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Original Article

Selective Approaches to Synthesize New Series of Heterocyclic Compounds Derived from Metronidazole

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ABSTRACT

A series of novel azo compounds was synthesized from Metronidazole through the reduction of its nitro group to an amine, yielding 2-(5-amino-2-methyl-1H-imidazol-1-yl) ethanol. The study comprised three main stages to produce new compounds with potential biological activity. In the first stage, the nitro group of Metronidazole was reduced to an amine. This intermediate then underwent two synthetic pathways. In the first pathway, Schiff bases were prepared by reacting the amine with various aldehydes, followed by conversion into heterocyclic derivatives. In the second pathway, the amine was transformed into a diazonium salt and subsequently coupled with phenolic compounds to obtain azo dyes. Specifically, the azo derivatives were synthesized by reacting compound with sodium nitrite at 0–5 °C, followed by coupling with several pharmaceutical compounds-paracetamol, 4-aminoantipyrine, Metronidazole reductase, sulfanilic acid, and salicylic acid-to yield compounds. Additionally, Schiff bases were synthesized by reacting compound with m-anisaldehyde, vanillin, and 3-nitrobenzaldehyde to produce compounds. These Schiff bases were then cyclized using thioglycolic acids and phthalic anhydrides to afford new heterocyclic compounds: thiazolidines and oxazepanes. The synthesized compounds were characterized by physical constants and spectral analyses, including infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy.

Keywords: Metronidazole, Oxazepane, Thiazolidine

Introduction

Metronidazole, an antibiotic used to treat bacterial and parasitic diseases, kills microorganisms by inhibiting DNA synthesis within the bacterial cell [1]. Additionally, it is employed to treat bacterial infections affecting various parts of the body such as the stomach, intestines [2], skin [3], joints, respiratory systems [4] and reproductive systems, among others [5]. *Metronidazole* was used as a starting material to prepare novel substituted imidazole rings. Imidazole is one of the important five-membered derivatives that contains two nitrogen atoms. These heterocycles are vital components of functional compounds that are widely used in many applications. They are the main components of a wide range of therapeutic substances and are also found in natural products. The most common imidazole synthesis involves the condensation of dicarbonyl compounds with ammonias [6] and aldehydes, or α-diketones [7] with amines or amidines [8]. These compounds can also be obtained by cyclization of amido-nitriles using a nickel catalyst [9] or by the reaction of amidines with an α-halogen ketone [10].

Imidazole exhibits a wide spectrum of pharmacological and biological activities such as antibacterial [11], antitumor [12], anti-inflammatory analgesic [13], enzyme inhibitory [14, 15], anticancer, and antidepressant [16, 17] properties. It also has applications including in agrochemicals, research dyes for solar cells, and other optical applications [18, 19]. Azo compounds have many different uses, such as in pharmaceuticals [20] and cosmetics, due to their greater stability compared to natural dyes. They are also used as industrial dyes and food colorants, and they exhibit antioxidant and antibacterial activities [21, 22]. The aim of this study was to use the nucleus of one of the pharmaceutical compounds and develop it by synthesizing new compounds that may have greater potential activity than the original substance. In this study, the nitro group in the *Metronidazole* compound was converted to an amine by reduction, after which Schiff bases were prepared and converted into several derivatives of heterocyclic compounds.

Experimental Section

Melting points (M.P.) were uncorrected using the thermal SMP30 UK M.P. apparatus. Infrared spectra were recorded using an Alpha II (ATIR) instrument. ^1H-NMR spectra were recorded using a Varian Agilent 499.53 MHz instrument, with DMSO-d6 as the internal solvent. All chemicals were supplied by Sigma–Aldrich, BHD, and Fluka companies.

Preparation of 2-(5-amino-2-methyl-1H-imidazol-1-yl) ethanol

Metronidazole (10 gm, 0.0584 mole) in 100 ml of 1:1 (methanol: water) was neutralized with 50% NaOH and then the mixture was refluxed in a water bath at 50–60°C [23]. The reducing agent was prepared by dissolving Na_2S (24 gm, 0.3076 mole) with sodium bicarbonate (8.4 gm, 0.1 mole) in 40 ml of water at 40–50°C and was added slowly to the solution until it precipitates The solvent was discarded by pouring, and the precipitate was washed several times with cold water to remove the base, giving a yellow powder (Rf 0.75 (benzene: methanol), 1.8 gm, 80%, m.p. 156°C).

