Research Article

Synthesis of New Potential Chemotherapeutic Agents Incorporating Naproxen Sub-Structure.

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ABSTRACT

A series of potential biologically active compounds have been synthesized through the derivatization of carboxyl group in Naproxen core structure involving the conversion the Naproxen to its methyl ester then to the acid hydrazide. The acid hydrazide of Naproxen was incorporated with hydrazones, diamide linkage, oxadiazole, pyrazolone, triazole, quinazoline and indole containing motifs. The targeted compounds have been achieved in a very good yield under conventional heat and irradiation conditions. All compounds have been characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra.

Keywords: Naproxen; anti-inflammatory; NSAID's.

INTRODUCTION

Naproxen, *(S)*-(+)-6-methoxy-a-methyl-2-naphthaleneacetic acid, is a non-steroidal anti-inflammatory drug used in painful inflammatory rheumatic and certain non-rheumatic conditions. Anti-inflammatory effects of naproxen are generally thought to be related to its inhibition of cyclooxygenase and consequent decrease in prostaglandin concentrations in various fluids and tissues[1]. Naproxen possesses the anti-inflammatory[2], anticonvulsant[3] and reduced ulcerogenic activity[4]. However, Naproxen, as other common anti-inflammatory drugs (NSAIDs) which are widely employed in the treatment of pain and inflammation, has been reported to be associated with a number of undesirable effects, which in particular include gastrointestinal (GI) toxicity[5]. The reported literatures confirm that gastrointestinal side effects of Naproxen and other aroylpropanoic acids are due to the presence of free carboxylic group in the parent drug[6]. Therefore, the temporarily mask or manipulation of the acidic group in NSAID's are promising means to reduce or to abolish the GI toxicity due to the local action mechanism[7-9]. So the glycolamide ester prodrugs were synthesized[10]. To reduce the gastrointestinal toxicity[11,12], it has been found that series of phenolic ester and amide derivatives of the NSAID naproxen had both anti-oxidative and anti-proliferative activity[13]. Furthermore, aliphatic and aromatic esters and amides, along with amide derivatives with covalently linked anti-oxidant moieties were prepared as potential prodrugs[14-17].

Hydrazone is a versatile moiety that exhibits a wide variety of biological activities[18]. A number of hydrazidehydrazones have been demonstrated to possess interesting anti-depressant[19], antibacterial, antifungal[20,21], anticonvulsant[22,23], anti-inflammatory[24,25], antimalarial[26] and anti-tuberculosis activities[27,28]. Organic compounds incorporating heterocyclic ring systems continue to attract considerable interest due to their wide range of biological activities[29]. A great number of established drugs bear heterocyclic system with certain substitutions and functionalization[30]. The oxadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings. Several pyrazoline substitution products are used in medicine as anti-inflammatory, analgesic, antioxidant, antipyretic, diuretic, antimicrobial and antidepressant[31].

In recent years, indole and Isatin derivatives have acquired conspicuous significance due to their wide spectrum of biological activities[32]. On the light of these observations, and as a continuation of our works on functionalization and incorporation of NSAID's core structures[33,34], we have synthesized series of new potential chemotherapeutic agents based Naproxen core structure and incorporated amide linkage, hydrazide-hydrazones and heterocyclic nucleus such as oxadizole, pyrazole, indole, triazole, thiophene and furan rings.

MATERIALS AND METHODS

General

Melting points were uncorrected and measured using open capillary method using Gallen Kamp melting point apparatus. The IR spectra were recorded by Perkin-Elmer FT-IR instrument using potassium bromide pellets. ^{1}HNMR, ^{13}CNMR spectra were recorded in deuterated chloroform (CDCl3), acetone CD3COCD3 or dimethylsulphoxide (DMSO-d6) with TMS as an internal standard on a JOEL 400 MHz instrument. Chemical shifts are expressed as [ppm], s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet, and b for broad. X-

ray has been measured at National Crystallography Services (NCS), Southampton, United Kingdom.

Materials

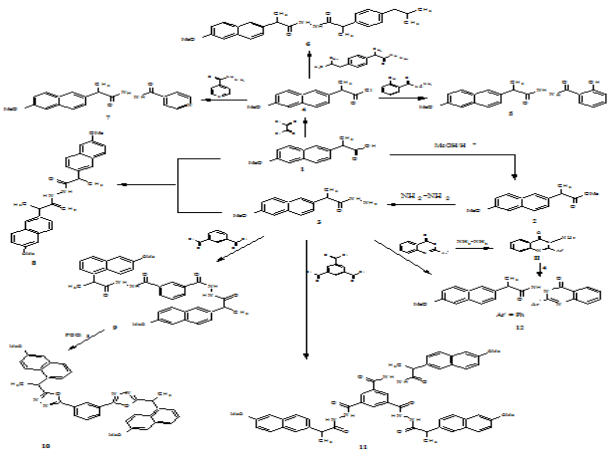
Naproxen has been purchased from Aldrich. Compounds such as methyl 2-(6-methoxynaphthalen-2-yl)propanoate **2**[35], 2-(6-methoxynaphthalen-2-yl)propanehydrazide **3**[36], 2-(6-methoxynaphthalen-2-yl)propanoyl chloride 4[37] and 3-amino-2-phenylquinazolin-4(3H)-one II[38] were synthesized according to the cited literatures.

The physical properties of the synthesized compounds are tabulated in Table 1.

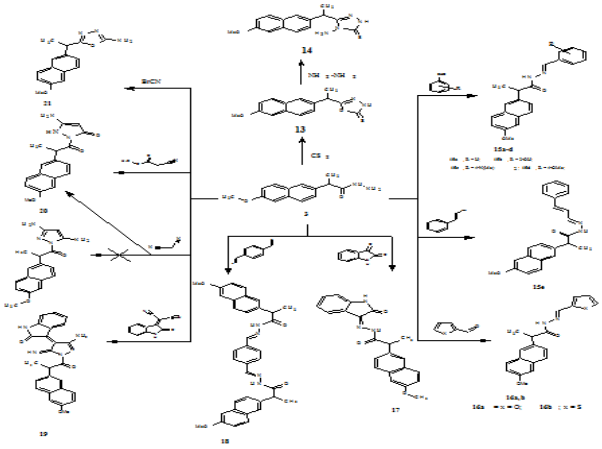
Table 1: Physical properties of Synthesized Compounds

No.	M.F	M. wt	Solvent	Yield%	M.P or B.P.(°C)
2	$C_{15}H_{16}O_3$	244.28574	Ethanol	82%	89-91
3	$C_{14}H_{16}N_2O_2$	244.29	Ethanol	85%	138-139
4	$C_{14}H_{13}ClO_2$	248.06	Ethanol	79%	93-94
6	$C_{21}H_{20}N_2O_4$	364.14	Ethanol	82%	209-211
6	$C_{27}H_{32}N_2O_3$	432.24	Ethanol	85%	200-202
7	$C_{20}H_{19}N_3O_3$	349.14	Dioxan	71%	251-253
8	$C_{28}H_{28}N_2O_4$	456.20	Dioxan	68%	237-239
9	$C_{36}H_{34}N_4O_6$	618.25	Dioxan	70%	229-232
10	$C_{36}H_{30}N_4O_4$	582.23	Ethanol	76%	109-112
11	$C_{51}H_{48}N_6O_9$	888.35	Ethanol/DMF	65%	291-294
12	$C_{28}H_{23}N_3O_3$	449.17	Ethanol	87%	143-145
13	$C_{15}H_{14}N_2O_2S$	286.08	Ethanol	89%	189-191
14	$C_{15}H_{16}N_4OS$	300.10	Ethanol	91%	152-153
15a	$C_{21}H_{20}N_2O_2$	332.15	Ethanol	92%	180-181
15b	$C_{21}H_{20}N_2O_3$	348.15	Ethanol	90%	169-171
15c	$C_{23}H_{25}N_3O_2$	375.46	Ethanol	92%	185-187
15d	$C_{23}H_{22}N_2O_2$	358.43	Ethanol	88%	173-176
15e	$C_{22}H_{22}N_2O_3$	362.42	Ethanol	89%	161-164
16a	$C_{19}H_{18}N_2O_3$	322.36	Ethanol	85%	165-166
16b	$C_{19}H_{18}N_2O_2S$	338.42	Ethanol	93%	186-188
17	$C_{22}H_{19}N_3O_3$	373.14	Ethanol	89%	194-196
18	$C_{27}H_{23}N_3O_3$	437.17	Ethanol	77%	205-208
19	$C_{36}H_{34}N_4O_4$	586.26	DMF	88%	293-295
20	$C_{17}H_{17}N_3O_3$	311.13	Ethanol	87%	183-185
21	C15H15N3O2	269.12	Ethanol/Dioxan	84%	220-222

The key compounds **3** and **4** have been employed as main precursors to produce multi-variety of naproxen containing compounds as shown in Schemes 1 and 2.



