, Sodium Periodate in Pharmaceutical Assays, Green Analytical Methods in Pharmaceutical Testing.

2.5. Search Strategy

2.5.1. Boolean Operators

- AND was used to combine key concepts (e.g., *"Oxidative Coupling Reactions" AND "Pharmaceutical Preparations" AND "Spectrophotometric"*).
- OR was used to expand the search with synonyms (e.g., *"Ferric Chloride" OR*

"Potassium Ferricyanide" OR "Ammonium Ceric Sulfate").

- NOT was applied to exclude unrelated studies (e.g., *"Spectrophotometric" NOT "Animal Studies"*).

2.5.2. Search Phrases

The search included phrases such as:

- "Oxidative Coupling Reactions in Pharmaceutical Determination"
- "Spectrophotometric determination of drugs using oxidative agents"
- "Role of oxidants in pharmaceutical analysis"
- "Oxidizing agents in spectrophotometric methods"
- "Oxidative coupling reaction for drug analysis"

2.5.3. Filters

The following filters were applied during the database searches:

- Publication Years: 2008–2025
- Article Types: Research articles and systematic reviews
- Language: English and Arabic

3. Applications

There are many pharmaceuticals that were quantified spectrophotometrically, and some of them can be listed as follows:

3.1. Pharmaceuticals Determined by Oxidative Coupling Reagents:

Oxidative coupling reactions have proven to be highly effective in the spectrophotometric determination of a broad range of pharmaceuticals across various therapeutic categories. Antibiotics such as tetracycline, procaine penicillin, nitrofurantoin, sulfamerazine, and sulfamethoxazole (SMX), which are widely used to treat bacterial infections including urinary tract infections, have been quantified using this approach (Hadi, 2008; Al-Kalissy and Mohammed, 2017; Hadi and Mouayed, 2017; AL-Okab, Mansour and Ahmed, 2018; Humeidy, 2019). Antiviral drugs, particularly Tenofovir disoproxil fumarate, essential in HIV therapy, have also been effectively analyzed using oxidative coupling (Varsha *et al.*, 2015). This method extends to cardiovascular and respiratory therapeutics as well. Tadalafil, prescribed for erectile dysfunction and pulmonary hypertension, and methyldopa, an antihypertensive catecholamine derivative, have both been successfully assessed via oxidative pathways (Pani Kumar *et al.*, 2013; Ghaib Allah, Ahmed and Tapabashi, 2022; Shakkor, Mohammed and Shakor, 2022; Shehab and Mohammed, 2022). Bronchodilators such as salbutamol sulfate and nasal decongestants like phenylephrine hydrochloride (PEH) have also been evaluated spectrophotometrically (Abdoon and Yahyaa, 2020; Ahmed, Anwar and Hattab, 2020). Oxidative coupling techniques have been utilized in the quantification of drugs for chronic conditions and systemic diseases. These include mesalazine, used for inflammatory bowel disease; saxagliptin (Onglyza), an antidiabetic agent; and mefenamic acid, indicated for musculoskeletal pain and inflammation (Al Abachi and Hadi, 2014; Gurrala *et al.*, 2022; Shehab and Mohammed, 2022). Likewise, antiepileptics such as carbamazepine, psychiatric drugs like chlorpromazine and chlordiazepoxide, and anti-anxiety agents from the benzodiazepine class have been determined using oxidative coupling methodologies (Fadhel, Abdulla and Sulaiman, 2016; T Humeidy, 2016; M. J. Ahmed and H. H. Abdullah, 2018). The method also encompasses

antiparasitic, antiviral, and gastrointestinal medications. Mebendazole, an effective broad-spectrum anthelmintic; loperamide hydrochloride, used as an antidiarrheal; and lamivudine, which targets both HIV and hepatitis B, have all been accurately analyzed using this technique (Rahul, Gurupadayya and Anil, 2011; Babu *et al.*, 2012; Shehab, Mohammed and Mahmood, 2021; Al-Shaker, Mohammed and Abdalkader, 2022). Additional applications include antipyretics like naproxen, NSAIDs such as tenoxicam and meloxicam, and oxyphedrine, a vasodilator used to manage coronary artery conditions (J. Mythri, B.S.Anusha, 2014; Mallikarjuna Rao and Gowrisankar, 2016; Hasan and Bakir, 2021). Furthermore, oxidative coupling has been instrumental in the analysis of compounds like raloxifene hydrochloride (RLX), used in osteoporosis and breast cancer prevention in postmenopausal women, and metadoxine, a hepatoprotective agent effective in early-stage liver disease (Kalyanaramu and Raghubabu, 2011; Unnisa *et al.*, 2011). Antihistamines such as loratadine, indicated for allergic rhinitis and urticaria, also fall within the range of compounds studied using this approach (Sujatha, Balmuralikrishna and Ramesh Raju, 2014). The oxidative coupling method offers significant advantages that make it highly attractive for pharmaceutical analysis. It is notably sensitive, allowing for the detection of minute drug concentrations an essential feature for quality control and pharmacokinetic studies (M. J. Ahmed and H. H. Abdullah, 2018). The methodology is also straightforward, minimizing the need for elaborate sample preparation, and is highly adaptable in basic laboratory settings (M. J. Ahmed and H. H. Abdullah, 2018). Its cost-effectiveness further adds to its appeal, especially in comparison to high-end techniques like HPLC. Rapid execution and environmentally benign conditions make it an exemplary tool in green analytical chemistry. Nevertheless, the technique is not without limitations. Instability of the colored reaction products can impair measurement accuracy, and complex sample matrices may introduce interfering substances that compromise selectivity (Qi *et al.*, 2020; Zhang *et al.*, 2020). Furthermore, the typically narrow linearity range restricts its applicability for samples with higher analyte concentrations (M. J. Ahmed and H. H. Abdullah, 2018). To ensure analytical reliability, these challenges necessitate meticulous optimization of reaction conditions and appropriate method validation.

3.2. Oxidizing Agents in Oxidative Coupling Reactions

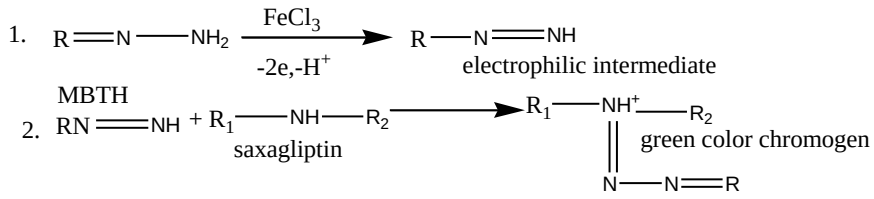
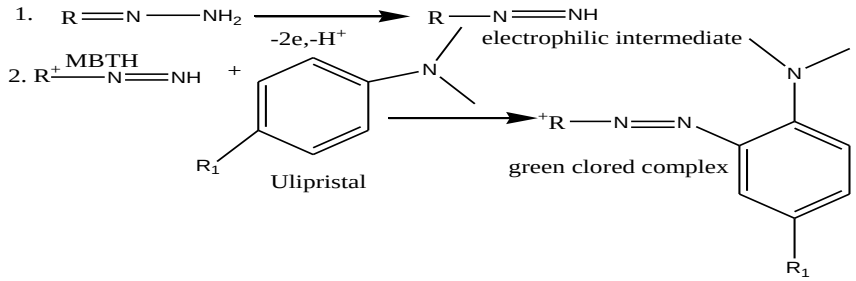
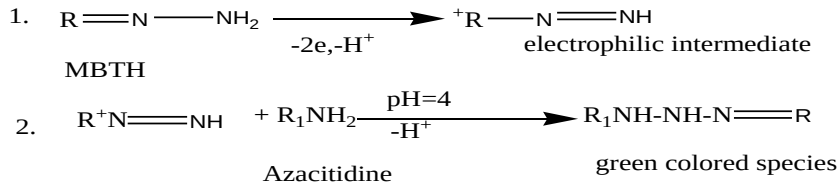
Oxidizing agents play a pivotal role in oxidative coupling reactions, acting as initiators that convert chromogenic reagents into reactive intermediates capable of forming colored complexes with target pharmaceutical compounds. Their selection has a critical influence on the sensitivity, specificity, and applicability of spectrophotometric methods. The most prominent and effective oxidants employed in this analytical context are discussed below.

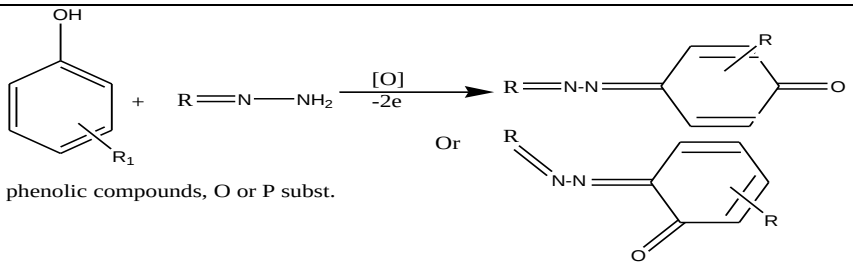
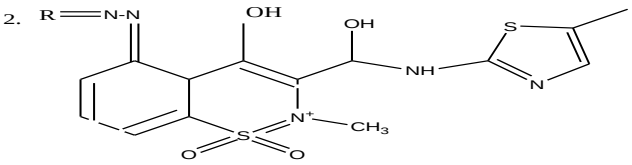
3.2.1. Ferric Chloride and Related Iron-Based Oxidants

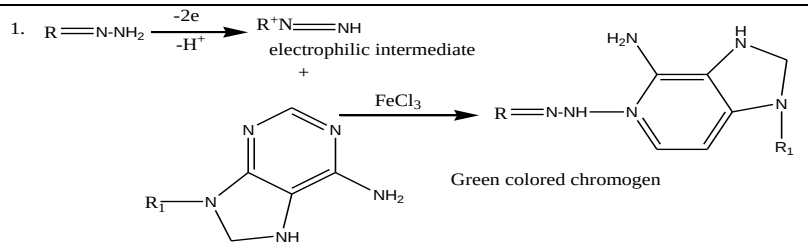
Ferric chloride has demonstrated exceptional oxidative strength, particularly in combination with coupling agents like MBTH (3-methylbenzothiazolinone hydrazone), facilitating the accurate spectrophotometric analysis of various pharmaceuticals. Its versatility is highlighted

through its pairing with different ligands, including MPDA and 4AP, which broaden its applicability across numerous drug classes. Additionally, ferric ion in the form of sulfate has been employed in the oxidation of paracetamol, enabling further reaction with nitroso-R-salt for quantitative analysis. The mechanisms and compound-specific details are provided in Tables 1–3.

Table 1: Role of an oxidant (ferric chloride) in coupling agent, MBTH, reactions.

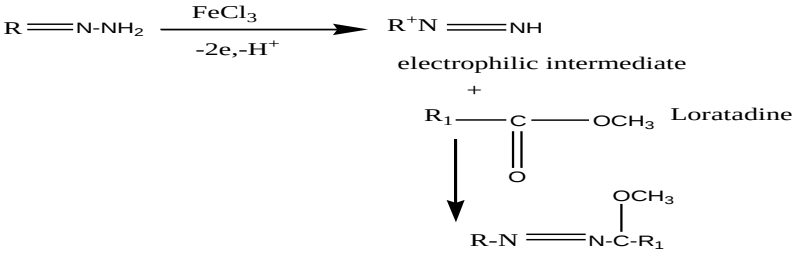
No	Drug	Concentration range µg/mL	Mechanism	pH	Ref.
1					
	Saxagliptin in pharmaceutical formulation	0.01-0.25			(Gurrala *et al.*, 2022)
2					
	Ulipristal acetate present in bulk and Tablet formulation	6.25 – 37.50			(Gorumutchu and , Venkata Nadh Ratnakaram, 2019)
3					
	Azacitidine in pharmaceutical formulations and blood	10 - 35		Acidic	(Ramachandra and Naidu, 2018)

4	 phenolic compounds, O or P subst. 1. $R{=}N{-}NH_2 \xrightarrow[-2e,-H^+]{2Fe(III)} {}^{+}R{-}N{=}NH + 2Fe(II)$ MBTH electrophilic intermediate	Total phenolic compounds in beverage samples	Acidic	(da Silva Granja *et al.*, 2018)
5	1. $R{=}N{-}NH_2 \xrightarrow[-2e,-H^+]{+\ FeCl_3} R{=}N^{-}NH^{+}$ MBTH electrophilic intermediate 2. $R{=}N^{-}NH^{+} + R_1\text{-}NH_2 \xrightarrow[-H^+]{pH\ 4.5} R{=}NH\text{-}NH{-}R_1$ reduced Azathioprine Green colored species	Azathioprine	Not reported	(Ramachandra and Naidu, 2017)
6	1. $R{=}N{-}NH_2 \xrightarrow[-2e,-H^+]{Fe(III)} R{=}N^{-}NH^{+}$ MBTH electrophilic intermediate 2. 	meloxicam (MLX) (A) and tenoxicam (TNX) (B)	Not reported	(Mallikarjuna *et al.*, 2016)
7	1. $R{=}N{-}NH_2 \xrightarrow[-2e,-H^+]{Fe(III)} R{=}N^{-}NH^{+}$ MBTH electrophilic intermediate + 2. R_1NH_2 Gemcitabine HCl $R\text{-}N{=}N\text{-}NH\text{-}R_1$ bluish -green colored complex	Gemcitabine HCl	Not reported	- (Reddy and Firadous, 2015)
8				



