RESEARCH ARTICLE

Synthesis and Characterization of some new Ibuprofen Derivatives and Study Antibacterial Activity

Khalida A. Thejeel*

Department of Geophysics, College of Remote Sensing and Geophysics, University of Al-Karkh for Science, Iraq

Received: 14th June, 2020; Revised: 05th July, 2020; Accepted: 10th August, 2020; Available Online: 25th September, 2020

ABSTRACT

The series of ibuprofen compounds (1–5) have been synthesized. Acid chloride (4-isobutylphenyl) acetyl chloride (1) was obtained from interaction ibuprofen with thionyl chloride, this compound (1) was treated with hydrazine to give acid hydrazide 2-(4-isobutylphenyl) acetohydrazide (2). Schiff's base of 2-(4-isobutylphenyl) acetohydrazide derivatives (3a–e) were prepared by refluxing (2) with different aromatic aldehydes and ketones. The (4-isobutylphenyl) acetyl chloride **(**1) converts to esters (4a–f) by reacting with alcohols, and with secondary amines to give amide compounds of (4-isobutylphenyl) acetyl chloride (5a–b). All structures of synthesized compounds have been confirmed by elemental analysis (C, H, and N) and spectral data (FT-IR and ^{1}H NMR). The prepared compounds (3a–e) and (4a–f) have been screened for their antibacterial activity for *S. aureus*, *B. subtilis*, *E. coli*, *P. aeuroginosa*, and were shown to have antibacterial activity.

Keywords: (4-isobutylphenyl) acetyl chloride, Amide derivatives, Antibacterial activity, Ibuprofen derivatives, Schiff's base.

International Journal of Drug Delivery Technology (2020); DOI: 10.25258/ijddt.10.3.26

How to cite this article: Thejeel KA. Synthesis and characterization of some new ibuprofen derivatives and study antibacterial activity. International Journal of Drug Delivery Technology. 2020;10(3):454-458.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Ibuprofen is 2-[4-isobutyl phenyl] propionic acid, Figure 1, it is the first of propionic acid derivatives introduced as a better alternative to aspirin in 1969.[1] It is a nonsteroidal anti-inflammatory drug (NSAID) with pronounced analgesic and antipyretic properties.[2] Various ibuprofen derivatives have been prepared to reduce side effects.[3-5] Recently, the profens have been come to demented this therapeutic class. Some of the available profen drugs are ibuprofen, naproxen, ketoprofen, and flurbiprofen.[6] Ibuprofen is given as esters, various salts, free acid, and other complexes are also used. These include lysing and salt of sodium, pyridoxine and guaiacol esters, and meglumine and iso-butanol ammonium derivatives.[7-9] Ibuprofen is used to relieve the symptoms (wide range) of illnesses, such as, headaches, backaches, period pain, cold and flu, migraine symptoms, and arthritis.[10]

Ibuprofen is produced as a racemate. It contains a chiral center in α-position of the propionate, it has two enantiomers, (S), and (R); the two enantiomers have different metabolism and biological effects, the S−(+) − the active form for ibuprofen.[11,12]

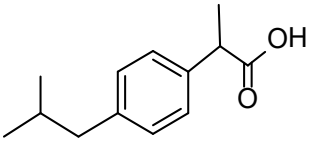


Figure 1: Ibuprofen

MATERIAL AND METHODS

Apparatus and Chemicals

All reagents and solvents are used from Merck, Fluka, and BDH. Melting points were recorded using hot stage Gallen Kamp melting point and uncorrected, England. Thin-layer chromatography (TLC) was carried out using Fertigfollen recoated sheets type polygram Silg, and the plates were developed with iodine vapor. Infrared spectra have been recorded using Shimadzu (8300) (FT-IR) infrared spectrometer, KBr disc in 4,000 to 600 cm^{-1} spectral range. ^{1}H NMR spectra have been recorded using NMR Spectrometer 400MHz, Bruker, Germany, using tetra methyl saline (internal standard) and DMSO-d_6 (solvent). The elemental analyses of C, H, and N have been performed using the Perkin-Elmer 240C analyzer.