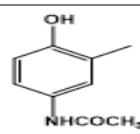
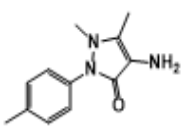
Preparation of Diazonium salts and azo compounds

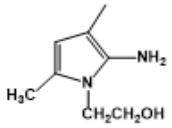
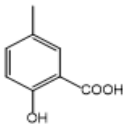
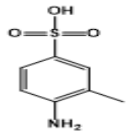
A mixture consisting of 7.58 gm (0.058 mole) of the reduced drug compound (1) was prepared in a large beaker [24]by combining equal quantities of concentrated hydrochloric acid (HCl) and water, each measuring 16 mL. To maintain a low temperature during the reaction, the beaker was placed in an ice bath, and the reaction temperature was kept below 5°C.

In a separating funnel, 4 gm (0.058 mole) of sodium nitrite were dissolved in 20 milliliters of water. This solution was then added drop by drop to the stirred mixture in the ice tub. If necessary, a few grams of crushed ice were added to keep the temperature below 5°C. The resulting solution was stirred for 5 minutes. In a separate beaker, phenol weighing 5.05 gm (0.054 mole) was mixed with 45 milliliters of 10% sodium hydroxide (NaOH) solution to prepare a phenolic solution. Similar to the previous step, this beaker was also immersed in the ice tub, and the temperature was maintained below 5°C by adding crushed ice directly into the mixture. The phenolic solution was vigorously stirred.

The cold diazonium salt solution, containing a few grams of crushed ice, was added drop by drop to the stirred phenolic solution in the ice tub. As a result, a red color developed, and crystals began to separate, forming azo compounds. After adding the diazonium salt solution, the mixture was allowed to stand in the ice bath for 30 minutes. The crystals were then filtered off and washed three times with cold water. Finally, the crystals were recrystallized from ethanol. The physical properties of the prepared compounds can be found in Table 1, while the Infrared (IR) and Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra are presented in Tables 4 and 5, respectively.

Table 1. Properties of Compounds (2-6)

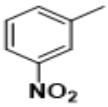
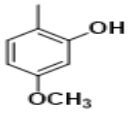
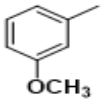
Comp. No.	Ar-OH	M.P.	Yield %	COLOR
2		145 – 146	70	Brown
3		170 -171 dec.	72	Dark brown

4		174 -176 dec.	75	White
5		183 – 185	80	Yellow
6		207-209	82	Brown

Preparing Schiff base substituted

The following method was used to synthesize a number of Schiff bases. A substituted amine ethanolic solution (0.01 mole in 40 mL absolute ethanol) was coupled with 2-(2-amino-5-methyl-1H-imidazol-1-yl) ethanol (1.02 gm, 0.01 mole) dissolved in 20 mL of absolute ethanol [25]. The resulting mixture was refluxed for 6 hours. Following the reflux, the reaction mixture was evaporated to reduce its volume and allowed to cool. The resulting Schiff base was filtered, washed with ethanol, and recrystallized from ethanol. The overall yield of the obtained Schiff bases was 75%. The physical properties of compounds (7–9) appear in Table 2, while their IR and ^{1}H-NMR spectral data in Tables 6 and 7, respectively.

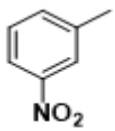
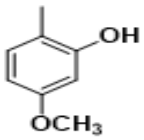
Table 2. Properties of Compounds (7-9)

Comp. No	R	M.P. (0C)	Yield %	Color
7		145 -146	70	Brown
8		209 dec.	78	Yellow
9		148-149	77	Dark brown

Preparation of 3-(substituted -4-thiazoldinone)

A mixture of 0.009 mol of eight to ten different substituted Schiff base compounds in 30 mL of absolute ethanol was combined with 0.009 mol of α-thiolacetic acid [26]. The resulting mixture was refluxed for 4 hours. After cooling, the product was recrystallized from ethanol to obtain a solid compound. Tables 3, 8, and 9 present the physical characteristics and the IR and ^{1}H-NMR spectra, respectively.