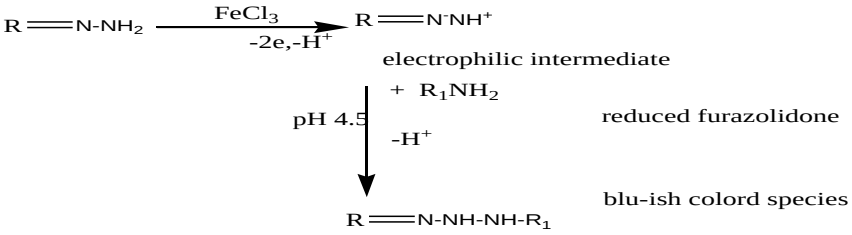
	Tenofovir disoproxil fumarate	50 – 250	-	(Varsha *et al.*, 2015)

9



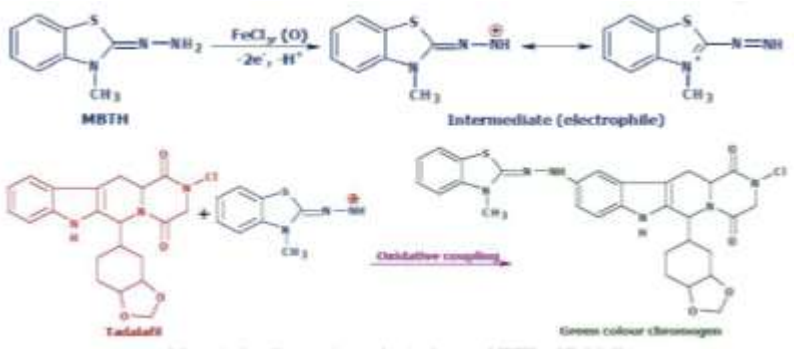
	Loratadine		-	(Sujatha, Balmuralikrishna and Ramesh Raju, 2014)

10

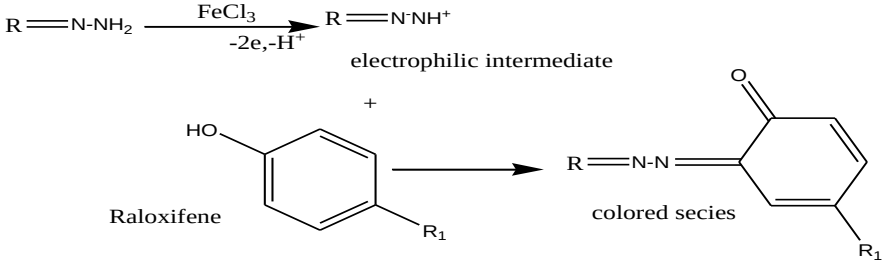
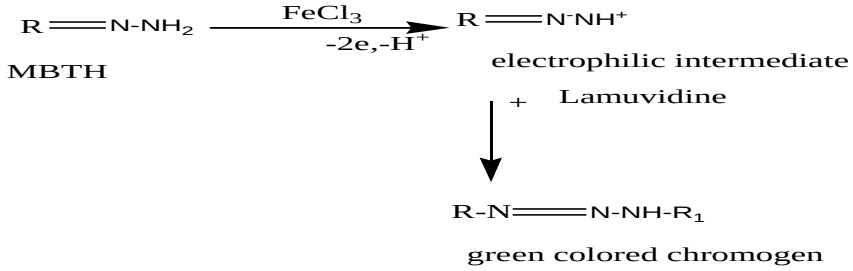
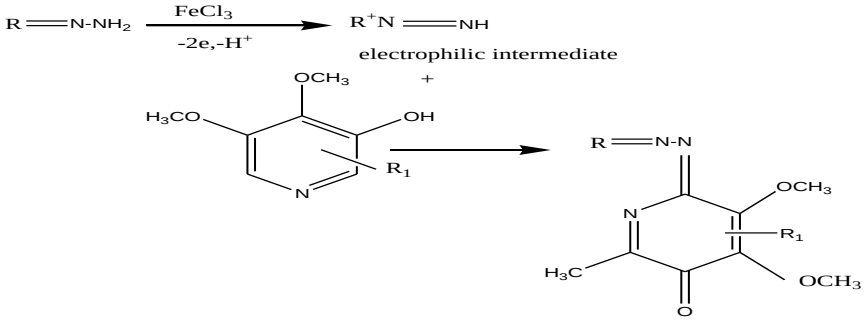


	Synthetic antimicrobial furazolidone	10-60 and 5-30 for blood sample	Acidic	(Ramachandra and Naidu, 2017)

11



	Tadalafil	2.12	-	(Anumolu *et al.*, 2013)

12		Raloxifene			(Kalyanaramu and Raghubabu, 2011)
13		Lamuvidine (LMV)	1-8		(Reddy, Gurupadaya and Kumar, 2011)
15		Metadoxine (MTD), 5-oxo-L-proline compound	2-10	-	(Unnisa *et al.*, 2011)

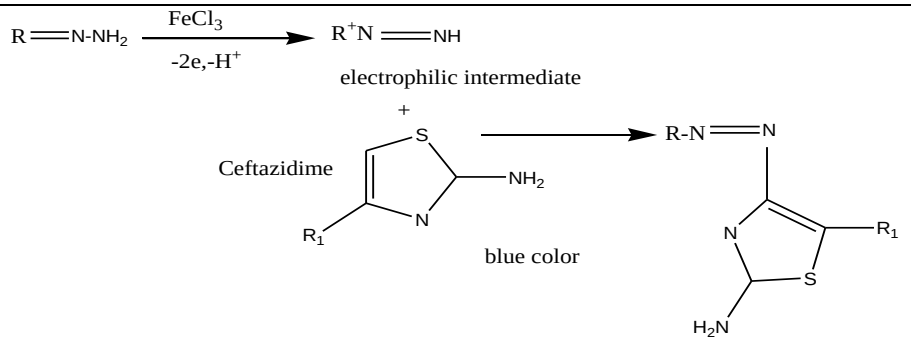
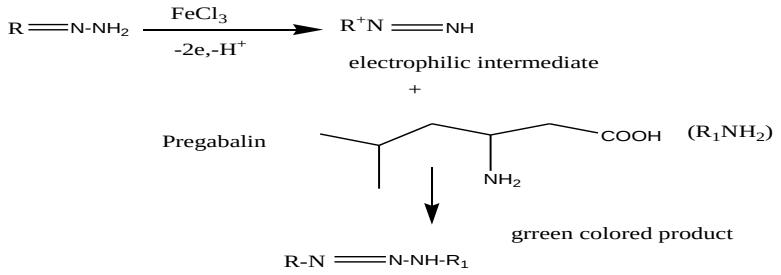
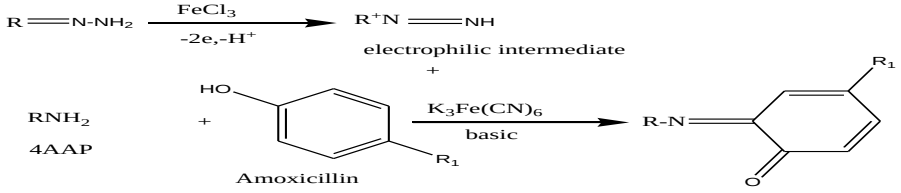
16					
	Ceftazidime (CFZM)	0.2–1.0		Acidic	(Hiremath, 2008)
17					
	,Pregabalin (PGB)	50-350			(Sowjanya *et al.*, 2011)
18	Bromhexine hydrochloride	5-25	Not found	acidic	(Raja *et al.*, 2010)

Table 2: Role of an oxidant (potassium or sodium ferricyanide) in oxidative coupling reactions.

No	Drug	Concentration range	Mechanism	pH	Ref.
1					
	Amoxicillin	5-100 µg/L		Basic	(Aljeboree and Alshirifi, 2019)

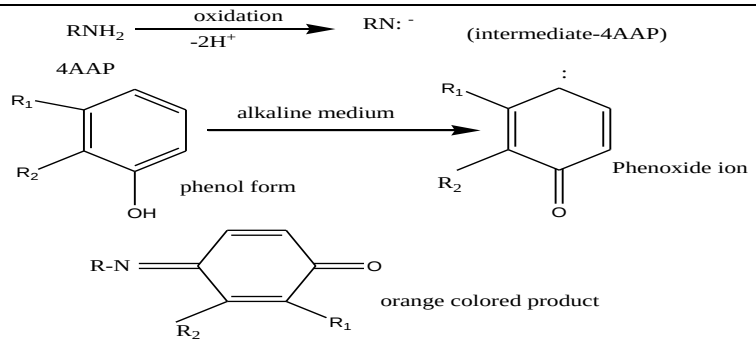
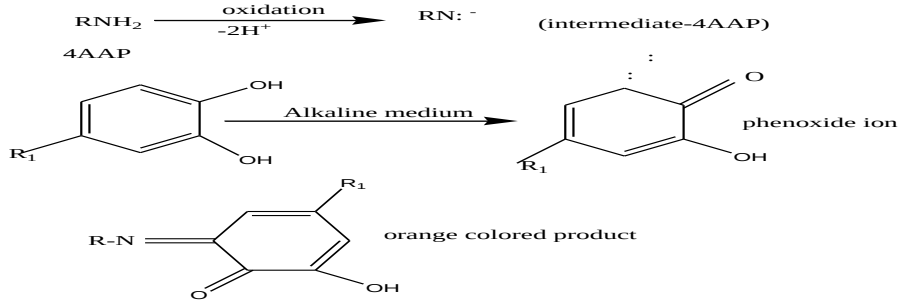
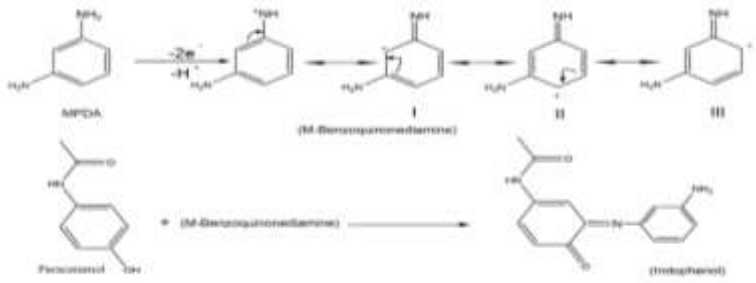
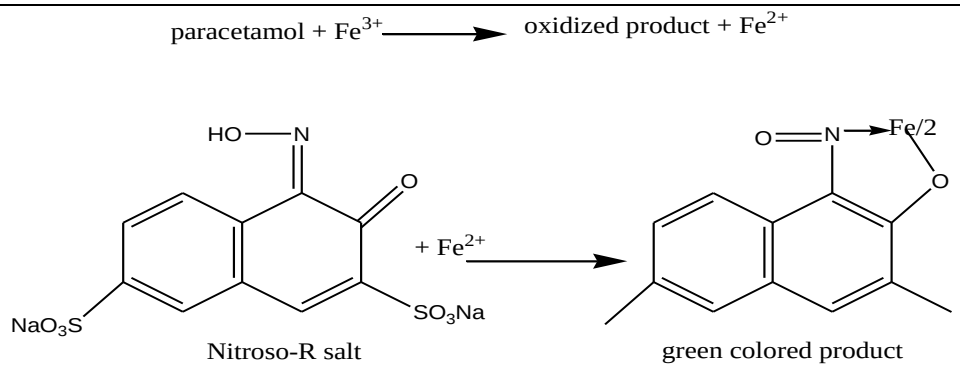
2					
	Tetracycline and Doxycycline	1-18 and 15-70		Basic	(Al-Kalissy and Mohammed, 2017)
3					
	Methyldopa	1-60		basic	(Al-Kalissy and Mohammed, 2014)

Table 3: Role of the oxidants, ferric chloride and ferric sulfate, in the reactions.

