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RESEARCH ARTICLE

Synthesis and Characterization of New Ligands attached to NSAIDs Moiety

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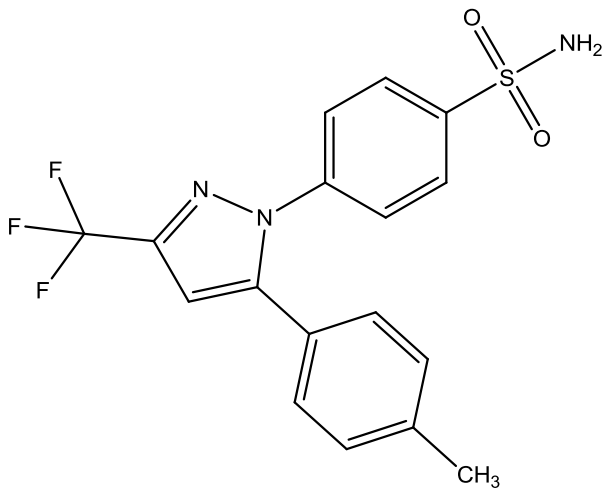
Abstract

A series of new analogues of Naproxen contain imidazole ring were synthesized (compound 7a-d). a group of amine derivatives incorporated in the carboxylate group of a naproxen, to increase its bulkiness were designed to be synthesized and evaluated as anti-inflammatory agents with expected inhibitory selectivity toward COX-2 enzyme. The anti-inflammatory activity of the tested analogues has been evaluated in comparison with propylene glycol 50%v/v (control group) and naproxen. The synthesis of the designed compounds has been successfully achieved. Purity and characterization of the synthesized compounds were confirmed by determination of physical properties (melting points and R_f values), FT-IR and ^{1}H-NMR spectroscopies.

INTRODUCTION

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) have been commonly used in both humans and animals as remedies to relieve pain and inflammation in different arthritic and postoperative conditions due to their three major activities, anti-inflammatory, antipyretic, and analgesic[(1)]. Some of the main indications for NSAID therapy include Rheumatoid Arthritis (RA), Osteoarthritis (OA), Acute gouty arthritis, ankylosing spondylitis, and Dysmenorrhea[(2)], however, NSAIDs are associated with a spectrum of upper gastrointestinal complications, ranging from endoscopic ulcers in 10–30% of patients, to serious ulcer complications in 1–2% of patients, although the exact incidence is changing [(3)]. Therefor there is a need to develop new anti-inflammatory and analgesic drugs without causing gastric injury. The mechanism of action of NSAIDs can be comprehended according to their effects on inflammation, pain, and fever [(4)]. The major mechanism by which the NSAIDs extract their therapeutic effects is inhibition of prostaglandin (PG) synthesis [(5)]. Specifically NSAIDs will cause almost complete blockade of the activity of the precursor enzymes , cyclooxygenase, the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins [(6)]. Three COX isoenzymes have been identified: COX-1, COX-2 and COX-3 [(7&8)], though COX-3 activity in human has not been confirmed [(9)]. COX-1 showed to be constitutionally present in low abundance in most human tissues, acting as a housekeeping enzyme by regulating normal physiological processes like the maintenance of gastric mucosal integrity, kidney function, and platelet aggregation [(10)]. Inhibition of COX-1 activity is considered a major contributor in the side effects associated with using NSAIDs [(11)]. While COX-2 is an inducible isoenzyme, expressed primarily in response to inflammation, but to some extent in other tissues including kidneys and brain [(12)]. Induction of COX-2 enzyme is associated with inflammation. Generally, the NSAIDs inhibit both COX-1 and COX-2[(13)]. The inhibition of the cyclooxygenase-2 reaction results in anti-inflammatory, analgesic and antipyretic effects. The substrate binding site of COX-1 differs from that of COX-2. COX-2 has a larger and more flexible substrate channel than that in COX-1 and a larger space at the site where inhibitors bind. The structural difference between COX-1 and COX-2 has allowed the development of COX-2 selective agents that differ from most of the traditional NSAIDs, which inhibit both COX-1 and COX-2 [(14)]. Most COX-2 inhibitors are diaryl-5-membered heterocyclic such as Celecoxib (I) has a central pyrazole ring and two adjacent phenyl substituents and Rofecoxib (II) has a central furanone ring and two adjacent phenyl substituents [(15)].

From this review we designed, synthesized and preliminary evaluated new Naproxen analogues by increase its bulkiness by incorporated the imidazole ring and tied it with different aldehydes. Also we masking the free carboxylic group that responsible for gastric irritant and this may shift its enzyme selectivity from COX-1towards COX-2 and reduce the side effects.



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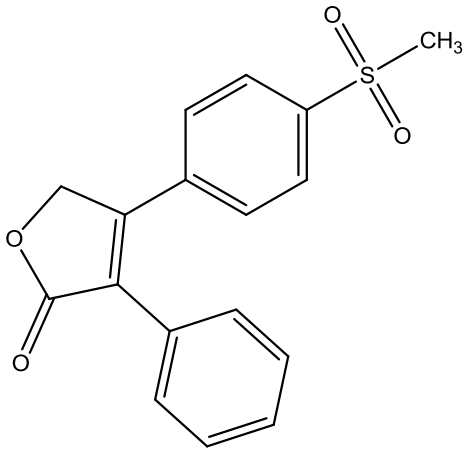


II

Methods:

All chemicals and reagents were obtained from the commercial supplier (Merck –Germany, sigma – Aldrich – Germany, BDH – England and Fluka –USA). Naproxen was supplied from SDI Company, Iraq. Melting points were determined by capillary method on Thomas Hoover apparatus (England). FT-IR spectra were recorded by using Shimadzu –Japan spectrophotometer and the determination of spectrophotometer and the determination of the spectra were performed by using KBr discs. Thin layer chromatography (TLC) was run on Kieslgel GF254 (60), Merck (Germany), to check the purity of the products as well as monitoring the progress of reactions. Compounds were revealed by reactivity by irradiation with UV light and chromatograms were eluted by Chloroform: methanol (85: 15) [16]. ^{1}HNMR spectra for target compounds were performed at University of Jordan /Faculty of science with Brucker AC-400F (400MHZ).

I- Chemistry:

The synthetic procedures for intermediat compounds [1a-4a] were we used glycine as spacer followed by synthesis of oxazol derivatives as intermediates [5a-5d] by using different aldehydes then generation of the final compounds [6a-6d] as new analogues of Naproxen were synthesized by using hydrazine hydrate are illustrated in scheme (1).

Synthesis of Glycine ethyl ester hydrochloride compound [1a]:

In the round bottomed flask (0.375g, 1mmol), Glycine was dissolved in 15 mL ethanol with stirring until the glycine completely melt. The solution was placed in ice path and the temperature was adjusted to -5 0C using the salt. The (0.4 mL, 5 mmol.) of thionyl chloride added as dropwise, the mixture was stirred vigorously for one hr at the same condition in ice path, then reached the temperature at the room temperature for 15 mins. The result product was refluxed for five hrs. with stirring, the HCl gas was liberated from the mixture, which that proved by the litmus paper indicating the red colour changed when exposure to the vapour of the condenser exsust. The precipitate was filtered and collected, washed with diethyl ether then it was re-crystallized from hot ethanol by slow addition of 15–20 ml ether followed by cooling at 0°C. The crystals were collected on the following day [17&18]. The percent yield, physical parameters, melting point and R_f values results are listed in Table (1).

Conversion of Glycine ethyl ester hydrochloride in to free Glycine ester [2a]:

Compound [1a] (0.103g,5 mmol) was dissolved in dry chloroform (15 mL) then triethylamine (10 mmol, 1 mL) was added dropwise over a period of 10 min at 0°Cwith continuous stirring for 2 hrs. The reaction mixture was then filtered and the chloroform layer was distilled off to get clear solution. The clear solution was directly used for the next coupling step [19].

Synthesis of 2-(6-methoxynaphthalen-2-yl)propanoyl chloride [3a]:

NSIAD (0.46g, 2 mmol) was dissolved in dry chloroform (20 mL) in a100ml round-bottomed flask. Thionyl chloride (6 mmol, 1.1 mL) was added dropwise over a period of 15 min. with cooling on ice bath. The mixture was refluxed for 3hrs at 65 °C with continuous stirring and monitored by evolution of HCl gas (which is detected by changing the color of Litmus paper into reddish when placed on the top of condenser) and changing the color of the solution from colorless into deep yellow. The reactions are often promoted by the addition of a drop of dimethylformamide (DMF) [20]. The excess of thionyl chloride and solvent (chloroform) was removed under reduced pressure and the residue was re-dissolving in dry chloroform (20 mL) and was re-evaporated to give an oily residue. This compound was directly used for the next coupling step with free Glycine esterride and solvent (chloroform) was removed under reduced pressure and the residue was re-dissolving in dry chloroform (20 mL) and was re-evaporated to give an oily residue. This compound was directly used for the next coupling step with free Glycine ester [21&22].

Synthesis of ethyl 2-(2-(6-methoxynaphthalen-2-yl)propanamido)acetate [4a]:

Glycine ethyl ester hydrochloride (0.139g, 0.1 mmol) and triethylamine (2 mL) was added in 20 mL dry chloroform and stirred for 1 h to neutralize ester hydrochloride. To this solution, acid chloride of Naproxen in dry chloroform was added slowly in dropwise manner at 0°C for 30 min followed by stirring at room temperature for 30 h and then the solvent was evaporated under reduced pressure. Crude product was dissolved in 10 mL ethyl acetate and washed three times with 10% aqueous sodium bicarbonate solution and with distilled water to remove the traces of unreacted Naproxen and alkali. Finally it was dried over anhydrous magnesium sulphate for whole night. The solution was filtered and the solvent was removed under reduced pressure to get the crude product. It was re-crystallized using alcohol-water mixture. Recrystallized product was filtered off, dried in air and stored in airtight container. This method was used to synthesize product [23]. The percent yield, physical parameters, melting point and R_f values results are listed in Table (1).

Synthesis of 2-(2-(6-methoxynaphthalen-2-yl)propanamido)acetic acid [5a]:

Ester compound (2.6 mmol, 1.2g) was dissolved in a minimum volume of ethanol 99%. The solution was cooled to 18 0C, and then sodium hydroxide (2N, 1.6 mL, 3.23 mmol) was added drop wise with continuous stirring over a period of 30 minutes. Stirring was continued at 18 0C for additional 3 hours. The reaction mixture then was acidified with HCl (2N, 1.6 mL, 3.23 mmol), excess of cold water was added and the compound was precipitated, then filtered and dried to give a white powder [24]. The percent yield, physical parameters, melting point and R_f values results are listed in Table (1).