Table 3. Physical characteristics constants for compounds (10-11)

Comp. NO.	R	M.P(°C)	Yield %	Color
10		187- 190	60	White
11		175-178	62	White

Preparation of 1- N- Metronidazole-1,3- phenyl oxazepine-4,7-dion

Phthalic anhydride (1.481 gm, 0.01 mol) in 30 mL of absolute ethanol was mixed with a variety of substituted Schiff bases and refluxed for 4 hours [27]. The solvent was evaporated under reduced pressure, and the resulting precipitate was washed with cold methanol. Following recrystallization from ethanol, a white powder weighing 0.885 g was obtained, corresponding to a 75% yield. Using a benzene: methanol solvent system, the resulting white powder showed a melting point of 179°C and an Rf value of 0.56 in thin-layer chromatography. The compound's infrared (IR) spectra revealed characteristic absorption bands at specific wavenumbers (cm^{-1}), which require further study and identification.

Results and Discussion

Metronidazole was used as a base material for the preparation of new derivatives, where the nitro group on the heterocyclic ring was converted to an amine, which can enter into several reactions [28], including conversion into diazonium salts as well as Schiff bases [29]. Infrared stretching vibrations at 3300 cm^{-1} belong to the amine group obtained from nitro reduction. Thus, the disappearance of the stretch bands of the symmetric and asymmetric NO_2 groups indicates the transformation of the nitro groups to the amine. In addition, the appearance of a new single signal for compound (1) in the NMR spectrum was due to the formed amine group, which was not present in the original compound (*Metronidazole*).

^{1}H NMR (ppm) – DMSO-d_6 comp. (1): 1.95 (s, CH_3, 3H on pyrrole ring); 2.38 (t, CH_2, 2H on pyrrole ring); 2.46 (t, CH_2, 2H primary alcohol); 3.68 (s, OH, 1H); 5.04 (s, NH_2, 2H); 8.01 (s, H, 1H pyrrole ring).

The amine group obtained in compound (1) was converted to a diazonium salt by reacting it with nitrous acid at 0–5°C. Subsequently, phenol derivatives were added to compound (2) to obtain new derivatives containing the azo group (3–8).

The identity of the resulting materials was confirmed by the infrared spectrum, which showed bands for the alcohol (OH) group at 3320–3208 cm^{-1}, (C=N) imine at 1666–1637 cm^{-1}, (N=N) azo group at 1472–1432 cm^{-1}, and the disappearance of the aldehyde stretching bands. All spectroscopic information is shown in Table 4. Additionally, nuclear magnetic resonance data show the same ranges as indicated in Table 5.

Table 4. IR. spectra for compounds (2-6)

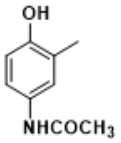
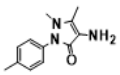
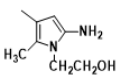
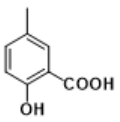
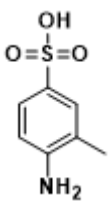
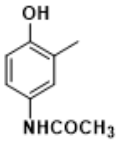
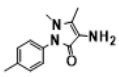
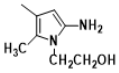
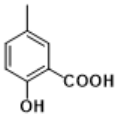
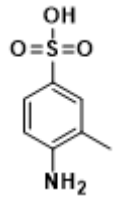
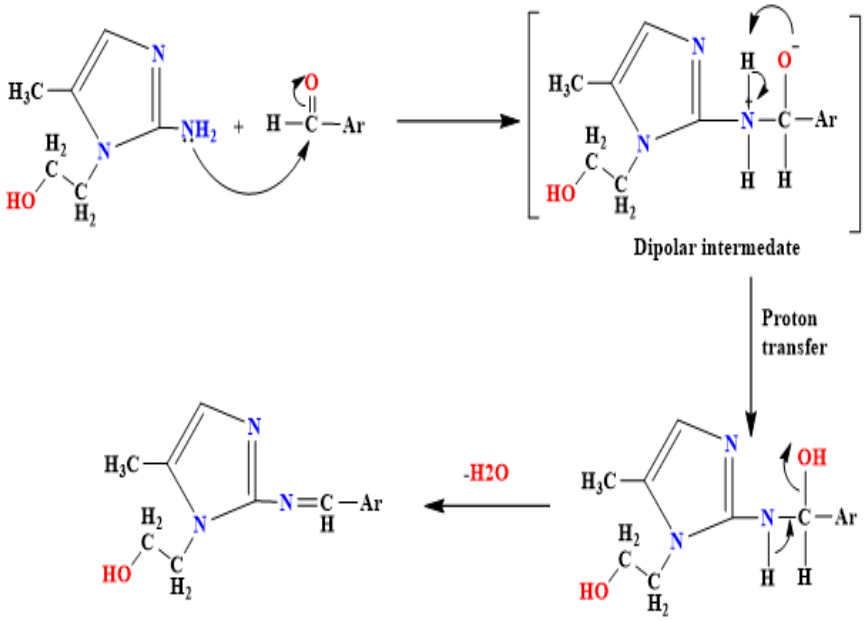
		IR, KBr, γ (cm^{-1})						
Com. NO.	**Ar-OH**	**OH**	**C-H Aromatic**	**C-H aliphatic**	**C=N**	**N=N**	**C-O**	**Other**
2		3208	3098	2956,2880	1637	1457	1072	1667 C=O Amid
3		3298	3045	2961,2880	1655	1455	1056	3321,3434 NH_2
4		3305	3088	2954,2912	1648	1432	1062	3398 3444 NH_2
5		3288	3088	2940,2832	1666	1458	1073	1740 C=O 2670 OH acid
6		3320	3032	2943,2845	1654	1444	1066	2670 OH sulphonic acid