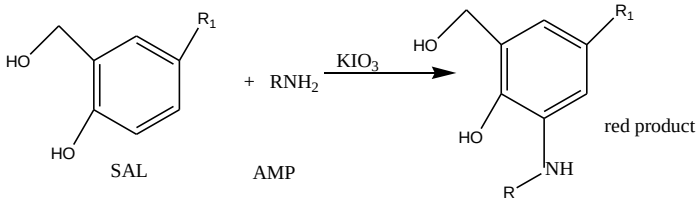
No	Drug	Concentration range	Mechanism	pH	Ref.
1					
	Paracetemol	0.189-3.78		basic	(Altahir and Shakir, 2023)

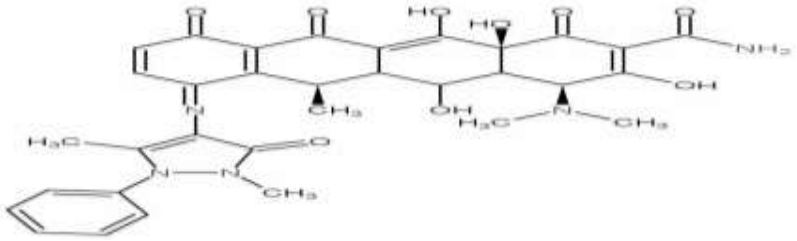
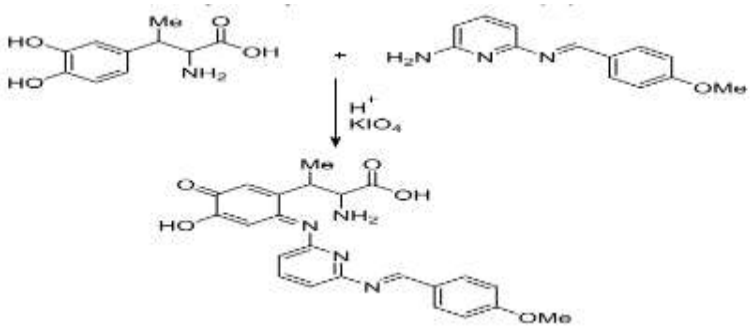
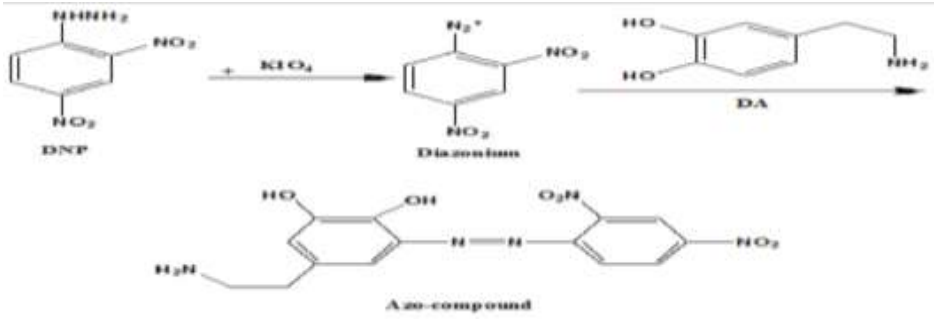
2					
	Paracetamol	0.1 – 2.0		-	(Sinan and SS, 2009)

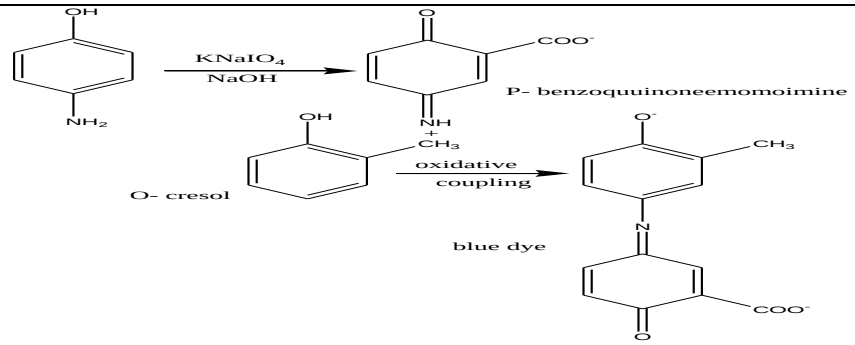
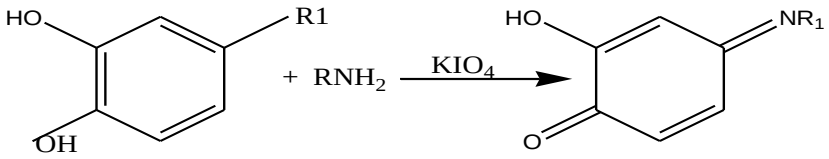
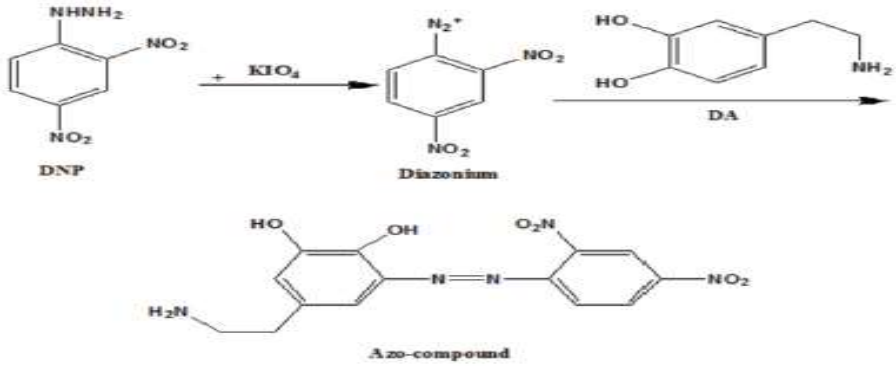
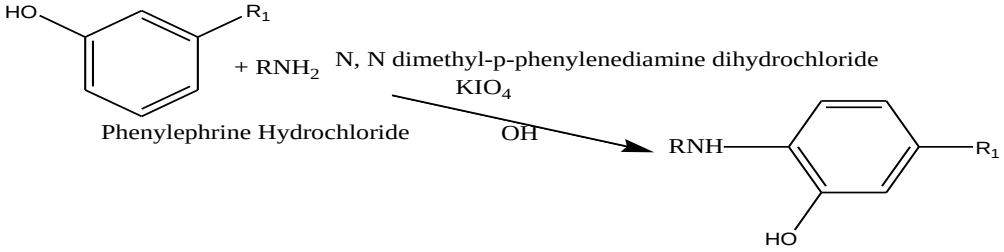
3.2.2. Periodate and Iodate Compounds

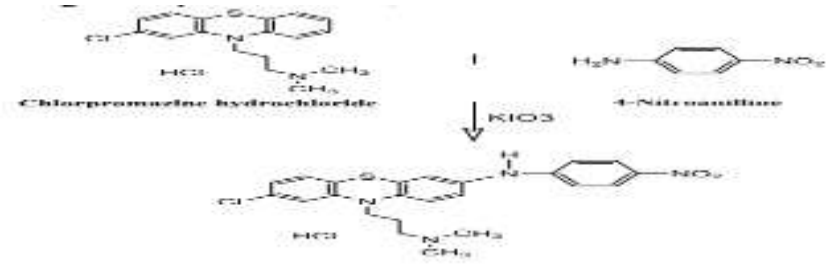
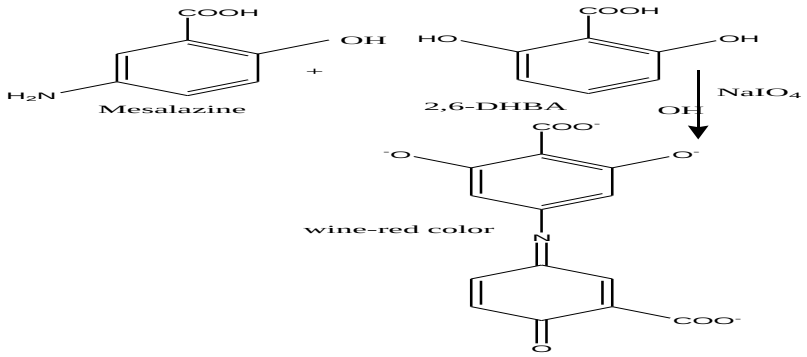
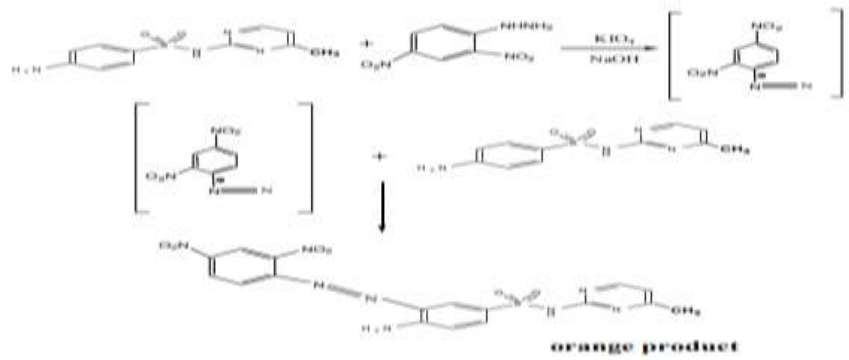
Sodium periodate, potassium periodate, and potassium iodate are among the most powerful and widely adopted oxidizing agents in oxidative coupling chemistry. Their high redox potential makes them ideal for activating a range of chromogenic reagents. These agents have been used effectively with coupling partners such as N,N-dimethyl-p-phenylenediamine dihydrochloride, MBTH, 2,6-diaminopyridine, and 2,4-dinitrophenylhydrazine (DNP) to determine numerous drug compounds with high sensitivity. The corresponding applications are compiled in Table 4.

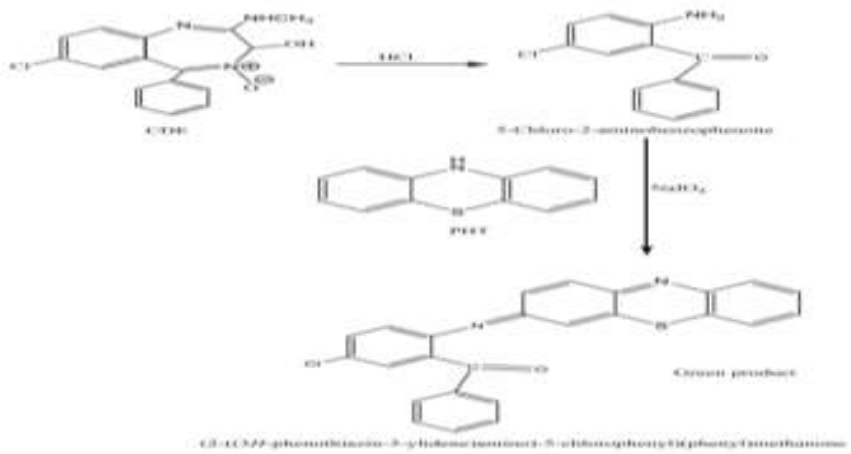
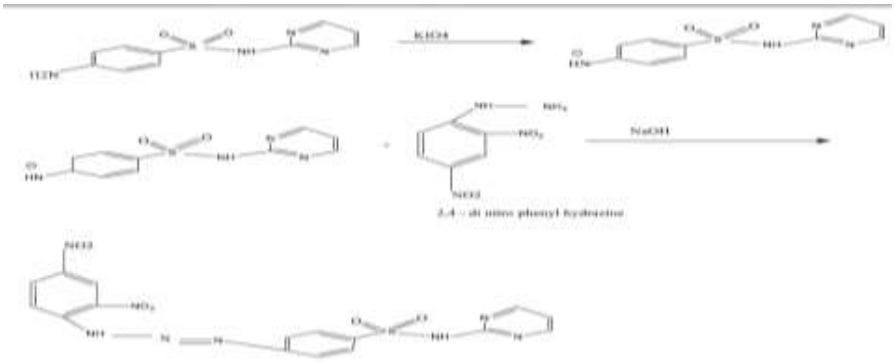
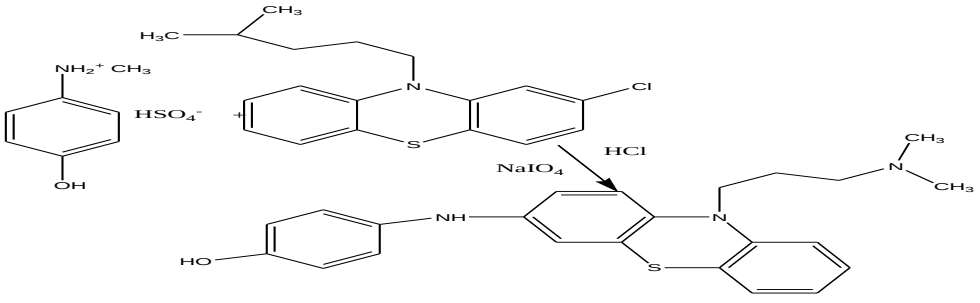
Table 4: Role of oxidants (sodium and potassium periodate or potassium iodate) in the oxidative coupling reactions.