Scheme 1



Scheme 2

General Procedure

Synthesis of 2-hydroxy-*N*'-[2-(6-methoxynaphthalen-2-yl)propanoyl]benzohydrazide 5

A mixture of equimolar quantities of **4** (0.01mol) and salicylic acid hydrazide (0.01mol) was refluxed for two hours in 50 ml dry THF. The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from ethanol to give **5** as brown crystals. IR(KBr cm^{-1}): (C=O amide 1652, 1678), (NH 3306), (C-H, Ar 2973), (C-H aliphatic 2933). 1H-NMR: (chloroform-D) δ at 1.6(d, CH_3), 3.8(q, C-H aliphatic), 3.7(s, -OCH_3), 11.2(s, OH phenolic), 8.1(s, -NH), 8.8(s, -NH), 7.3,7.0(s, Ar, 2H for naphthalene ring), 7.2,7.4(d, Ar, 2H for naphthalene ring), 7.08, 7.6(d, Ar, 2H for naphthalene ring), 7.3(t, Ar, 1H in benzene ring), 7.07(t, Ar, 1H), 6.8(d, Ar, 1H), 7.6(d, Ar, 1H). ^{13}C-NMR: 173,168(C=O amide), 155(C-O Ar), 55(CH_3-O), 19(CH_3), 46(C-H aliphatic), 114, 132, 120, 127(C-H, Ar, in benzene ring), 130, 133(C=C Ar for two fused ring in naproxen), 134(C-C Ar for naphthalene attached to isopropyl. In x-ray structure of **5**[39](Fig. 1) the N1—N2 bond length of 1.427 (8) A, indicates a single bond. The naphthalene ring (C1—C10) is planar, with a maximum deviation of -0.007 (7) A for the C4 atom. This ring makes a dihedral angle of 84.5 (3)° with the hydroxyl benzene ring. The —C14(═O)—N1(H)—N2(H)—C15(═O)— torsion angle is 70.7 (7)°. An intramolecular O—H · · · O hydrogen bond which generates an S(6) ring motif is observed in the molecular structure. The crystal structure of **5** is stabilized by intermolecular N—H · · · O and C—H · · · O hydrogen bonds (Fig. 2) which connect molecules into supra-molecular layers in the *ab* plane.

Synthesis of 2-(4-Isobutyl-phenyl)-propionic acid N'-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-hydrazide 6

A mixture of equimolar amounts of **4** (0.01mol) and Ibuprofen acid hydrazide (0.01mol) was refluxed for two hours in 50 ml dry THF.

The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from ethanol to give **6** as a white powder. IR(KBr cm^{-1}): (C=O amide 1640,1651), (C-H aliphatic, 2870-2954), (Ar, 3039), (NH-3204).

^{1}H-NMR: (DMSO-d6) δ at 1.0 (d, $(CH_3)_2$), 1.9(m, 1H aliphatic), 2.55(d, -CH_2-), 1.6(d, 3H aliphatic), 3.5(quartet,1H), 3.6(s, OCH_3), 7.0(dd, Ar, J=8.14 for ibuprofen ring), 7.43, 6.9(s, Ar), 7.18,7.54(d, Ar for naphthalene ring(, 7.5, 7.01(d, Ar for naphthalene ring), 6.8(s, 2H, NH). ^{13}C-NMR: 171,172(C=O), 19(CH_3), 18(CH_3), 23$(CH_3)_2$, 44(CH_2aliphatic), 42(C-H aliphatic), 44(C-H aliphatic), 31(C-H aliphatic tertiary), 55(CH_3-O), 131,130(C=C Ar for ibuprofen ring), 140, 137(=C-Ar for ibuprofen ring)128.0, 128.1, 134, 130(C=C Ar for naproxen attached to isopropyl), 131, 135(C=C Ar for two fused ring in naproxen), 117, 127, 105(C=C Ar), 156(C-O Ar).

Synthesis of *N*'-[2-(6-methoxynaphthalen-2-yl)propanoyl]pyridine-4-carbohydrazide 7

A mixture of equimolar quantities of **4** (0.01mol) and isoniazid (0.01mol) was refluxed for two hours in 50 ml dry THF. The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from ethanol to give **7** as a white powder. IR(KBr cm^{-1}): (C=O amide 1637, 1696), (NH 3133), (C-H, Ar 3052), (C-H aliphatic 2954). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, CH_3), 3.7(q, C-H aliphatic), 3.8(s, CH_3-O), 7.3,7.0(s, Ar in naphthalene nuclei), 7.15,7.4(d, Ar in naphthalene nuclei), 7.1, 7.6(d, Ar in naphthalene ring), 7.8(d, Ar, 2H), 8.9(d, Ar, 2H), 6.9(s,2H,-NH). ^{13}C-NMR: 165, 172(C=O amide), 21(CH_3), 42(C-H aliphatic), 59(CH3-O), 151(2C, Ar in pyridine nuclei), 121(2C, Ar in pyridine nuclei), 116, 126, 153, 103, 130, 126, 124, 132, 125, 122(10C, Ar in naphthalene).

Synthesis of 2-(6-Methoxy-naphthalen-2-yl)-propionic acid N'-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-hydrazid 8

A mixture of equimolar quantities of **4** (0.01mol) and **3** (0.01mol) was refluxed for two hours in 50 ml dry THF. The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from ethanol to give **8** as a white powder. IR(KBr cm^{-1}): (C=O amide, 1645), (NH, 3190), (C-H aliphatic 2838-2936), (C-H, Ar 2974). ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 6H, $2CH_3$), 3.3(s, 6H, $2OCH_3$), 3.7(q, j=6.8, 2C-H aliphatic), 7.0(s, 2H, Ar in 2naphthaline nuclei), 7.3(s, 2H, Ar in two naphthaline nuclei**)**, 7.01, 7.6(d, 4H, Ar in two naphthaline nuclei), 7.25, 7.6(d, 4H, Ar in 2 naphthaline nuclei). ^{13}C-NMR: 172(C=O amide), 55(2C,-OCH_3), 43(2C,C-H aliphatic), 18(2C, CH_3), 157, 137, 133, 129, 128, 127, 126, 125, 119, 106(20C, Ar, in 2naphthaline nucleus). **MS (EI, 70 eV), m/z (Irel, %):** a molecular ion peak (M.+) at m/z=456,7.5%, base peak at m/z=185, 100%.

Synthesis of *N'1,N'3*-bis{(E)-2-[2-(6-methoxynaphthalen-2-yl)propanoyl]hydrazinecarbonyl} benzene 9

A mixture of (0.02mol) from **3** and (0.01mol) of benzene-1,3-dicarbonyl dichloride was refluxed for two hours in 50 ml dry THF. The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from Dioxan to give **9** as a brown powder. IR (KBr cm^{-1}): (C=O amide, 1640, 1651), (-NH, 3200), (C-H aliphatic 2843-2935), (C-H, Ar 2978-3010). ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 6H, $2CH_3$), 3.6(s, 6H, -OCH_3), 3.9(q, 2H, C-H aliphatic), 8.6(s, 1H, Ar in Benzene ring), 8.0(dd, 2H, j=1.37 in benzene ring), 7.5(t, 1H, Ar in benzene ring), 10.2(s,2H,-NH), 10.4(s,2H,-NH), 12H, Ar, in two naphthalene nucleus were appeared in the range of 6.8-7.5. ^{13}C-NMR: 173, 165(C=O amide), 19(2C, CH_3), 43(2C,C-H aliphatic), 55(2C,-OCH_3), 131(2C, Ar in benzene ring), 134(2C, Ar in benzene ring), 129, 127(2C, Ar in benzene ring), 106, 119, 125, 127.4, 127, 128, 129.6, 133.7, 137, 157(20C, Ar in two naphthalene nucleus, each two carbons have one signal).

Synthesis of 1,3-bis[2-[1-(6-methoxynaphthalen-2-yl)ethyl]-1,3,4-oxadiazole]benzene 10

A mixture of 0.001mole of compound **9** and 5ml of $POCl_3$ was refluxed for four hours. The mixture was cooled and poured onto crushed ice then neutralized with $NaHCO_3$ solution 20%.

