Chemical Methodologies 5(2021) 416-421

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research Article

Modification of Creatinine to Form New Oxazepane Ring and Study Their Antioxidant Activity

Raed M. Muhiebes[1,*], Entesar O.Al-Tamimi[2]

[1]*Department of Biochemistry, College of Medicine, University of Misan, Iraq*
[2]*Department of Chemistry, College of Science, University of Baghdad, Jadiriya, Baghdad, Iraq*

ARTICLE INFO

Article history

Submitted: 2021-07-20
Revised: 2021-08-04
Accepted: 2021-08-12
Manuscript ID: CHEMM-2107-1353
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Behrouz Jamalvandi
Editor who approved publication:
Dr. Abdolkarim Zare

DOI: 10.22034/chemm.2021.135020

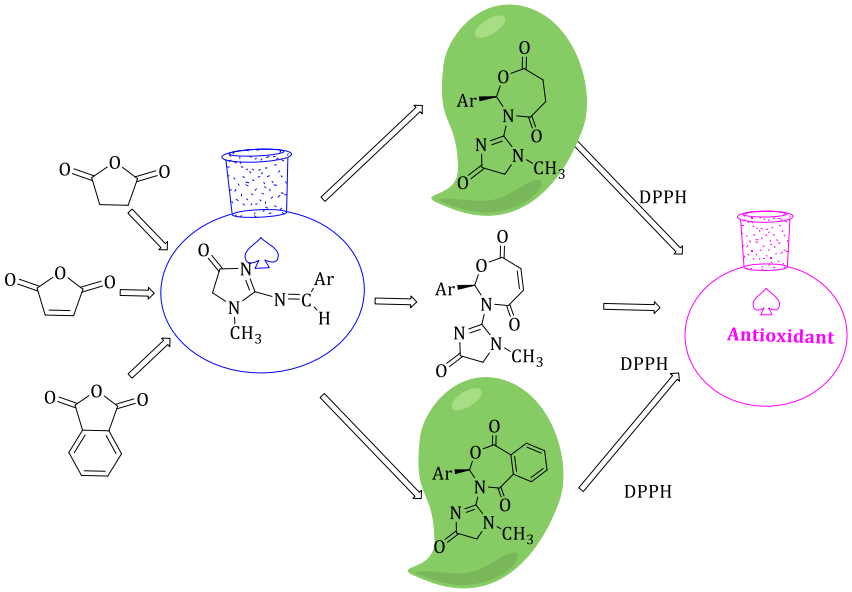
KEYWORDS

Schiff base
Oxazapane derivatives
Antioxidant activity

ABSTRACT

In this research new creatinine Schiff bases (1a, 1b, and 1c) were synthesized from the reaction of aromatic aldehydes (4-nitrobenzaldehyde,4-amino benzaldehyde, and cinnamaldehyde) with creatinine, in few drops of glacial CH_3COOH as a catalyst in C_2H_5OH. Then, seven-member rings were prepared (oxazepine) (2a-4c) on creatinine form treatment of imines with (phthalic, maleic, and succinic anhydrides. Synthesized compounds were identified by IR, melting point, and ^{1}H-NMR of some of them. Some of the prepared compounds were studded with antioxidant activity.

GRAPHICAL ABSTRACT



* Corresponding author: Raed M. Muhiebes
✉ E-mail: raadmuslim7@gmail.com
© 2021 by SPC (Sami Publishing Company)

Introduction

Azomethines are types of compounds that contain an imine group, synthesized from condensation of a $^{0}1$ aliphatic and aromatic amine with aldehydes and ketones. They are widely used as starting materials in the preparation of organic, bio-organic, organometallic, and industrial compounds via ring closure, cycloaddition, and substitution reactions [1-3]. Oxazepine derivatives were presented in 1965 to be used in mental ease characterized by anxiety and stress [4]. Oxazepine is an unsaturated seven membered containing heteroatoms O and N in the positions (1) and (2), respectively, in addition to 5 carbon atoms. It is prepared by the pericyclic cycloaddition of the imine with anhydrides [5]. Oxazepine and derivatives have medical and biological applications [6]. Oxazepine derivatives were found to exhibit a vast variety of biological activities like antibacterial, antifungal, hypnotic muscle relaxant, antagonistic, inflammatory and antiepileptic [7].