Methods of Synthesis

Synthesis of (4-Isobutylphenyl) Acetyl Chloride (1)[15]

A 0.01 mole (ibuprofen) was added to a 50 mL round bottom flask with stirring. In the ice bath, the reaction was cooled for 10 minutes and 10 mL thionyl chloride was then introduced into the reaction. After 25 minutes reaction, the reaction

*Author for Correspondence: khalidath1971@yahoo.com

refluxed at about 60 to 70ºC until no bubbles were generated in the flask. The excess of thionyl chloride has been removed by rotating evaporation to get compound (4-isobutylphenyl) acetyl chloride (1).

Synthesis of 2-(4-Isobutylphenyl) Acetohydrazide (2)[16]

To a stirred solution of compound (1) (0.005 mole) in dry benzene (15 mL), a mixture of hydrazine (0.005 mole) was added dropwise. The mixture was then refluxed for about 4 hours. After cooling, benzene was removed, the product was collected, and recrystallized using an appropriate solvent.

Synthesis of N-Substituted-2-(4-Isobutylphenyl) Propanehydrazide (3a–e)[17]

To a stirred solution of compound (2) (0.005 mole) in absolute ethanol (15mL) the appropriated aromatic aldehydes or ketones (0.005 mole) was added. The mixture refluxed for 3 hours, then cooled at room temperature. The precipitate filtered to remove excess solvent and recrystallized using an appropriate solvent.

Synthesis Esters of (4-Isobutylphenyl) Acetyl Chloride (4a–f)[18]

To a solution of compound (1) (0.005 mole) in dry benzene (25 mL), alcohol (0.005 mole) was added, the mixture refluxed for 6 hours. After that, excess benzene filtered off to obtain esters (4a–f). The products were recrystallized by using an appropriate solvent.

Synthesis Amide Derivatives of (4-Isobutylphenyl) Acetyl Chloride (5a and b)[19,20]

To the solution of compound (1) (0.005 mole) in dry benzene (15 mL), sec-amine (0.005 mole) added, the mixture then refluxed for about 4 hours. Excess benzene was filtered off to obtain (5a–d). The physical properties of compounds (5a–d) The

Table 1: Physical and analytical data of the prepared compounds[1-5]

