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Chemical Design, Synthesis And Biological Evaluoation Of Mutual Prodrug Of Gabapentin With Different Types Of Phenolic And Alcoholic Antioxidants

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ABSTRACT

This work concern about finding the best effective way to optimizing therapeutic characteristics of gabapentin, by retarding neuronal and gastrointestinal adverse effects through masking of carboxyl group chemically, and increase its analgesic This is achieved by design and synthesis different types of ester derivatives of gabapentin as mutual pro drugs with some of phenolic and alcoholic antioxidants. Pro moieties like; thymol and eugenol, umbilliferon and some other types of phenolic and alcoholic antioxidant ,with the aim of getting synergistic effect as these antioxidants considered as natural analgesic having analgesic and anti-inflammatory activity. The chemical structures of these compounds were confirmed and characterized using Fourier transform infrared spectroscopy (FTIR), 1H-NMR spectroscopy and some physicochemical parameters . The synthesized final compounds (3a–3g) were tested to evaluate their anti- inflammatory, antifungal and antibacterial activity against gram negative and gram positive bacteria. Anti-inflammatory activity in rats using egg-white induced edema method of inflammation . All of the synthesized compound showed anti-inflammatory activity compared to the control group (dimethyl sulfoxide) and gabapentin ; however eugenol conjugate (3f) and thymol conjugate (3a) demonstrate more significant anti-inflammatory activity than the other derivative. The antibacterial and antifungal activity for these compounds evaluated by well diffusion method and the results revealed that compound 3a have the best antibacterial and antifungal activity

Keywords: gabapentin , anti-bacterial, Mutual prodrug

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INTRODUCTION

Gabapentin [1-(aminomethyl)cyclohexane acetic acid] is an anti-epileptic agent, originally developed as a gamma-aminobutyric acid (GABA)-mimetic compound to treat spasticity, and has been shown to have potent anticonvulsive effects. Initially approved only for use in partial seizures, it soon showed great promising results in the pain relieve of chronic syndromes, especially neuro-pathic pain. It is a novel drug used for the treatment of postoperative pain with antihyperalgesic properties and a unique mechanism of action. Gabapentin and the related, more potent compound pregabalin have been shown to be beneficial in the treatment of neuropathic pain as well as postoperative pain following spinal surgery and hysterectomy[1,2].

Gabapentin bioavailability and pharmacokinetics properties varias with the dose decreases from about 60% at a 300 mg dose to about 35% at dose 1000 mg, and The free acidic –COOH in its structure is responsible in a great deal for the gastric irritation and other gastrointestinal problem's by most of the traditional analgesics.[3,4]

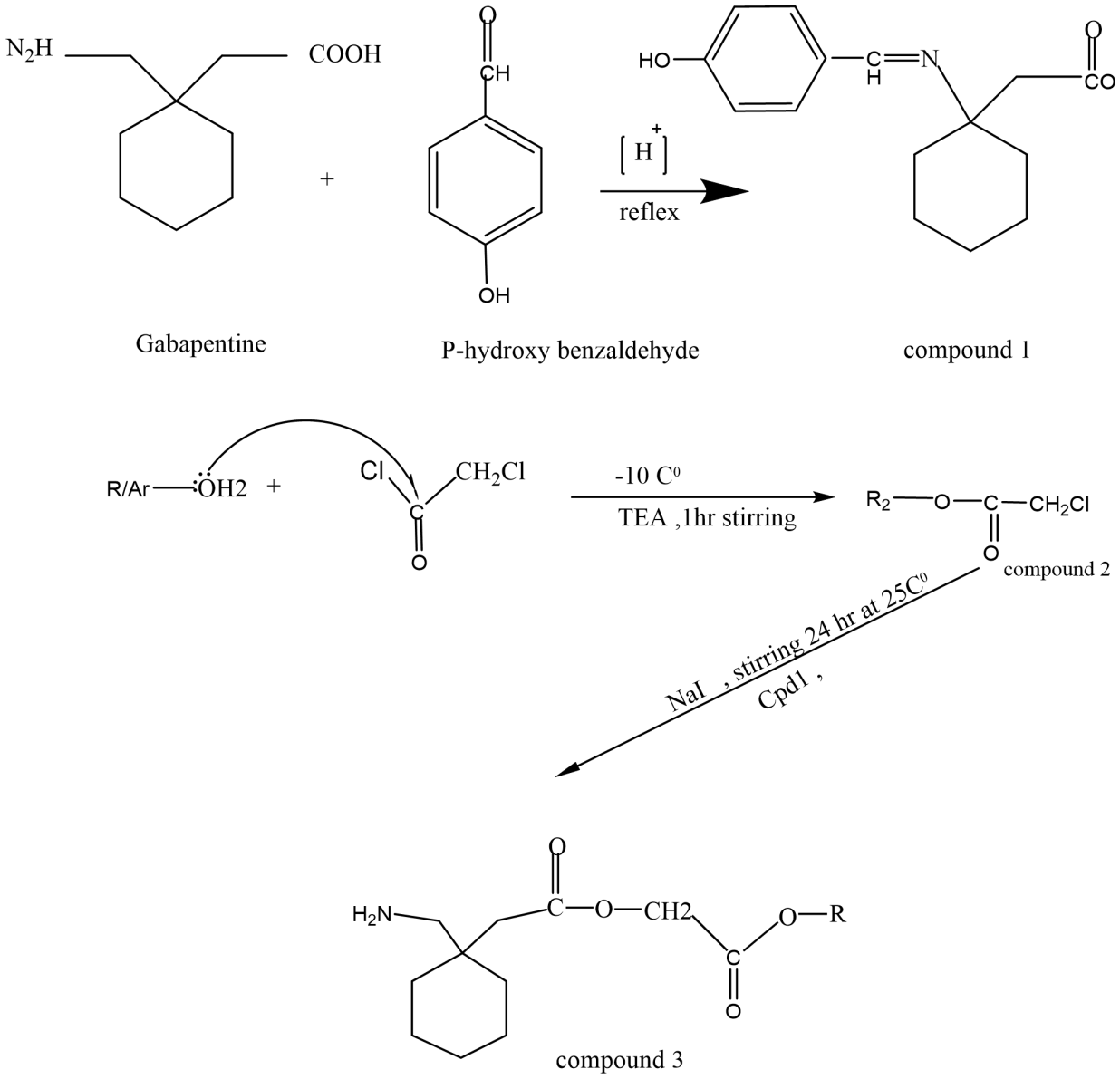
To overcome these pharmaco-kinetic limitations, gabapentin has been designed as a gabapentin prodrug, by combining it with different types of natural phenolic and alcoholic antioxidant with the aim of increasing its efficacy by getting synergistic effect as these antioxidants considered as natural analgesic having analgesic and anti-inflammatory activity which is absorbed by high-capacity nutrient transporters throughout the small and large intestines, and is rapidly and extensively converted by nonspecific esterase to gabapentin, delivering dose up to twice daily[5].