Material and methods

All starting chemical compounds were obtained from Fluka, Sigma- Aldrich, Alfa Aesar, Japan and BDH and used without further purification. The Stuart melting point apparater was used to measure melting points. IR Affinity-1 Shimadzu as KBr disc, results are given in cm^{-1}, ^{1}HNMR Bruker Spectra spin ultra-shield magnets 300 MHz instruments, using DMSO-d_6 solvent and TMS as an internal reference used to identify the organic inhibitor.

Synthesis of new Schiff bases (1a, 1b, 1c) [8]

New imines are prepared from the reaction of creatinine (0.5 g, 0.1 mol), with different aldehydes (0.1 mol), in 25ml absolute C_2H_5OH and trace of CH_3COOH. This mixture was refluxed for (10-12 hrs). The excess solvent was evaporated and the formed product was recrystallized from EtOH.

Synthesis of oxazepine derivatives (2a-4c) [9]

A mixture of Schiff base [1a, 1b, 1c] (0.01 mol) and (phthalic anhydride, maleic anhydride, and succinic anhydride (0.05 g, 0.01 mol) was dissolved in (25 ml) dry C_6H_6. The reaction mix was refluxed for (16-18 hrs.) at (70-75 °C). The excess solvent was evaporated and the formed product was recrystallized from CH_3CH_2OH.

Determination of Antioxidant Capacity [10]

The experiment was performed using the modified blois method for DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging activity (1958). 2 ml of aqueous extracts at various concentrations were combined with 1ml of a 0.1 mM DPPH solution in methanol (Alfa Aesar, Japan) (250-1000 PPM). After that, the mixture was incubated for 30 minutes in the dark at room temperature. 1 cc of DPPH solution was mixed with distilled water to make the control. A spectrophotometer was used to test the absorbance against a blank at 517 nm. Higher DPPH free radical scavenging activity is shown by a lower absorbance of the reaction mixture. The standard was ascorbic acid (Merck, India). Triplicate samples were made and quantified using the following equation; the percentage of scavenging activity of each extract on DPPH radical was estimated as percent inhibition of DPPH (1%):

$1\% = [(A_o - A_s)/A_o] \times 100$

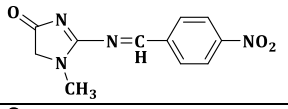
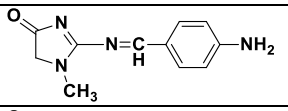
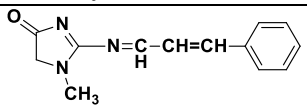
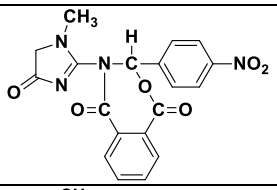
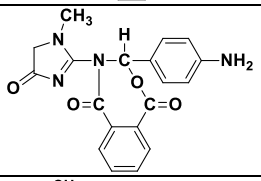
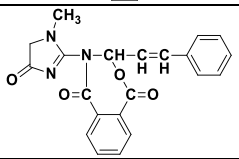
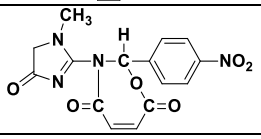
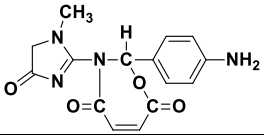
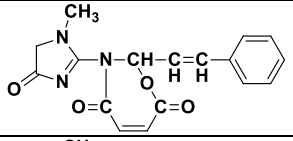
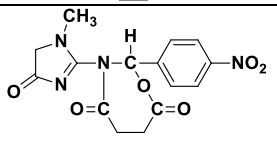
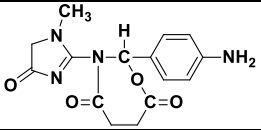
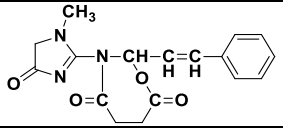
All physical properties are listed in Table 1.