% clad. (found)			*Mol. Form. (Mol. Wt.)*	*Recrystallized solvent*	*Yield%*	*M.P. (ºC)*	*Comp. Name*	*Comp. Code*
N	*H*	*C*						
-	-	-	$C_{13}H_{17}ClO$ (224.73)	-	-	-	2-(4-isobutylphenyl) propanoylchloride	1
12.72 (12.66)	9.15 (9.04)	70.87 (70.95)	$C_{13}H_{20}N_2O$ (220.31)	Ethanol	85	205-207	2-(4-isobutylphenyl) propanehydrazide	2
11.89 (11.73)	6.56 (6.49)	67.97 (68.21)	$C_{20}H_{23}N_3O_3$ (353.41)	Ethanol	83	> 280	N-(2-nitrobenzylidene)2-(4-isobutylphenyl) propane hydrazide	3a
9.09 (8.98)	7.84 (7.77)	77.89 (77.98)	$C_{20}H_{24}N_2O$ (308.19)	Benzene	66	238-240	N-benzylidene-2-(4-isobutylphenyl) propanehydrazide	3b
8.64 (8.53)	7.46 (7.38)	74.04 (74.22)	$C_{20}H_{24}N_2O_2$ (324.42)	Ethanol	72	253-255	N-(4-hydroxy benzylidene)-2-(4-isobutylphenyl) propanehydrazide	3c
11.96 (11.82)	8.32 (8.25)	75.18 (75.62)	$C_{22}H_{29}N_3O$ (351.49)	Ethanol	70	240-242	N-(4-(dimethyl amino) benzylidene)-2-(4-isobutyl phenyl) propane hydrazide	3d
7.14 (7.01)	7.19 (7.11)	73.44 (73.63)	$C_{24}H_{28}N_2O_3$ (392.49)	Ethanol	69	257-260	2-(4-isobutylphenyl)-N'-(1-(3-oxochroman-2-yl) ethylidene) propanehydrazide	3e