The obtained precipitate was collected and recrystallized from ethanol to give **10** as brown powder. IR(KBr cm^{-1}): (C=N in oxadiazole ring 1606), (C-H aliphatic 2869-2935), (C-H, Ar, 3031). ^{1}H-NMR: (Acetone-d6) δ at 1.8(d, 6H, $2CH_3$), 3.5(s, 6H,2 –OCH_3), 3.8(q, 2H, C-H aliphatic), 7.8(s, 1H in benzene ring), 8.1(dd, j=2.7, 2H in benzene ring), 7.7(t,1H, in benzene ring), 12H, Ar in two naphthalene nucleus were appeared in the range of 7.0-7.7. ^{13}C-NMR: 161(2C, in oxadiazole ring), 160(2C, in oxadiazole ring), 19(2C, $2CH_3$), 37(2C, C-H aliphatic), 55(2C, 2-OCH_3), 127(2C, Ar in benzene ring), 135(2C, Ar in benzene ring), 130,127(2C, Ar in benzene ring), 105, 119, 124 ,125, 127, 129, 130, 134, 135, 158(20C, Ar in two naphthalene nucleus, each two carbons have one signal). **MS (EI, 70 eV), m/z (Irel, %):** a molecular ion peak (M.+) at m/z=583,6.3%, base peak at m/z=140, 100%.

Synthesis of *N'1,N'3, N'5*-tris{2-[2-(6-methoxynaphthalen-2-yl)propanoyl]hydrazinecarbonyl} benzene 11

A mixture of (0.03mole) of **3** and (0.01mole) of benzene-1,3,5-tricarbonyl trichloride was refluxed for 3hr in 25ml of dry THF.

The mixture was cooled and poured onto crushed ice. The precipitate that formed was collected and recrystallized from ethanol/DMF to give **11** as a white powder. IR(KBr cm^{-1}): (C=O amide, 1665,1679), (NH, 3191), C-H aliphatic, 2868-2935), (C-H, Ar, 2973-3040). ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 9H, $3CH_3$), 3.8(s, 9H, $3OCH_3$), 8.4(s, 3H in benzene ring), 10.3(s, 3H, 3NH-), 10.6(s, 3H, 3NH-), 18H, Ar in three naphthalene nucleus were appeared in the range of 7.1-7.8. ^{13}C-NMR: 171, 176(C=O amide), 20(3C, $3CH_3$), 43(3C, 3C-H aliphatic), 58(3C, 3-OCH_3), 130(3C, 3C-H, Ar in Benzene ring), 135(3C, Ar, in benzene ring), 105, 118, 125, 125.5, 127, 128, 129, 133, 134, 158(30C, Ar in three naphthalene nucleus, each three carbons have one signal.

Synthesis of 2-(6-Methoxy-naphthalen-2-yl)-N-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-propionamide 12

Compound **12** has been synthesized in two different ways.

Method 1

An equimolar ratio of **3** and the appropriate substituted-4H-3,1-benzoxazin-4-one was dissolved and refluxed in 30ml pyridine for 8hours. The reaction mixture was poured on cold water to afford a solid product. The crude product was filtered off, washed diluted hydrochloric acid followed by cold ethanol then recrystallized from ethanol to furnish a fine brownish powder of **12**.

Method 2

A mixture of equimolar quantities of **4** (0.01mol) and 3-amino-2-phenylquinazolin-4(3H)-one **II** [38] (0.01mol) was refluxed for 10hrs in 50 ml of freshly distilled dry pyridine. The mixture was cooled and poured onto crushed ice and acidified with conc. HCl. The precipitate that formed was collected and washed twice with water then recrystallized from ethanol to give **12** as a brown powder. IR (KBr cm^{-1}): (C=O amide, 1632), (C=O cyclic amide, 1685), (-NH, 3258), (C-H aliphatic 2867-2935), (C-H, Ar 3021-3058). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 4.0(q,1H, C-H aliphatic), 3.8(s, 3H, -OCH_3), 8.9(s, 1H, -NH), 7.8(d, 1H, Ar in quinazoline nuclei), 7.5(d, 1H, Ar in quinazoline nuclei), 7.6(t, 1H, Ar in q quinazoline nuclei), 7.7(t, 1H, Ar in quinazoline nuclei), 5H, Ar in benzene ring attached to quinazoline nuclei were appeared in the range of 6.8-7.7, 6H, Ar in naphthalene nuclei were appeared in the range of 6.8-7.6. ^{13}C-NMR: 169,172(C=O amide and cyclic amide), 19(1C, CH_3), 43(C-H aliphatic), 57(1C, -OCH_3), 126, 127, 127.5, 135, 123, 153, 166 (7C, Ar in quinazoline nuclei), 134, 126.5, 129, 131(4signals for 6C, Ar in benzene ring attached to quinazoline nuclei), 134.3, 128.7, 126.9, 126.1, 133.9, 129.9, 107, 157, 119, 129.6(10 signals for 10C in naphthalene nuclei).

5-[1-(6-methoxynaphthalen-2-yl)ethyl]-1,3,4-oxadiazole-2(3*H*)-thione 13

A mixture of 0.005mol from **3**, 0.01mol of KOH in 100ml ethanol and 0.2mol of CS_2 was refluxed for 23hr (the reaction time was monitored by the evolution of H_2S). The mixture was cooled and poured onto crushed ice then acidified with HCl. The precipitate was collected, washed with water twice then recrystallized from ethanol to give **13** as a pure yellow powder. IR (KBr cm^{-1}): (C=S thione 1161), (C=N, in oxadiazole ring 1607), (-NH, 3235), (2935, C-H aliphatic), (2975, C-H, Ar). ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 3H, CH_3), 3.9(q, 1H, C-H aliphatic), 3.6(s, 3H, -OCH_3), 5.9(s, 1H, -NH), 7.0(s, 1H, Ar), 7.3(s, 1H, Ar), 7.6(d, 1H, Ar), 7.2(d, 1H, Ar), 6.9(d, 1H, Ar), 7.4(d, 1H, Ar). ^{13}C-NMR: 14(1C, CH_3), 40(1C, C-H aliphatic), 57(1C, -OCH_3), 152(1C, -O-C=N in oxadiazole ring), 165(1C, C=S), 157, 117, 127, 128, 133, 107, 125, 132, 127.5, 125.4(10C, Ar in naphthalene nuclei).

Synthesis of 4-amino-5-[1-(6-methoxynaphthalen-2-yl)ethyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 14

A mixture of 0.001mol of **13** and 0.06mol of hydrazine hydrate 80% in 50ml of ethanol was refluxed for 5hr. The mixture was cooled, and poured onto crushed ice, the solid that formed was collected and recrystallized from ethanol to give **14** as a pink powder. IR(KBr cm^{-1}): (C=S thione, 1164), (C=N 1605 in triazole ring), (NH, 3316), (C-H aliphatic 2868-2935), (C-H, Ar 2981-3092). ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 3H, CH_3), 3.2(q, 1H, C-H aliphatic), 3.8(s, 3H, -OCH_3), 3.4(s, 2H, -NH_2), 5.9(s, 1H, -NH), 6H, Ar in naphthalene nuclei were appeared in the rage of 6.8-7.7. ^{13}C-NMR: 179(C=S in oxadiazole ring), 151(C=N in oxadiazole ring), 15(1C, CH_3), 41(C-H aliphatic), 58(1C, -

OCH_3), (10C, Ar in naphthalene nuclei were appeared in the range of 106-158).

General synthesis of 2-(6-methoxynaphthalen-2-yl)-*N*'-[(*E*)-arylmethylidene]propanehydrazide 15a-d, 15e and **16a,b**

Microwave Irradiation Method

A mixture of an equimolar ratio of appropriate aromatic aldehydes (0.0.1mol) and naproxen hydrazide **3** (0.01mol) along with few drops of catalytic glacial acetic acid was transferred to a conical flask and subjected to microwave irradiation for 2 minutes. The solid mass that obtained was collected and recrystallized from ethanol.

Conventional Method

An equimolar ratio of the appropriate aldehydes (0.01mmol) and naproxen acid hydrazide **3** (0.01mol) with few drops of glacial acetic acid as a catalyst was refluxed in 20ml of absolute ethanol for 4-5hr. The mixture was cooled and concentrated to half volume and the precipitate that formed was collected and recrystallized from ethanol to give the corresponding arylmethylidene propanehydrazides **15a-d**, **15e** and **16a,b**.