The target compounds are designed as mutual prodrug of different types of alcoholic and phenolic antioxidants that are conjugated with gabapentin, a well known anticonvulsant and neuro-analgesic drug, through acetyl spacer[6,7]. Gabapentin was reacted with p-hydroxy benzaldehyde to protect the free amine group via converting it to imine (gabapentin - schiff base).

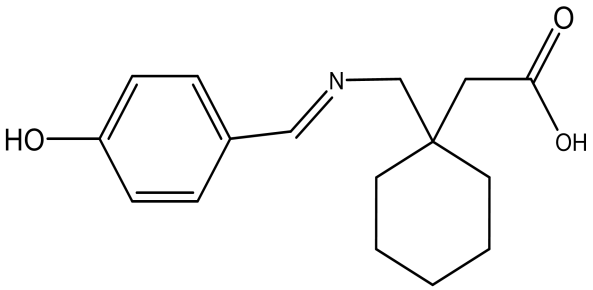
On the other hand different types of antioxidant of the mutual prodrugs like(Menthol,thymol,Eugenol,guaicol,sesamol,umbiliferon and vanillin) were synthesized using acetyl spacer (-OCH2COO-) .[7]

MATERIALS AND METHODS

gabapentin(as free drug) and antioxidants bought from Hyper Chem company (China). Solvent and other reagent that used through reaction were bought from the chemicals store of college of the pharmacy. The monitoring of the reactions was done by thin layer chromatography (TLC), the mobile phase solvent systems used are toluene : ethyl acetate (2:1) .Electronic melting point apparatus (Stuart SMP30) was used to determine all melting points in this study. FTIR spectrophotometer (Schimadzu, Japan), were done by thin film technique. 1H-NMR spectra were obtained on BRUKER model Ultra shield 500 MHz spectrophotometer, using Dimethyl sulfoxide (DMSO) as a solvent.



2.3.1: Synthesis of gabapentin- p-OH- benzaldehyde schiff base (compound1)[8,9,10]



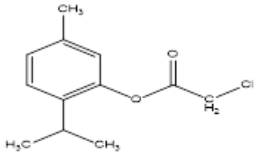
In (100ml) round bottom flask equipped with stirrer and reflux condenser, solution of gabapentin (1.723g / 10 mmol) in absolute methanol (99%) (40ml) was added, then a mixture of 10 mmol p-hydroxy benzaldehyde 1.22 gm and one to three drops of glacial acetic acid in absolute methanol (3ml) was added drop wise to the first solution. The reaction mixture was reflex for (5 hr). After the completion of the reaction, methanol was removed by rotary evaporator; yellow residue was collected and recrystallized from absolute ethanol (99%) to give yellow crystals of compound.

Synthesis of antioxidant-chloroacetyl chloride derivatives comp.2(a-g)[11,12]

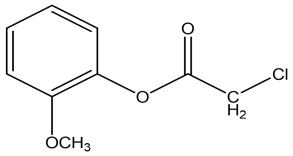
An appropriate amount of each antioxidant 10 mmole[1.5 gm (a-thymol) -1.24gm (B-guaiacol)- 1.56gm (c-menthol)- 1.6 (d-vanillin)-1.38gm (e-sesamol)-2.406gm (f-eugenol)-1.6gm (g-umbiliferon)was mixed respectively with trimethylamine (0.01mole,1.4ml), 25ml of dichloromethane was placed above the mixture in a round bottom flask and then the mixture was cooled to -10°C, using an ice bath . A mixture of chloroacetylchloride (0.01mole/0.8ml) in chloroform 25ml was prepared and was added drop-wise to the antioxidant mixture over a period of 1hr., with continuous stirring, the temperature of reaction mixture was kept at -10ºC during the addition; the resultant mixture was stirred over night at -10°C. Then washing using separatory funnel with three different solutions as follows; 5% HCl (3×50 ml), 5% NaOH (3×50 ml), Brine solution (2×25ml). The intermediate of the antioxidant-chloroacetylchloride was collected by evaporating the solvent using a hot air stream. Then recrystallization of the resultant intermediate was done with petroleum ether (60-80) °C and ethyl acetate (25:1)

Synthesis of mutual prodrugs (gabapentin-antioxidant) [13]

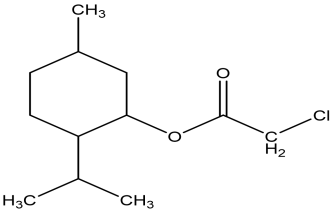
(a) 2-isopropyl-5-methylphenyl 2-chloroacetate
Thymol-chloroacetyl derivative