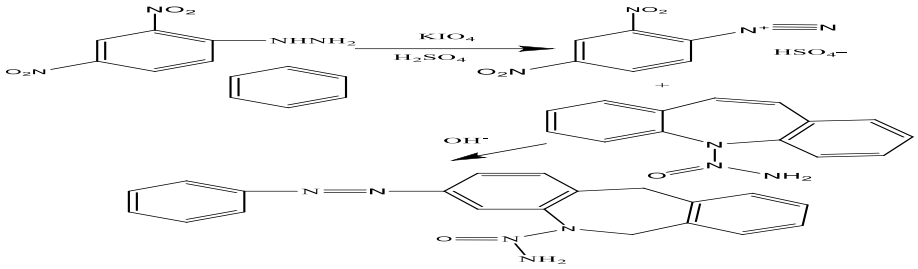
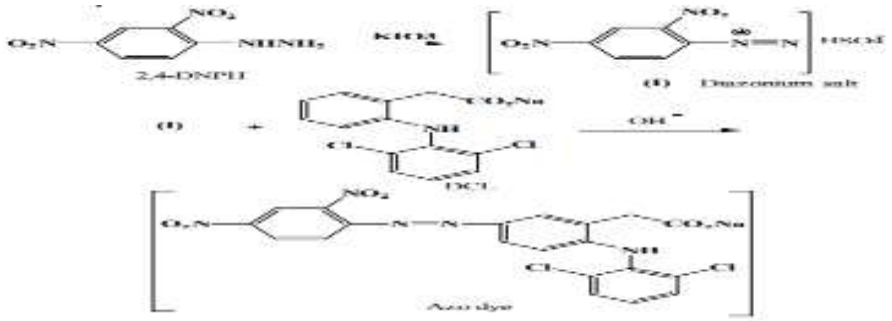
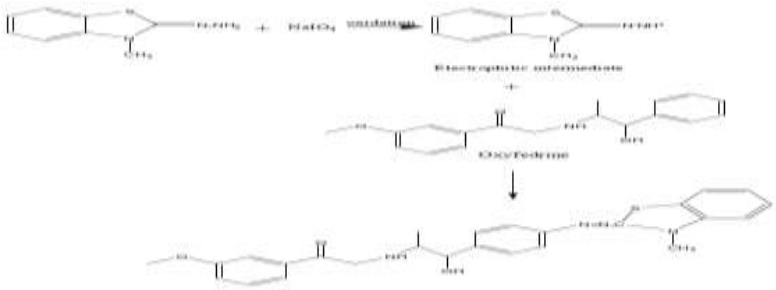
No	Drug	Concentration range, µg/mL	Mechanism	pH	Ref.
1					
	Salbutamol sulfate (SAL)	2–32		-	(Abdoon and Yahyaa, 2020)
2	Salbutamol sulphate (SBS)	0.2-16	Not found	basic	(Al-Safar and Al-Enizzi, 2022)

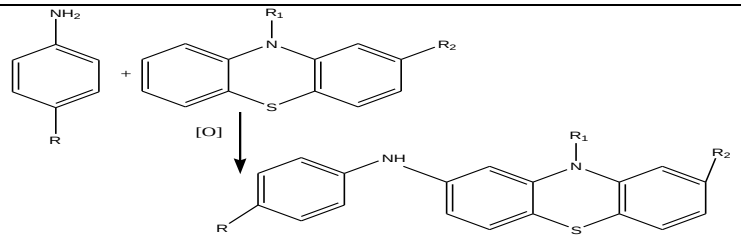
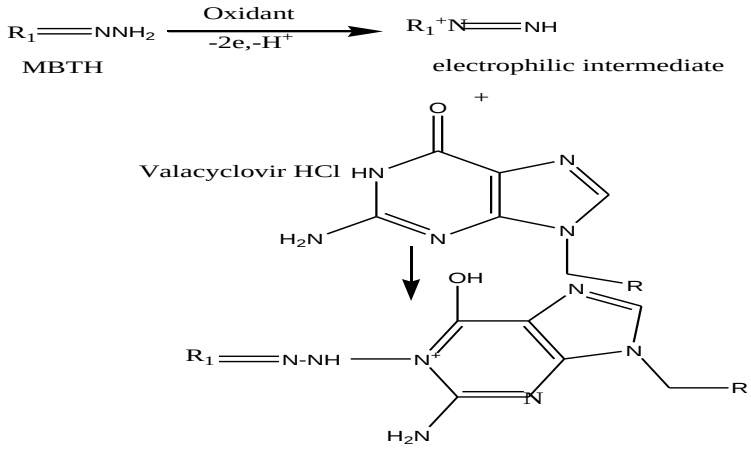
3					
	Doxycycline	5 - 110		basic	(Khalaf and Othman, 2022)
4					
	Methyldopa (MDP	5.0- 40			(Shakkor, Mohammed and Shakor, 2022)
5	Carvedilol	5-35	Not found	Buffer sol.	(Abduljabbar and Ali, 2022)
6					
	Dopamine,	5 - 50		basic	(Ramadan, Almasri and Khayal, 2020)

7					
	Mesalazine	0.4 – 12		basic	(Salih, 2020)
8	Azithromycin (AZT)	3- 44	Not reported	acidic	(Hussein, Abdulrahman and Raheem, 2020)
9					
	Methyldopa (MDP)	2 - 24		-	(Humeidy, Salman and Hashim, 2020).
10					
	Dopamine (DA),	5 - 50		basic	(Ramadan, Almasri and Khayal, 2020)
11					
	Phenylephrine	4 - 22		basic	(Ahmed,

					Anwar and Hattab, 2020)
12					
	Chlorpromazine hydrochloride (CPZ)	5–40		acidic	(Al-rashidy and Shareef, 2019)
13					
	Mesalazine	0.5-12.5		Basic	(Aziz and Sultan, 2019)
14					
	Sulfamerazine (SMZ)	2.5-55		basic	(Humeidy, 2019)

15					
	Chlordiazepoxide (CDE)	0.1−50		-	(M. J. Ahmed and H. H. Abdullah, 2018)
16					
	Sulphadiazine veterinary	3-15		basic	(Ahmed and Khaleel, 2018)
17					
	Chlorpromazine hydrochloride	1-20		acidic	(Khanfous, Nasser and AL-Rufaie, 2017)
18	Doxycycline h (DCH)	3 –72	Not found	basic	(Awad and Taki, 2021)

19					
	Carbamazepine (CRN)	4-50		basic	(Fadhel, Abdulla and Sulaiman, 2017)
20					
	Diclofenac sodium (DCL),	0.5-40		basic	(Dikran and Mahmood, 2017)
21					
	Oxyfedrine	6 -1		-	(J. Mythri, B.S.Anusha, 2014)
22	Methyldopa in pharmaceutical preparations	0.1–10	Not found		(AL-Da'amy and AL-Moswi, 2014)

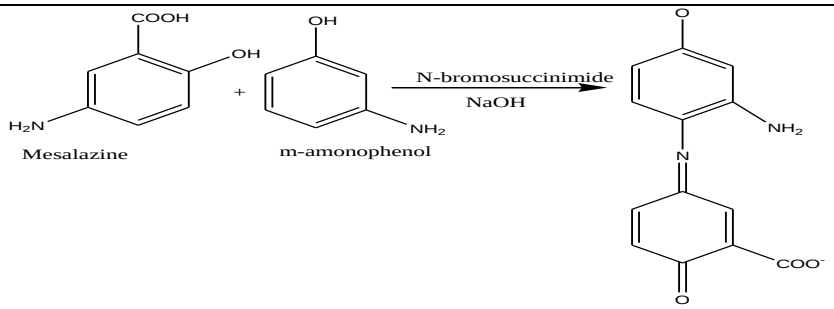
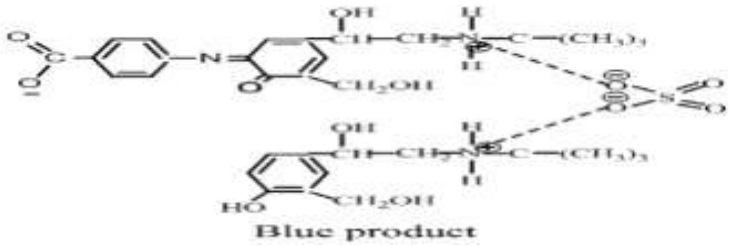
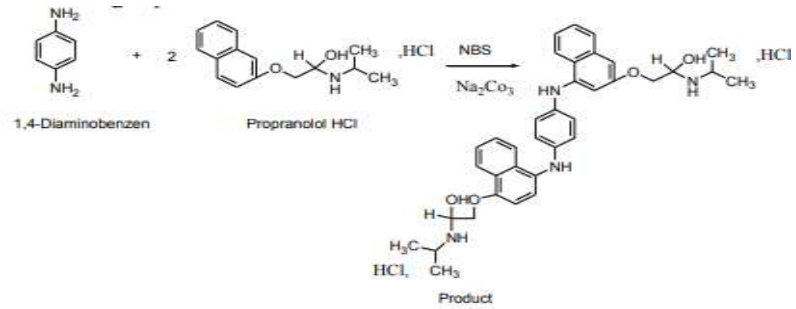
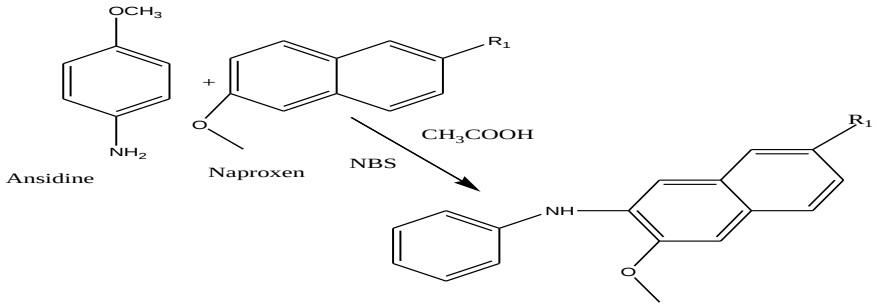
23					
	Chlorpromazine hydrochloride	0.5 – 11.2		acidic	(Al-Rufaie, 2013)
24					
	Val acyclovir HCl	2-10		-	(Siva Ramakrishna *et al.*, 2012)

3.2.3. N-Bromosuccinimide and N-Chlorosuccinimide

Both N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) have proven to be highly effective halogen-based oxidants in oxidative coupling reactions. These agents facilitate the detection of various pharmaceuticals by enabling coupling with agents such as 1,4-diaminobenzene, m-aminophenol, p-aminobenzoic acid (PABA), and aniline derivatives like ansidine and CB. Their successful implementation in spectrophotometric protocols is summarized in Table 5.

Table 5: Role of oxidants (N-bromosuccinimide and N-chlorosuccinimide) in the oxidative coupling reactions.

No	Drug	Concentration range	Mechanism	pH	Ref.
1	CTZ solution (A) and CTZ solution (B)	Not reported	Not reported	Acidic	(Hasan and Bakir, 2021)

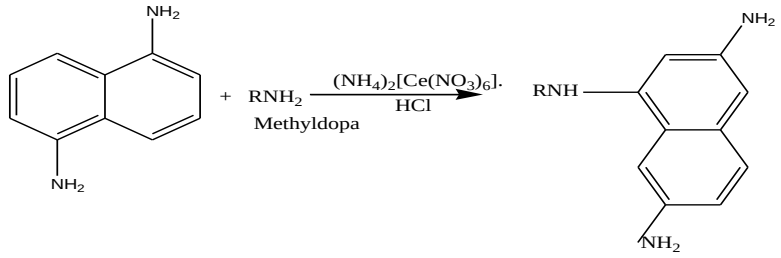
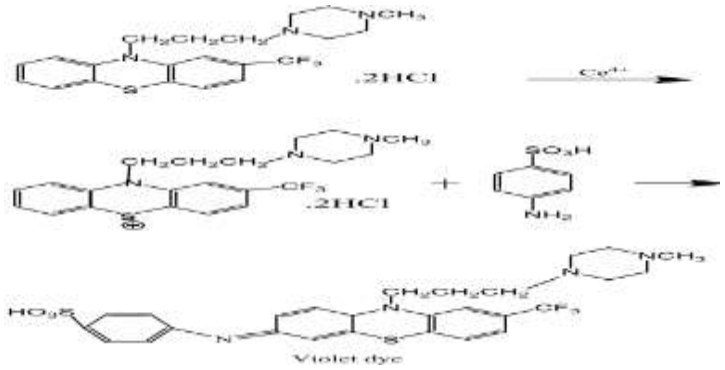
2					
	Mesalazine	1.25-30		basic	(Aziz and Sultan, 2019)
3					
	Salbutamol Sulphate	0.2- 0.02		basic	(Othman, 2021)
4					
	Mesalazine	2.5-0.75		Basic	(Mohammed, Ibrahim and AL-Niaimi, 2018)
5					

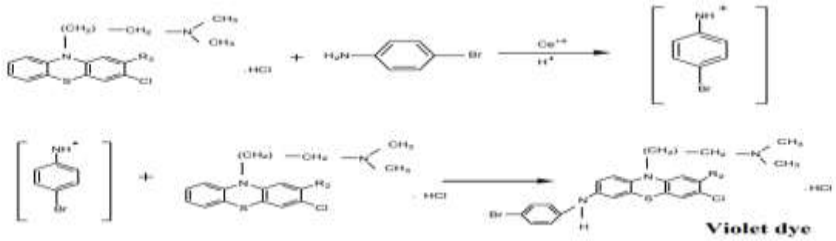
	Naproxen	1-28 mg/mL	acidic	(Nasser, Atiya and Baker, 2017)

3.2.4. Ammonium Ceric Sulfate

Ammonium ceric sulfate is one of the most reliable and stable oxidants used in analytical chemistry. Its consistent oxidative power has been utilized to develop robust spectrophotometric methods involving a wide array of coupling agents, including sulphanilic acid, p-bromoaniline, 5-diaminonaphthalene, MBTH, and p-nitroaniline. These combinations have enabled precise quantification of diverse pharmaceuticals, as detailed in Table 6.