Table 5. 1H-NMR spectra for compounds (2-6)

Com.NO.	Ar-OH	^{1}H NMR (ppm) – DMSO-d6
2		3.07 (t, CH_3, 3H on pyrrole ring);3.28 (t, CH_2, 2H on pyrrole ring); 3.31 (t, CH_2, 2H primary alcohol); 3.36 (s, OH, 1H); 4.77 (s, CH_3, 3H acetyl); 6.65 (t,1H, aromatic ring); 7.32 (t,1H, aromatic ring); 7.44 (d,H,1H pyrrole ring); 7.95 (t,H,1H aromatic ring); 9.12 (s, NH, 1H aromatic amine); 9.64(s, OH, 1H phenol).
3		1.23 (s, CH_3, on pyrrole ring) 1.75 (s, CH_3, 3H on pyrrole ring); 2.68 (s, CH_3, on N-atom heterocyclic ring); 3.07 (t, CH_2, 2H on pyrrole ring); 3.14 (t, CH_2, 2H primary alcohol); 3.35 (s, OH, 1H); 7.25 (d,2H, aromatic ring); 7.32 (d,2H, aromatic ring);7.44 (d,2H, NH_2) 7.62 (d,H,1H pyrrole ring); 7.84 (t,H,1H aromatic ring).
4		2.05 (s, CH_3, 6H on two pyrrole ring); 3.17 (t, CH_2, 4H on two pyrrole ring); 3.26 (t, CH_2, 4H two primary alcohol); 3.32 (s, OH, 2H); 6.68 (s, NH_2, 2H) 7.92 (d, H, 1H pyrrole ring); 8.04 (d, H,1H pyrrole ring).
5		1.75 (t, CH_3, 3H on pyrrole ring);2.06 (t, CH_2, 2H on pyrrole ring); 2.10 (t, CH_2, 2H primary alcohol); 3.44 (s, OH, 1H); 7.33 (t,1H, aromatic ring); 7.49 (t,1H, aromatic ring); 7.57 (d,H,1H pyrrole ring); 7.88 (t,H,1H aromatic ring); 8.06(s, OH, 1H phenol); 10.10 (s, CO_2H, 1H).
6		2.29 (t, CH_3, 3H on pyrrole ring);3.07 (t, CH_2, 2H on pyrrole ring); 3.18 (t, CH_2, 2H primary alcohol); 3.36 (s, OH, 1H); 7.54 (t,1H, aromatic ring); 7.68 (d,H,1H pyrrole ring);8.05 (t,1H, aromatic ring); 8.62 (t,H,1H aromatic ring); 7.14(s, NH, 2H); 11.52 (s, SO_3H, 1H).

Also, the compounds (3-nitrobenzaldehyde, vanillin, 3-anisaldehyde) were used to convert the amine group in compound (1) into Schiff bases (7–9) in the presence of drops of glacial acetic acid, and the mixture was refluxed for 3 hours by the mechanism shown below [30].