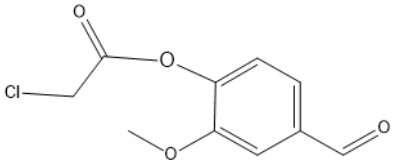
(b) 2-methoxyphenyl 2-chloroacetate
Guaiacol- chloroacetyl derivative



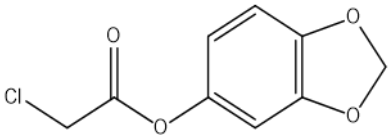
(c) 2-isoprpyl-5-methylcyclohexyl 2-chloroacetate
Menthol- chloroacetyl derivative



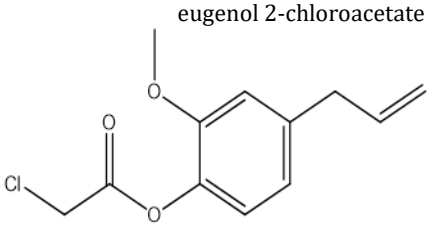
(d) 4-formyl-2-methoxyphenyl 2-chloroacetate
Vanillin-chloroacetyl dervative



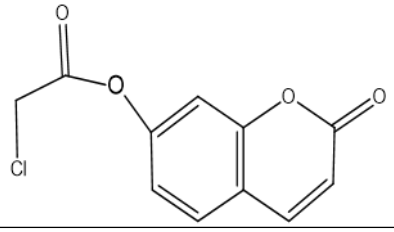
(e) benzo[d][1,3]dioxol-5-yl 2-chloroacetate
sesamol2-chloroacetate



4-allyl-2-methoxyphenyl 2-chloroacetate
eugenol 2-chloroacetate



(g) 2-oxo-2H-chromen-7-yl 2-chloroacetate
Umbiliferon 2-chloroacetate



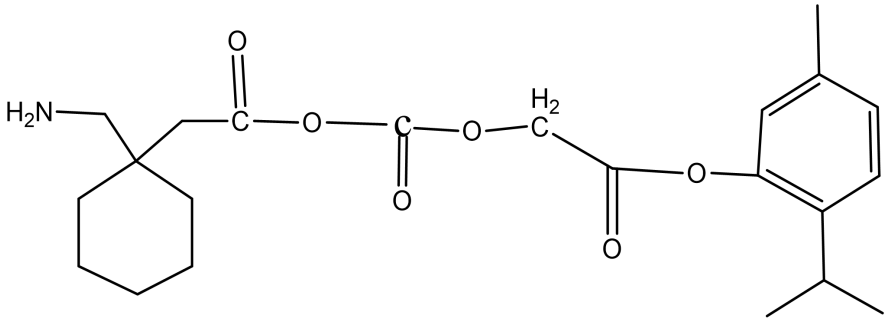
The following mixtures were prepared:

- Compound 1 [10 mmole/ (2.75gm).
- Compound 2 Chloro - acetyl derivatives 10 mmole [2.267gm (***a***) - 2.006gm (***b***) - 2.327gm (***c***)-2.29gm ***(d)***- 2.14 gm ***(e)*** – 2.40gm ***(f)*** - 2.38***(g)***].
- TEA (10 mmole/1.4ml).
- sodium iodide (10mmole/1.5gm).

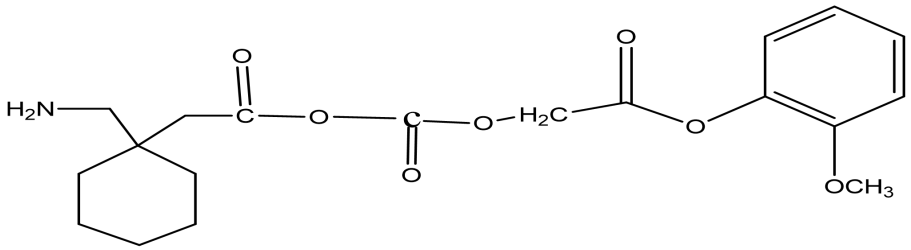
All mixtures were stirred overnight at 25 C. Then after, poured down into ice slush, stirred, and extracted using Chloroform solution (25 ml, used four times).

The resultant organic layer was washed over with 50 ml of 2% Sodium Thiosulphate (used three times), 50 ml of 5% Sodium Hydroxide (used three times), 50 ml of 5% Hydrochloride (also used three times), and finally washed with 25 ml of Brine solution (used twice). The organic layer dried over anhydrous sodium sulphate and was filtered using under pressure circumstances to remove the solvent to obtain the Gabapentin – anti oxidant mutual prodrugs (*3a,3b,3c,3d,3e,3f,3g*). The derivatives then re – crystallized from Petroleum Ether and Ethyl – Acetate (25:1).

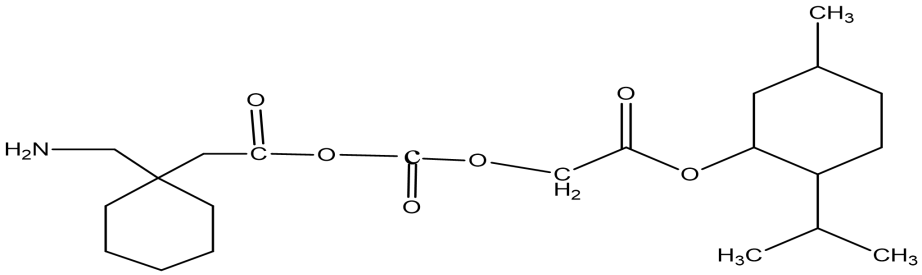
(3a) *2-isopropyl-5-methylphenyl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)*