Table 6: Role of oxidant (Ammonium ceric sulfate) in the oxidative coupling reactions.

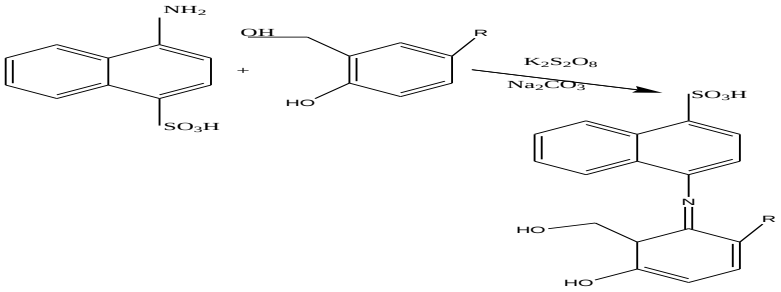
No	Drug	Concentration range, µg/mL	Mechanism	pH	Ref.
1					
	Methyldopa	5.4 - 39.6		acidic	(Ghaib Allah, Ahmed and Tapabashi, 2022)
2	Chlorpromazine Hydrochloride	12 - 46		acidic	(Anwar, 2018)
3					
	Trifluoperazine hydrochloride (TFPH)	0.5 – 20		-	(Abdurahman and Mahmoud, 2016)

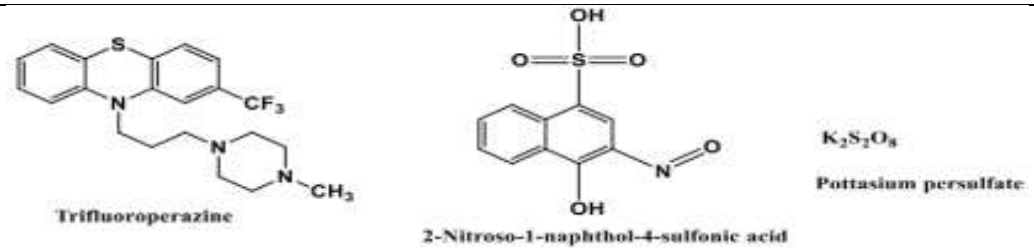
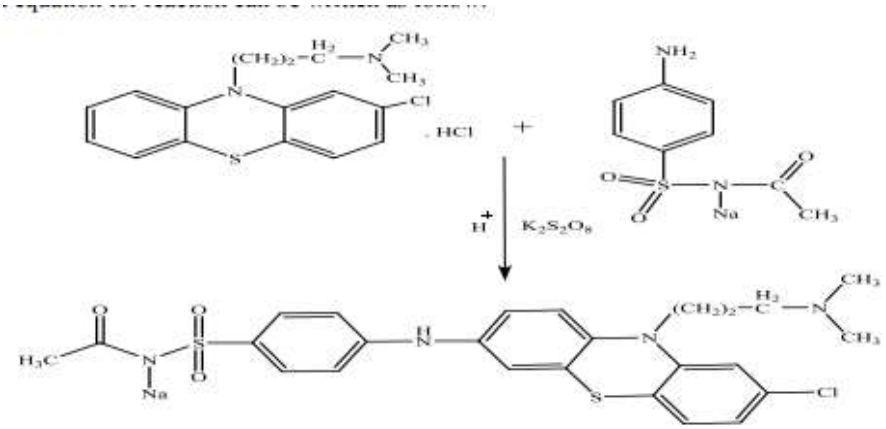
4					
	Chlorpromazine Hydrochloride	2.5 - 30		acidic	(T Humeidy, 2016)
5	Miglitol (MIG), carvedilol (CRV), alverine citrate (ALV)	10-30 for MIG, 20-100 for CRV and 50-250 for ALV,	Not found	-	(Vijayalakshmi *et al.*, 2016)

3.2.5. Persulfate Compounds

Ammonium, potassium, and sodium persulfate salts are strong inorganic oxidizers with significant analytical potential due to their high oxidation potentials and stability. Persulfate ions have been widely used in oxidative coupling with ligands such as 2-nitroso-1-naphthol-4-sulfonic acid, mesalazine (MES), 4-(methylamino)phenol sulfate (Metol), sodium sulphacetamide, and 1-naphthylamine-4-sulfonic acid. These methods provide reliable and reproducible quantification of pharmaceutical analytes, as presented in Table 7 (Reisner, 2016).

Table 7: Role of oxidant (persulfate compounds) in the oxidative coupling reactions.

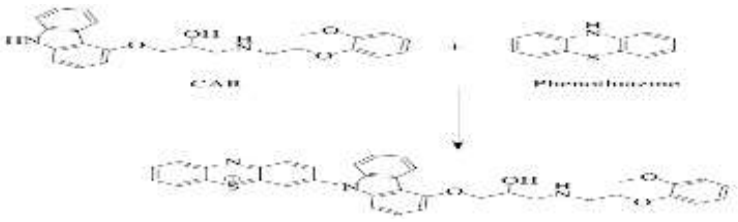
No	Drug	Concentration range, µg/ml	Mechanism	pH	Ref.
1	Dopamine (DM)	2.7 -31.25		basic	(Nejres and Najem, 2023)
2					
	Salbutamol, 4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl) phenol	5–23		Basic	(Hussein, Ahmed and Mohammed, 2021)

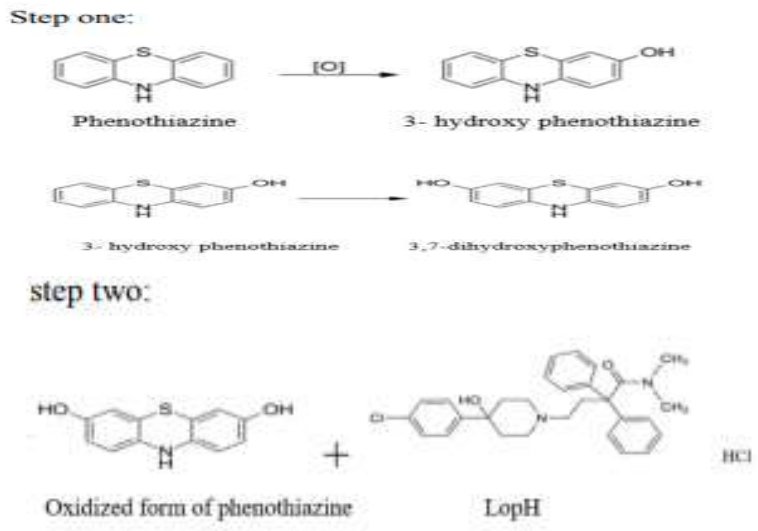
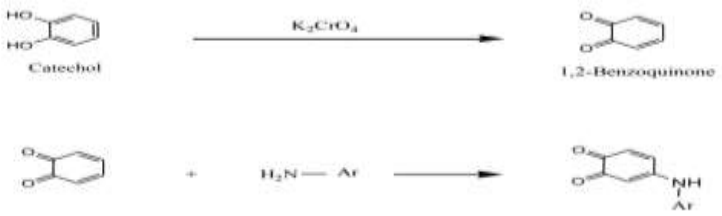
4					
	Trifluoperazine Hydrochloride	12–36		acidic	(Jalal, 2020)
5					
	Chlorpromazine hydrochloride	2 – 20		acidic	(Ahmed, Khazaal and Ahmed, 2018)
6	Doxycycline Hyclate	2 – 44	Not found	basic	(Al-Rufaie, 2013)

3.2.6. Potassium Dichromate

Potassium dichromate, especially under acidic conditions, acts as a powerful oxidizing agent suitable for spectrophotometric analysis. It has been successfully used to oxidize pharmaceutical preparations and facilitate coupling with agents such as phenothiazine and pyrocatechol. The analytical applications and compound details are summarized in Table 8.

Table 8: Role of the oxidant, potassium dichromate, in the oxidative coupling reactions

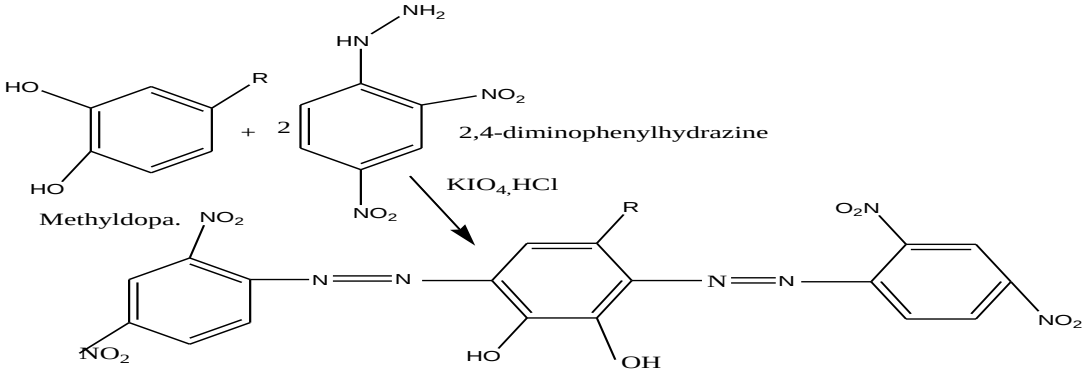
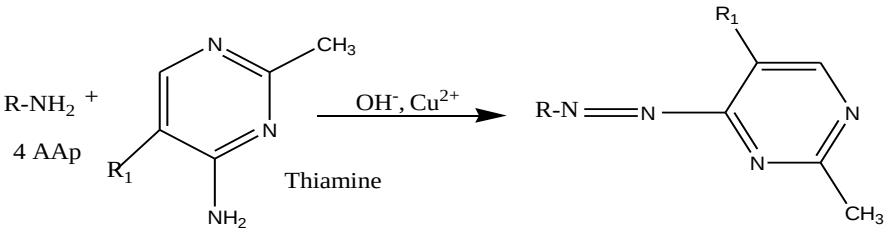
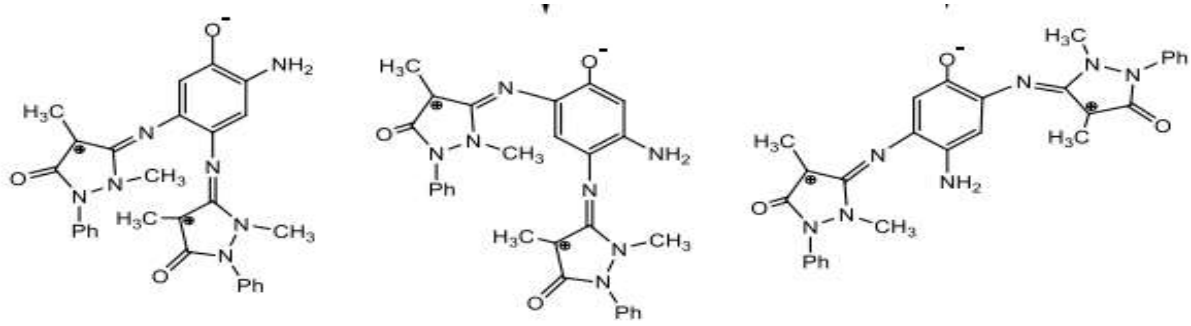
No	Drug	Concentration range	Mechanism	pH	Ref.
1					

	Carvedilol	1 to 12 mg/mL.		acidic	(Mohammed , Omar and Shihab, 2022)
2	Mebendazole	4-140	Not found	-	(Al-Shaker, Mohammed and Abdalkader, 2022)
3					
	Loperamide hydrochloride (LopH)	0.8 - 40		-	(Shehab, Mohammed and Mahmood, 2021)
4					
	Mesalazine	(0.4-10 mg/mL.		Acidic	(Shihab, 2011)

3.2.7. Copper Sulfate

Though less frequently employed, copper sulfate has shown potential as an alternative oxidizing agent in oxidative coupling methods. Its application has been demonstrated in reactions involving coupling agents such as terephthalic acid and 4-aminoantipyrine (4-AAP). These methods, while limited in prevalence, offer additional avenues for drug determination and are documented in Table 9, with contributions primarily from Reem A. Al-Luhaiby and colleagues (Al-Luhaiby and Shehab, 2022).