General procedure for the Synthesis of Oxazol derivatives of Naproxen [6a-6d]:

Aromatic benzaldehyde (1 mmol), compound 5a (0.287g, 1 mmol), anhydrous sodium acetate (1.9 mmol) and (7 mL) of acetic anhydride placed in a conical flask of 100 mL. Heated for 2 hr on water bath with constant stirring. Orange colour crystals formed immediately. Made it cool and added water (10 mL) and kept in refrigerator overnight. Then filtered and dried. Recrystallized with acetic acid to give the final compounds (6a-6d) [25]. The percent yield, physical parameters, melting point and R_f values results are listed in Table (1).

General procedure for synthesis of final compound [7a-7d]:

To a mixture of compound (5a–d) (0.001 mmol) in dry pyridine (5mL) and hydrazine hydrate (99%) (1ml) was added. The reaction mixture was refluxed for 20hs. Then, the mixture was allowed to cool to room temperature and pyridine was removed. The product was recrystallized from ethanol to afford the desired compound [26]. The percent yield, physical parameters, melting point and R_f values results are listed in Table (1).

II- Pharmacology:

Albino rats of either sex weighing (150 ± 10 g) were supplied by the animal house of the College of Pharmacy, Al-Mustansirya University and were housed in the same location under standardized conditions. Animals were fed commercial chaw and had free access to water ad libitum. Animals were divided into six groups (each group consist of 6 rats) as follow.

Group A: six rats served as control; and treated with the vehicle (i.p) (propylene glycol 50% v/v).

Group B: six rats treated with naproxen as reference substance in a dose of 2.5mg/ kg (i.p)[132]suspended in propylene glycol 50% (v/v) [27].

Group C-F: six rats/group treated with the tested compounds (7a, 7b, 7c and 7d) in doses that determined below. (Suspended in propylene glycol 50% v/v).

Anti-inflammatory activity:

Anti-inflammatory Effect of Tested Compounds was studied using egg-white induced edema model. Acute inflammation was produced by a subcutaneous injection of 0.05ml of egg-white into the planter side of the hind paw of the rats after 30 minutes i.p. administration of the drugs or their vehicle. The paw thickness was measured by vernea at seven time intervals (0, 30, 60, 120, 180, 240,300 minutes) after drugs administration [28]. The data was

expressed as the mean ± SEM (standard error of the mean) and results were analyzed for statistical significance using student t-test (Two Sample Assuming Equal Variances) for comparison between mean values. While comparisons between different groups were made using ANOVA (analysis of variance): Two factors without Replication. Probability (P) value of less than 0.05 was considered significant.

Results and Discussion:

The synthesis of compounds [7a-d] was carried out through the reaction were summarized in Scheme (1), the prepared compounds was characterized in FT-IR, ^{1}HNMR spectroscopies, melting points and pharmacological activity examined.

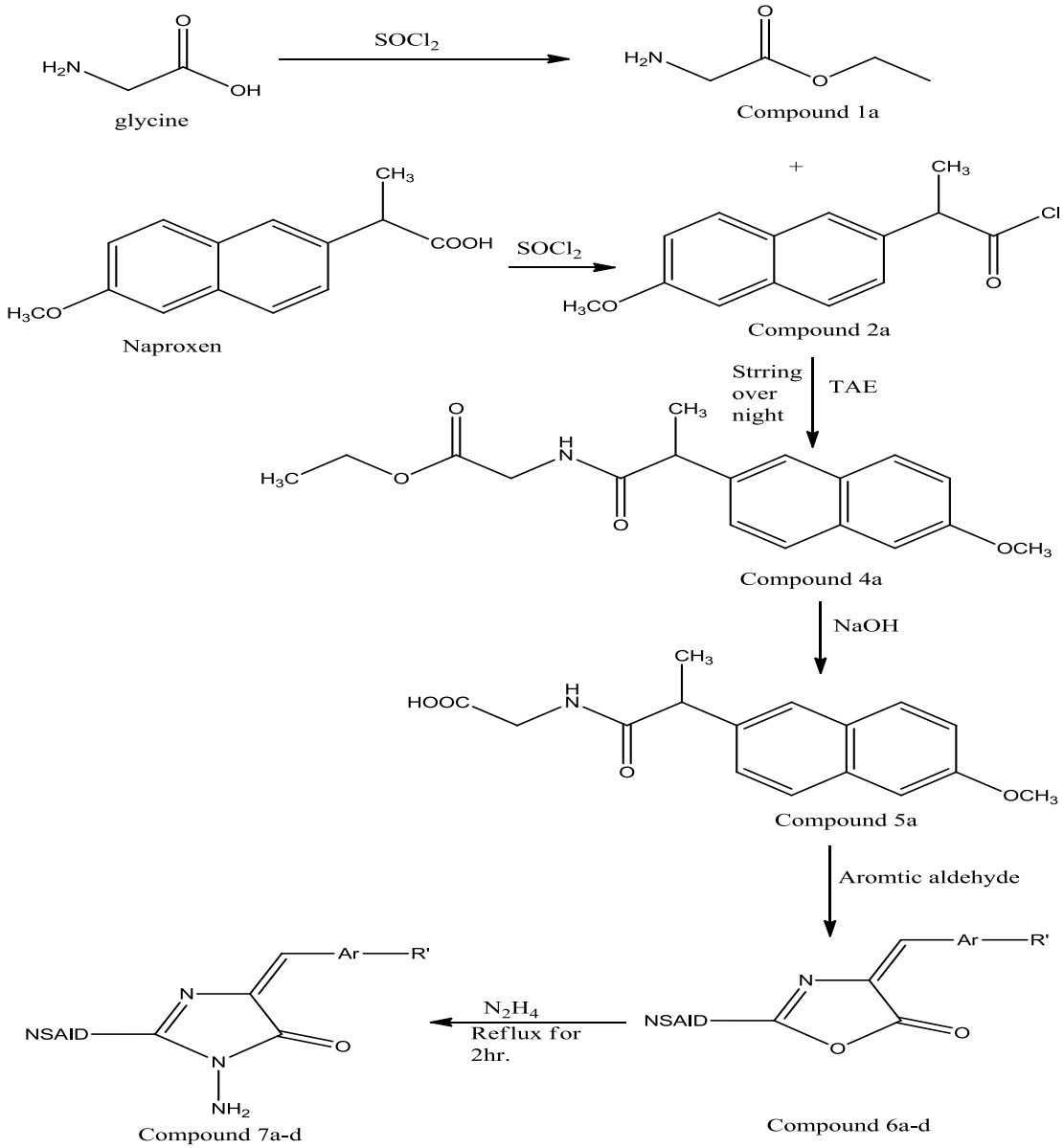
IR spectra of compound [1a], Fig.2 show (cm−1): 3477 (N-H), 2976 (CH_3), 1745 (C=O), 1249 (C-O-C stretching), 1134 (C-N). IR spectra of compound [4a], Fig. 3 show (cm−1): 3290 (N-H), 3068 (C-H of aromatic ring), 2976 and 2933 (C-H_3 asymmetric and symmetric), 1793 (C=O of ester), 1651 (C=O of amide), 1456 (C=C of aromatic), 1296 (C-O-C), 1261 (O-CH_3). IR spectra of compound [5a], Fig.4 show (cm−1): 3415 (OH), 3311 (NH), 3061 (C-H of aromatic), 2935 and 2843 (C-H asymmetric and symmetric), 1612 (Broad and twin band belong to C=O stretching of carboxylic and amide), 1510 (C=C of aromatic), 1313 (C-O-C), 1265 (O-CH_3). IR spectra of(E)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)-4-(4-nitrobenzylidene)oxazol-5(4H)-one (compound 6a), Fig.5 show (cm−1): 3107 (C-H of alken), 3051 (C-H of aromatic), 2939 and 2839 (C-H asymmetric and symmetric), 1799 (C=O of ester), 1658 (C=N), 1602 (C=C of aromatic), 1514 (N=O), 1340 (N-O), 1263 (C-O-C). IR spectra of (E)-4-(4-chlorobenzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)oxazol-5(4H)-one (compound 6b), Fig.6 show (cm−1): 3053 (C-H of aromatic), 2935 and 2841 (C-H asymmetric and symmetric), 1801 (C=O of ester), 1656 (C=N), 1599 (C=C of aromatic), 1267 (C-O-C). IR spectra of (E)-4-(4-methoxybenzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)oxazol-5(4H)-one (compound 6c), Fig.7 show (cm−1): 3055 (C-H of aromatic), 2939 and 2843 (CH_3 asymmetric and symmetric), 1795 (C=O of ester), 1658 (C=N), 1602 and 1504 (C=C of aromatic), 1267 (C-O-C). IR spectra of (E)-4-(4-(dimethylamino)benzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)oxazol-5(4H)-one (compound 6d), Fig.8 show (cm−1): 3053 (C-H of aromatic), 2935 and 2841 (CH_3 asymmetric and symmetric), 1801 (C=O of ester), 1658 (C=N), 1599 (C=C of aromatic), 1265 (C-O-C). IR spectra of (E)-1-amino-2-(1-(7-methoxynaphthalen-3-yl)ethyl)-4-(4-nitrobenzylidene)-1H-imidazol-5(4H)-one (compound 7a), Fig.9 show (cm−1): 3423 and 3288 (N-H stretching of NH_2), 3066 (C-H of aromatic), 2924 (C-H of CH_3), 1631 (C=O stretching of amide), 1600, 1577 and 1508 (C=C stretching of aromatic overlap with C=N), 1234 (N-C stretching for amide group). IR spectra of (E)-1-amino-4-(4-chlorobenzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)-1H-imidazol-5(4H)-one (compound 7b), Fig.10 show (cm−1): 3385 and 3265 (N-H stretching of NH_2), 3055 (C-H stretching of aromatic), 2935 and 2841 (C-H stretching vibration of CH_3), 1660 (C=O stretching of amide), 1633 (C=N stretching), 1606 (C=C of aromatic), 1265 (C-O-C), 1205 (N-C for amide group). IR spectra of (E)-1-amino-4-(4-methoxybenzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)-1H-imidazol-5(4H)-one (compound 7c), Fig.11 show (cm−1): 3392 and 3221 (N-H stretching of NH_2), 3059 (C-H stretching of aromatic), 2933 and 2850 (C-H stretching vibration of CH_3), 1633 (C=O stretching of amide), 1608 (C=N stretching), 1545 (C=C of aromatic), 1263 (C-O-C), 1213 (N-C for amide group). IR spectra of (E)-1-amino-4-(4-(dimethylamino)benzylidene)-2-(1-(7-methoxynaphthalen-3-yl)ethyl)-1H-imidazol-5(4H)-one (compound 7d), Fig.12 show (cm−1): 3441 and 3246 (N-H stretching of NH_2), 3061 (C-H stretching of aromatic), 2989 and 2912 (C-H stretching vibration of CH_3), 1641 (C=O stretching of amide), 1604 (C=N stretching), 1548 (C=C of aromatic), 1261 (C-O-C), 1209 (N-C for amide group).