	8.16 (8.08)	81.04 (81.13)	$C_{20}H_{24}O_2$ (296.40)	Ethanol	45	165-167	benzyl 2-(4-isobutylphenyl) propanoate	4a
	9.99 (9.92)	77.82 77.91))	$C_{17}H_{26}O_2$ (262.39)	Benzene	66	141-143	sec-butyl 2-(4-isobutylphenyl) propanoate	4b
	9.99 (9.91)	77.82 (77.90)	$C_{17}H_{26}O_2$ (262.39)	Benzene	71	148-150	butyl 2-(4-isobutylphenyl) propanoate	4c
	9.99 (9.93)	77.82 (77.91)	$C_{17}H_{26}O_2$ (262.39)	Ethanol	62	133-136	sec-butyl 2-(4-isobutylphenyl) propanoate	4d
	10.2 1 (10.11)	78.41 (78.55)	$C_{18}H_{28}O_2$ (276.42)	Ethanol	74	151-153	pentyl 2-(4-isobutylphenyl) propanoate	4e
	10.41 (10.40)	78.57 (78.61)	$C_{19}H_{30}O_2$ (290.44)	Benzene	67	147-150	hexan-2-yl 2-(4-isobutylphenyl) propanoate	4f
3.92 (3.69)	7.61 (7.58)	83.99 (84.38)	$C_{25}H_{27}NO$ (357.49)	Benzene	63	145-148	2-(4-isobutylphenyl)-N,N-diphenyl propanamide	5a
5.36 (5.22)	10.41 (10.37)	78.11 (78.36)	$C_{17}H_{27}NO$ (261.40)	Chloroform	55	136-138	N,N-diethyl-2-(4-isobutylphenyl) propanamide	5b

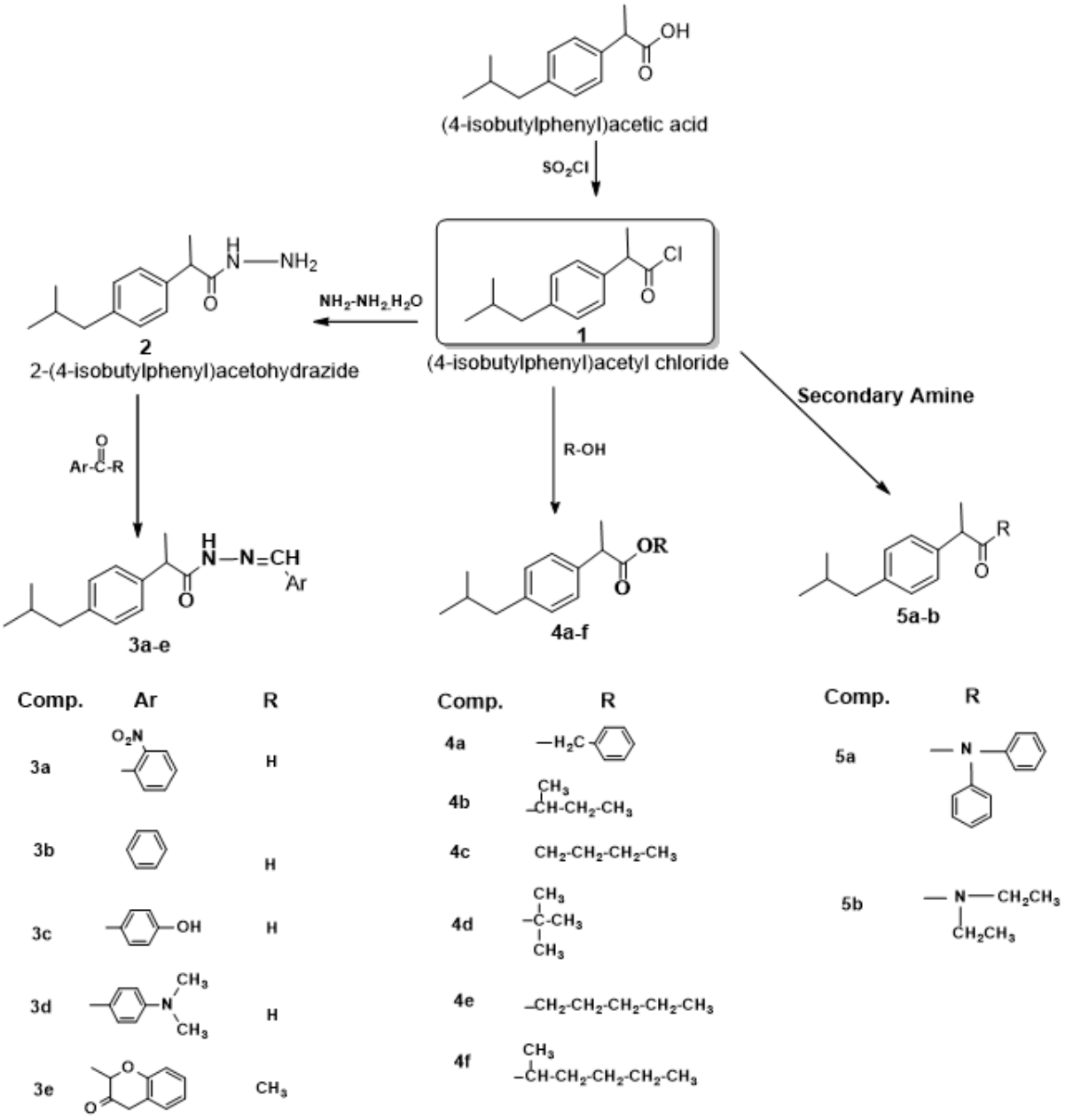
products were recrystallized by using an appropriate solvent. The physical properties of synthesized compounds (1–5) are shown in Table 1.