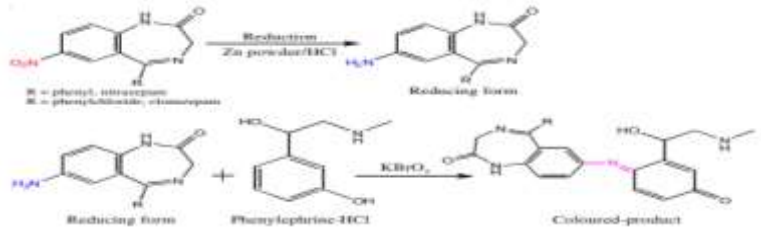
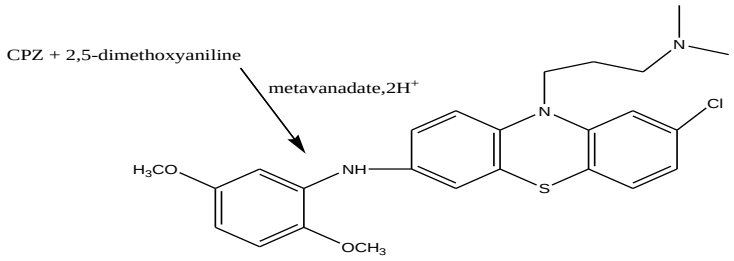
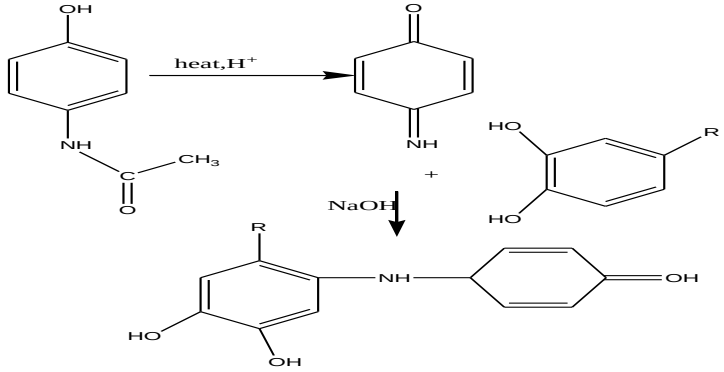
Table 9: Role of the oxidant, copper sulfate, in the oxidative coupling reactions

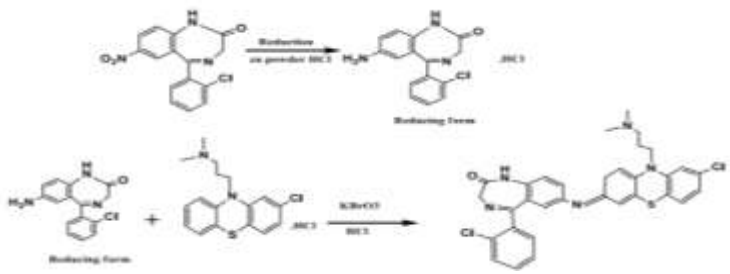
No	Drug	Concentration range, µg/mL	Mechanism	pH	Ref.
1					
	Methyldopa.	1-30		acidic	(AL-ghanam and AL-Enizzi, 2022)
2	Resorcinol	4-18	Not found	basic	(Al-Luhaiby and Shehab, 2022)
3					
	Thiamine hydrochloride	0.2-18		basic	(Al-Luhaiby and Al-Enizzi, 2020)
4	Isomers of aminophenol in the presence of Cu^{2+} and OH^- and 2 moles of 4-AAP,the dye is 				
	Aminophenol isomers (o-aminophenol, m-aminophenol and p-aminophenol).	1-20, 1-24, and 1-7		basic	(Al-Luhaiby and Al-Enizzi, 2020)

3.2.8. Other Oxidizing Agents

In addition to the commonly used oxidants, several lesser-known agents have been occasionally employed in oxidative coupling reactions. These include ammonium vanadate, atmospheric oxygen, and potassium bromate. Though rare, their usage with specific coupling agents such as 2,5-dimethoxyaniline, methyldopa, chlorpromazine hydrochloride (CPZ.HCl), and phenylephrine hydrochloride has been reported and summarized in Table 10.

Table 10: Role of some oxidants, rarely used, in the oxidative coupling reactions

No	Drug	Concentration range, µg/mL	Mechanism	pH	Ref.
1					
	Benzodiazepine Drugs (Clonazepam and Nitrazepam)	2-60 and 5-90		-	(Mahdi and Kadim, 2018)
2					
	Chlorpromazine hydrochloride (CPZ)	0.05– 14		acidic	(Ali and Kadhim, 2016)
3					
	Paracetamol	10–100		basic	(Thanoon, Raheed and Hasan, 2021)

4		Clonazepam (CZP)	0.05–3.5	acidic	(Saddam and Kadhim, 2019)

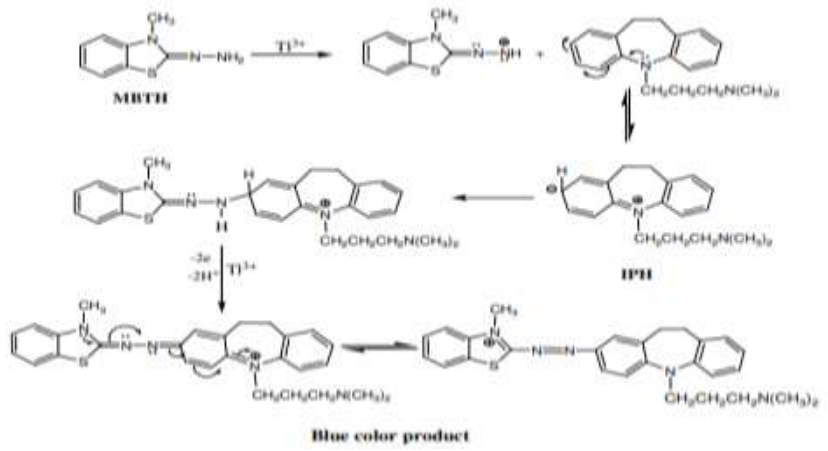
3.3. Determination of oxidants by oxidative coupling:

The role of oxidizing agents was not limited to the determination of pharmaceutical preparations by oxidative coupling reactions, but rather, such reactions were exploited in the spectrophotometric determination of these agents. It is possible to review these agents that were estimated using the coupling agents, phenoxazine (PNZ), 10, 11-dihydro-5-H-dibenzo [b, f] azepine (IDB), and imipramine hydrochloride (IPH), as shown in Table 11.

Table 11: Using some oxidative coupling reactions for the determination of oxidants

No	Oxidant, oxidized compound	Concentration range, μg/mL	Mechanism	pH	Ref.
1	Iron(III) in environmental water and soil samples, 2-amino-2′,5-dichlorobenzophenone (MCB) or 2-amino-5-chloro-2'-fluorobenzophenone (MFB)	0.31-1.2121 and 0.42-1.41	Not found	acidic	(Al Okab and Galil, 2012)
2	Thallium (III) in Water and Urine Samples, 2-hydrazono-3-methyl-2,3-dihydrobenzo[*d*]thiazole hydrochloride, (MBTH)	0.1-4	The mechanism is shown as (P Nagaraja *et al.*, 2009)	acidic	(Padmaraj aiah Nagaraja *et al.*, 2009)

3



Thallium(III) thallium(I)	and	0.1-5	Acidic	(P Nagaraja *et al.*, 2009)

Enas Samer Thanoon *et al.* were able to estimate paracetamol in drug formulations indirectly through the hydrolysis of this drug, resulting in paminophenol, which was oxidized by dissolved oxygen to benzoquinoneimine. This product, in turn, reacted in the basic medium with methyldopa to produce a highly stable indophenol dye, as shown in Figure 1 below.

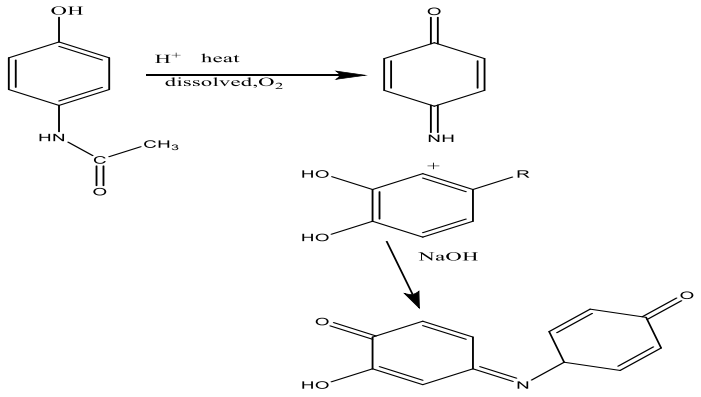


Figure 1: proposed mechanism for reacting the drug after hydrolysis process

Moreover, the role of nanoparticles cannot be overlooked, as they were used in the determination of hydrogen peroxide using pyrocatechol and MBTH. In this method, percatechol was oxidized by hydrogen peroxide in the presence of Fe_2O_3 nanoparticles(Chamaraja, 2017), producing quinone, which in turn couples with MBTH, forming an intense red complex that can be measured at a maximum wavelength of 510 nm, as shown in Figure 2.

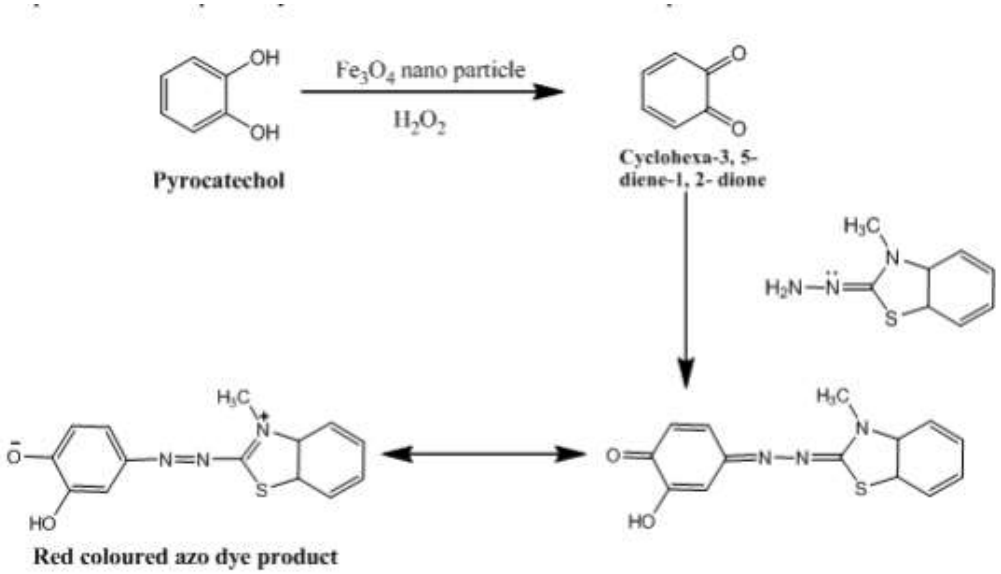


Figure 2: The role of Fe_2O_3 nanoparticles in the oxidation of Pyrocatechol

3.4. Potential Limitations

Spectrophotometric determination of oxidants via oxidative coupling reactions presents several limitations. Interference from coexisting oxidants can hinder accurate quantification, often necessitating additional sample purification steps (Al Okab and Galil, 2012). Furthermore, the specificity of these reactions is sometimes inadequate, resulting in cross-reactivity with structurally similar compounds (Gurrala *et al.*, 2022). The instability of oxidized intermediates poses another challenge, as degradation over time may compromise measurement accuracy (M. J. Ahmed and H. H. Abdullah, 2018). In many cases, the method exhibits a narrow detection range, limiting its applicability to specific concentration thresholds (Ahmed, 2018). Additionally, fluctuations in experimental parameters such as pH and temperature can negatively impact reproducibility (Singh *et al.*, 2021). These challenges highlight the importance of method optimization and stringent control of analytical conditions to ensure reliability. Among the oxidizing agents examined, ferric chloride and potassium periodate were the most commonly utilized, owing to their high oxidation potential and broad compatibility with various chromogenic ligands. Conversely, agents like copper sulfate and ammonium vanadate were employed in fewer studies, likely due to lower reactivity or insufficient validation for pharmaceutical applications. These findings underscore the need for systematic comparative studies to evaluate the trade-offs among reactivity, stability, and selectivity in choosing suitable oxidants for spectrophotometric analyses.