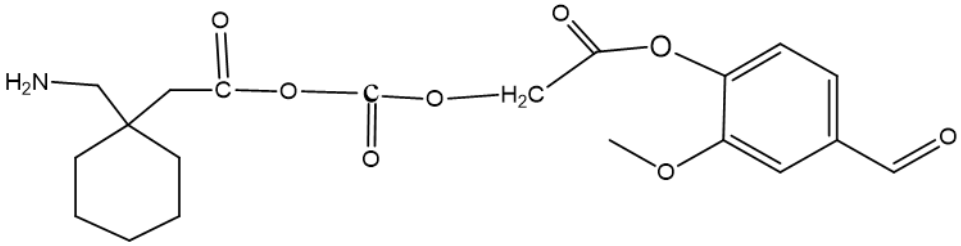
3B) 2- methoxyphenyl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)



(3C) 2- isopropyl-5-methylcyclohexyl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)

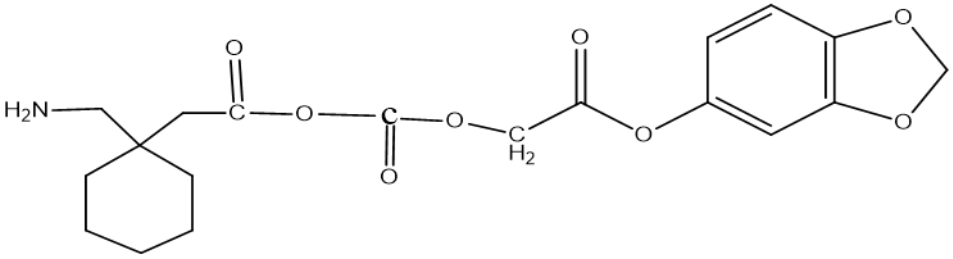


(3d) *4-formyl-2-methoxyphenyl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)*

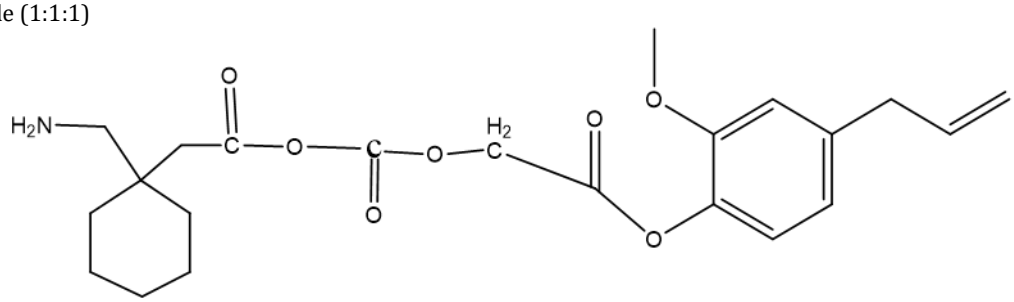


(3e)

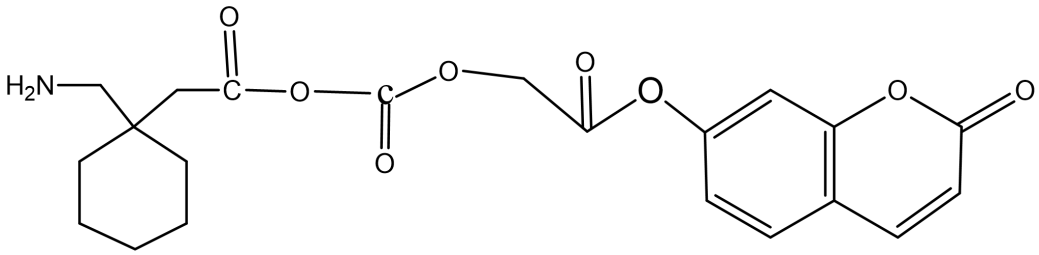
benzo[d][1,3]dioxol-5-yl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)



(3f) 4-allyl-2-methoxyphenyl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)



(3g) *2-oxo-2H-chromen-7-yl 2-methoxyacetate compound with methyl 2-(1-(aminomethyl)cyclohexyl)acetate and formaldehyde (1:1:1)*



Compound (1) Yield = 85%, R*f* = 0.93, IR: 2858.51 and 2931.80(C-H) stretching vibration of aromatic, 1681.93 (C=O) stretching vibration of COOH, 1589.34 (C=N) stretching vibration of amide, 1523.76 (C=C) stretching vibrati0n of aromatic, 1450 and 1396.46 (OH) strtching vibration of carboxylic acid, 1311.59 bending .vibration of phenolic (OH) , 1176.58 (C-O) assym .stretching vibration. H^1NMR : 1.3-1.5(6H) Complex,protons of cyclohexane ring of gabapentin , 2.6-2.8(4H) Complex,protons of cyclohexane ring of gabapentin, 3.2(2H) S, protons of methylene group of gabapentin α to C=O group, 3.7(2H) S, protons of methylene group of gabapentin α to NH2 group, 4.9 (1H)Singlet, proton of phenolic group, 6.8-7.0(2H) Doublet, aromatic protons ortho to phenolic group, 7.2-7.5(2H) Doublet, aromatic protons ortho to imine group, 7.9(2H) Singlet,proton of imine group (Schiff base) , 9.9(1H) Singlet, proton of hydroxy group of benzaldehyde.