Antibacterial Activity

The agar well diffusion method.[21] Barry AL. Procedure for testing antimicrobial agents in agar media. In Antibiotics in Laboratory Medicine[22] employed for determining the antibacterial activity of some synthesized compounds (3a–e), (4a–f), and (5a and b) against gram-positive bacteria *S. aureus*, *B. subtilis*, and gram-negative bacteria *E. coli*, *P. aeruginosa* compounds have been screened for their antibacterial activity for bacterial species by using Mueller Hinton agar to determine the activity of the chosen synthesized compounds. The concentration of selected compounds under test 500 µg/mL in DMSO. Wells were made by the medium is extracted with a sterile cork hole borer (6 mm) in each plate, which was streaked with test bacterial. These plates were incubated at 37ºC for 24 hours The drug ampicillin was tested under similar conditions for comparison. The zone inhibition produced by each compound was measured in mm. The results of antibacterial studies have been given in Table 4.

RESULTS AND DISCUSSION

In this work, the carboxylic group of ibuprofen was modified into various derivatives acid chloride, hydrazine, Schiff's bases, esters, and amide, the reaction sequences have been outlined in Scheme 1.



Scheme 1

Table 2: Spectral data for synthesized compounds

Comp. Code	*FT-IR spectral data (cm^{-1})*
1	34300-,2500(O-H), 3037(C-H Arom.), 2960,2929(C-H Aliph.), 1710(C=O Acid), 1588,1510(C=C Arom.), 720(C-Cl).
2	3495,3442(NH_2), 3273(NH), 3037(C-H Arom.), 2964,2931(C-H Aliph.), 1687(C=O Amide), 1588,1512(C=C Arom.).
3a	3281(NH), 3042(C-H Arom.), 2955,2927(C-H Aliph.),1621(CH=N), 1589,1516(C=C Arom.), 1511, 1348(NO_2).
3b	3277(NH), 3047(C-H Arom.), 2958, 2931(C-H Aliph.), 1622 (CH=N), 1578,1520(C=C Arom.).
3c	3283(NH), 3039(C-H Arom.), 2964, 2930(C-H Aliph.), 1617(CH=N), 1588,1529(C=C Arom.), 3449(O-H Phenolic), 1196(C-O).
3d	3279(NH), 3040(C-H Arom.), 2967, 2931(C-H Aliph.), 1619(CH=N), 1581,1522(C=C Arom.), 1315(C-N).
3e	3268(NH), 3033(C-H Arom.), 2974, 2934(C-H Aliph.), 1624(CH=N), 1579,1511(C=C Arom.), 1641(C=O), 1154(C-O-C).
4a	3039(C-H Arom.), 2971,2934(C-H Aliph.), 1575,1521(C=C Arom.), 1748 (C=O Ester), 1154(C-O-C).
4b	3037(C-H Arom.), 2979, 2931(C-H Aliph.), 1578, 1518(C=C Arom.), 1744 (C=O Ester), 1160(C-O-C).
4c	3033(C-H Arom.), 2981, 2939(C-H Aliph.), 1569, 1514(C=C Arom.), 1738(C=O Ester), 1159(C-O-C).
4d	3034(C-H Arom.), 2969, 2926(C-H Aliph.), 1570, 1522(C=C Arom.), 1737 (C=O Ester), 1149(C-O-C).
4e	3040(C-H Arom.), 2978,2933(C-H Aliph.), 1576,1511(C=C Arom.), 1736 (C=O Ester), 1164(C-O-C).
4f	3029(C-H Arom.), 2972, 2940(C-H Aliph.), 1589, 1524(C=C Arom.), 1740 (C=O Ester), 1158(C-O-C).
5a	3029(C-H Arom.), 2972, 2940(C-H Aliph.), 1589, 1524(C=C Arom.), 1660 (C=O Amide), 1348(C-N).
5b	3029(C-H Arom.), 2972, 2940(C-H Aliph.), 1589, 1524(C=C Arom.), 1658 (C=O Amide), 1351(C-N).

Table 3: ^{1}H NMR spectral data for synthesized compounds

Comp. Code	*^{1}H NMR spectral data (δ ppm)*
2	0.91(d,6H, $CH(CH_3)_2$); 1.28(d,3H, $CH\text{-}CH_3$); 1.82(m,1H, $CH(CH_3)_2$); 2.0(s,2H, NH_2); 2.43(d,2H, ($CH\text{-}CH_2$-Ar); 3.52(q,1H, $CH\text{-}CH_3$); 7.05-7.24(m,4H, Ar-H); 8.0(s,1H, NH).
3a	0.91(d,6H,$CH(CH_3)_2$); 1.28(d,3H,$CH\text{-}CH_3$) ; 1.82(m,1H,$CH(CH_3)_2$); 2.45(d,2H,($CH\text{-}CH_2$-Ar); 3.52(q,1H,$CH\text{-}CH_3$); 7.05-8.09(m,8H,Ar-H); 8.54(s,1H,N=CH).
4a	0.91(d,6H, $CH(CH_3)_2$); 1.61(d,3H, $CH\text{-}CH_3$); 1.82(m,1H, $CH(CH_3)_2$); 2.43(d,2H, ($CH\text{-}CH_2$-Ar); 3.78(q,1H, $CH\text{-}CH_3$); 5.34(s,2H, O-CH_2-Ar); 7.05-7.47(m,9H, Ar-H).
5a	0.91(d,6H,$CH(CH_3)_2$); 1.28(d,3H,$CH\text{-}CH_3$) ; 1.82(m,1H,$CH(CH_3)_2$); 2.43(d,2H,($CH\text{-}CH_2$-Ar); 3.52(q,1H,$CH\text{-}CH_3$); 7.05-7.47(m,9H,Ar-H).