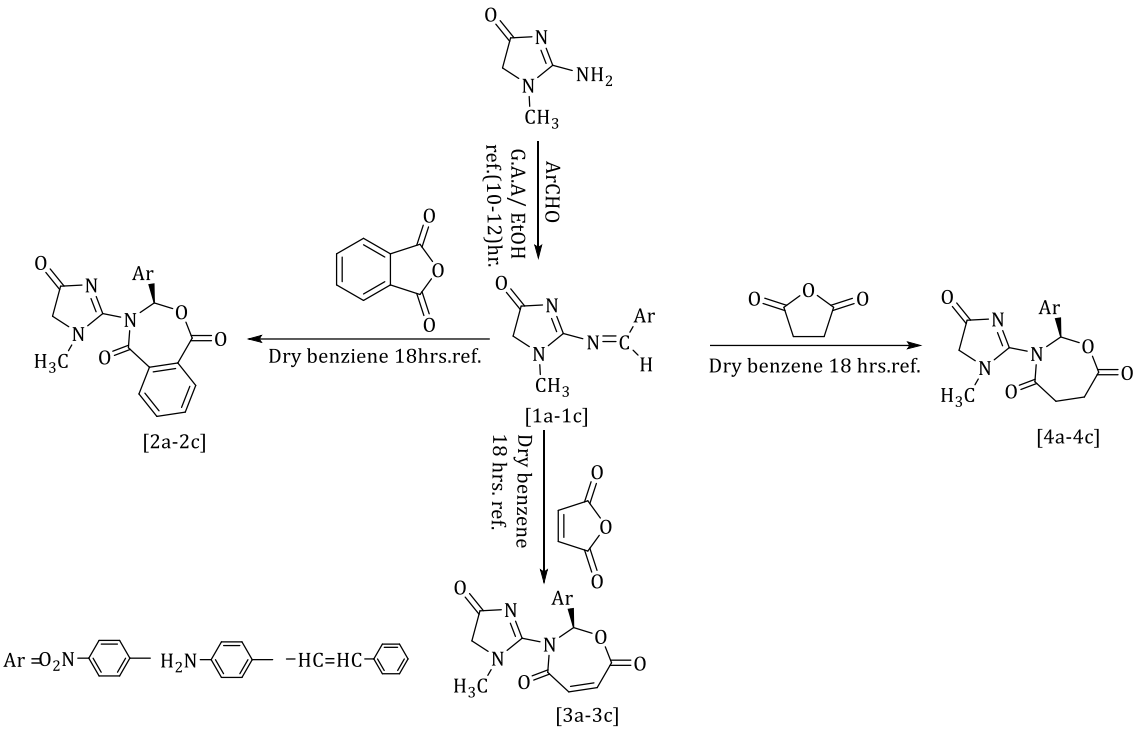
Result and Dissection

This research involved the synthesis of new oxazepine compounds from reaction of Phthalic, Maliec, Succunic anhydrides with Schiff bases. These different synthesized compounds that are presented are summarized in Scheme 1.

Compounds [1a-1c] were prepared from condensation of Creatinine with (4-nitrobenzaldehyde, 4-amino benzaldehyde, and cinnamaldehyde) in the presence of glacial acetic acids as a catalyst (Scheme1). Compounds [1a-1c] were afforded as white, brown and yellow colors of (90%, 88% and 75%) yields with a melting point of (220-222 °C, 230-232 °C and 182-184 °C), respectively.