Compound (2a) Yield = 72%, R*f* = 0.93, IR: 2962, 2973 and 2873.94(C-H) stretching vibration of CH3 and CH2,1759.08(C=O) stretching vibration of ester, 1620, 1577,and 1504 (C=C) stretching vibration of aromatic, 1459(C-H) bending of CH3 & CH2, 1149.44(C-O) stretching vibration, 1234 Asymmetric (C–O–C) stretching vibration, 813 (C-Cl) stretching vibration

Compound (2b) Yield = 69%, R*f* = 0.91, IR

3005, (C-H) stretching vibration of aromatic,2951 and 2839(C-H) stretching vibration of CH3 1770 (C=O) stretching vibration of ester, 1604 and 1500 (C=C) stretching vibration of aromatic 1469 and1435 (C-H) bending of CH3 & CH2, 1195 and 1145 (C-O) stretching vibration, 1107 (C-O) stretching vibration of ether, 1257 Aryl(C-O) stretching vibration of aromaticEther, 756.10 (C-Cl) stretching vibration

Compound (2c) Yield = 80%, R*f* = 0.73, IR:

2954.95, (C-H) stretching vibration of CH3 and CH2 , 2920.23 and 2870.08(C-H) stretching vibration of CH3 and CH2 , 1735.93(C=O) stretching vibration of ester, 1454.33 and 1369.46(C-H) bending of CH3 & CH2, 1180 and 1149.57 (C-O) stretching vibration, 1303.88 Asymmetric (C–O–C) stretching vibration, 790 and 771.53(C-Cl) stretching vibration

Compound (2d) Yield = 65%, R*f* = 0.81, IR2931.50(C-J vibration of CH2, 833.25 and 790.81(C-Cl) stretching vibration

Compound (3a) Yield = 72%, R*f* = 0.93, IR: 3290.5(NH2) stretching vibration of primary amine, 2958.80, (C-H) asym. stretching vibration of CH3, 2927.94 and 2858.51(C-H)asym. stretching vibration of CH2, 1762.94 and 1678.07 (C=O) stretching vibration of ester, 1616.53(C=C) stretching vibration of aromatic, 1585.49 Bend. vibration of (N-H), 1450.47and 1381 (C-H) bending vibration of CH3 and CH2, 1234.44 (C–O–C) stretching vibration, 1153.43 Asymmetric (C-O) stretching vibration, 779 C-H out of plane bending 1,2 substituted aromatic .H^1NMR: 1.2(6H) Doublet ,protons of methyl group of iso propyl, 1.9-2.1(6H) Complex,protons of cyclohexane ring of gabapentin, 2.4-2.6 (4H) Complex,protons of cycloh exane ring of gabapentin, 3.1(2H) S, protons of methylene group of gabapentin α to C=O group , 3.3(3H) S, protons of methyl group, 3.6 (2H) S, protons of methylene group of gabapentin α to NH2 group, 3.8 (1H) Complex-protons of CH of isopropyl group, 4.2 (2H) S, protons of methylene group of gabapentin α to ester, 4.6 (2H) S, protons of methylene group of gabapentin, 7.4(1H) Doublet, aromatic protons ortho to CH3 group, 7.5(1H) S,aromatic proton ortho to ester and methyl group, 7.9(1H) Doublet,aromatic proton meta to ester group .

Compound (3b) Yield = 71%, R*f* = 0.91, IR: 3197.98(NH2) stretching vibration of primary amine, 3097 (C-H) stretching vibration of aromatic, 2927.94 and 2870 (C-H) stretching vibration of CH3, 1697.36 and 1674 (C=O) stretching vibration of ester, , 1543 (C=C) stretching vibration of aromatic, 1438.90, 1419 and 1381 C-H bend.vibration of CH3 and CH2, 1257 Aryl(C-O) stretching vibration of aromatic ether, 1199 (C-O) stretching vibration of ether. H^1 NMR1.1-1.26H Complex,protons of cyclohexane ring of gabapentin, 1.65(4H) Complex,protons of cyclohexane ring of gabapentin, 2.17(2H) S, protons of methylene group of

gabapentin α to C=O group , 2.57(2H) S, protons of methylene group of gabapentin α to NH2 group, 3.83(3H) S, protons of methoxy group, 5.02 (2H) S, protons of methylene group of gabapentin α to ester . 5.11(2H) S, protons of methylene group of gabapentin, 6.98(1H) Multiplate, aromatic protons alpha to ester group, 6.96 (2H) Multiplate,o,p protons to methoxy group, 7.15 (2H) Multiplate o,p protons to ester group

Compound (3c) Yield = 73%, R*f* = 0.78, IR: 3340.71 and 3317.56(NH2) stretching vibration of primary amine, 2951, 2920.23 and 2870.08 (C-H) stretching vibration of CH3 and CH2 , 1739.79 and 1685.79(C=O) stretching vibration of ester, 1454.33 and 1369.46(C-H) bending of CH3 & CH2, 1180 and 1149.57(C-O) stretching vibration, 1311 Asymmetric (C–O–C) stretching vibration. H^1 NMR: 0.6(3H) Doublet, protons of methyl group, 0.7(6H) Doublet. protons of methyl groups of isopropyl group 0.8-1.0 (10H) Complex, protons of cyclohexane ring, 1.1-1.3(9H) Complex, protons of cyclohexane ringβ to ester group, 1.4-1.6(1H) Complex,protons of C-H of isopropyl group, 1.9-2.1(1H) M, protons of cyclohexane ring α to methyl group, 3.1(2H) S, protons of methylene group of gabapentin α to C=O group, 3.2(2H) S, protons of methylene group of gabapentin α to NH2 group, 4.2(1H) Complex, protons of cyclohexane ring , 4.3- 4.4(1H) S, protons of methylene group of gabapentin α to ester, 4.71H S, protons of methylene group of gabapentin

Compound (3d) Yield = 65%, R*f* = 0.56, IR; 3197.98 (NH2) stretching vibration of primary amine, 3097.68(C-H) stretching vibration of aromatic, 2927.94, 2870 and 2843.07 (C-H) stretching vibration of CH3 , 1697.36 (C=O) stretching vibration of ester, 1674.21 (C=O) stretching vibration of aldehyde, 1492.90 stretching vibration of aromatic (C=C), 1438.90, 1419.61 and 1381.03(C-H) bending vibration of CH3 and CH2, 1273 Aryl(C-O) stretching vibration of aromatic ether, 1145 (C-O) stretching vibration 0f aromatic,H^1 NMR 1.1-1.2(6H) Complex,protons of cyclohexane ring of gabapentin2.19-2.3(6H) Complex,protons of cyclohexane ring of gabapentin, 3.0(4H) S, protons of methylene group of gabapentin α to C=O group, 3.2(2H) S, protons of methylene group of gabapentin α to NH2 group, 3.4 (3H) S. protons of methoxy group 4.3(2H) S. protons of methylene group of gabapentin α to ester, 4.8 (1 H) S. protons of methylene group of gabapentin, 6.5-6.8(2H) M. aromatic protons alpha to ester group, 7.0(2H) S,aromatic protons α to aldehyde and methyl group, 7.2-7.3(1H) M. aromatic proton α-β unsaturated system, 9.1(1H) S, proton of aldehyde group