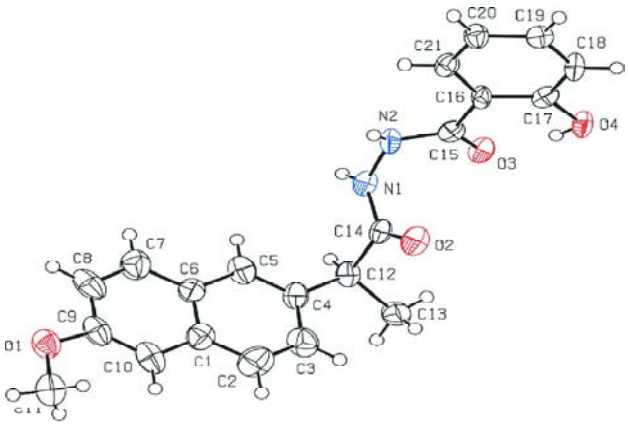


Figure 1: The molecular structure of 5, showing the labeling of the non-H atoms and displacement ellipsoids drawn at the 50 probability level

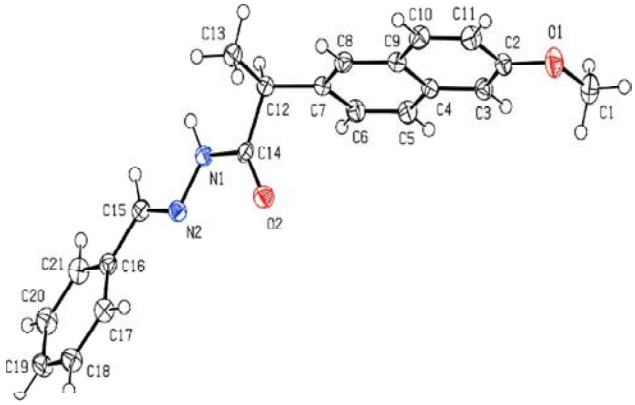


Figure 3: Perspective view of the 15a with 50% probability displacement ellipsoids

2-(6-methoxynaphthalen-2-yl)-*N*'-[(*E*)-phenylmethylidene]propanehydrazide 15a

This product was obtained as yellow crystal. IR(KBr cm^{-1}): (C=O amide, 1664), (C=N, 1605), (-NH, 3238), (C-H aliphatic, 2896-2968), (C-H, Ar, 3058). ^{1}H-NMR: (DMSO-d6) δ at 1.5(d, 3H, CH_3), 3.8(s, 3H, -OCH_3), 4.7(q, 1H, C-H aliphatic), 8.2(s, 1H, -CH=N-), 11.3(s, 1H, -NH), 11H, Ar in naphthalene nuclei and benzene ring were appeared in the rage of 7.2-7.9. ^{13}C-NMR:175(C=O, amide), 160(1C, C=N), 18(1C, CH_3), 44(1C, C-H aliphatic), 55((1C, -OCH_3), 126.9(2C, Ar, in Benzene ring), 126.7(2C, Ar, in Benzene ring), 128.7(1C, Ar in Benzene ring), 128.8(1C, Ar in benzene ring), (10C, Ar in naphthalene nuclei were appeared in the range of 105-157). The x-ray crystal structure of **15a** (Fig. 3) showed the naphthalene ring system (C2–C11) is essentially planar with an r.m.s. deviation of 0.003 A and makes a dihedral angle of 77.57 (12)° with the terminal phenyl ring (C16–C21). In the crystal structure, the molecules exist in the "extended" form. The packing consists of ribbons of molecules extending parallel to *c* (Fig. 4) and associated *via* N—H · · · O and weak C—H · · · O hydrogen bonds (Fig. 5). In addition, C—H · · · π interactions are observed.

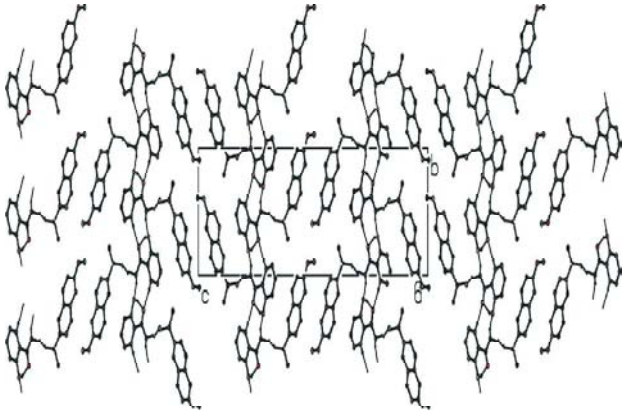


Figure 2: View of the packing and hydrogen bonding (dashed lines) of **5** down the *a* axis, in the unit-cell. H atoms not involved in hydrogen bonds have been omitted for clarity

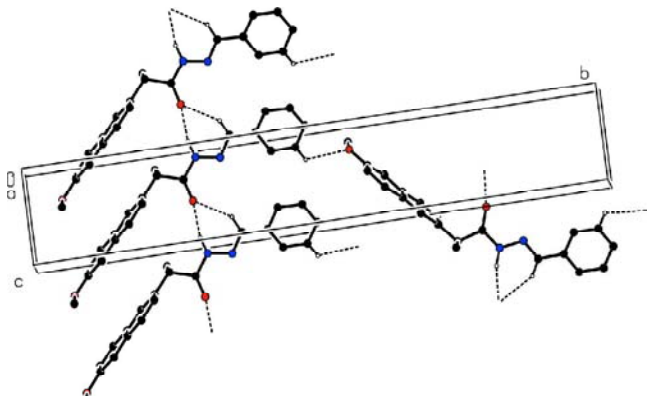


Figure 4: The hydrogen bonding (dotted lines) viewed along the *a* axis of 15a

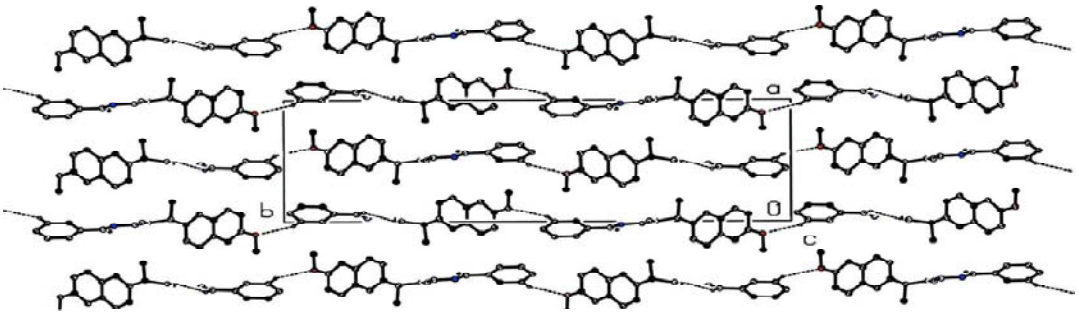


Figure 5: Packing viewed along the c axis showing the ribbon like structure with intra-ribbon C—H·O hydrogen bonds

_N_'-[(_E_)-(2-hydroxyphenyl)methylidene]-2-(6-methoxynaphthalen-2-yl)propanehydrazide 15b

This product was obtained as yellow powder. IR(KBr cm^{-1}): (C=O amide, 1657), (C=N, 1609), (-NH, 3201), (C-H aliphatic, 2881-2961), (C-H, Ar, 3050). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 3.7(s, 3H, -OCH_3), 4.3(q, 1H, C-H aliphatic), 8.1(s, 1H, -CH=N-), 9.1(s, 1H, -NH), 10.2(s, 1H, OH), 6.9(d, 1H, Ar in benzene), 7.2(t, 1H, Ar in benzene), 6.8(t, 1H, Ar in benzene ring), 7.3(d, 1H, Ar in benzene ring), (6H, Ar in naphthalene nuclei were appeared in the range of 6.85-7.7). ^{13}C-NMR: 171(C=O, amide), 161(1C, C=N), 19(1C, CH_3), 45(1C, C-H aliphatic), 56((1C, -OCH_3), (16C, Ar in naphthalene nuclei and benzene ring were appeared in the.

2-(6-Methoxy-naphthalen-2-yl)-propionic acid (4-dimethylamino-benzylidene)-hydrazide 15c

This product was obtained as orange powder. IR (KBr cm^{-1}): (C=O amide, 1651), (C=N, 1615), (-NH, 3195), (C-H aliphatic, 2868-2945), (C-H, Ar, 3047). ^{1}H-NMR: (DMSO-d6) δ at 1.56(d, 3H, CH_3), 3.8(s, 3H, -OCH_3), 4.0(q, 1H, C-H aliphatic), 2.7(s, 6H,2CH_3), 7.3(d, 2H, Ar in benzene ring), 6.5(d, 2H, Ar in benzene ring), 8.2(s, 1H, -CH=N-), 9.1(s, 1H, -NH), (6H, Ar in naphthalene nuclei were appeared in the range of 6.9-7.6). ^{13}C-NMR: 174(C=O, amide), 159(1C, C=N), 18(1C, CH_3), 43(1C, C-H aliphatic), 54(1C, -OCH_3), 129(2C, Ar in benzene ring), 115(2C, Ar, in benzene ring), 145(1C, Ar in benzene ring), 121(1C, Ar in benzene ring), (10C, Ar in naphthalene nuclei were appeared in the range of 105-155).