4. Conclusion

This comprehensive review has demonstrated the significant role that oxidizing agents play in the spectrophotometric determination of pharmaceutical compounds via oxidative coupling reactions. A wide range of oxidants has been successfully employed, with most reactions occurring under mild conditions, notably at room temperature, which enhances operational simplicity. Despite these advantages, certain limitations were observed, including narrow linear ranges in some methods and the need for pH

adjustment in specific cases, which may complicate the analysis. Nevertheless, the methods exhibit commendable sensitivity and acceptable selectivity, rendering them suitable for routine pharmaceutical analysis. Moreover, the reactions are generally environmentally benign and free from hazardous reagents, aligning with green analytical chemistry principles. The stability of the colored complexes was generally sufficient for accurate quantification. A key finding is that the presence of an amine group or an additional reactive site in the drug molecule is often essential for successful coupling. Overall, oxidative coupling reactions present a promising, efficient, and sustainable approach to pharmaceutical analysis, though further optimization and standardization are recommended to enhance robustness and broaden applicability.

References

Al Abachi, M.Q. and Hadi, H. (2014) 'Simple, rapid and sensitive method for the determination of mefenamic acid in pharmaceutical preparations', *Journal of Analytical Chemistry*, 69, pp. 769–776.

Abdoon, F.M. and Yahyaa, S.Y. (2020) 'Validated spectrophotometric approach for determination of salbutamol sulfate in pure and pharmaceutical dosage forms using oxidative coupling reaction', *Journal of King Saud University-Science*, 32(1), pp. 709–715.

Abduljabbar, A.T. and Ali, N.H. (2022) 'Spectrophotometric Determination Of Carvedilol In Some Pharmaceuticals Via An Oxidative Coupling Reaction', *Journal of Pharmaceutical Negative Results*, pp. 2951–2962.

Abdurahman, M.T. and Mahmoud, K.M. (2016) 'Spectrophotometric Determination of Trifluoperazine Hy-drochloride Using Oxidative Coupling Reaction', *International Journal Of Innovative Research In Technology & Science*, 4(6), pp. 23–27.

Afify, K.K., Abdelsalam, R.A. and Hadad, G.M. (2018) 'HPLC determination of Metronidazole in pure form, pharmaceutical dosage form and spiked urine.', *Records of Pharmaceutical and Biomedical Sciences*, 2(2), pp. 46–51.

Ahmed, A.M.K., Anwar, S.M. and Hattab, A.H. (2020) 'Spectrophotometric determination of phenylephrine hydrochloride in pharmaceutical preparations by oxidative coupling reaction', *Int. J. Drug Delivery Technol.*, 10, pp. 323–327.

Ahmed, A.M.K., Khazaal, A.S. and Ahmed, A.H. (2018) 'Spectrophotometric Determination of Methyl Paraben in Pharmaceutical Formulations by Oxidative Coupling Reaction', *Tikrit Journal of Pure Science*, 21(6), pp. 85–89.

Ahmed, M.J. (2018) 'Spectrophotometric Determination of Chlordiazepoxide in Pharmaceutical Formulations via Oxidative Coupling Reaction with Phenothiazine', *Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512)*, pp. 7–14.

Ahmed, N.A.A.L.S. and Khaleel, A.I. (2018) 'Spectrophotometric determination of sulphadiazine Using 2, 4–dinitrophenylhydrazine as Coupling Reagent', *Tikrit Journal of Pure Science*, 23(8), pp. 77–82.

AL-Da'amy, M.A.A. and AL-Moswi, R.F. (2014) 'Spectrophotometric determination of

methyldopa in pharmaceutical preparation via oxidative coupling organic reaction with para-phenylenediamine in the presence of potassium periodate', *Abstract of Emerging Trends in Scientific Research*, 1, pp. 1–53.

AL-ghanam, D.N.A. and AL-Enizzi, M.S.S. (2022) 'Spectrophotometric determination of methyldopa by oxidative coupling reactions using 2, 4-dinitrophenylhydrazine reagent', *Tikrit Journal of Pure Science*, 27(5), pp. 16–22.

Al-Kalissy, R.S. and Mohammed, A.K. (2014) 'Spectrophotometric method for the determination of methyldopa by oxidizing coupling reaction with 4-aminoantipyrine', *Journal of University of Babylon for Pure and Applied Sciences*, 28(3), pp. 1–12. Available at: https://portal.arid.my/Publications/d9f062d7-f03d-4d90-b954-8d7f8730a71b.pdf.

Al-Kalissy, R.S. and Mohammed, A.K. (2017) 'Spectrophotometric method for the determination of tetracycline and doxycycline by oxidizing coupling reaction with 4-aminoantipyrine', *Ibn AL-Haitham Journal For Pure and Applied Science*, 28(3), pp. 154–168.

Al-Luhaiby, R.A. and Al-Enizzi, M.S. (2020) 'Spectrophotometric Determination of Aminophenol Isomers Via Oxidative Coupling Reaction with 4-Aminoantipyrine', *Journal of Education and Science*, 29(3), pp. 68–84.

Al-Luhaiby, R.A. and Shehab, A.A. (2022) 'Spectrophotometric Determination of Resorcinol Using Oxidative Coupling Reactions', *College Of Basic Education Research Journal*, 18(4), pp. 744–754.

AL-Okab, R.A., Mansour, S.A. and Ahmed, N.A. (2018) 'Development green spectrophotometric method for determination of sulfamethoxazole in pure and pharmaceutical formulations', *Pharm Anal Acta*, 9(5), pp. 15–19.

Al-rashidy, A.A.M. and Shareef, A.K.A.A.M.F. (2019) 'Spectrophotometric Determination of Chlorpromazine Hydrochloride using 4-nitroanilline by oxidative coupling reaction', *Baghdad Science Journal*, 16(1 Supplement).

Al-Rufaie, M.M. (2013) 'Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction', *Iraqi National Journal of Chemistry*, 51, pp. 338–347.

Al-Safar, M.A. and Al-Enizzi, M.S. (2022) 'Spectrophotometric determination of salbutamol via oxidative coupling reaction using reagent benzidine', in *AIP Conference Proceedings*. AIP Publishing LLC, p. 40001.

Al-Shaker, Y.M.S., Mohammed, D.H. and Abdalkader, H.M. (2022) 'Spectrophotometric Method for the Determination of Mebendazol in Different Formulation', *Pakistan Journal of Medical & Health Sciences*, 16(04), p. 913.

Ali, S.M. and Kadhim, K.H. (2016) 'Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pure and Pharmaceutical formulation by Using The Organic Reagent 2-5 dimethoxyaniline.', *Research Journal Of Pharmaceutical Biological And Chemical Sciences*, 7(5), pp. 640–650.

Aljeboree, A.M. and Alshirifi, A.N. (2019)

'Determination of Phenylephrine Hydrochloride and Amoxicillin in a Binary Mixture using Derivative Spectrophotometry Methods', *International Journal of Pharmaceutical Quality Assurance*, 10(03), pp. 168–177.

Altahir, B.M. and Shakir, S.M. (2023) 'Determination of paracetemol in pharmaceutical preparations samples by spectrophotometer using meta phenylenediamine as a chromogenic agent', in *AIP Conference Proceedings*. AIP Publishing LLC, p. 50003.

Anumolu, P.D. *et al.* (2013) 'Development of dissolution test method for drotaverine hydrochloride/mefenamic acid combination using derivative spectrophotometry', *Tropical Journal of Pharmaceutical Research*, 12(2), pp. 227–232.

Anwar, S.M. (2018) 'Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pharmaceutical Preparations by Oxidative Coupling reaction.', *Kirkuk University Journal-Scientific Studies*, 13(3), pp. 23–36.

Awad, F.H. and Taki, A.G. (2021) 'Spectrophotometric determination of doxycycline via oxidation reduction reactions', *Egyptian Journal of Chemistry*, 64(11), pp. 6615–6621.

Aziz, A.T. and Sultan, S.H. (2019) 'Spectrophotometric Determination of Mesalazine in Pharmaceutical Preparations by Oxidative Coupling Reactions with m-Aminophenol and 2, 6-Dihydroxybenzoic Acid', *Baghdad Science Journal*, 16(4 Supplement).

Babu, A.B. *et al.* (2012) 'Spectrophotometric determination of lamivudine in pure and tablet forms', *E-journal of Chemistry*, 9(2), pp. 569–575.

Battu, S., Gandu, V. and Nenavathu, B.P. (2020) 'Simple spectrophotometric method for estimation of drugs using chloramine-t and indigo caramine dye couple.', *Asian J Biomed Pharmaceut Sci*, 10(69), p. 19.

Chamaraja, N.A. (2017) 'Fe3O4 Nano Particle Catalysed Spectrophotometric Method for the Quantification of Hydrogen Peroxide using Pyrocatechol and 3-Methyl-2 Benzothiazolinehydrazone Hydrochloride: Applications in Water, Vegetables and Milk samples', *Chem. Sci. Rev. Lett.*, 6(23), pp. 1443–1451.

Dikran, S.B. and Mahmood, R.M. (2017) 'Spectrophotometric determination of diclofenac sodium using 2, 4-dinitrophenylhydrazine in pure form and pharmaceutical preparations', *Ibn AL-Haitham Journal For Pure and Applied Science*, 28(3), pp. 129–141.

Fadhel, S.R., Abdulla, N.I. and Sulaiman, I.D. (2016) 'The Spectrophotometric Determination of Olanzapine via Coupling with Diazotized p-Nitroaniline', *Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512)*, 25(1), pp. 42–49.

Fadhel, S.R., Abdulla, N.I. and Sulaiman, I.D. (2017) 'Spectrophotometric determination of carbamazepine via oxidative coupling reaction with 2, 4-dinitrophenyl hydrazine', *Ibn AL-Haitham Journal For Pure and Applied Science*, 29(1).

Ghaib Allah, N.M., Ahmed, A.M.K. and

Tapabashi, N.O. (2022) 'Spectrophotometric Determination of Methyldopa in Pure and Pharmaceutical Preparations by the Oxidative Coupling Reaction with 1, 5-Diaminonaphthalene in the Presence of Ammonium Ceric (IV) Nitrate', *Kirkuk University Journal-Scientific Studies*, 17(4), pp. 42–49.

Gorumutchu, G.P. and , Venkata Nadh Ratnakaram, K.V. (2019) 'Ulipristal acetate determination using MBTH', *International Journal Of Research In Pharmaceutical Sciences*, 10(4), pp. 3369–3375.

Gurrala, S. *et al.* (2022) 'Response Surface Methodology in Spectrophotometric Estimation of Saxagliptin, Derivatization with MBTH and Ninhydrin', *Turkish Journal of Pharmaceutical Sciences*, 19(1), p. 9.

Hadi, H. (2008) 'Spectrophotometric determination of Procaine penicillin in pure and pharmaceutical formulations using metol', *Um-Salama Science Journal*, 5, pp. 137–142.

Hadi, H. and Mouayed, M. (2017) 'Determination of nitrofurantoin in pharmaceutical preparations using flow injection-spectrophotometry', *Journal of the Association of Arab Universities for Basic and Applied Sciences*, 24, pp. 74–80.

Hasan, G.A. and Bakir, M.H. (2021) 'Spectrophotometric Determination of Naproxen using Metol reagent by Oxidative Coupling Reaction', in *IOP Conference Series: Materials Science and Engineering*. IOP Publishing, p. 12079.

Hiremath, B. (2008) 'Bennikallu Hire Mathada, Mruthyunjayaswamy', *Acta Pharm*, 58, pp. 275–285.

Humeidy, I.T. (2019) 'Spectrophotometric method for Determination of sulfamerazine Using 2, 4-dinitrophenylhydrazineReagent', in *Journal of Physics: Conference Series*. IOP Publishing, p. 52022.

Humeidy, I.T., Salman, S.A. and Hashim, K.K. (2020) 'Spectrophotometric Determination of Methyldopa With 2, 6-Diaminopyridine Reagent Using Oxidative Coupling Reaction', *Journal of Engineering Science and Technology*, 15(3), pp. 1824–1839.

Hussein, A.D., Abdulrahman, M.T. and Raheem, A.S. (2020) 'UV Spectrophotometric Development and HPLC Methods for Estimation of Paracetamol in Oral Syrup Formulation: Validation, Comparison and Application', *International Journal of Psychosocial Rehabilitation*, 24(04).

Hussein, K.S., Ahmed, A.M.K. and Mohammed, F.Y. (2021) 'Spectrophotometric determination of salbutamol by oxidative coupling reaction with 1-Naphthylamine-4-sulfonic acid in the presence of potassium per sulfate', *Medical Journal of Babylon*, 18(3), p. 249.

Ibrahem, L.I. and Rashid, Q.N. (2022) 'Spectrophotometric determination of nystatin in its pharmaceutical preparations', in *AIP Conference Proceedings*. AIP Publishing LLC, p. 20034.