Scheme 1. The Mechanism of preparation Schiff base

The infrared spectrum showed bands for the alcohol (OH) group at 3397–3209 cm^{-1} and for the (C=N) imine and imidazole ring between 1707–1632 cm^{-1}, besides the disappearance of the stretching bands of the two amine groups as in Tables 6 and 7 showing the IR and NMR spectra.

Table 6. IR. The spectra for compounds (7-9)

		IR, KBr, γ (cm^{-1})					
Comp. No	**R**	**OH**	**C-H Aromatic**	**C-H aliphatic**	**C=N,**	**C-O**	**Other**

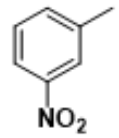
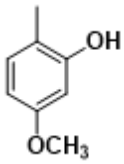
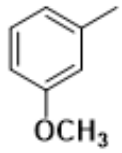
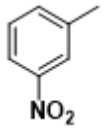
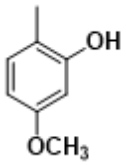
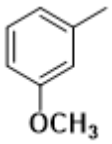
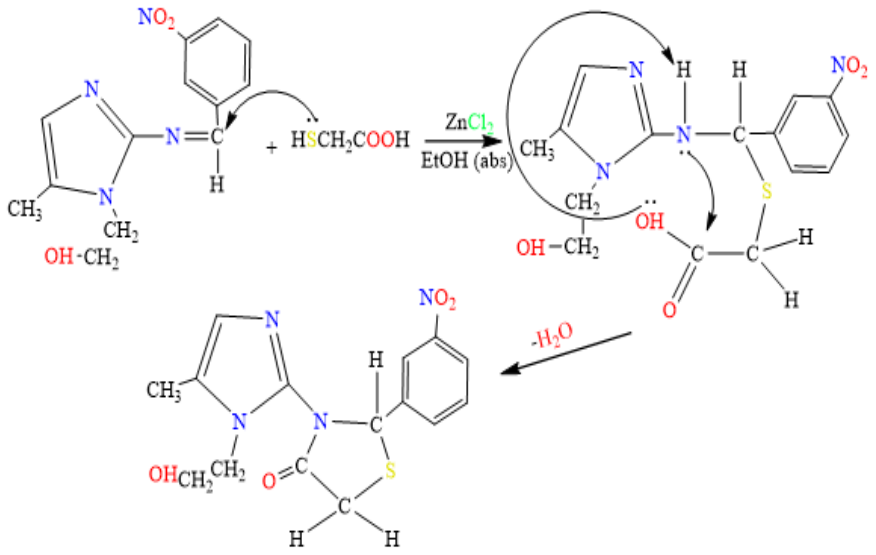
				C=N cyclic			
7		3209	3099	2981, 2847	1707, 1635	1072	1553,1366 Sym. & Assy. NO_2
8		3213	3043	2976, 2834	1659, 1632	1072	1201,1113 Sym. & Assy. C-O-C
9		3397	3083	2990, 2851	1651, 1633	1078	1237,1121 Sym. & Assy. C-O-C

Table 7. 1H-NMR spectra for compounds (7-9)

Comp. No	R	^{1}H NMR (ppm) – DMSO-d6
7		1.94 (t, CH_3, 3H on pyrrole ring);2.42 (t, CH_2, 2H on pyrrole ring); 2.78 (t, CH_2, 2H primary alcohol); 3.67 (s, OH, 1H); 4.39 (s, N=CH, 1H); 7.59 (t,1H, aromatic ring); 7.79 (t,1H, aromatic ring); 7.90 (d,H,1H pyrrole ring); 8.02 (d,H,1H aromatic ring); 8.11 (d,H,1H aromatic ring).
8		2.41 (t, CH_3, 3H on pyrrole ring);2.45 (t, CH_2, 2H on pyrrole ring); 2.58 (t, CH_2, 2H primary alcohol);3.68 (s, OCH_3,3H); 3.78 (s, OH, 1H); 4.35 (s, N=CH, 1H); 6.60 (t,1H, aromatic ring); 7.20 (t,1H, aromatic ring); 7.24 (d,H,1H aromatic ring); 8.02 (d,H,1H pyrrole ring); 9.51 (s,OH,1H phenol ring).
9		1.94 (t, CH_3, 3H on pyrrole ring);2.45 (t, CH_2, 2H on pyrrole ring); 2.54 (t, CH_2, 2H primary alcohol);3.67 (s, OCH_3,3H); 3.75 (s, OH, 1H); 4.40 (s, N=CH, 1H); 6.94 (t,1H, aromatic ring); 7.23 (t,1H, aromatic ring); 7.44 (d,H,1H aromatic ring); 7.48 (d,H,1H aromatic ring); 8.06 (d,H,1H pyrrole ring).