2-(6-methoxynaphthalen-2-yl)-_N_'-[(_E_)-(4-methoxyphenyl)methylidene]propanehydrazide 15d

This product was obtained as a white powder. IR(KBr cm^{-1}): (C=O amide, 1667), (C=N, 1601), (-NH, 3225), (C-H aliphatic, 2866-2949), (C-H, Ar, 3061). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 3.9(q, 1H, C-H aliphatic), 3.8(s, 3H, -OCH_3), 3.7(s, 3H, -OCH_3), 6.9(d, 2H, Ar in benzene ring), 7.4(d, 2H, Ar in benzene ring), 8.2(s, 1H, -CH=N-), 11.2(s, 1H, -NH), (6H, Ar in naphthalene nuclei were appeared in the range of 6.8-7.6).^{13}C-NMR: 175(C=O, amide), 158(1C, C=N), 17(1C, CH_3), 43(1C, C-H aliphatic), 55, 57(2C, -OCH_3), 116(2C, Ar in benzene ring), 132(2C, Ar in benzene ring), 161(1C, Ar, -C-O in benzene ring), 121(1C, Ar in benzene ring), (10C, Ar in naphthalene nuclei were appeared in the range of 107-155).

2-(6-methoxynaphthalen-2-yl)-_N_'-[(1_E_,2_E_)-3-phenylprop-2-en-1-ylidene]propanehydrazide 15e

This product was obtained as a yellow powder. IR(KBr cm^{-1}): (C=O amide, 1658), (C=N, 1609), (-NH, 3211), (C-H aliphatic, 2866-2949), (C-H, Ar, 3061). ^{1}H-NMR: (DMSO-d6) δ at 18(d, 3H, CH_3), 4.0(q, 1H, C-H aliphatic), 3.6(s, 3H, -OCH_3), 8.0(s, 1H, -CH=N-), 6.5(d, 1H, -CH=, alkene), 5.7(d, 1H, -CH=, alkene), 9.5(s, 1H, -NH), 7.4(d, 2H, Ar in benzene ring), 7.3(t, 2H, Ar in benzene ring), 7.2(t, 1H, Ar in benzene ring), (6H, Ar in naphthalene nuclei were appeared in the range of 7.0-7.7). ^{13}C-NMR: 176(C=O, amide), 155(1C, C=N), 18(1C, CH_3), 44(1C, C-H aliphatic), 57(1C, -OCH_3), 117(1C, -C=C-), 135(1C, -C=C-), 125(2C, Ar in benzene ring), 127(2C, Ar in benzene ring), 126(1C, Ar in benzene ring), 134(1C, Ar in benzene ring), (10C, Ar in naphthaline nuclei were appeared in the range of 108-156).

_N_'-[(_E_)-furan-2-ylmethylidene]-2-(6-methoxynaphthalen-2-yl)propanehydrazide 16a

This product was obtained as yellow powder. IR(KBr cm^{-1}): (C=O amide, 1656), (C=N, 1607), (-NH, 3197), (C-H aliphatic, 2934), (C-H, Ar, 3051). ^{1}H-NMR: (DMSO-d6) δ at 1.5(d, 3H, CH_3), 4.1(q, 1H, C-H aliphatic), 3.6(s, 3H, -OCH_3), 7.6(s, 1H, -CH=N-), 6.2(d, 1H, Ar in furan ring), 6.4(t, 1H, Ar in furan ring), 7.0(d, 1H, Ar in furan ring), (6H, Ar in naphthalene nuclei were appeared in the range of 6.7-7.5). ^{13}C-NMR: 172(C=O, amide), 159(1C, C=N), 15(1C, CH_3), 41(1C, C-H aliphatic), 54(1C, -OCH_3), 126(2C, Ar in furan ring), 148(1C, Ar, -C-O in furan ring), 146(1C, Ar, -O-C- in furan ring), (10C, Ar in naphthalene nuclei were appeared in the range of 108-159).

2-(6-methoxynaphthalen-2-yl)-_N_'-[(_E_)-thiophen-2-ylmethylidene]propanehydrazide 16b

This product was obtained as a brown powder. IR(KBr cm^{-1}): (C=O amide, 1662), (C=N, 1600), (-NH, 3190), (C-H aliphatic,2969-2956), (C-H, Ar, 3037). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 3.9(q, 1H, C-H aliphatic), 3.8(s, 3H, -OCH_3), 7.7(s, 1H, -CH=N-), 8.5(s, 1H, -NH), 6.6(d, 1H, Ar in thiophene ring), 6.5(t, 1H, Ar in thiophene ring), 7.1(d, 1H, Ar in thiophene ring), 7.8(d, 1H, Ar), 7.3(d, 1H, Ar), 7.9(d, 1H, Ar), 7.6(d, 1H, Ar),7.0(s, 1H, Ar), 7.4(s, 1H, Ar). ^{13}C-NMR: 170(C=O, amide), 155(1C, C=N), 17(1C, CH_3), 42(1C, C-H aliphatic), 56(1C, -OCH_3), 129(2C, Ar in thiophene ring), 157(1C, Ar, -C-O in thiophene ring),

114(1C, Ar, -C-O in thiophene ring), (10C, Ar in naphthalene nuclei were appeared in the range of 106-156).

Synthesis of 2-(6-methoxynaphthalen-2-yl)-*N*'-[(3*Z*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]propanehydrazide 17

A mixture of an equimolar ratio of isatin (0.0.1mol) and naproxen hydrazide **3** (0.01mol) along with few drops of catalytic glacial acetic acid was transferred to a conical flask and subjected to microwave irradiation for 2 minutes. The solid mass that obtained was collected and recrystallized from ethanol to give **17** as a yellow powder. IR(KBr cm^{-1}): (C=O amide, 1699), (C=O cyclic amide, 1718), (C=N, 1620), (-NH, 3234), (C-H aliphatic, 2867-2950), (C-H, Ar, 3024-3048). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 4.0(q, 1H, C-H aliphatic), 3.6(s, 3H, -OCH_3), 8.1(s, 1H, -NH in indol ring), 8.6(s, 1H, -NH), 7.8(d, 1H, Ar in indole nuclei), 7.4(t, 1H, Ar in indole nuclei), 7.1(t, 1H, Ar in indole ring), 7.6(d, 1H, Ar in indole nuclei), 7.53(s, 1H, Ar), 7.2(d, 1H, Ar), 7.59(d, 1H, Ar), 6.8(s, 1H, Ar), 7.1(d, 1H, Ar), 7.65(d, 1H, Ar). ^{13}C-NMR: 172, 162(C=O, amide), 157(1C, C=N), 16(1C, CH_3), 44(1C, C-H aliphatic), 57(1C, -OCH_3), (10C, Ar in naphthalene nuclei were appeared in the range of 109-158). (6C, Ar in indole nuclei were appeared in the range of 119-139).

Synthesis of 1,4-bis [2-(6-methoxynaphthalen-2-yl)-N'-[(E)-methylidene]propanehydrazide]benzene 18

A mixture of 0.001mol of benzene-1,4-dicarbaldehyde and 0.002mol of naproxen hydrazide **3** in 50 ml of absolute ethanol with few drops of glacial acetic acid was refluxed for 4hr. The mixture was concentrated to half and the precipitate that formed was collected and recrystallized from DMF to afford **18** as a yellow powder. IR (KBr cm^{-1}): (C=O amide, 1662), (C=N, 1605), (-NH, 3268), (C-H aliphatic, 2864-2955), (C-H, Ar, 3070). ^{1}H-NMR: (DMSO-d6) δ at 1.7(d, 6H, 2CH_3), 4.0(q, 2H, 2C-H aliphatic), 3.8(s, 6H, 2OCH_3), 8.0(s, 2H, -CH=N-), 8.4(s, 2H, -NH), 7.8(dd, 4H, Ar in benzene ring), 8.1(s, 2H, -CH=N), 7.0(s, 2H, Ar), 7.05(d, 2H, Ar), 7.6(d, 2H, Ar), 7.48(s, 2H, Ar), 7.2(d, 2H, Ar), 7.58(d, 2H, Ar). ^{13}C-NMR: 175(2C, C=O, amide), 153(2C, -C=NH), 19(2C, 2CH_3), 42(2C, 2C-H aliphatic), 58(2C, 2OCH_3), 128(4C, -CH=, Ar in benzene ring), 135(2C, Ar in benzene ring), (20C, Ar in naphthalene nuclei were appeared in the range of 107-156).