^{1}HNMR spectra of compound [7a], Fig.13 show (400 MHz, MeOD): δ 1.57 (d, 3H, for CH_3 protonsof naproxen), 3.74 (s, 3H, for OCH_3 protons of naproxen), 3.92 (q, 1H, for CH protons of naproxen), 4.60 (s, 2H, for NH_2 amide proton), 7.18 (d, 2H, for CH protons ortho to methoxy), 7.3 (s, 1H, for CH protons for ethylene), 7.4-7.8 (m, 8H, for naphthalene & aromatic protons). ^{1}HNMR spectra of compound [7b], Fig.14 show (400 MHz, MeOD): δ 1.50 (d, 3H, for CH_3 protonsof naproxen), 3.9 (s, 3H, for OCH_3 protons of naproxen), 4.2 (q, 1H, for CH protons of naproxen), 4.61 (s, 2H, for NH_2 amide proton), 7.1-7.13 (m, 4H, for CH protons ortho to methoxy & chloro), 7.2 (s, 1H, for CH protons for ethylene), 7.4-7.74 (m, 6H, for naphthalene & aromatic protons). ^{1}HNMR spectra of compound [7c], Fig.15 show (400 MHz, DMSO): δ 1.41 (d, 3H, for CH_3 protonsof naproxen), 3.38 (q, 1H, for CH proton of methane), 3.80 (s, 3H, for-OCH_3 protons of naproxen), 3.81 (s, 3H, for-OCH_3 protons of aromatic ring), 4.04 (s, 2H, for NH_2 amide protons), 7.13 (d, 2H, for aromatic ortho protons to methoxy), 7.16 (d, 2H, for aromatic ortho protons to methoxy), 7.28 (s, 1H, for CH proton of ethylene), 7.4-7.79 (complex, 6H, for naphthalene & aromatic protons). ^{1}HNMR spectra of compound [7d], Fig.16 show (400 MHz, DMSO): δ 1.55 (d, 3H, for CH_3 protons of naproxen), 3.78 (q, 1H, for CH proton of naproxen), 3.84 (s, 6H, for-$N(CH_3)_2$ protons of aromatic ring), 3.94 (s, 3H, for-OCH_3 protons of naproxen), 4.29 (s, 2H, for NH2 amide proton), 6.7-6.8 (d, 2H, for aromatic protons ortho to N-dimethyl), 7.1 (d, 2H, for aromatic protons ortho to methoxy), 7.3 (s, 1H, for CH proton for ethylene), 7.4-7.79 (m, 6H, for naphthalene & aromatic protons).

The most widely used primary test to screen new anti-inflammatory agents' measure the ability of the compound to reduce local edema induced in the rat paw by injection of an irritant agent [29]. The anti-inflammatory activity of the tested analogues has been evaluated in comparison with propylene glycol 50%v/v (control group) and naproxen. Table (2) explains the effect of tested compounds (7a-7d) in comparison to propylene glycol 50%v/v and naproxen.
The reference drug as well as the tested compounds produced significant reduction of paw edema in comparison to the effect of control group (propylene glycol 50%v/v). All tested compounds significantly limited the edema in paw rats, the onset of nitro containing analogue and chloro containing analogues (compounds 7a & 7b) started at time 60 min. while the remaining compounds and naproxen started at 120 min.
Nitro containing analogue exhibited significantly ($P<0.05$) potent anti-inflammatory effect than naproxen (50mg/kg, i.p.) at 60-300 min., while remaining analogues exhibited comparable anti-inflammatory effect at 120 – 300 min.
However, the effect of all tested analogues continued till the end of experiment time with statistically significant ($P<0.05$) reduction in paw edema thickness as shown in Figure (1).

Table (1): The physical properties and Rf values of the intermediates and final products:

Compounds and intermediates	Moleculer formula	Molecular weight	Description	% yield	Melting point ^{o}C	R_f value
1a	$C_4H_9NO_2$	103	White crystals	79	146-148	A=0.7 B=0.62
4a	$C_{18}H_{21}NO_4$	315	Off white powder	55	84-86	A=0.81 B=0.54
5a	$C_{16}H_{17}NO_4$	287	White crystals	73	167-168	A=0.73 B=0.57
6a	$C_{23}H_{18}N_2O_5$	402	Orange powder	62	140-141	A=0.88 B=0.61
6b	$C_{23}H_{18}ClNO_3$	391	Pale yellow powder	40	131-133	A=0.78 B=0.67
6c	$C_{24}H_{21}NO_4$	387	Yellow powder	35	127-128`	A=0.61 B=0.42
6d	$C_{25}H_{24}N_2O_3$	400	Brown powder	50	135-136	A=0.56 B=0.61
Compound7a	$C_{23}H_{20}N_4O_4$	416	Pale Orange powder	46	149-151	A=0.27 B=0.35
Compound7b	$C_{23}H_{20}ClN_3O_2$	405	White powder	38	155-157	A=0.46 B=0.68
Compound7c	$C_{24}H_{23}N_3O_3$	401	Yellow powder	40	164-166	A=0.62 B=0.77
Compound7d	$C_{25}H_{26}N_4O_2$	414	Deep brown powder	57	145-147	A=0.73 B=0.60



Scheme (1): Synthesis of routs of target compounds.

Where R'= NO2, compound 6a&7a
R'= Cl, compound 6b&7b
R'= OCH3, compound 6c&7c
R'= N(CH3)2, compound 6d&7d

Table (2): The anti-inflammatory effect of propylene glycol, naproxen and compounds (7a-7d) on egg-white induced paw

	compounds	Time (min)						
		0	30	60	120	180	240	300
Paw Thickness (mm) / n=6	Control	4.05±0.09	5.35±0.06	6.21± 0.01	6.88±0.03	7.61±0.09	6.70±0.03	5.41±0.04
	Naproxen	4.03±0.04	5.32±0.04	6.11±0.05	5.60±0.02^{*a}	5.39±0.07^{*a}	5.15±0.04^{*a}	4.61±0.06^{*a}
	7a	3.99±0.02	5.27±0.05	5.84±0.03*	5.17±0.08^{*b}	4.92±0.02^{*b}	4.22±0.07^{*b}	4.13±0.01^{*b}
	7b	4.0±0.07	5.29±0.06	5.90±0.03*	5.53±0.06^{*a}	5.17±0.09^{*a}	4.91±0.03^{*a}	4.55±0.05^{*a}
	7c	3.98±0.07	5.27±0.08	6.10±0.06	5.61±0.01^{*a}	5.27±0.08^{*a}	4.95±0.05^{*a}	4.71±0.02^{*a}
	7d	4.01±0.05	5.30±0.09	6.18±0.07	5.57±0.03^{*a}	5.31±0.08^{*a}	4.92±0.04^{*a}	4.56±0.10^{*a}

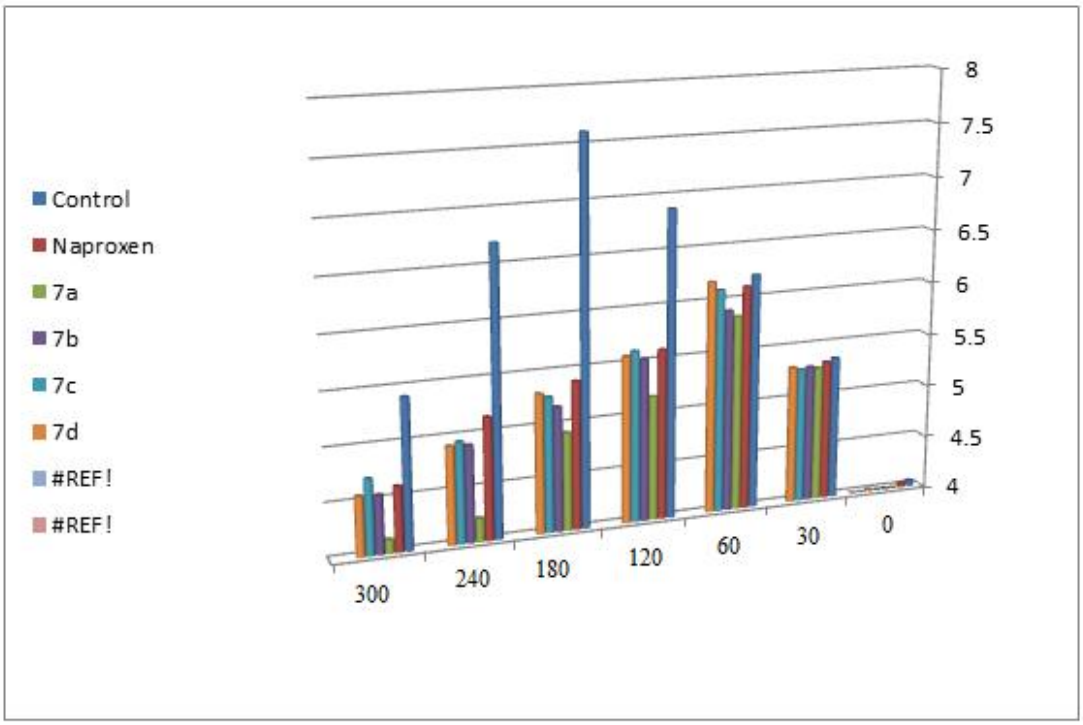


Figure (1): Effect of naproxen, propylene glycol and compounds 7a-d on egg-white induced paw edema in rats
Results are expressed as mean ± SEM (n = 6 for each group)