Compound (3e) Yield = 53%, R*f* = 0.79, IR: 3194 (NH2) stretching vibration of primary amine, 3097.68(C-H) stretching vibration of aromatic, 2927.94, 2870 and 2843.07(C-H) stretching vibration of CH3, 1697.36(C=O) stretching vibration of ester, 1674.21(C=O) stretching vibration of aldehyde,1492.90 stretching vibration of aromatic (C=C), 1438.90, 1419.61 and 1381.03 (C-H) bending vibration of CH3 and CH2, 1273 and 1273 Aryl(C-O) stretching vibration of aromatic ether, 1149 (C-O) stretching vibration . H^1 NMR : 1.37-1.49(6H) Complex,protons of cyclohexane ring of gabapentin, 2.35-2.77(4H) Complex,protons of cyclohexane ring of gabapentin , 3.2(2H) S, protons of methylene group of gabapentin α to C=O group, 3.53(2H) S. protons of methylene group of gabapentin α to NH2 group, 3.9(2H) Complex, protons of both benzylic and allylic position, 4.1(3H) S. protons of methoxy group, 5.3(2H) S. protons of methylene group, 6.7-7.0(1H) Complex, protons of aromatic ring, 7.5-7.7(1H) Dublet, protons of aromatic ring.

Table (1) Antibacterial activity of quinolone derivative

Compound(3f) Yield = 67%, R*f* = 0.83, IR: 3317.56(NH2) stretching vibration of primary amine,2927.94 (C-H) stretching vibration of aromatic,2854.65 (C-H) stretching vibration of CH2 and CH3,1751.36(C=O) stretching vibration of ester,1662.64 (C=C) stretching vibration of aliphatic ethelen,1600.92and1512.19 (C=C) stretching vibration of aromatic, 1450 and 1388 (C-H) bending of CH3 & CH2,1149.75(C-O) stretching vibration of ether,995.27 and 848.68 (C=C) stretching vibration of alkene. H^1 NMR: 1.2-1.4(6H) Complex,protons of cyclohexane ring of gabapentin, 2.4-2.6(4H) Complex,protons of cyclohexane ring of gabapentin, 3.3(2H) S, protons of methylene group of gabapentin α to C=O group, 3.7(2H) S, protons of methylene group of gabapentin α to NH2 group, 3.9(2H) Complex, protons of both benzylic and allylic position, 4.3(2H)S, protons of methoxy group, (3H) 4.1 S, protons of methylene group of gabapentin α to ester, 4.4-4.6 (2H) Complex, vinyllic proton, 4.9 (1H) S, protons of methylene group of gabapentin, 5.3(1H) Complex, vinyllic proton, 6.7-6.9 (1H) M., aromatic protons ,7.1-7.3(1H) Multiplate, aromatic protonsα to allylic and methoxy group, 7.4-7.6 (1H) M. aromatic protons ortho to ester group.

Compound(3g) Yield = 65%, R*f* = 0.52, IR: 3197.98(NH2) stretching vibration of primary amine,3097 (C-H) stretching vibration of aromatic,2927.94 ,2970.08 and 2843.07(C-H) stretching vibration of CH2 , 1755.22(C=O) stretching vibration of ester group of heterocyclic ring, 1697.36 and 1674.21 (C=O) stretching vibration of ester, 1570 (C=C) stretching vibration of aromatic, 1438.90, 1419.61 and 1381.03 (C-H) bending vibration of CH2 , 1.3-1.5(6H) Complex,protons of cyclohexane ring of gabapentin , 2.6-2.8(4H) Complex,protons of cyclohexan, ring of gabapentin , 3.2(2H) S, protons of methylene group of gabapentin α to C=O group, 3.7 (2H) S,protons of methylene group of gabapentin α to NH2 group, 4.1(2H) S, protons of methylene group of gabapentin α to ester, 4.4(2H) S, protons of methylene group of gabapentin, 4.6 (1H) D. ,protonα to C=Ogroub of pyran-2-n one ring, 6.2-6.4 (2H) Complex, aromatic protons α to ester groubs , 6.7(1H) Doublet aromatic protons , 7.4(1H) Doublet proton of pyran-2-onering as α-β-unsaturated ketone

RESULT AND DISCUSSION

Antibacterial Activity [14]

The synthesized final compounds (3a-3g) were tested to evaluate their antimicrobial activity against gram negative, gram positive bacteria & fungi, this evaluation was done using well diffusion method, the standard compounds used as an antifungal agents were(clotrimazole & nystatin) while the antibacterial agents were (amoxicillin ,ciprofloxacin & naitrofurantoin). DMSO was chosen as a solvent and as control

Compound name	Conc. µg/ml	Staph aureus.	Strep. pneumoniae	klebsilla pneumoniae	E.coli
		Gram posative		Gram.negative	
		Zone of inhibition			
Amoxicillin	10^3	1.5	zero	zero	**zero**
ciprofloxacin	10^3	3	3.5	3	**zero**
nitrofurantoin	10^3	2	1.5	1	**1.5**
DMSO	Control & solvent	zero	Zero	zero	**zero**
3a	10^3	3	2.5	1.8	**2**
3b	10^3	1	1.2	zero	**1.7**
3c	10^3	1.5	1.3	1.3	**1.3**
3d	10^3	1.2	1.2	1.3	**zero**
3e	10^3	1.3	1.5	zero	**zero**
3f	10^3	1.5	1.2	1.5	**1.5**
3g	10^3	1	1.3	zero	**zero**

It was observed that 2a have shown the most potent and widest spectrum of antibacterial activity including both gram positive and gram negative bacteria, and very close with its activity to ciprofloxacin with 3f coming in the second place showing a smaller inhibition zone than 3a while e and 3g were more selective for gram positive. It was noted that all synthetic compounds shows better and wider antibacterial activity than amoxicillin thymol conjugate 3a had improved antibacterial activity.