Table 1: Some physical properties and FT-IR spectral data $cm^{-1}$of syntheses compounds (1a-4c)

No.	Structure	m.p. ^0C	Color	Yield%	Major FT-IR Absorption Cm-1						
					1/ν(C-H) aromatic 2/ν(C-H)	ν(C=O) (ester ring)	ν(C=O) (amide ring)	1/ν(C=N) 2/ν(C- N)	1/ ν(C-O) 2/ν(O-C-O)	ν(C=C) arom.	Other bands
1a		220- 222	White	90	1/3043 2 /2910	---	1701	1/ 1668 2/ 1336	1244 1140	1506 1593	ν(NO_2) 1500 1336
1b		230- 232	Brown	88	1/ 3060 2/ 2906	---	1693	1/ 1662 2/1352	1244 1150	1507 1594	ν(NH_2) 3421
1c		182- 184	yellow	75	1/ 3028 2 /2927	---	1701	1/ 1660 2 /1338	1240 1145	1577 1594	ν(C-H) olef. 1635
2a		172-174	white	90	1/ 3040 2/2945	1745	1705	1/ 1654 2/ 1361	1/123 2 2/108 7	1600 1556	ν(NO_2) 1555 1361
2b		136- 138	Orange	90	1/ 3091 2/ 2900	1764	1697	1/ 1685 2/ 1359	1/ 1259 2/ 1109	1500 1585	ν(NH_2) 3421
2c		170- 172	yellow	70	1/ 3030 2/ 2897	1764	1697	1/ 1610 2/ 1361	1/ 1259 2/ 1170	1508 1585	ν(C=C) olef. 3084
3a		200-202	Off white	85	1/ 3059 2/ 2926	1750	1707	1/ 1637 2/ 1359	1/126 5 2/110 9	1500 1593	ν(NO_2) 1520 1370
3b		164-166	Orange	66	1/ 3059 2/ 2933	1720	1707	1/ 1618 2/ 1396	1/ 1240 2/ 1107	1523 1600	ν(NH_2) 3356
3c		120- 122	Brown	55	1/ 3201 2/ 2927	1745	1707	1/ 1637 2/ 1361	1/126 5 2/105 6	1500 1593	ν(C=C) olef. 3059
4a		180-182	Off white	50	1/ 3040 2/ 2931	1740	1697	1/ 1620 2/ 1340	1/123 6 2/117 6	1500 1600	ν(NO_2) 1311 1510
4b		178-180	yellow	60	1/ 3040 2/ 2931	1760	1697	1/ 1630 2/ 1330	1/ 1245 2/ 1118	1508 1575	ν(NH_2) 3421
4c		108-110	yellow	60	1/ 3059 2/ 2931	1770	1699	1/ 1620 2/ 1350	1/ 1255 2/ 1178	1500 1595	ν(C=C) olef. 3130



Scheme 1: synthesis of subs. heterocyclic on creatinine

The antioxidant activity of compounds [1a-1c] in the Figure (1a) shows the high antioxidant reactivity of compound 1c (Figures 1, 2, and 3).

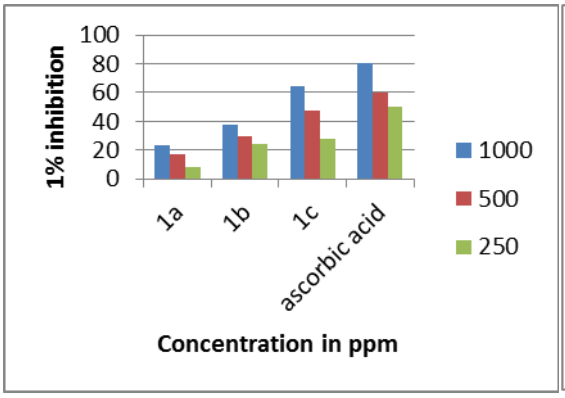


Figure 1: 1% inhibition Schiff bases (1a, 1b, 1c)