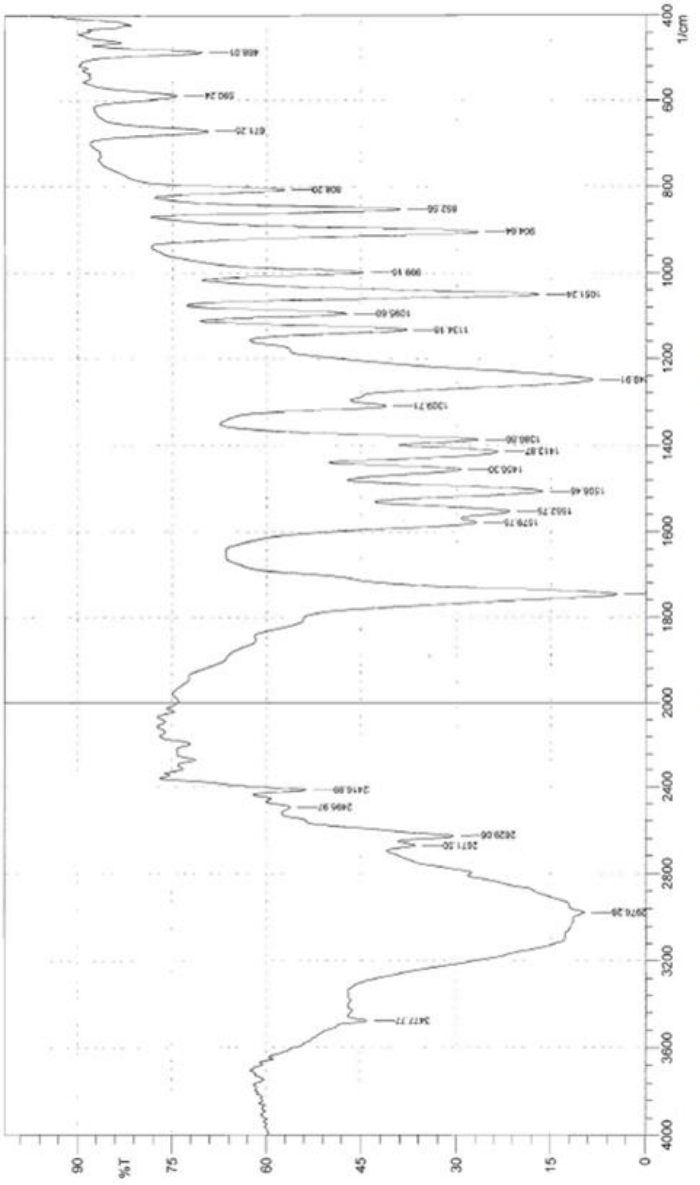


Figure 2: FT-IR sectrum of compound (1a) using KBr disc

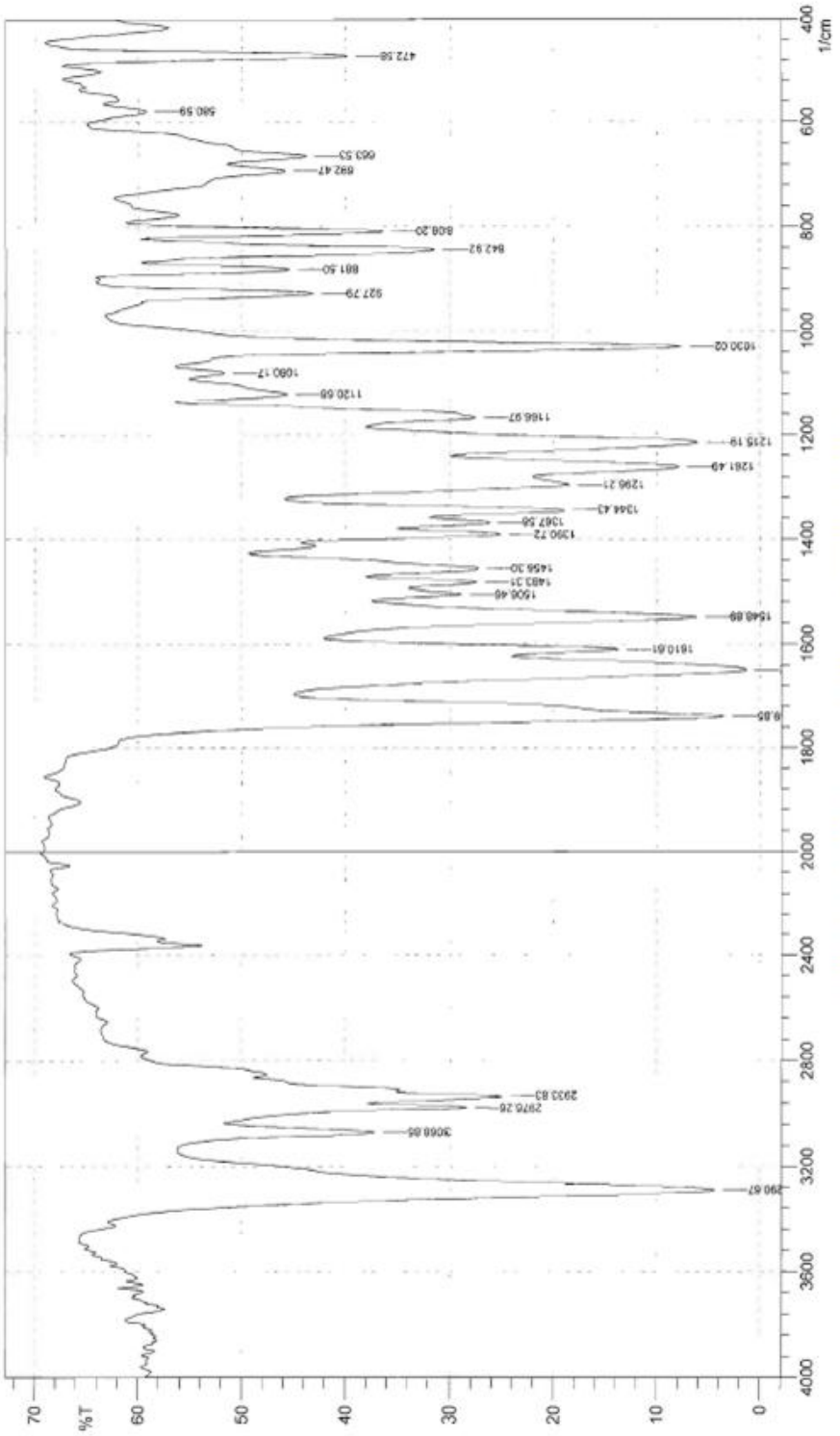


Figure 3 : FT-IR spectrum of compound (4a) using KBr disc

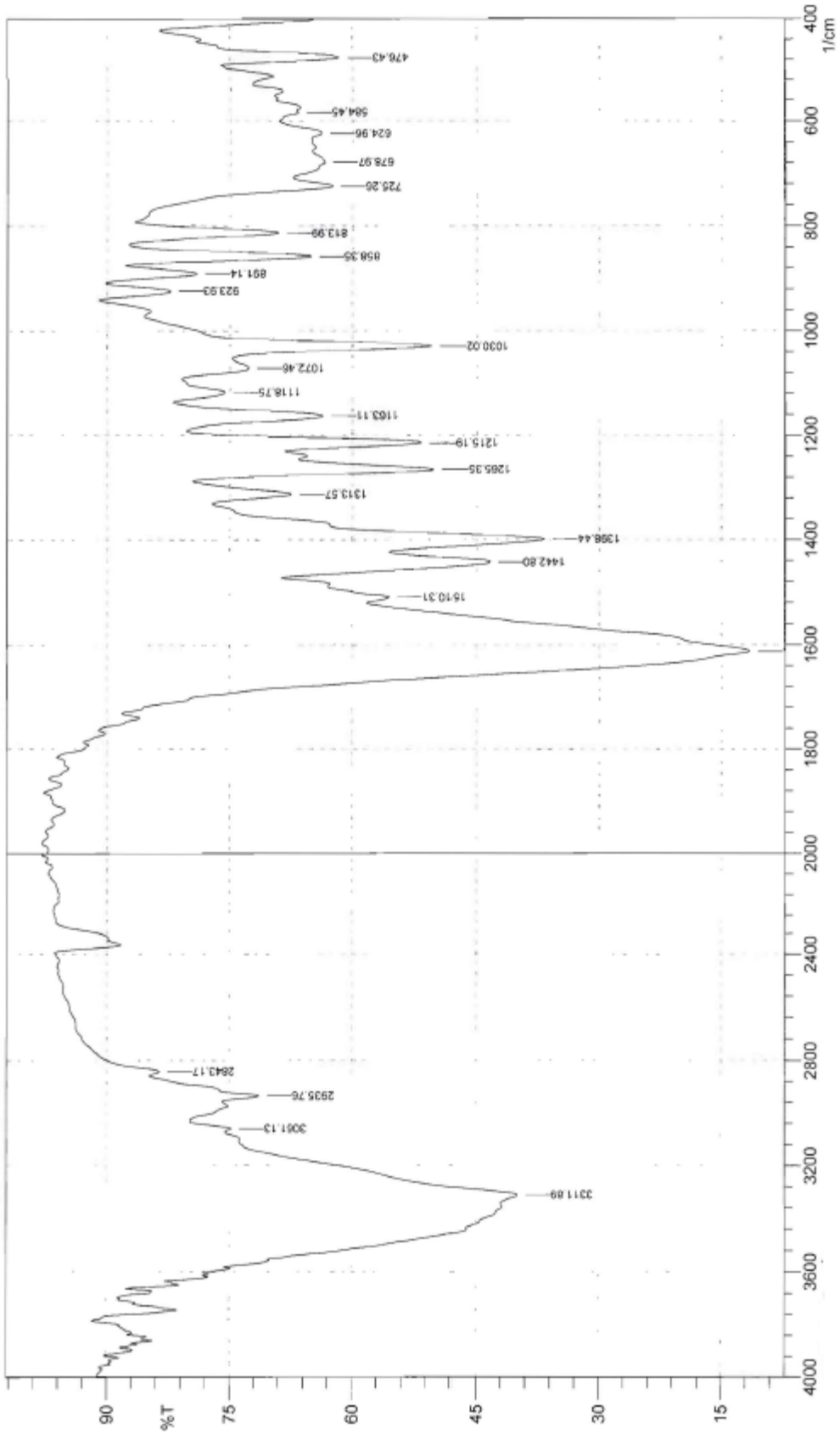


Figure 4 : FT-IR spectrum of compound (5a) using KBr disc

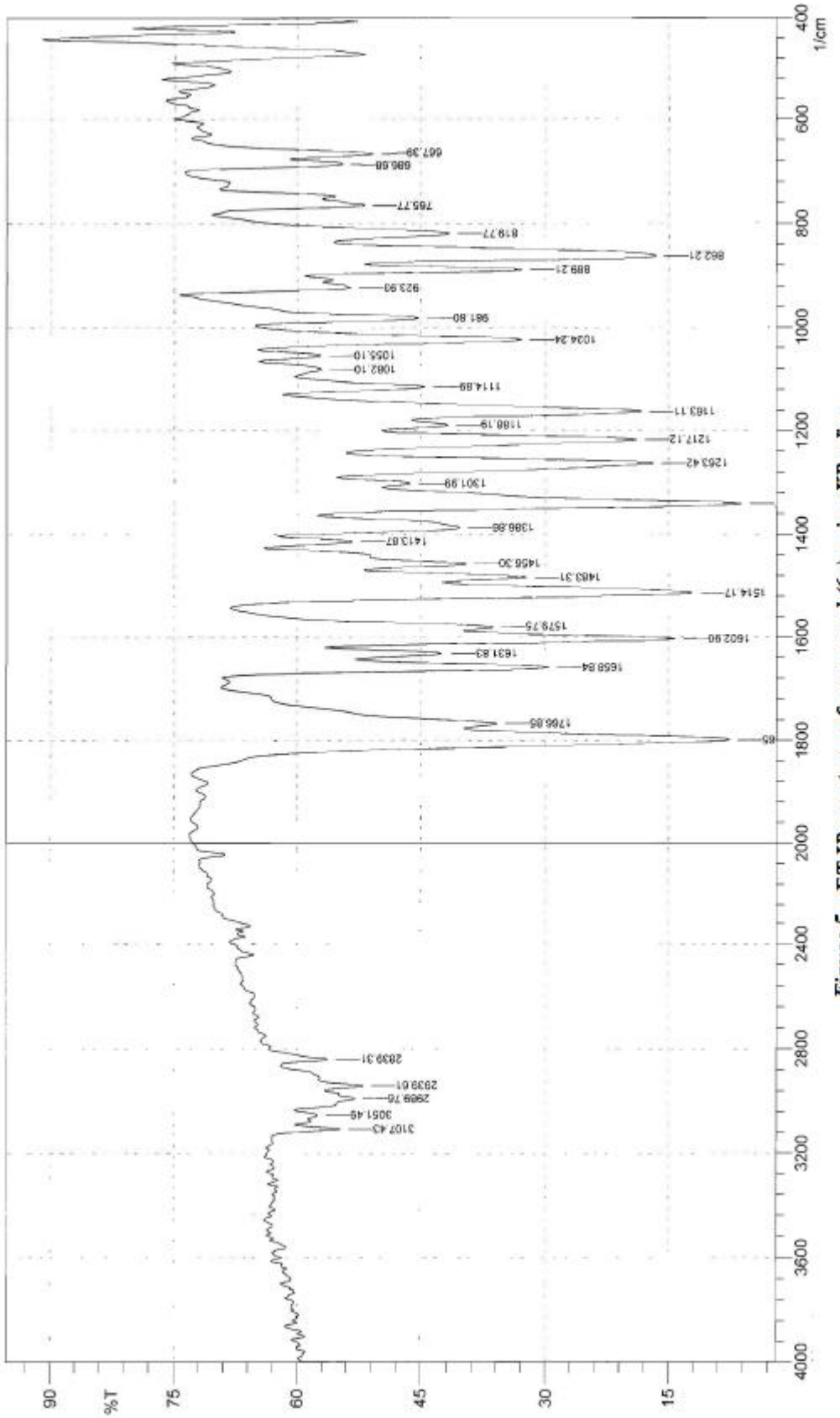