Antifungal Activity [14]

The final compounds (3a-3g)subjected to antifungal activity test to evaluate their efficacy by well diffusion method, the standard drugs used as an antifungal are (clotrimazole and nystatin) while DiMethyl sulfoxide was chosen as a solvent and control

Table (2) Antifungal activity of quinolone derivative

Compound name	*Conc.µg/ml*	Candida albicans / zone of inhibition
clotrimazole	10^3	***2.5***
nystatin	10^3	***zero***
DMSO	10^3	***zero***
3a	10^3	***2***
3b	10^3	***zero***
3c	10^3	***1.5***
3d	10^3	***1.3***
3e	10^3	***zero***
3f	10^3	***1.5***
3g	10^3	***1***

3a, have the stronger inhibition activity against c.albicans among the syntheyic dervatives and comparable inhibition to clotrimazole due to the strong antibacterial and antifungal activity of thymol which agreed with Marchese.A.etal study ,with 3c and 3f derivatives come the second after 3a

Anti-Inflammatory Activity[15,16,17]

This section will discuss the results of evaluation of tested compounds as anti-inflammatory agents using paw-edema method by induction of acute inflammation with subcutaneous injection of undiluted egg white to the intra planter side of the left hind paw of the rat. The subcutaneous injection of egg-white into the rat paw produces inflammation resulting from plasma extravasations increased tissue water and plasma protein exudation along with neutrophil extravasations, which are all due to the metabolism of arachidonic acid This *in vivo* method has advantages over other methods because of the fast evaluation by measuring the inflammation at the beginning and throughout short time course, high paw sensitivity for inflammation, no use of anesthesia, cost effectiveness, method closeness to human nature and easy handling of the method.

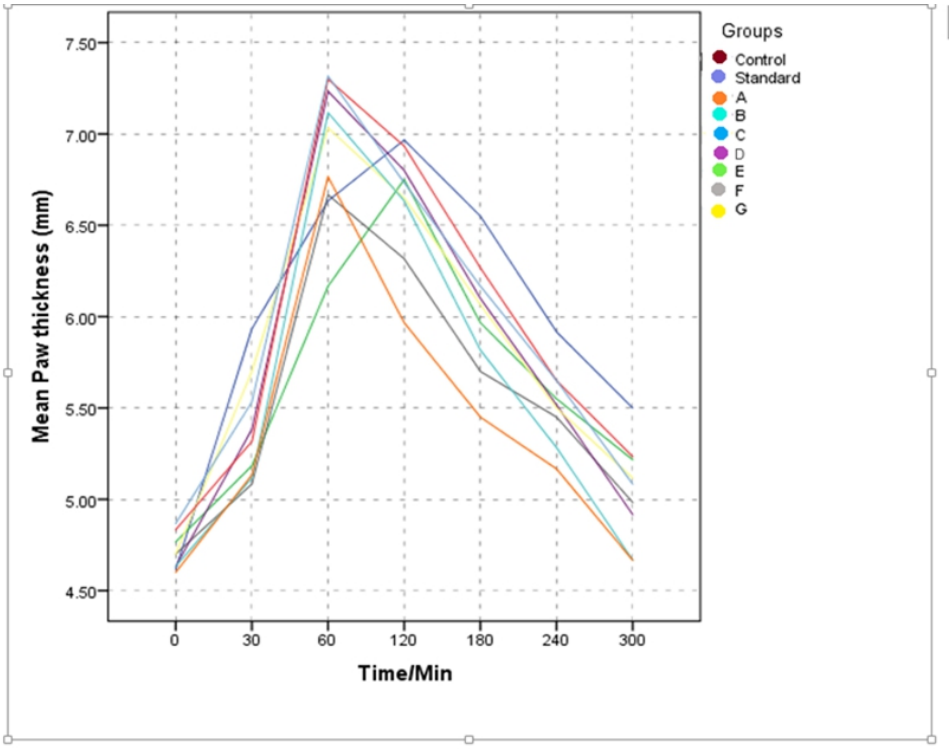
Table (3) Anti-inflammatory activity of control,standard(gabapentin) and gabapentin-antioxidants derivatives(3A-3G) on egg-white induced paw edema in rat hand paw