Table 4: Antibacterial activity of prepared compounds (3a–e), (4a–f), and (5a and b)

	Zone of inhibition (mm)			
	Gram-positive bacteria		*Gram-positive bacteria*	
Compound No.	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeuroginosa*
3a	17	16	15	15
3b	15	14	14	13
3c	14	16	13	15
3d	15	15	13	14
3e	15	16	14	13
4a	12	13	13	12
4b	12	12	13	10
4c	12	11	12	11
4d	11	11	13	11
4e	11	11	12	11
4f	12	12	11	12
5a	11	12	12	11
5b	11	14	13	12
Ampicillin (standard)	22	23	24	20

The acid hydrazide (2) was prepared by reaction of ibuprofen and thionyl chloride, then treated with hydrazine hydrate, the compound (2) converted into Schiff's bases (3a–e), using different ketones and aldehydes, structures of synthesized compounds confirmed by elemental analysis, FT-IR and ^{1}H NMR, the FT-IR of all Schiff's bases were showed absorption at between 1,617 to 1,624 cm^{-1} for C=N vibration and at between 3,268 to 3,283 cm^{-1} for N-H vibration, ^{1}H NMR spectrum of (3a) showed singlet at δ = 8.54 ppm for N=CH proton.

Compounds (4a–f) were prepared by esterification of acid 1 with different alcohols, FT-IR spectra of them display absorption band at 1,149 to 1,164 cm^{-1} for C-O-C, 1,737 to 1,748 cm^{-1} for C=O ester, ^{1}H NMR spectrum of 4a showed singlet at δ = 5.34 ppm for O-CH_2-Ar protons.

Amides (5a and b) were synthesized from secondary amines and acid chloride (1), the structure of them were deduced from FT-IR, ^{1}H NMR spectra and have been confirmed by C, H, and N analysis, the FT-IR of compounds (5a and b) showed characteristic band for C=O amide at 1,658 to 1,660 cm^{-1} and C-N at 1,348 to 1,351 cm^{-1}, ^{1}H NMR spectrum of (5a) appeared as multiple at 1.82 ppm for $CH(CH_3)_2$ and quartet at 3.52 ppm for -$CH\text{-}CH_3$.

All of FT-IR spectral data for synthesized compounds (1–5) that associated and their functional groups appeared in expected regions, Table 2. The ^{1}H NMR spectral data of some compounds (2, 3a, 4a, and 5a) were listed in Table 3.

The newly prepared compounds (3a–e), (4a–f), and (5a and b) were tested for antibacterial activity contra bacterial species, gram-positive bacteria *S. aureus*, *B. subtilis*, and gram-

negative bacteria *E. coli*, *P. aeruginosa* were showing signification antibacterial activity; the tested compounds were exhibited moderate to good inhibition, Table 4.

The antibacterial activity of tested compounds was determined via measuring the diameter inhibition zone and compared with the standard drug (ampicillin).[13,14]

CONCLUSIONS

The newly prepared compounds were supported by elemental analysis (C, H, and N), and spectral data (FT-IR and ^{1}H NMR), and showing signification antibacterial activity, were exhibited moderate to good inhibition.

ACKNOWLEDGMENTS

Special thanks to the University of Al-Karkh for Science, for their help and support to complete the research.