Figure 5 : FT-IR spectrum of compound (6a) using KBr disc

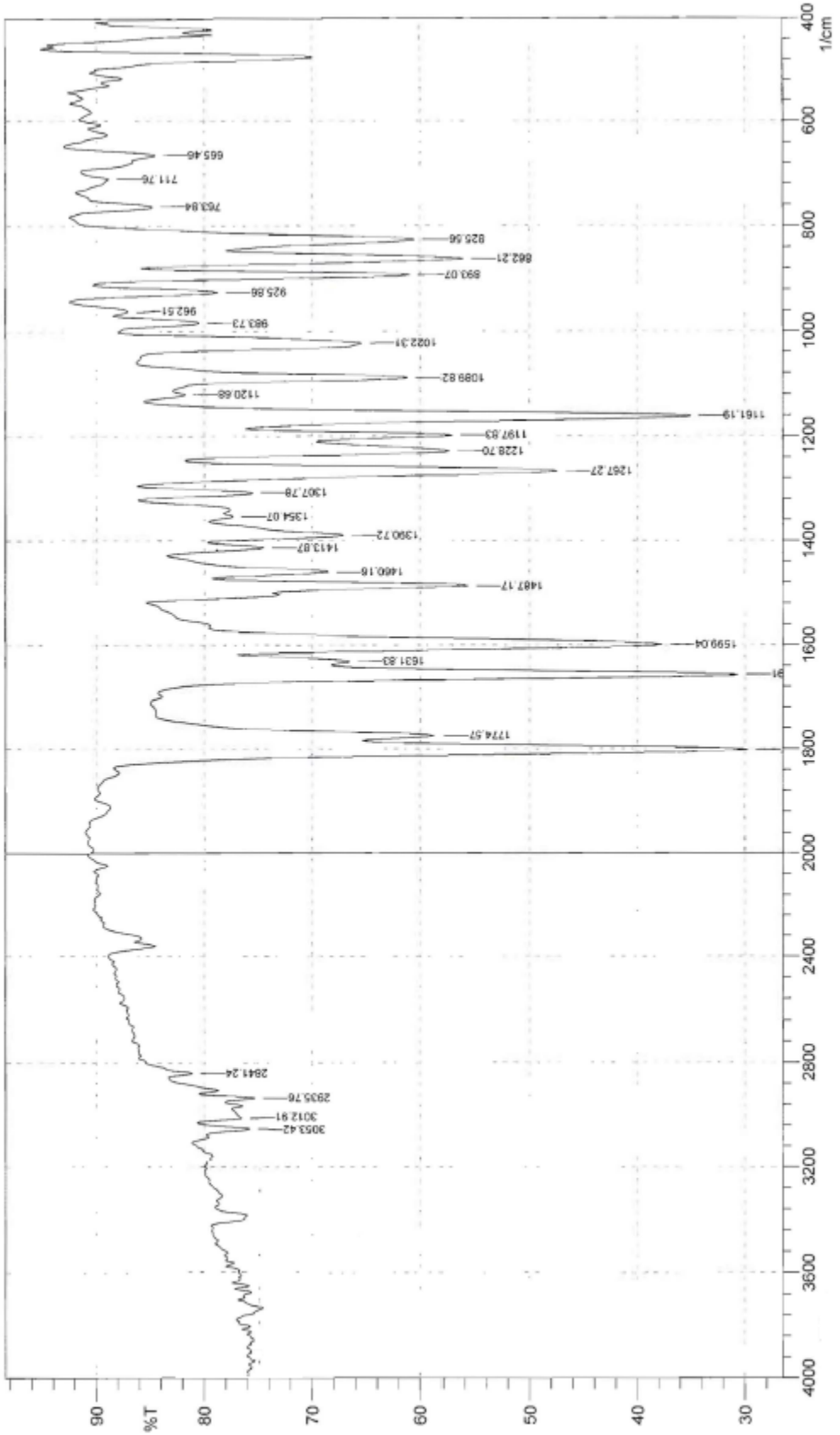


Figure 6 : FT-IR spectrum of compound (6b) using KBr disc

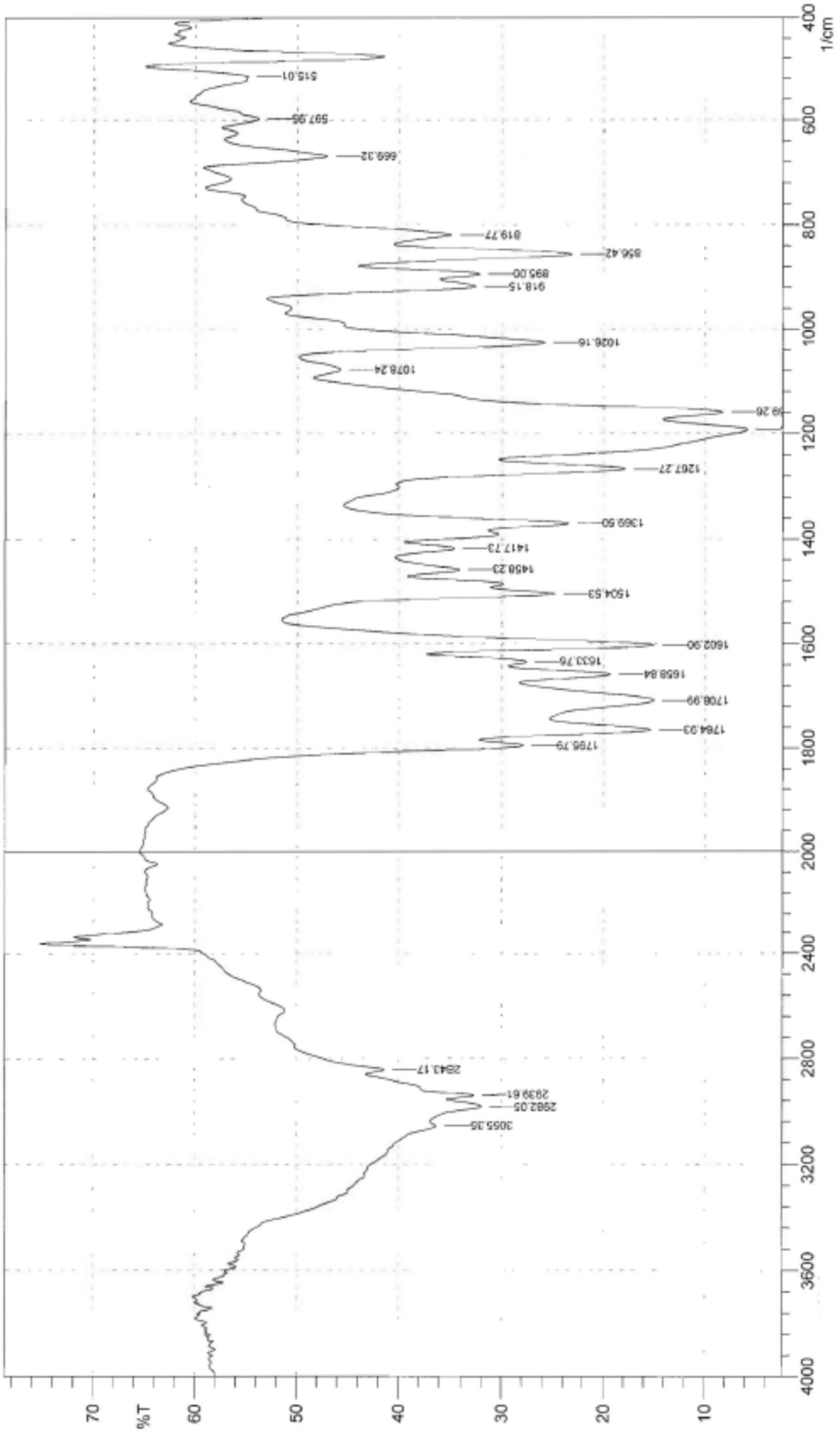


Figure 7 : FT-IR spectrum of compound (6c) using KBr disc

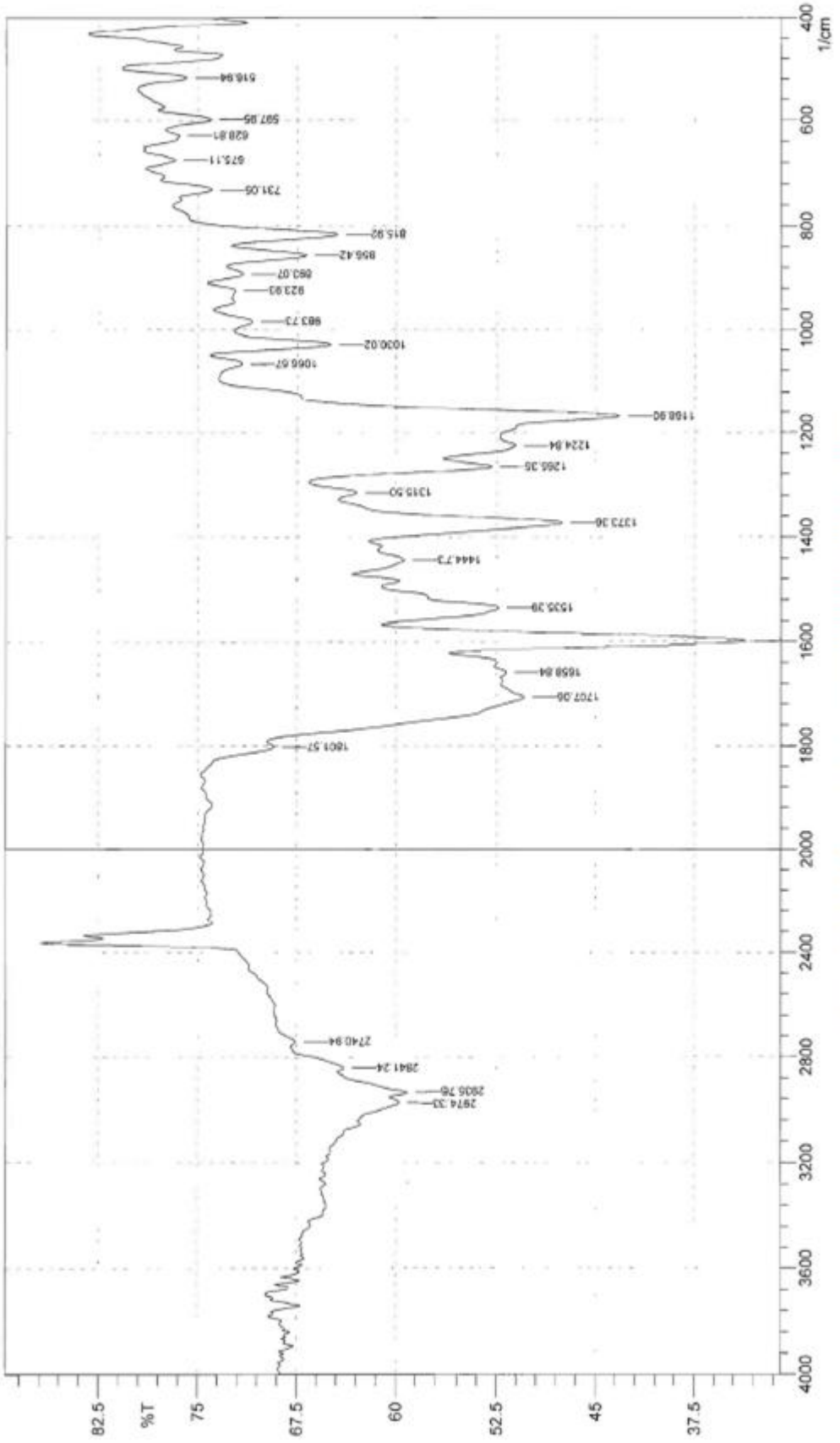