Synthesis of 3-{3-Amino-5-imino-1-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-1,5-dihydro-pyrazol-4-ylidene}-1,3-dihydro-indol-2-one 19

A mixture of an equimolar ratio of naproxen hydrazide **3** and (2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)propanedinitrile in 25ml of ethanol and few drops of TEA was refluxed for 10hr. The mixture was cooled and poured onto crushed ice. The precipitate that formed was collected and washed with water then recrystallized from ethanol to give **19** as a yellow powder. IR(KBr cm^{-1}): (C=O amide, 1689),(C=O cyclic amide, 1707), (C=N, 1618), (-NH, 3183), (C-H aliphatic, 2936-2975), (C-H, Ar, 3997-3068). MS(EI, 70ev), m/z(%): a molecular ion peak (M^+) at m/z= 439, 41.76%, base peak at m/z=80, 100%. ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 3.9(q, 1H, C-H aliphatic), 3.8(s, 3H, -OCH_3), 5.9(s, 2H, -NH_2), 6.1(s, 1H, NH), 8.3(s, 1H, -NH in indole ring), 7.65(d, 1H, Ar in indole nuclei), 7.2(t, 1H, Ar in indole nuclei), 6.8(t, 1H, Ar in indole nuclei), 7.3(d, 1H, Ar in indole nuclei), (6H, Ar in naphthalene nuclei were appeared in the range of 6.8-7.6). ^{13}C-NMR: 174,164(2C, C=O, amide), 163(1C,-C=NH), 154(1C, -N=C-NH_2 in pyrazole ring), 146, 123(2C, -C=C- between indole nuclei and pyrazole ring), 121, 125, 124, 127.4, 126.5, 137(6C, Ar in indole moiety), 16(1C, CH_3), 45(1C, C-H aliphatic), 55(1C, -OCH_3), 129, 127, 134, 128.3, 133.5, 125.7, 128.1, 119, 157, 106(10C, Ar in naphthalene nuclei).

Synthesis of 5-amino-2-[2-(6-methoxynaphthalen-2-yl)propanoyl]-1,2-dihydro-3*H*-pyrazol-3-one 20

A mixture of equimolar quantities of naproxen hydrazide **3** (0.01mol) and methyl cyanoacetate (0.01mol) in 25ml of ethanol with few drops of TEA was refluxed for 7hr. The mixture was cooled and concentrated to half. The precipitate that formed was collected and recrystallized from ethanol to furnish **20** as yellow crystal.

On reaction of **3** with malononitrile under same reaction condition, it did not give the expected diamino-pyrazole derivative (see Scheme 2), instead it deposited same product **20**.

IR (KBr cm^{-1}): (C=O cyclic amide, 1674), (C=O amide 1660), (-NH, 3232), (C-H aliphatic, 2933-2963), (C-H, Ar, 3049). MS (EI, 70ev), m/z(%): a molecular ion peak (M^+) at m/z= 311.1, 6.2%, base peak at m/z=185, 100%. ^{1}H-NMR: (DMSO-d6) δ at 1.4(d, 3H, CH_3), 4.7(q, 1H, C-H aliphatic), 3.8(s, 3H, OCH_3), 8.9(s, 1H, -NH), 4.8(s, 2H, -NH_2), 2.8(s, 1H, -C=H in pyrazolone ring),(6H, Ar in naphthalene nuclei were appeared in the range of 6.9-7.6. ^{13}C-NMR: 175(C=O, cyclic amide), 158(C=O amide), 168(1C, =C-NH_2 in pyrazolone ring), 17(1C, CH_3), 44(1C, C-H aliphatic), 55(1C, -OCH_3), 71(1C, -C=C- in pyrazolone ring), (10C, Ar in naphthalene nuclei were appeared in the range of 105-157).

Synthesis of 5-[1-(6-methoxynaphthalen-2-yl)ethyl]-1,3,4-oxadiazol-2-amine 21

A mixture of (0.005mol) of naproxen hydrazide **3** and (0.0075mol) of bromocyanogene in 25ml of methanol was refluxed for 10hr. The mixture was cooled and poured onto crushed ice then neutralized with sodium bicarbonate. The precipitate that formed was washed with water then collected and recrystallized from ethanol/Dioxan to furnish **21** as pinky crystals. IR (KBr cm^{-1}): (C=N of oxadiazole ring 1613), (-NH_2 3115, 3290), (C-H aliphatic 2863-2930), (C-H, Ar, 3035). ^{1}H-NMR: (DMSO-d6) δ at 1.6(d, 3H, CH_3), 4.3(q, 1H, C-H aliphatic), 3.3(s, 3H, -OCH_3), 3.9(s, 2H, -NH_2), (6H, Ar in naphthalene nuclei were appeared in the range of 6.9-7.8). ^{13}C-NMR: 19(1C, CH_3), 38(1C, C-H aliphatic), 55(1C, -OCH_3), 161, 163(2C, 2C=N in oxadiazole ring), 157(1C, Ar, -C-O-in naphthalene

nuclei), 105, 118, 125.3, 125.9, 127.2, 128.4, 129.1, 133.3, 136.4(9C, Ar in naphthalene nuclei).

RESULTS AND DISCUSSION

Compound **5** was confirmed by X-ray which confirmed the crystal structure of its mono crystal as shown in Fig(1). In addition, this compound was proofed by IR, ^{1}H-NMR, ^{13}C-NMR. Compound **6** was proofed by IR which showed two vC=O at 1640, 1651 and vNH at 3204. ^{1}H-NMR of **6** showed a significant signal at 7.0(dd, j=8.1) belongs to aromatic protons of Ibuprofen. Also, six aromatic protons of naphthalene nuclei were appeared in the range of 6.9-7.5. The two proton of NH-NH were appeared at 6.8 as a singlet signal. ^{13}C-NMR of **6** showed two signals at 171, 172ppm belong to two C=O amide and these two signals disappeared in DEPT confirming the structure. Also, the aliphatic carbon atoms showed 8 signals in the range of 18-55, the signal at 44ppm appeared in DEPT downward confirming that this signal belongs to $-CH_2$ in the structure. Compound **7** was proofed by IR which showed two vC=O at 1637, 1696, vNH at 3133 and vC-H aromatic at 3052. ^{1}H-NMR of **7** showed 3 signals for 7 aliphatic protons in the Naproxen moiety as s, d, q. The most significant signals were at (d, 7.8, 2H, Ar) and at 8.9(d, 8.9, 2H, Ar) which belong to the aromatic protons in pyridine. The –NHNH two protons were appeared at (s, 6.9ppm). ^{13}C-NMR of **7** showed two signals at 165, 172 belong to the C=O and these two signals were disappeared in DEPT confirming the structure. Also, there are 13signals in the range of 103-153 belong to the aromatic carbon atoms in the structure, five of these 13 signals were disappeared in DEPT confirming that these carbon were not attached to hydrogen atoms. Compound **8** was proofed by mass spectrum which showed the molecular ion peak at (M^{+}) at m/z= 456, 7.5% and the base peak at 185, 100%. ^{1}H-NMR of **8** showed the total number of the structure which is 28proton. Significant signal was appeared at (10.1, s, 2H) which belongs to –NHNH-, this shifting towards the downfield could be justified to the probability of the tautomerism between NH and the oxygen atom of the amide group. ^{13}C-NMR of **8** showed a significant signal at 172 belongs to two C=O amide, because the structure is identical, the two C=O gave one signal and this signal was disappeared in DEPT. Compound **9** was proofed by IR which showed two vC=O bands at 1640, 1651 and vNH band at 3200, vC-H aliphatic at 2843-2935 and vC-H aromatic in the range of 2978-3010. ^{1}H-NMR of **9** showed a significant signal at (t, 7.5) belongs to 1H in benzene ring and another characteristic signal at (dd, 8.0, j=1.37) belongs to identical 2H in Benzene ring. ^{13}C-NMR of **9** showed two signal at 173,165 belong to C=O amide in the structure and these two signals were disappeared in DEPT. Compound **10** was proofed by mass spectrum which showed the molecular ion peak at (M^{+}) at m/z= 583, 6.3% and the base peak at 140, 100%. IR spectrum of **10** showed the disappearance of the amide bands at 1640, 1651 which were in **9** and the appearance of new band at 1606 which belongs to vC=N band in oxadiazole ring. IR also showed the disappearance of vNH band at 3200 confirming the formation of the Oxadiazole ring. ^{1}H-NMR of **10** was very similar to ^{1}H-NMR of **9** except that the signal of –NHNH- in **9** was disappeared in **10** confirming the formation of the five membered ring. ^{13}C-NMR of **10** also was very similar to ^{13}C-NMR of **9** except that the signals of two C=O amide group at 173, 165 in **9** were disappeared and instead of them the signals of two C=N at 161,160 were appeared. On comparison with DEPT these two signals at 161, 160 were disappeared in DEPT. Compound **11** was proofed by IR which showed two vC=O amide bands at 1665, 1679 and vNH at 3191. ^{1}H-NMR of **11** showed a very significant signal at (s, 8.4, 3H) belongs to three protons in benzene ring. The protons of three _NHNH_ groups were appeared at 10.3, 10.6 as singlet signal, again, this shifting towards the downfield could be justified to the probability of the tautomerism between NH and the oxygen atom of the amide group. ^{13}C-NMR of **11** showed two signals at 171,176 belong to six C=O amide group and these two signals were disappeared in DEPT. The aliphatic carbon atoms which were 9 carbon atoms gave three signals in the range of 18-55ppm (each three identical carbon gave one signal). Compound **12** was proofed by IR which showed two vC=O bands at 1632 amide and at 1685 cyclic amide. Another characteristic band was at 3258 which belongs to vNH. ^{1}H-NMR of **12** showed the protons attached to the aliphatic carbons in naproxen at (1.6, d, 3H), (4.0, q, 1H), (3.8, s, 3H) and the aromatic protons of the quinazoline nuclei at (7.8, d, 1H), (7.5, d, 1H), 7.6, t, 1H), (7.7, t, 1H) confirming that the naproxen have incorporated with quinazoline nuclei. ^{13}C-NMR of **12** showed two signals at 169, 172 belong to C=O amide and C=O cyclic amide and these two signals were disappeared in DEPT. Compound **13** was proofed by IR which showed a band at 1161 belongs to vC=S (thione). Another bands at 1607, 3235 belong to vC=N in Oxadiazole ring and vNH- respectively. ^{1}H-NMR of **13** showed the characteristic band at (5.9, s, 1H) belongs to –NH. The signal of the protons attached to the aliphatic carbon atoms were appeared at (1.4, d, CH_3), (3.9, q, 1H), (3.6, s, 3H). In addition, six aromatic protons were appeared in the range of 6.9-7.6. ^{13}C-NMR of **13** showed a signal at 165 belongs to C=S, and at 152 belongs to –O-C=N in oxadiazole ring. These two signals were disappeared in DEPT. Compound **14** was proofed by IR which showed vC=S (thione) band at 1164, vNH- at 3316 and vC=N band at 1605 in triazole ring. ^{1}H-NMR of **14** showed two significant signals, the first one at (3.4, s, 2H, -NH2) and the second one at (5.9, s, 1H, -NH). The rest of the spectrum is approximately similar to other compounds. ^{13}C-NMR of **14** exhibited two significant signal at 173 belongs to C=S and at151 belongs to –O-C=N in oxadiazole ring. The aromatic carbons gave 10 signal in the range of 106-158, while the aliphatic carbons gave three signals at 15, 41, 58. Compounds **15a-e, 16a-b** were proofed by IR which showed the band of vC=O in seven compounds in the range of 1651-1667, vC=N in seven compounds in the range of 1600-1615 and vNH- in seven compounds in the range of 3190-3238. ^{1}H-NMR of **15a-e**