REFERENCES

1. Ibtihal Q) 2014) Synthesis and antimicrobial activity of Ibuprofen Derivatives. Natural Science, 6 (2): 47-53.
2. Ravi G. *et al*. (1996) Structural basis for selective inhibition of cyclooxygenase-2 by anti- inflammatory agents. Letters to Nature, 384: 644-649.
3. Selinsky BS, Gupta CT and Loll PJ (2001) Structural analysis of NSAID binding by prostaglandin H2 synthase: time-dependent and time-independent inhibitors elicit identical enzyme conformations. Biochemistry, 40: 5172– 5180.
4. Tripathi KD (2003) Non-steroidal anti-inflammatory drugs and anti-pyretic Analgesics. Essentials of medical pharmacology. 5th edition. Jaypee Brothers, New Delhi.
5. Bushra R and Aslam N (2010) An overview of clinical pharmacology of Ibuprofen. Oman Medical Journal, 25: 1655-1661.
6. Woods KW, McCrisken RW, Michaelides M R, Wada CK, Hulkower, KW and Bell RW (2001) Thiazole analogues of NSAIDs of indomethacin as selective COX–2 inhibitors. Bioorg. Med. Chem.Lett., 11: 1325–1328.
7. Potthast H, Dressman JP, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H and Barends DM (2005) Bio waiver Monographs for Immediate Release Solid Oral Dosage Forms: Ibuprofen. Journal of Pharmaceutical Science, 94: 10-14.
8. Warner TD, Giuliano F, Vaynovie I, Bukasa A, Mitche JA and Vave JR (1999) Non-steroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastro intestinal toxicity a full *in vitro* analysis. Proceedings of National Academy Science of USA, 96: 7563-7568.
9. Tan SC, Patel BK, Jackson SH, Swift CG and Hutt JA (2002) Stereo selectivity of ibuprofen metabolism and pharmacokinetics following the administration of the racemate to healthy volunteers. Xenobiotica, 32: 683- 697.
10. Amit S, Kalgutkar B , Brenda C and Lawrence J (2000) Ester and Amide Derivatives of the Nonsteroidal Anti-inflammatory Drug, Indomethacin, as Selective Cyclooxygenase-2 Inhibitors. *J. Med. Chem.,* 43 (15): 2860–2870.
11. Hijazi A, Suhad N, Mohanad D and Hadeel F (2016) Synthesis, characterization and antimicrobial activity of zinc (II) ibuprofen complexes with nitrogen-based ligands. Journal of Coordination Chemistry, 69(6): 1110–1122.
12. Latif Abuhijleh A (1997) Synthesis and characterization of copper-ibuprofen are complexes with 2,2'-bipyridine and 1,10-phenanthrolines and their hydrolytic activities in phosphate diester cleavage. Polyhedron, 16(4): 733 -740.
13. Fenlon CH and Cynamon MH (1986) Comparative *in vitro* activities of ciprofloxacin and other 4-quinolines against micro bacterium tuberculosis and micro bacterium intracellular, *Antimicrob. Agents Chemother,* 29: 386–388.
14. Davis R, Markham A and Balfour JA (1996) Ciprofloxacin, An updated review of its pharmacology, therapeutic efficacy and tolerability. *Drug,.*51:1019–1074.
15. Heying D, *et al*. (2016) Synthesis and Controlled Release Behavior of Biodegradable Polymers with Pendant Ibuprofen Group. International Journal of Polymer Science, Article ID 5861419: 8-15.
16. Shaaban K, Mustafa R and Sabry H (2013) Functionalization of Ibuprofen Core Structure Compound: Synthesis of New Potential Chemotherapeutic Agents Incorporating Ibuprofen Substructure. Chemical Science Journal, CSJ-97: 1-10.
17. Asmaa S, *et al*. (2015) Synthesis, Reactions and Antimicrobial Activity of Some New 3-Substituted Indole Derivatives. International Journal of Organic Chemistry, 5: 81-99.
18. Xuan Z, Xing L, Tao G, Xun S and Zhi-rong Z (2012) *In vitro* and *in vivo* investigation of dexibuprofen derivatives for CNS delivery. Acta Pharmac ologica Sinica., 33: 279–288.
19. Ayad M. R. Raauf, Rafah F. Al-Smaism, Khalida A. Thejeel and Hala Ayad M. Rasheed (2018) Synthesis, characterization and antimicrobial study via new heterocyclic derivatives of trimethoprim. Natural Product Research, ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal.
20. Attia AJK (2003) PhD Thesis. Al-Mustansiriya University. College of science, Iraq.
21. Barry AL (1991) Procedure for testing antimicrobial agents in agar media. In Antibiotics in Laboratory Medicine. Corian. V.L. (Ed.). Williams and Wilkins. Baltimore. MD. USA.
22. MacLowry JD, Jaqua MJ and Selepak, ST (1970) Detailed methodology and implementation of a semi automated serial dilution micro technique for antimicrobial susceptibility testing. *Appl. Microbial,* 20:46–53.