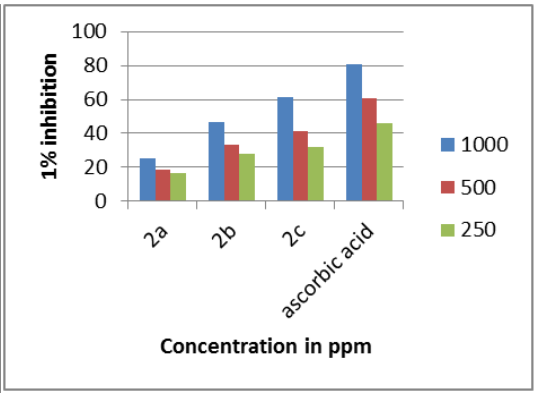


Figure 2: 1% inhibition of oxazepine (2a, 2b, 2c)

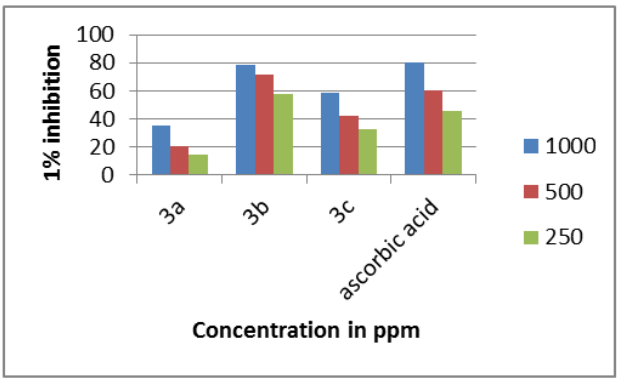


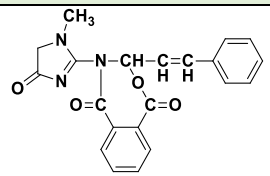
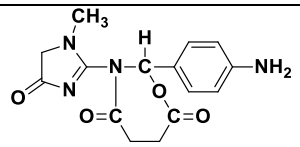
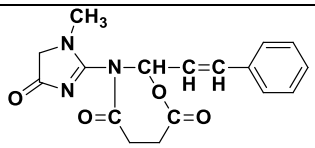
Figure 3: 1% inhibition of oxazepine (3a, 3b, 3c)

The FT-IR spectrum data of compounds (1a-1c) show the vanishing of the carbonyl group of the CHO at 1680-1710 cm^{-1} and appearance of 1660-1668 cm^{-1} bands indicative of the formation of (C=N) group [11]. Compounds [1a-1c] were reacted with Phthalic, Maliec, and Succunic anhydrides to give oxazepine derivatives [2a-4c] in dry benzene as a solvent.

The FT-IR spectrum data of the (2a-4c) show the vanishing of the stretching absorption bands of the (C=N) group of the imine compounds and the absorption bands seven-membered compounds and show the appearance of the stretching absorption bands at 1770-1720 cm^{-1} indicative of lactone boned formation besides the characteristic bands of the remained groups in the structure [12], FT-IR spectrum date of compounds [2a-4c] as shown in Table 1.

The ^{1}H-NMR spectrum of compound 2b in DMSO showed δ(ppm), singlet in 2.25 (3H, N-CH_3) protons of imidazole ring, singlet in 3.03 (2H, CH_2-C=O), singlet in 3.80 (1H, N-CH-O), singlet in 3.12(2H, Ar-NH_2) multiple in 7.38-7.82 (8H, Ar-H), and spectrum of compound 4a showed δ(ppm) at singlet in 2.75 (3H, CH_3), singlet in 2.96 (2H, CH_2), singlet in 3.81 (1H, -CH), triplets in 2.13 (2H, CH_2=CO-N), triplets in 2.34(2H, CH_2=CO-O), and multiples in 7..23-7.73 (4H, Ar-H). Other chemical shifts, δ (ppm) of compounds 2c, 4b, 4c, are given in Table2.