Figure 8 : FT-IR spectrum of compound (6d) using KBr disc

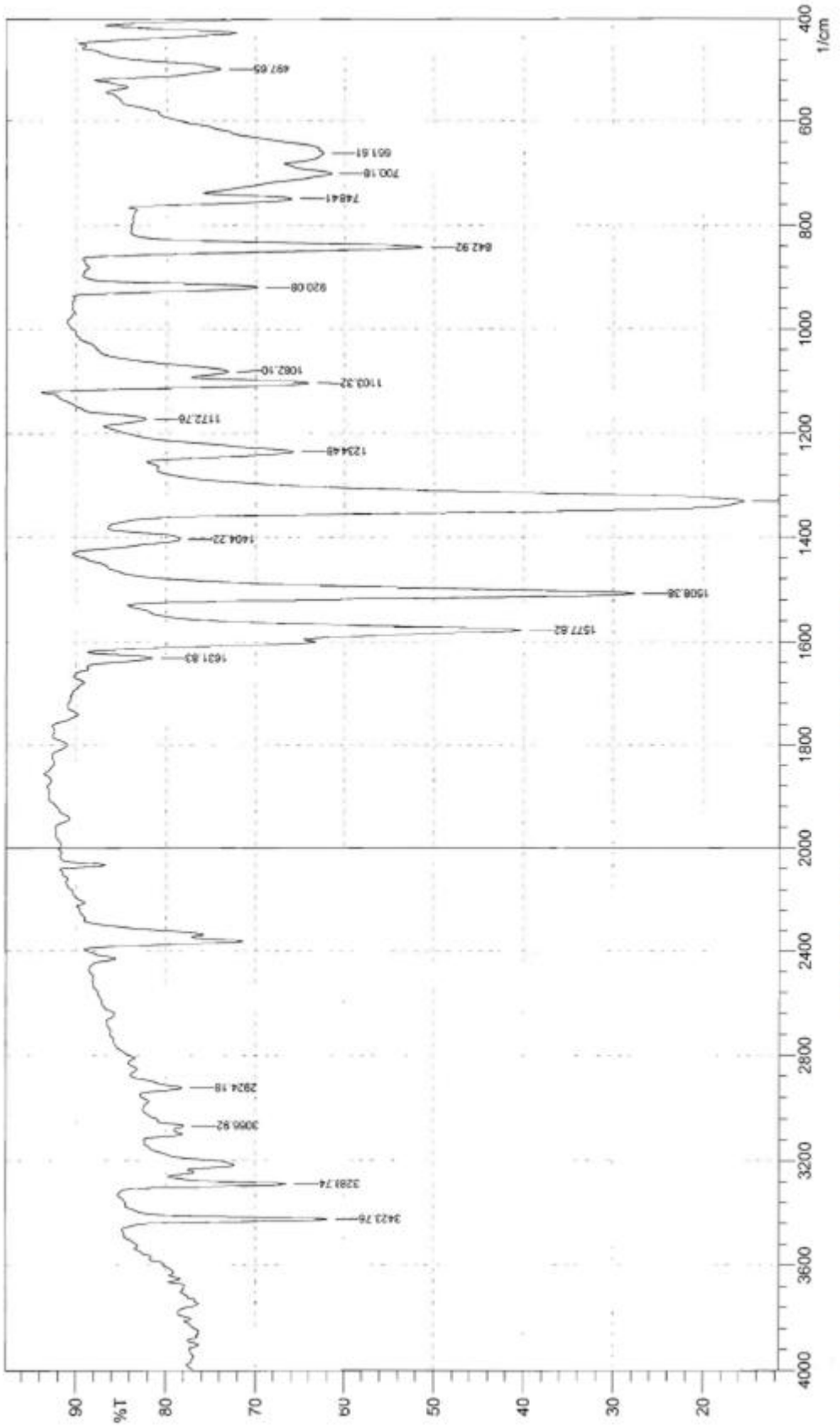


Figure 9 : FT-IR spectrum of compound (7a) using KBr disc

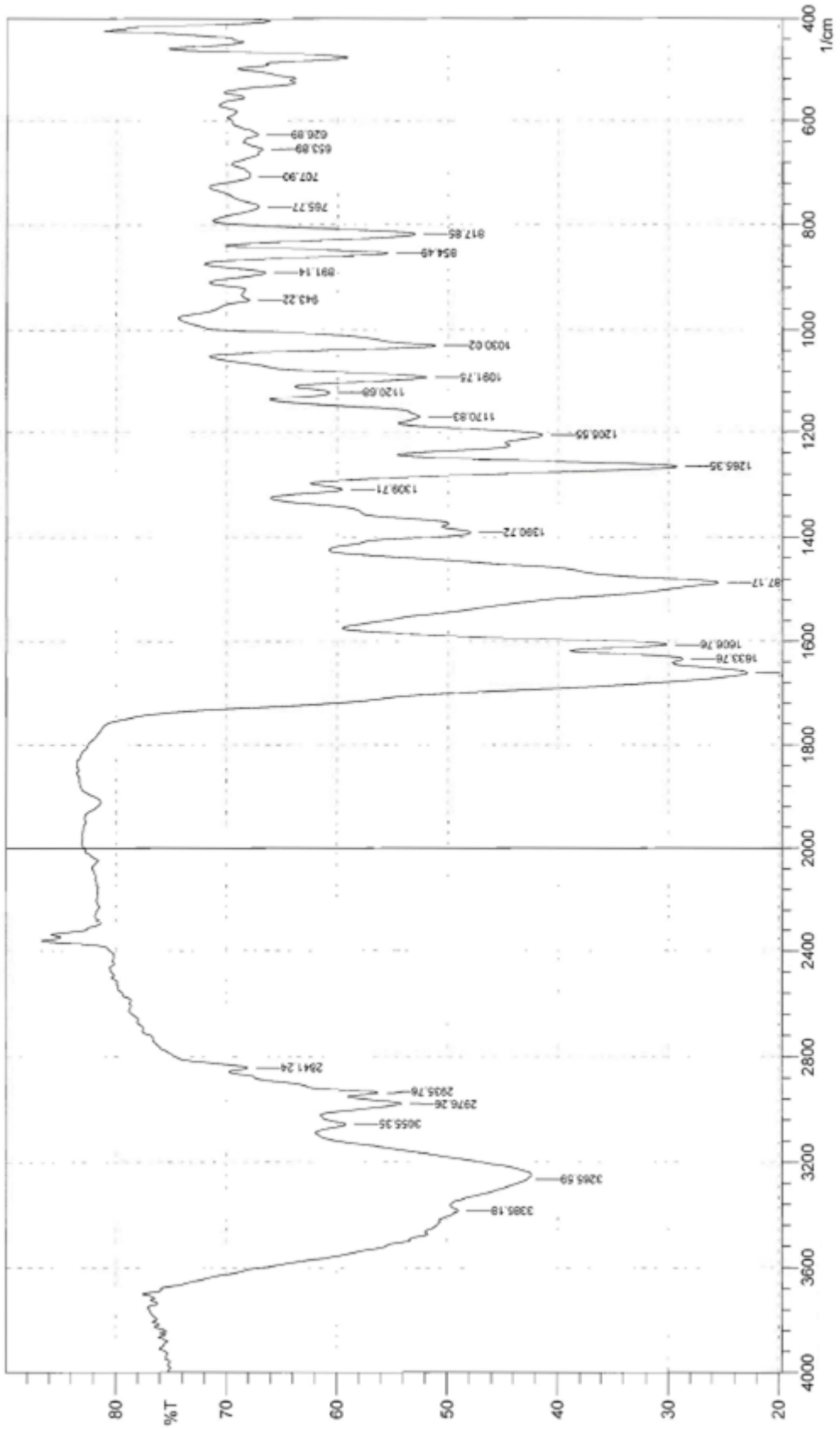


Figure 10 : FT-IR spectrum of compound (7b) using KBr disc

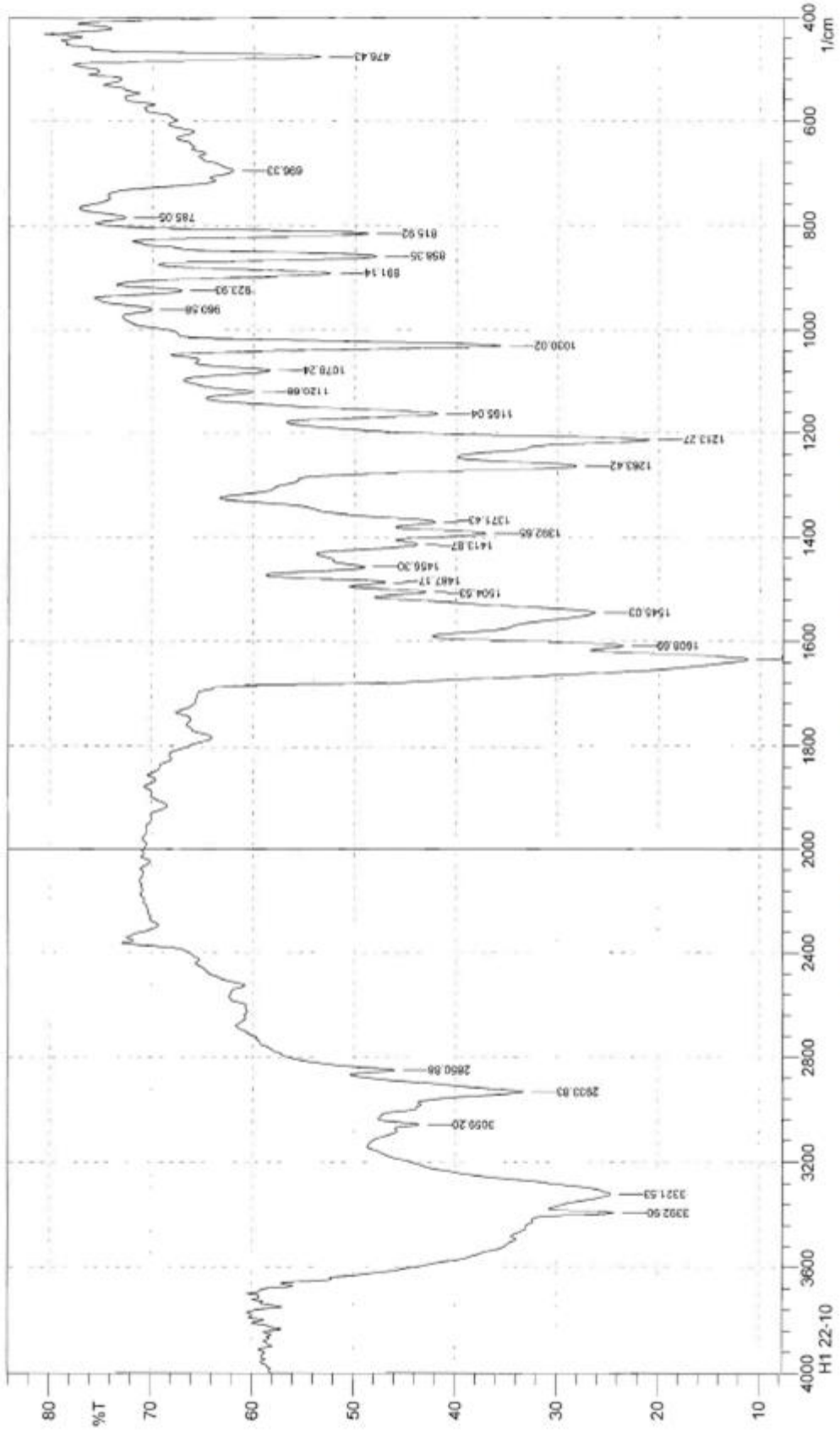