Thioglycolic acid was used to convert the C=N bond in compounds (7–9) into thiazolidine-3-one (10, 11) heterocyclic compounds in the presence of anhydrous zinc chloride, and the mixture was refluxed for 6 hours. The reaction is summarized by the mechanism shown below [31].



Scheme 2. Mechanism of preparation of Thiazolidine.

According to the infrared spectrum, bands for compounds (10 & 11) appear at 3387–3211 cm^{-1} for the alcohol (OH) group, 1735 cm^{-1} for the C=O group, and 1648–1654 cm^{-1} for the (C=N) group in the imidazole ring, and the C=N stretching band from the ring disappears. Additionally, nuclear magnetic resonance data show the same ranges as indicated in Table 9. All spectroscopic information is shown in Table 8.

Table 8. IR. Spectra for compounds (10-12)

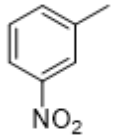
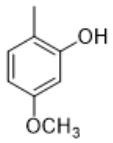
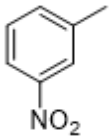
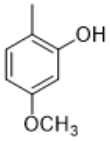
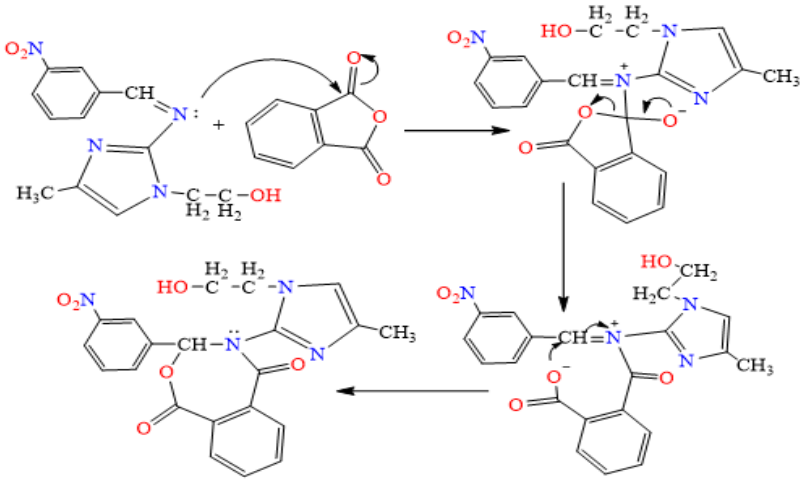
		IR, KBr, γ (cm^{-1})							
Comp. NO.	**R**	**OH**	**C-H Aromatic**	**C-H aliphatic**	**C=O**	**C=N**	**C-O**	**C-S-C**	**Other**
10		3211	3061	2981, 2938	1735	1648	1032	1157, 1003	1534,1366 Sym. & Assy. NO_2
11		3387	3063	2981, 2849	1735	1654	1072	1157, 989	1240,1036 Sym. & Assy. C-O-C
12	--	3152	3068	2868, 2826	1700, 1668	1606	1070	--	1526,1386 Sym. & Assy. NO_2

Table 9. 1H-NMR spectra for compounds (10-12)