showed the significant signal which belongs to –CH=N as a singlet signal in the range of 8.0-8.2ppm for **15a-e**. Another significant signal which belongs to –NH was appeared as a singlet in the range of 9.1-11.3 for **15a-e**. Compound **15b** showed a signal at (10.2, s, 1H) belongs to phenolic OH. Compound **15c** showed a significant signal at (2.7, s, 6H) belongs to $–N(CH_3)_2$ group. Compound **15d** exhibited two characteristic signals the first one at (6.5, d, 1H) belongs to –CH= in alkene and the second one at (5.7, d, 1H) belongs to–CH= in the conjugated system of cinnamaldehyde. Compound **15e** showed a significant signal at (3.8, s, 3H) belongs to methoxy group in anesaldehyde. The rest of protons in **15a-e** were appeared in the same manner and same locations approximately as that with previous compounds. ^{1}H-NMR of **16a-b** showed the aromatic protons of furan and thiophene in the range of 6.2-7.1ppm. ^{13}C-NMR of compounds **15a-e, 16a-b** showed the significant signals which belongs to C=O amide in the range of 170-176 for **15a-e** and **16a-b**. The signal of C=N was appeared in the range of 155-161 in the seven compounds. The signals of C=O and C=N were disappeared in DEPT. The signals of aromatic carbons in furan ring was appeared at 126, 148, 146. The signals of aromatic carbons in thiophene ring were appeared at 113, 129, 152 ppm confirming the incorporation of these two rings with naproxen moiety.

Compound **17** was proofed by IR which showed νC=O amide band at 1699 and νC=O cyclic amide at 1718, νNH at 3234 and the νC=N band was appeared at 1620. ^{1}H-NMR of **17** showed two characteristic signals the first one at (8.1, s, 1H) belongs to –NH in indole nuclei and the second one at (8.6, s, 1H) belongs to NH proton in Naproxen moiety. Four protons in indole nuclei were appeared in the range of 7.1-7.8 as a d, t, t, d signals respectively. In addition, the signals of naproxen moiety were appeared in the range of 6.8-7.6. ^{13}C-NMR of **17** showed the two C=O amide signal at 172, 162 and the signal of C=N at 157ppm. On comparison with DEPT, these three signals were disappeared confirming the existence of them and the structure of the compound. Compound **18** was proofed by IR which showed the νC=O amide band at 1662, νC=N band at 1605 and νNH at 3268. In addition, ^{1}H-NMR showed the significant signal at (8.0, s, 2H) which belongs to two –CH=N- in the structure. The signal of two identical –NH group's was appeared at (8.4, s, 2H) confirming the structure. The most characteristic signal was at (7.8, dd, 4H) which belongs to four protons in benzene ring. The total number of aliphatic and aromatic protons in naproxen nuclei was multiplied confirming that the structure contains two naproxen moieties. ^{13}C-NMR of **18** showed one significant signal for two identical C=O amide group at 175 which on DEPT was disappeared. The other characteristic signal was at 153ppm for two –CH=N- group confirming the incorporation of two naproxen nuclei through two imine linkages. Compound **19** was proofed by mass spectrum which showed the molecular ion peak at (M^+) at m/z= 439, 41.7% and the base peak at 80, 100%. IR spectrum of **19** showed two C=O bands. The first one at 1689 for νC=O amide and the second one for νC=O cyclic amide at 1707. νNH band appeared at 3183 and νC=N band at 1618. The most significant signals in ^{1}H-NMR of **19** was at (5.9, s, 2H) belongs to $–NH_2$, at (6.1, s, 1H) belongs to C=NH and at (8.3, s, 1H) belongs to –NH in indole nuclei. The total number of aromatic protons was 10 in the range of 6.8-7.6ppm confirming the incorporation of naproxen moiety with indole nuclei. ^{13}C-NMR of **19** showed two significant signal at 174, 164 belongs to two C=O amide in the structure. Another two significant signals were at 163 belongs to –C=NH and at 154 belongs to $–N=C-NH_2$ in pyrazoline ring.

On comparison with DEPT these four signals were disappeared confirming its existence. Compound **20** was proofed by mass spectrum which showed the molecular ion peak at (M^+) at m/z= 311.1, 6.2% and the base peak at 185, 100%. IR spectrum for **20** showed the two ν C=O amide bands at 1660, 1674. Also, the band of νNH was appeared at 3232. ^{1}H-NMR of **20** showed the two characteristic signals of –NH at (8.9, s, 1H) and of $–NH_2$ at (4.8, s2H). Another significant signal appeared at (2.8, s, 1H) belongs to –C=H proton in pyrazolone ring. The usual signals of Naproxen protons attached to aliphatic and aromatic carbons were appeared in the same locations as with previous compounds. ^{13}C-NMR of **20** showed two C=O amide group at 175 for cyclic amide and at 174 for amide group and these two signals were disappeared in DEPT. Also, there is another important signal at 168 belongs to $=C-NH_2$ which also disappeared in DEPT.

Compound **21** was proofed by IR which showed νC=N band of oxadiazole ring at 1613, νNH_2 band at 3115, 3290. ^{1}H-NMR of **21** showed the characteristic signal at (3.9, s, 2H) which belongs to $–NH_2$. ^{13}C-NMR of **21** showed two characteristic signals at 161, 163 which belong to two C=N group in Oxadiazole ring which on comparison with DEPT were disappeared confirming the formation of this ring.

CONCLUSION

We herein report the synthesis of various scaffold naproxen structure compounds in different ways of functionality such as amides, imines, heterocyclic motifs and merging other NSAIDs through hydrazide-hydrazone linkage for the purpose of masking the carboxylic group in the parent drug. This will give a potential safe therapeutic applications and a wide range of biological potency for all the newly synthesized compounds incorporated naproxen core structure.