Figure 11: FT-IR spectrum of compound (7c) using KBr disc

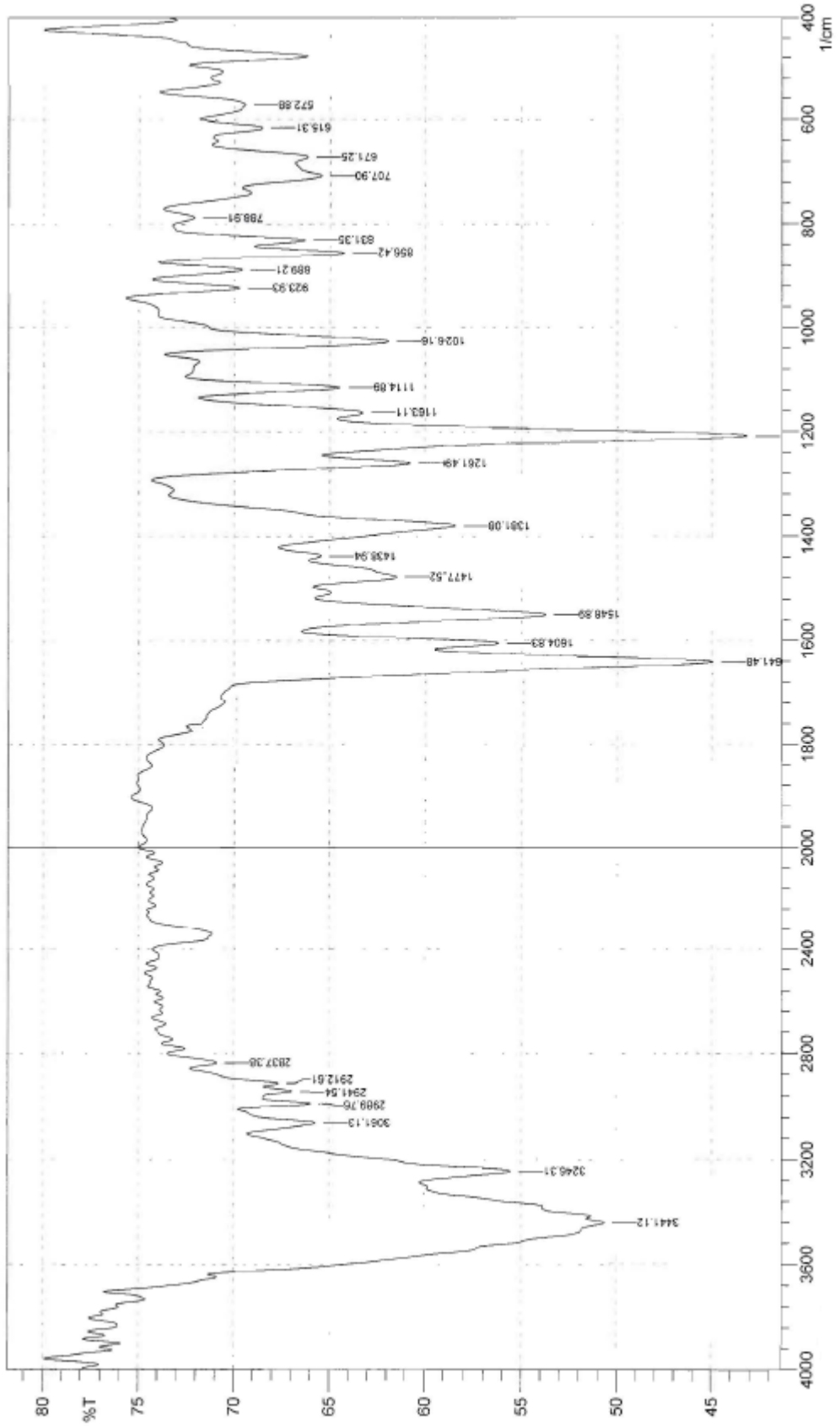


Figure 12 : FT-IR spectrum of compound (7d) using KBr disc

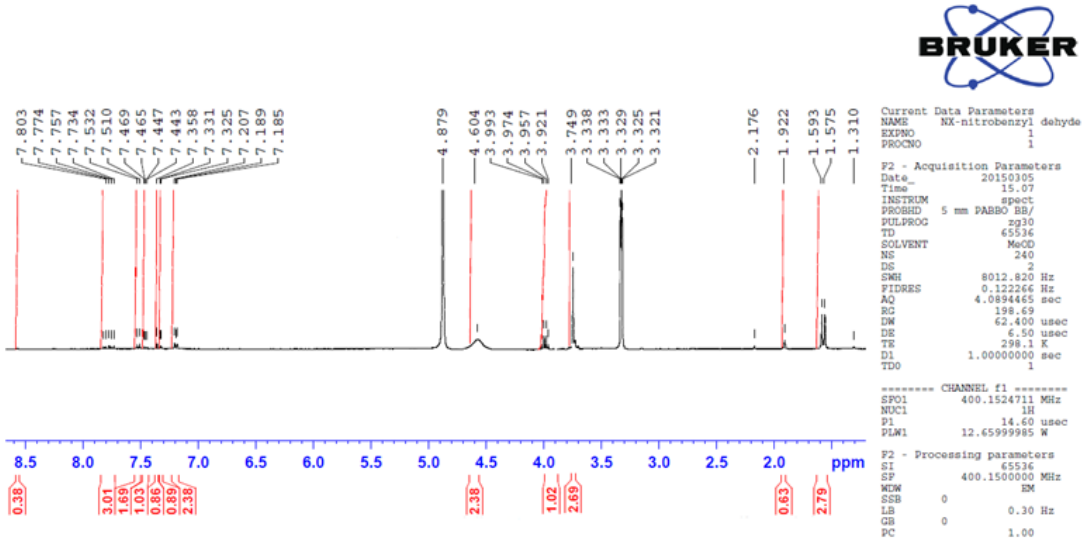


Figure 13 : [1]H-NMR spectrum of compound (7a)

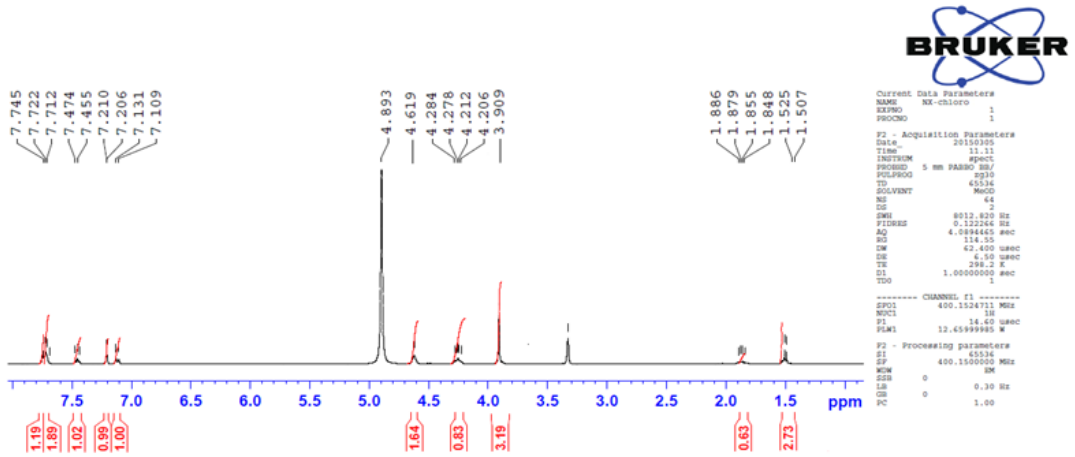


Figure 14 : [1]H-NMR spectrum of compound (7b)