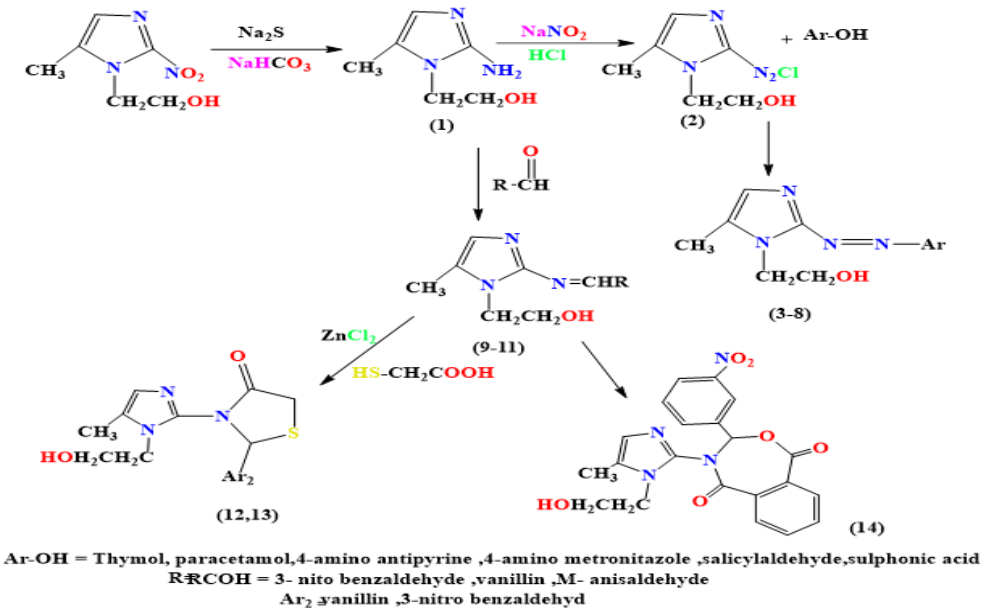
Comp. NO.	**R**	**^{1}H NMR (ppm) – DMSO-d6**
10		1.90 (t, CH_3, 3H on pyrrole ring);2.17 (t, CH_2, 2H on pyrrole ring); 2.49 (t, CH_2, 2H primary alcohol); 3.03 (s, CH, 1H thiazolidine ring); 3.36 (s, OH, 1H); 3.95 (s, CH_2-C=O, 2H thiazolidine ring); 7.12 (t,1H, aromatic ring); 7.55 (t,1H, aromatic ring); 7.92 (d,H,1H pyrrole ring); 8.01 (d,H,1H aromatic ring); 8.46 (d,H,1H aromatic ring).
11		1.91 (t, CH_3, 3H on pyrrole ring);1.97 (t, CH_2, 2H on pyrrole ring); 2.00 (t, CH_2, 2H primary alcohol); 2.10 (s, CH, 1H thiazolidine ring); 3.36 (s, OH, 1H); 3.44 (s, OCH_3,3H); 3.90 (s, CH_2-C=O, 2H thiazolidine ring); 7.14 (t,1H, aromatic ring); 7.37 (t,1H, aromatic ring); 7.93 (d,H,1H aromatic ring); 8.16 (d,H,1H pyrrole ring); 9.40 (s,OH,1H phenol ring).
12	--	2.08 (t, CH_3, 3H on pyrrole ring);2.34 (t, CH_2, 2H on pyrrole ring); 2.54 (t, CH_2, 2H primary alcohol); 3.28 (s, CH-O, 1H oxazipane ring); 3.36 (s, OH, 1H); 7.44 (t,1H, aromatic ring); 7.53 (t,1H, aromatic ring); 7.95 (d,H,1H pyrrole ring); 8.05 (d,H,1H aromatic ring); 8.07 (d,H,1H aromatic ring).

Also, one of the prepared Schiff bases (3-nitrobenzene) was converted into the oxazepane ring (12) using phthalic anhydride and the mechanism below shows the course of the reaction: [31]



Scheme 3. Mechanism of preparation of Oxazepine

The IR spectra showed specific bands for compound (12) at 3152 cm^{-1} for the (OH) group, 1700 and 1668 cm^{-1} for the C=O group, and 1606 cm^{-1} for the (C=N) group in the imidazole ring. This is followed by the lose of the C=N stretching band outside the ring(32)(33). Tables 8 and 9 show the IR and NMR spectra for compound (12). The following synthetic route was used to create each compound:



Scheme 4. The Synthetic route of compounds

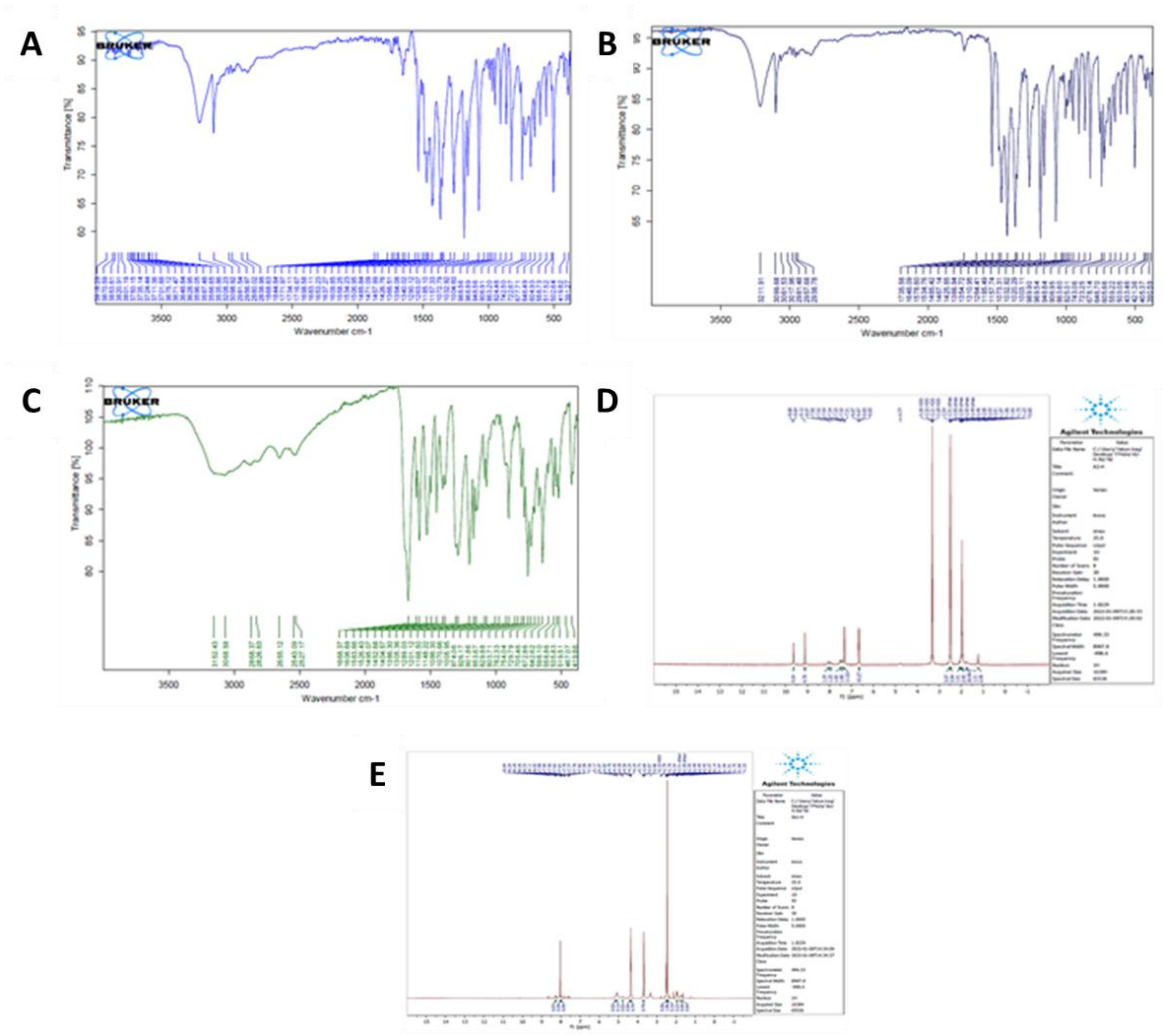


Figure 1. A. IR Spectra for compound (2); B. IR Spectra for compound (10); C. IR Spectra for compound (12); D. 1H-NMR Spectra for compound (2); and E. 1H-NMR Spectra for compound (7)

Conclusion

Using *Metronidazole* as a starting material, many new compounds were prepared makingf heterocyclic organic compounds with novel derivatives. Reducing the nitro group in *Metronidazole* to an amine group and then converting it into diazonium salts was the first step in the synthesis of these compounds. Furthermore, new derivatives of heterocyclic compounds were produced by utilizing Schiff bases. All synthetic compounds were identified and characterized using Infrared Spectroscopy (IR) and Proton Nuclear Magnetic Resonance (^{1}H NMR).

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Conflict of Interest

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

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