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REFERENCES

1. Panderi I, Parissi-Poulout M, Second-derivative Spectrophotometric Determination of Naproxen in the Presence of its Metabolite in Human Plasma, Analyst, 119, 1994, 697-701.
2. Khanna S, Madan M, Vangoori A, Banerjee R, Thaimattam R, Jafar Sadik Basha SK, Ramesh M, Casturi SR and Pal M, Evaluation of glycolamide esters of indomethacin as potential cyclo oxygenase-2 (COX2) inhibitors, Bio org Med Chem., 14(4), 2006, 4820-4833.
3. Bhaduri J, Hota D and Acharya SB. Role of prostraglandin synthesis inhibitors on chemically induced seizures, Indian J experimental Biol. 33, 1995, 667-681.
4. Poonam Dharmani, Vijay Kumar Kuchibhotla, Rakesh Maurya, Sudhir Srivatsava, Sharad Sharma and Gautam Palit, Evaluation of Anti ulcerogenic and Ulcer healing properties of Ocimum sanctum Linn, J Ethnopharmacology., 93, 2004, 197-206.
5. Neeraj A, Chandrasekar MJN and Sara UVS, Synthesis, Chemical Hydrolysis and Bioavailability Evaluation of Poly(HEMA)-Ibuprofen Conjugate as Macromolecular Prodrug, International Journal of Drug Delivery Technology, 2(1), 2010, 12-17.
6. Asif H, Amide derivatives of sulfonamides and isoniazid: synthesis and biological evaluation, Acta Poloniae Pharmaceutica-Drug Research, 66(5), 2009, 513-521.
7. Parmeshwari K.H, Prashant R.M, Rajani G, Prodrug designing of NSAID's, Mini-Reviews in Medicinal Chemistry, 9, 2009, 124-139.
8. Alert A, Chemical Aspects of Selective Toxicity. Nature, 182, 1958, 421-423.
9. Bundgaard H, Novel chemical approaches in prodrug design, Drugs Future, 16, 1991, 443-458.
10. Lalit Kumar Wadha and Pritam Dev Sharma. Glycolamide esters of 6-methoxt-2-napthylacetic acid as potential prodrugs synthetic and spectral studies, Indian J. Chem., 34B, 1995, 408-415.
11. Khan MS and Akhter M. Glyceride derivatives as potential prodrugs, synthesis, biological activity and kinetic studies of glyceride derivatives of mefenamic acid, Pharmazie., 60(2), 2005, 110-114.
12. Nalini CN, Ramachandran S, Kavitha K., Glycolamide Esters of Naproxen as Potential Prodrugs - Synthesis, Spectral Studies and Preliminary Pharmacological Screening, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2 (3), 2011, Jul – Sep.
13. Hellberg M.R., Namil A., Delgado P., Novel esters and amides of nonsteroidal antiinflammatory carboxylic acids as antioxidants and antiproliferative agents. J Med Chem., 42, 1999, 267–276.
14. Zovko M., Zorc B., Jadrijevic´-Mladar Takac M., The novel fenoprofenamides – synthesis and spectroscopic characterization. Acta Pharm., 51, 2001, 107–115.
15. Zovko M., Zorc B., Jadrijevic´-Mladar Takac., The novel ketoprofenamides – synthesis and spectroscopic characterization, Croat Chem Acta, 76, 2003, 335–341.
16. Kourounakis P.N., Tsiakitzis K., Kourounakis A.P, Reduction of gastrointestinal toxicity of NSAIDs via molecular modifications leading to antioxidant anti-inflammatory drugs. Toxicology, 144, 2000, 205–210.
17. Marko M, Branca Z, Lana P., 2007. Fenoprofen and Ketoprofen Amides as Potential Antitumor Agents, Chem Biol Drug Des., 69, 2007, 222–226.
18. Goldie U, Suman B, Sunil K, Therapeutic Review Exploring Antimicrobial Potential of Hydrazones as Promising Lead, Der Pharma Chemica, 3(1), 2011, 250-268.
19. Mohareb R.M, El-Sharkawy K.A, Hussein M.M., Synthesis of hydrazide-hydrazone derivatives and their evaluation of antidepressant, sedative and analgesic agents, Journal of pharmaceutical sciences and research, 2(4), 2010, 185-196.
20. Rallas S, Gulerman N and Erdeniz H., Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines, II FARMACO, 57(2), 2002, 171-174.
21. Gursoy A, Terzioglu N and Otuk G., Synthesis of some new hydrazide-hydrazones, thiosemicarbazides and thiazolidinones as possible antimicrobials, Eur. J. Med. Chem., 32, 1997, 753-757.
22. Rahman V.M, Mukhtar S, Ansari W.H, Synthesis, stereochemistry and biological activity of some novel long alkyl chain substituted thiazolidin-4-ones and thiazan-4-one from 10-undecenoic acid hydrazide, Eur. J. Med. Chem., 40, 2005, 173-184.
23. Dimmock J.R, Vashishtha S. C and Stables J.P., Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds, Eur. J. Med. Chem., 35, 2000, 241-248.
24. Sava G, Perissin L, Lassiani L, Antiinflammatory action of hydrosoluble dimethyl-triazenes on the carrageen ininduced edema in guinea pigs, Chem. Biol. Interact., 53, 1985, 37-43.
25. Xia Y.I, Chuan-Dong F, Zhao B.X, Synthesis and structure-activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide hydrazone derivatives as potential agents A549 lung cancer cells, Eur. J. Med.Chem., 43, 2008, 2347-2353.
26. Melnyk P, Leroux V, Serghergert C, Design, synthesis and *in vitro* antimalarial activity of an acylhydrazone library, Bioorg. Med. Chem. Lett., 16, 2006, 31-35.
27. Ajani O.O, Obafemi C.A, Nwinyi O.C, Microwave assisted synthesis and antimicrobial activity of 2-quinoxalinone-3-hydrazone derivatives, Bioorg. Med. Chem., 18, 2010, 214-221.
28. Zheng L.W, Wu L.L, Zhao B.X, Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells, Bioorg. Med. Chem., 17, 2009, 1957-1962.
29. Mustafa M.A,Alaa H.J and Jawad K.S., Synthesis, Characterization and Evaluation of Biological Activity of New Heterocyclic Compounds Containing 1,2,4-Triazole and 1,3,4-Thiadiazole Rings, International Journal of Applied Science and Technology, 2(10), 2012, December.

30. Amanpreet S.K and Wakode S. R., 2012. Synthesis of Some Benzimidazole Derivatives and Evaluation of their Antimicrobial Activity, International Journal of Pharmaceutical frontier research., 2(2), 2012, 56-67.

31. Kalpesh P, Jayachandrane E, Ravi S, Synthesis, characterization and anthelmintic activity (Perituma Posthuma) of new oxadizole corporate with imidazole and pyrazole, International Journal of Pharma and Bio Sciences. 1(3), 2010, Jul-Sep.

32. Manju P, Neeraj K.S, Priyanka, Synthetic and biological multiplicity of Isatin: A review, Journal of Advanced Scientific Research. 2(2), 2011, 35-44.

33. Shaaban K. M, Albayati M.R, Walid A. M. O, Functionalization of ibuprofen core structure compound: Part1. Synthesis of potential chemotherapeutic agents incorporated ibuprofen substructure and their *in vitro* antimicrobial study, Journal of Chemical and Pharmaceutical Research, 4(7), 2012, 3505-3517.

34. Shaaban K M, Albayati M.R, Sabry H.H.Y, Functionalization of Ibuprofen Core Structure Compound: Synthesis of New Potential Chemotherapeutic Agents Incorporating Ibuprofen Substructure. Chemical Sciences Journal, 2013, CSJ-97.

35. Furniss BS, Hannaford AJ, Smith PWG, Vogel's Text Book Of Practical Organic Chemistry. Longman Scientific & Technical, London. Co-published in the United States with John Wiley & Sons Inc., New York, 5th edition, 1988, 695.

36. Amir M and Kumar S., Anti-inflammatory and Gastro Sparing Activity of Some New Indomethacin Derivatives, Arch. Pharm. Chem. Life Sci., 338, 2005, 24-31.

37. Eric J.F.F, Jaco K, Caroline A.M.K, Low Molecular Weight Proteins as Carriers for Renal Drug Targeting. Preparation of Drug-Protein Conjugates and Drug-Spacer Derivatives and Their Catabolism in Renal Cortex Homogenates and Lysosomal Lysates, J. Med. Chem., 35, 1992, 1246-1259.

38. Veerachamy A, Viswas R.S, Gnanavel V, Synthesis, Analgesic, Anti-inflammatory and Antibacterial Activities of Some Novel 2-Phenyl-3-substituted Quinazolin-4(3*H*) Ones, Biol. Pharm. Bull. 25(11), 2002, 1432—1435.

39. Shaaban K.M, Peter N.H, Mehmet A, 2-Hydroxy-N'-[2-(6-methoxynaphthalen-2-yl)propanoyl]benzohydrazide, Acta Cryst. E68, 2012, o1251–o1252.

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