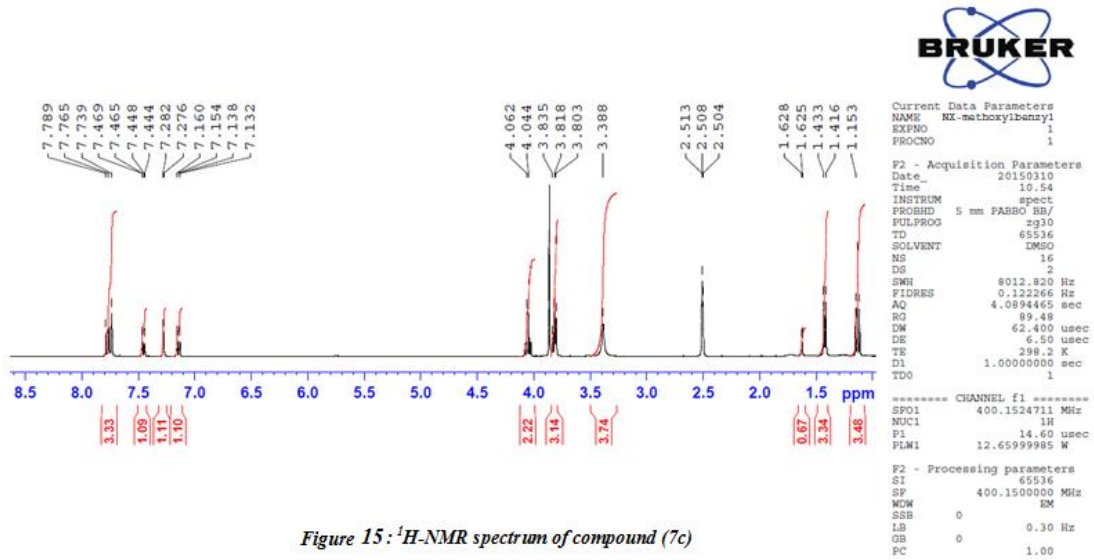


Figure 15: ^{1}H-NMR spectrum of compound (7c)

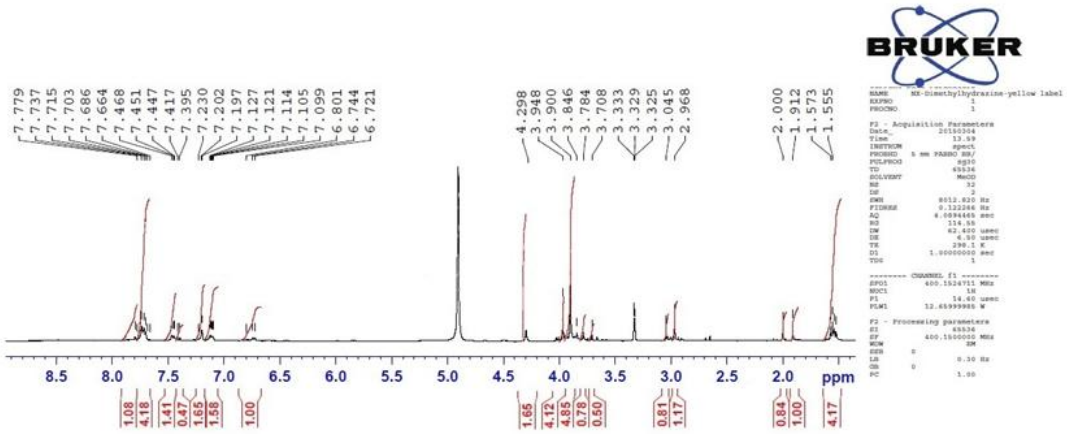


Figure 16: 1H-NMR spectrum of compound (7d)

Conclusions:

The synthesis of the designed compounds has been successfully achieved. Identification and characterization of the synthesized analogues was confirmed by ^{1}H-NMR spectra, FT-IR spectroscopy and determination of physical properties. Our study of the acute anti-inflammatory activity indicated that nitro containing analogue has faster onset of action and significantly more effect than naproxen

References:

1- Modi C. M., Mody S.K., Patel H.B., Dudhatra G.B., Kumar A. and Avale M.: Toxicopathological overview of analgesic and anti-inflammatory drugs. **Journal of Applied Pharmaceutical Science**.(2012); 149-157.

2- Sam Harirforoosh, Waheed Asghar, and Fakhreddin Jamali: Adverse Effects of Nonsteroidal Antiinflammatory Drugs: An Update of Gastrointestinal, Cardiovascular and Renal Complications. **J Pharm Pharm Sci**.(2013); 821 - 847

3- Ward R. Identifying and assessing benefit-risk in primary care—a family physician's perspective. **Rheumatology**. (2010).

4- Carin E. Dugowson, MD, Gnanashanmugam P.: Nonsteroidal Anti-Inflammatory Drugs. **Phys Med Rehabil Clin N Am**, 17(2006) 347-354.

5- Vane JR, Botting RM.: The mechanism of action of aspirin. **Thromb Res** (2003); 110-255.

6- Tagreed N, Omar A.: Synthesis and Preliminary Pharmacological Evaluation of Esters and Amides Derivatives of Naproxen as Potential Anti-Inflammatory Agents. **Iraqi J Pharm Sci**, (2013), Vol.22(1).
7- Marnett, L.J., Rowlinson, S.W., Goodwin, D.C., Kalgutkar and A.S. Lanzo, C.A.: Arachidonic acid oxygenation by COX-1 and COX-2. Mechanisms of catalysis and inhibition. **J. Biol. Chem.** (1999), 274: 22903-22906.
8- Chandrasekharan, N.V. Dai, H. Roos, K.L. Evanson and N.K. et al.: Cox-3, a COX-1variant inhibited by acetaminophen and other analgesic antipyretic drugs. **Proc. Natl. Acad. Sci.** (2002), 99: 13926-13931.
9- Dinchuk, J.E. Lui, R.Q. and Trzaskos J.M.:COX-3 in the wrong frame in mind. **Immunol. Lett.** (2003), 86: 121.
10- Inger L. Meek, Mart A.F.J. van de Laar and Harald E. Vonkeman: Non-Steroidal Anti-Inflammatory Drugs: **An Overview of Cardiovascular Risks. Pharmaceuticals** (2010), 3, 2146-2162.
11- Van, J.; Botting, J, Selective COX-2 inhibitors. **Pharmacology, clinical effects and therapeutic potential, Kluwer Academic publishers, Dordrecht**; 1998, pp. 19-26.
12- Kerr S.COX-2-selective NSAIDs. **National Prescribing Service.** (2010).
13- Choy, E. H. and Panayi, G. S.: Mechanism of disease: cytokine pathways and joint inflammation in rheumatoid arthritis. **New England Journal of Medicine.**(2001);344(12):907-916.
14- Monther F. Mahdi: Synthesis and Preliminary Pharmacological Evaluation of New Non-steroidal Anti-inflammatory Agents. **Ph.D. Thesis, College of Pharmacy, Baghdad University, Baghdad,** (2006).
15- Filiz Sayin, SedefKir : Determination of Diflunisal in Tablets Using Derivative UV Spectrophotometric Methods. **FABAD J. Pharm. Sci.** (2004); 29: 121-126.
16- Pradip, K.; Jee, B. and Amidon, G.L.: **J. Pharm. Sci.** (1981); 70: 1299.
17- Ali B.T., Monther F. M. and Mohammed H. M. "Design, synthesis, and hydrolysis study of mutual prodrugs of NSAIDS with different antioxidants via glycolic acid spacer"; **Pharmacieglobale**, 5 December (2012), ISSN 0976-8157.
18- Shriner, R.L.; Hermann, C.K.F.; Morrill, T.C.; Curtin, D.Y. and Fusan, R.C.: "The Identification of Organic Compounds" (8th ed.). **John Wiley and Sons, Inc. U.S.A**; (2004); pp. 247-350.
19-Dhanseshwar SS, and Metreyi S.; "Preliminary studies on gastro-protective chimeric derivative of biphenyl acetic acid for rheumatoid arthritis**"; International Journal off Pharmacy and Pharmaceutical Sciences**; (2012); Vol. 4, Issue 1; ISSN- 0975-1491.
20- Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. Helv. Chim.Acta 1959, 42, 1653–1658. (b) Bruckner, R. "Advanced Organic Chemistry, Reaction Mechanisms; **Harcourt/Academic: San Diego**; (2002); p 239.
21- Mehta N, Aggarwal S, Thareja S, Mallal P, Misra M, Bhardwaj TR; and Kumar M; "Synthesis, pharmacological and toxicological evaluation of amide derivative of ibuprofen" ; **International Journal of Chem Tech Research**; Jan-Mar (2010); Vol.2; No.1, pp 233-238.
22- Saraswathi R, Lokesh U., Thandapani AB, Venkatakrishnan R, Meera R, and Devi P; "Synthesis and pharmacological screening of N-substituted amide ester derivative& other derivative of naproxen for anti-inflammatory activity"; **International Journal of Drug Formulation & Research** Mar.-Apr. (2011), Vol. 2(2) 237-248; ISSN 2229-5054.
23- Mishra A; Veerasamy R; Kumar Jain P; Kumar Dixit V and Agrawal RK;" Synthesis, characterization and pharmacological evaluation of amide prodrugs of Flurbiprofen"; **J. Braz. Chem. Soc.** vol.19 no.1 São Paulo (2008).
24- Munther F. mahdi, Abdul-Rassoul Weis and Samira Fingan;" Synthesis and preliminary pharmacological evaluation of aminobenzensulfonamides derivatives of diflunisal as a anti-inflammatory agents"; **Irq J Pharm.** Vol. 7&8. No.1. (2008).
25- Mariappan G, Saha BP, Datta S, Kumar D and Haldar PK. Design, synthesis and antidiabetic evaluation of oxazolone derivatives. **J. Chem. Sci.** Vol 123, No. 3, (2011), pp. 335-341.
26- Maysoon A.A. Al-Soodani, Abdulwahab H. M. Ali, Mohammed F.Al-Marjani and AbdulJabar K. Atia. Synthesis and Biological activity of some complexes of (2-phenyl-4-arylidine imidazole-5- one) with some transition metal ions. **International Journal of Advanced Research** (2014), Volume 2, Issue 3 , 399-408.
27- Lichtenberger, L. M.; Dial, E.J.; Romero, J. J.; et al: Naproxen-PC: A GI safe and highly effective anti-inflammatory. **Inflammopharmacolog**. (2008); 16: 1-5.
28- Naser, N.H.; Mahdi, M.F and Omar, T.N.A.: Synthesis and Preliminary Pharmacological Evaluation of New Analogues of Diclofenac as Potential Anti-inflammatory Agents. **Iraqi J Pharm Sci**.(2011); 20(1).
29- Amresh, G.; Zeashan, H.; Singh, P. N.; et al: Prostaglandin mediated anti-inflammatory and analgesic activity of Cissampelos pareira. **Acta Pharmaceutica Sciencia**. (2007); 49: 153-160.