Table2: ^{1}HNMR spectral data for some synthesized derivatives

Structure	^{1}HNMR signals data,δ(ppm)
	2.65(s,3H,N-C<u>H</u>$_3$),2.91(s,2H,C<u>H</u>$_2$),3.84-3.87(d,1H,C<u>H</u>),5.31-5.41(t,1H,C<u>H</u>=CH-Ar),5.59-5.61(d,1H,CH=C<u>H</u>-Ar), 6.49-7.72(m,9H,Ar-<u>H</u>)
	1.35 (s,3H ,N-C<u>H</u>$_3$),2.89 (s,2H ,C<u>H</u>$_2$),3.12(s,1H ,C<u>H</u>),3.34-3.68(t,2H,C<u>H</u>$_2$C=O)4.16 (s,2H , N<u>H</u>$_2$),7.21-8.08 (m,4H , Ar-<u>H</u>)
	1.21(s,3H,N-C<u>H</u>$_3$),2.39(s,2H,C<u>H</u>$_2$),2.75(d,1H,C<u>H</u>),3.11-3.48(t,1H,C<u>H</u>=CH-Ar),3.67-4.07(t,2H,C<u>H</u>$_2$C=O)6.48-6.54(d,1H,CH=C<u>H</u>-Ar),7.30-8.12(m,5H,Ar-<u>H</u>)

Conclusion

The antioxidant activity of the compounds was compared with standard ascorbic acid. Among the newly synthesized Schiff bases and oxazepine derivatives, compounds (1c, 2c, and 3b) possess better antioxidant activity than compounds (1b, 1a, 2b, 2a, 3a and 3c), as shown in Figures 1a, 1b and 1c.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

References

[1]. Amina M., Tariq M., Elsegood M.R., Weaver G.W., *J. Nucl. Med. Radiat. Ther.,* 2016, **7**:1 [PDF], [Google scholar]

[2]. Hussain Z., Yousif E., Ahmed A., Altaie A., *Org. Med. Chem. Lett.,* 2014, 4:1 [Crossref], [Google scholar], [Publisher]

[3]. Mangalam K.R., *Int. Res. J. Pharm.,* 2018, **9**:153 [Crossref], [Google scholar], [Publisher]

[4]. Zhao X., Zhang J., Zheng Z., Xu R., *Molecules* 2017, **22**:53 [Crossref], [Google scholar], [Publisher]

[5]. Deka M.J., Indukuri K., Sultana S., Borah M., Saikia A.K., *J. Org. Chem.,* 2015, **80**:4349 [Crossref], [Google scholar], [Publisher]

[6]. Bera T., Singh B., Hamlin T.A., Sahoo S.C., Saha J., *J. Org. Chem.,* 2019, **84**:15255 [Crossref], [Google scholar], [Publisher]

[7]. Nihad T.I., *Int. J. Org. Chem.,* 2017, **7**:219 [Crossref], [Google scholar], [Publisher]

[8]. Mumtaz A., Mahmud T., Elsegood M.R., Weaver G.W., *J. Nucl. Med. Radiat. Ther.,* 2016, **7**:6 [PDF], [Google scholar]

[9]. Ahmed A., Mahdi S., Hussein A., Hamed A., Yousif E., *Al-Nahrain J. Sci*., 2015, **18**:22 [Crossref], [Google scholar], [Publisher]

[10]. Deepshikha G., *Int. J. Pharm. Sci. Res.,* 2015, **6**:546 [PDF], [Google scholar]

[11]. Budevska B.O., Sum S.T., Jones T.J., *Appl. Spectrosc*., 2003, **52**:124 [Crossref], [Google scholar], [Publisher]

[12]. Keller W.D., Lusebrink T.R., Sederholm C.H., *J. Chem. Phys.,* 1966, **44**:782 [Crossref], [Google scholar], [Publisher]

HOW TO CITE THIS ARTICLE
Raed M. Muhiebes, Entesar O.Al-Tamimi. Modification of Creatinine to Form New Oxazepane Ring and Study Their Antioxidant Activity, Chem. Methodol., 2021, 5(5) 416-421
DOI: 10.22034/chemm.2021.135020
URL: http://www.chemmethod.com/article_135020.html