J. Mythri, B.S.Anusha, and M.S.R. (2014) 'Visible Spectrophotometric Determination Of Oxyfedrine Through Oxidative Coupling Reaction In Bulk Sample And Dosage Forms', *Journal of Chemical and Pharmaceutical Sciences*, (Special Issue), pp. 54–56.

Jalal, M.T. (2020) 'Spectrophotometric

determination of trifluoperazine hydrochloride in pharmaceutical preparations by oxidative coupling reaction', *Systematic Reviews in Pharmacy*, 11(6), pp. 58–68.

Kalyanaramu, B. and Raghubabu, K. (2011) 'Development of new visible spectrophotometric methods for determination of benidipine hydrochloride in bulk and formulations based on oxidative coupling and diazo coupling reactions', *Int. J. Pharm. Biol. Sci*, 1, pp. 57–66.

Khalaf, N.M. and Othman, N.S. (2022) 'Determination of Doxycycline as Pure and in Pharmaceutical Preparation (Capsule) Using 4-Aminoantipyrine in Presence of Potassium Periodate', *Rafidain Journal of Science*, 31(4), pp. 15–28.

Khanfous, S.N., Nasser, N.A.H. and AL-Rufaie, M.M. (2017) 'Modern spectrophotometric approach for assessment chlorpromazine hydrochloride drug', *Iranian Journal of Organic Chemistry*, 9(3), pp. 2161–2167.

M. J. Ahmed and H. H. Abdullah (2018) 'Spectrophotometric Determination of Chlordiazepoxide in Pharmaceutical Formulations via Oxidative Coupling Reaction with Phenothiazine', *Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512)*, 27(2), pp. 7–14.

Mahdi, M.I. and Kadim, K.H. (2018) 'Spectrophotometric determination for benzodiazepine drugs (clonazepam and nitrazepam) in pure and pharmaceuticals preparation', *Asian J. Chem*, 30(12), pp. 2686–2692.

Mallikarjuna, H. *et al.* (2016) 'Spectrophotometric determination of some nonsteroidal anti-inflammatory drugs by oxidative coupling reaction', *Austin J Anal Pharma Chem*, 3, pp. 1–6.

Mallikarjuna Rao, N. and Gowrisankar, D. (2016) 'Development and Validation of Novel stability indicating UV spectrophotometric method for the estimation of Cinacalcet Hydrochloride in bulk and tablet dosage forms', *Indian Drugs*, 53(12), p. 31.

Manasa, M. *et al.* (2018) 'Method Development And Validation Of Norethindrone By Uv-Visible Spectrophotometer In Bulk And Pharmaceutical Dosage Form', *World Journal of Pharmaceutical research*, 7(7), pp. 2160–2165.

Marcel, S. *et al.* (2018) 'Validation of HPLC-UV method for determination of amoxicillin Trihydrate in capsule', *Annals of Advances in Chemistry*, 2, pp. 55–72.

Mohammed, D.H., Omar, F.K. and Shihab, E.A. (2022) 'Spectrophotometric determination of carvedilol via oxidative coupling reaction', *Journal of Global Scientific Research*, 7(3), pp. 2135–2144.

Mohammed, I.S., Ibrahim, M.K. and AL-Niaimi, A.F.D. (2018) 'A simple and sensitive colorimetric method for the determination of Propranolol hydrochloride in pure and pharmaceutical preparation via oxidative coupling organic reaction', *Journal of Pharmaceutical Sciences and Research*, 10(12), p. 3025.

Nagaraja, Padmarajaiah *et al.* (2009) 'Rapid and sensitive spectrophotometric method for the determination of the trace amount of thallium (III) in water and urine samples by new oxidative coupling reaction', *Journal of the*

Mexican Chemical Society, 53(4), pp. 201–208.

Nagaraja, P *et al.* (2009) 'Spectrophotometric determination of the trace amount of thallium in water and urine samples by novel oxidative coupling reaction', *E-Journal of Chemistry*, 6(4), pp. 1153–1163.

Nasser, K.A., Atiya, G.A. and Baker, M.H. (2017) 'Spectrophotometric determination of Naproxen in the pharmaceutical Preparations Via Oxidative Coupling of Naproxen with Ansidine', *Diyala Journal For Pure Science*, 13(1-part 1).

Nejres, A.M. and Najem, M.A. (2023) 'A Novel Yttrium (III) Complex for Estimating Dopamine in Pure and Pharmaceutical Dosage Forms', *Biomedicine and Chemical Sciences*, 2(1), pp. 23–30.

Al Okab, R.A. and Galil, M.A.S. (2012) 'New oxidative electrophilic coupling reactions and their application to spectrophotometric determination of iron (III) in environmental waters, soils and industrial effluent samples', *Facta universitatis-series: Physics, Chemistry and Technology*, 10(1), pp. 27–36.

Onikienko, S. *et al.* (2022) 'The Effects of H2S and Recombinant Human Hsp70 on Inflammation Induced by SARS and Other Agents In Vitro and In Vivo', *Biomedicines*, 10(9), p. 2155.

Othman, N.S. (2021) 'p-Aminobenzoic Acid as a New Reagent in Spectrophotometric Determination of Salbutamol Sulphate Via Oxidative Coupling Reaction', *ITALIENISCH*, 11(2), pp. 264–270.

Pani Kumar, A.D. *et al.* (2013) 'Spectrophotometric quantification of tadalafil by oxidative coupling reaction with MBTH reagent', *Anal Chem Ind J*, 13(9), pp. 361–364.

Qi, Y. *et al.* (2020) 'An aptamer-based colorimetric sensing of acetamiprid in environmental samples: Convenience, sensitivity and practicability', *Sensors and Actuators B: Chemical*, 304, p. 127359.

Rahul, R.M.B., Gurupadayya, B.M. and Anil, K.T. (2011) 'Determination of Stavudine as an Antiretroviral Drug against HIV by Selective Oxidation Methods', *Journal of Applied Chemical Research*, 18, pp. 20–28.

Raja, G. *et al.* (2010) 'Simple colorimetric assay for micro gram determination of bromhexine hydrochloride with MBTH and 2, 2'bipyridyl', *International Journal of Pharma Sciences and Research.*, 1, pp. 90–94.

Ramachandra, B. and Naidu, N.V. (2017) 'UV-Visible Spectrophotometric Determination of Azathioprine in Pharmaceutical Formulations Based on Oxidative coupling reaction with MBTH', *Int. J. Pharmaceut. Chem. Anal*, 4, pp. 117–139.

Ramachandra, B. and Naidu, N.V. (2018) 'Determination of Azacitidine by Spectrophotometric Method', *Open Journal of Medicinal Chemistry*, 8(2), pp. 15–21.

Ramadan, M.A.A., Almasri, I. and Khayal, G. (2020) 'Spectrophotometric determination of dopamine in bulk and dosage forms using 2, 4-dinitrophenylhydrazine', *Turkish Journal of Pharmaceutical Sciences*, 17(6), p. 679.

Reddy, M.B., Gurupadayya, B.M. and Kumar, T.A. (2011) 'Spectrophotometric determination of lamuvidine using acidic dye and coupling reagent', *Indian Journal of*

Chemical Technology, 18, pp. 431–438.

Reddy, M.S. and Firadous, S. (2015) 'Spectrophotometric estimation of gemcitabine HCl in pharmaceutical dosage form via oxidative coupling reaction', *Chem Sci Transactions*, 4, pp. 1102–1106.

Reisner, T. (2016) ''Application Of Persulfate For Water And Wastewater Treatment'. MSc Thesis, Tallinn University of Technology.

Saddam, N.S. and Kadhim, K.H. (2019) 'Spectrophotometric determination of drug clonazepam in pure form and pharmaceutical tablets by oxidative coupling reaction with chlorpromazine hydrochloride', *Int. J. Pharm. Qual. Assu*, 10(02), pp. 342–348.

Salih, E.S. (2020) 'Spectrophotometric Assay of Mesalazine in Pharmaceutical Preparations Via Oxidative coupling reaction with o-cresol and sodium metaperiodate', *Journal of Education and Science*, 29(1), pp. 279–292.

Serra, T.M.D.B.D.H. dos R. (2021) 'Development and validation of RP-HPLC method for simultaneous determination of lamivudine, stavudine, and zidovudine in perfusate samples: Application to the Single-Pass Intestinal Perfusion (SPIP) studies', *Brazilian Journal of Pharmaceutical Sciences*, 57, pp. 1–12. Available at: https://doi.org/https://doi.org/10.1590/s2175-97902020000419073.

Shakkor, S.J., Mohammed, N. and Shakor, S.R. (2022) 'Spectrophotometric Method for Determination of Methyldopa in Bure and Pharmaceutical Formulation Based on Oxidative Coupling Reaction', *Chemical Methodologies*, 6, pp. 851–860.

Shehab, A.A. and Mohammed, D.H. (2022) 'Indirect Spectroscopic Determination of Carvedilol and Propranolol Hydrochloride in Its Pure Form Using Methyl Orange Dye and Applying to Their Pharmaceutical Preparations', *College Of Basic Education Research Journal*, 18(1), pp. 996–1029.

Shehab, A.A., Mohammed, D.H. and Mahmood, H.S. (2021) 'Spectrophotometric Determination of Loperamide Hydrochloride in Pure and Pharmaceutical Dosage Forms Using Oxidative Coupling Reaction', *Egyptian Journal of Chemistry*, 64(12), pp. 7371–7376.

Shihab, I.A. (2011) 'Spectrophotometric determination of mesalazine via oxidative coupling reaction', *Tikrit Journal of Pure Science*, 16, pp. 64–69.

da Silva Granja, B. *et al.* (2018) 'Exploring MBTH as a spectrophotometric probe for the determination of total phenolic compounds in beverage samples', *Analytical Methods*, 10(19), pp. 2197–2204.

Sinan, R. and SS, A. (2009) 'Nitroso-R-salt as a sensitive spectrophotometric reagent for the determination of paracetamol in pharmaceutical preparations', *Baghdad Sci J*, 6, pp. 570–577.

Singh, A. *et al.* (2021) 'Recent advances in electrochemical biosensors: Applications, challenges, and future scope', *Biosensors*, 11(9), p. 336.

Siva Ramakrishna, V. *et al.* (2012) 'Method development and determination of valacyclovir HCl in pharmaceutical dosage forms by visible spectrophotometry', *Int J PharmTech Res*, 4, pp. 1009–1014.

Sowjanya, K. *et al.* (2011) 'Spectrophotometric

determination of pregabalin using Gibb's and MBTH reagent in pharmaceutical dosage form', *Der Pharma Chemica*, 3(1), pp. 112–122.

Sujatha, G., Swami, P.Y. and Venkateshwarlu, G. (2016) 'Spectrophotometric determination of drugs in bulk and in pharmaceutical dosage forms by using tetracyanoethylene', *Materials Today: Proceedings*, 3(10), pp. 3652–3659.

Sujatha, T., Balmuralikrishna, K. and Ramesh Raju, R. (2014) 'Visible Spectrophotometric determination of Loratadine through oxidative coupling reaction in bulk and its pharmaceutical preparations', *Int. J. of ChemTech Res*, 6(2), pp. 1091–1096.

T Humeidy, I. (2016) 'Spectrophotometric determination of Chlorpromazine Hydrochloride by oxidative coupling reaction with P-Bromo aniline using Ammonium Ceric Sulphate Dihydrate', *Kirkuk University Journal-Scientific Studies*, 11(1), pp. 1–19.

Thanoon, E.S., Raheed, L.A. and Hasan, I.Y. (2021) 'Oxidative Coupling-Base Reaction for the Indirect Spectrophotometric Determination of Paracetamol in Drug Formulations', *International Journal on Engineering, Science and Technology (IJonEST)*, 3(1), pp. 72–78.

Unnisa, A. *et al.* (2011) 'New Spectrophotometric Methods For Estimation Of Metadoxine In Bulk And Pharmaceutical Formulations Based On Oxidative Coupling And Charge-Transfer Complex Formation Reactions', *International Journal*, 9(1), pp. 403–411.

Varsha, M.S. *et al.* (2015) 'Development of new spectrophotometric method for estimation of tenofovir disoproxil fumarate using MBTH reagent', *International Current Pharmaceutical Journal*, 4(4), pp. 378–381.

Vijayalakshmi, R. *et al.* (2016) 'Colorimetric estimation of few pharmaceutical agents miglitol, carvedilol and alverine citrate in pure and tablet dosage forms using MBTH', *Der Pharma Chemica*, 6(2), pp. 20–23.

Zhang, X. *et al.* (2020) 'Rationale of 3, 3′, 5, 5′-tetramethylbenzidine as the chromogenic substrate in colorimetric analysis', *Analytical Chemistry*, 92(18), pp. 12400–12406.