Time	0 min	30 min	60 min	120 min	180 min	240 min	300 min	LSD
control	C4.61±0.19	B5.93±0.17a	A6.63±0.16c	A6.96±0.19a	A6.55±0.22a	B5.91±0.14a	B5.50±0.11a	0.504
standard	E4.76±0.16	DE5.18±0.20bc	B6.16±0.22d	A6.75±0.12a	BC5.96±0.06bcd	CD5.55±0.03bc	D5.21±0.09ab	0.4215
A	D4.70±0.16	CD5.08±0.15c	A6.66±0.23bc	A6.31±0.13bc	B5.70±0.17de	BC5.45±0.13bcd	CD4.98±0.18bc	0.4922
B	E4.63±0.21	D5.38±0.16bc	A7.23±0.12a	B6.80±0.07a	C6.10±0.13bcd	D5.51±0.04bcd	E4.91±0.12bc	0.3868
C	E4.70±0.18	BC5.70±0.22ab	A7.03±0.17abc	A6.65±0.19ab	B6.06±0.18bcd	CD5.50±0.16bcd	DE5.11±0.18ab	0.5408
D	D4.83±0.17	C5.31±0.19bc	A7.30±0.11a	A6.93±0.13a	B6.26±0.16ab	C5.65±0.16ab	CD5.23±0.17ab	0.467
E	E4.63±0.21	D5.11±0.16c	A7.11±0.13ab	B6.63±0.06ab	C5.81±0.08cde	D5.28±0.06cd	E4.66±0.13c	0.3818
F	E4.60±0.22	CD5.13±0.20c	A6.76±0.09bc	B5.96±0.13c	C5.45±0.14e	CD5.16±0.15d	DE4.66±0.21c	0.5013
G	E4.86±0.14	D5.53±0.20abc	A7.31±0.14a	B6.73±0.05a	C6.16±0.09abc	D5.65±0.12ab	E5.08±0.14abc	0.4004
LSD	0.5353 NS	0.5399	0.465	0.3776	0.4271	0.3577	0.4481	

Means with a different small letter in the same column are significantly different (P≤ 0.05)
Means with a different capital letter in the same row are significantly different (P≤ 0.05)

The differences among groups at zero time were not significant while the differences were significant (P≤ 0.05) among groups for all other times. The mean of paw thickness was significantly (P≤ 0.05) higher in the control group as compared with standard, A, B, D, E, and F at 30 min.

The mean of paw thickness inhibition of the control (6.96 mm) and the standard (6.75 mm) reached a peak at 120 min, whereas the means of other groups reached the peak at 60 min, that's means that gabapentin-antioxidant derivatives has advantage over both standerd and control by having faster onset of action . After peak all groups showed a gradual decreasing along with advanced time.with the significant inhibition seen with derivatives of gabapentin with eugenol in the first place, thymol in second place and sesamol to the place ,and gabapentin with umbiliferon and gabapentin with guaicol derivatives have comparable inhibition in the paw hand thikness of the rat, the other two derivatives of gabapentin with vanillin and menthol showed poor reduction in aw thickness, can be attributed to its various anti-inflammatory mechanisms, also due to the electronic and hydrophobic characters of the substituents.



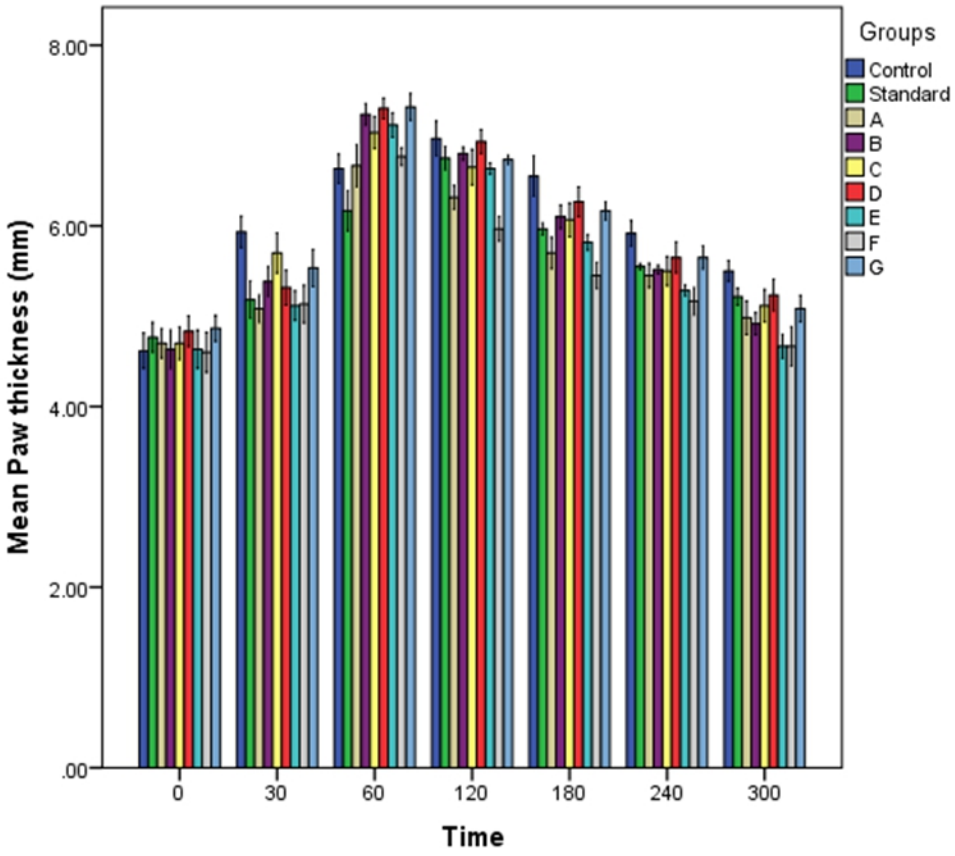


figure (3-) Anti-inflammatory activity of control, gabapentin and gabapentin dervatives on egg-white induced paw edema in rat

CONCLUSION

1. The synthetic procedure for the designed target compounds was
successfully achieved
2. Identification and charectrization of the synthezied compound were
achieved by using IR spectroscopy, 1H-NMR spectroscopy, melting points and *R*f values.
3. The preliminary antimicrobial activity study revealed that the synthesized final compounds (3a) demonstrate significant antibacterial and antifungal activity.
4. The Preliminary study of anti-inflammatory activity showed that gabapentin – antioxidant conjugated derivatives (3a, 3e and 3f) have more potent effect to gabapentin alone
while gabapentin with antioxidant (guaicol and umbiliferon) showed comparable inhibition in the paw hand thikness of the rat, the other two derivatives of gabapentin with vanillin and menthol showed poor reduction in aw thickness

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