RESEARCH ARTICLE

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Functionalization of Ibuprofen Core Structure Compound: Synthesis of New Potential Chemotherapeutic Agents Incorporating Ibuprofen Substructure

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Abstract

New series of potential biologically active agents have been synthesized by functionalization of ibuprofen core structure involving hydrazidic, heterocyclic, quinone and indole containing motifs. The targeted products have been achieved in a very good yield (average 75%) under conventional heat and irradiation conditions. All compounds have been characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra.

Keywords: Ibuprofen; anti-inflammatory; NSAID; biologically active compounds.

1. Introduction

Ibuprofen (IBU) is the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects [1, 2]. Ibuprofen is used clinically in the treatment of chronic articular rheumatism, pain, fever and inflammation, but to obtain good therapeutic effects, repeated administration is inevitable. Frequent medication of IBU, however, is well known to cause serious gastrointestinal damage, like other NSAIDs. A possible way to solve this problem is to derivatize the carboxylic functional group of the IBU to produce prodrug [3].

Hydrazines and their derivatives constitute an important class of compounds that has found wide utility in organic synthesis [4, 5] and employed as reagents for the derivatization and characterization of carbonyl compounds. Recently the N-N linkage has been used as a key structural motif in various bioactive agents. In particular, an increasing number of N-N bond-containing heterocycles and peptidomimetics have made their way into commercial applications as pharmaceutical and agricultural agents [6, 7].

Heterocyclic ring containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties [8].

In the last few decades, the chemistry of five-membered heterocyclic rings has received considerable attention owing to their synthetic and effective biological importance. Derivatives of 1,3,4–oxadiazole, 1,3,4-triazole, indole and pyrazole have been found to possess a wide spectrum of biological activities [9-16].

Further to our research program on synthesis of bio-active molecules [17-19] we continued to synthesize incorporated NSAID's sub-structure derivatives based on our significant data on the biological activities of ibuprofen containing compounds part 1 [20]. Such observations have prompted us to extend our study on synthesis of new potential biologically active derivatives based ibuprofen core structure and incorporated with hydrazidic linkage and heterocyclic ring such as pyrazole, oxadiazole , triazole, indole, piperazine, thiophene and furan ring (see Schemes 1 and 2).

2. Methods

Melting points are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. The IR spectra were recorded with Perkin-Elmer FT-IR instrument using potassium bromide pellets. ^{1}HNMR, ^{13}CNMR spectra were recorded in deuterated chloroform ($CDCl_3$), acetone CD_3COCD_3 or dimethylsulphoxide (DMSO-d_6) 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.

2.1 Materials

Ibuprofen has been purchased from Aldrich. Compounds such as ethyl 2-[4-(2-methylpropyl)phenyl]propanoate **2** [21], 2-[4-(2-methylpropyl)phenyl]propanoyl chloride **3** [22], 2-[4-(2-methylpropyl)phenyl]propanehydrazide **4** [23] were synthesized according to the cited literature. The physical properties of the synthesized compounds are tabulated in Table 1.

Synthesis of 1-(3-Mercapto-2-methyl-propionyl)-pyrrolidine-2-carboxylic acid N'-[2-(4-isobutyl-phenyl)-propionyl]-hydrazide 5:

A mixture of equimolar quantities of **3** (0.01mol) and captopril hydrazide (0.01 mol) 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 a white powder. IR(KBr cm^{-1}): (C=O amide and ketone1630, 1642 and 1675 respectively), (NH 3238), (C-H aliphatic 2869-2954), (Ar, 3052). ^{1}H-NMR: (Aceton-d_6) δ at 0.0.85(d,$(CH_3)_2$), 1.3(d, 3H aliphatic), 1.9(m, 1H aliphatic), 2.5(d, -CH_2-), 3.5(q, 1H), 7.0(dd, Ar, J=1.87),9.0(s,NH,2H), 2.0(t,SH), 4.2(t, 1H aliphatic), 2.3(q, 2H aliphatic), 1.9(m, 2H aliphatic), 3.1(t , 2H aliphatic), 1.1(d, 3H aliphatic), 2.8(m, 1H aliphatic). ^{13}C-NMR**:** 171, 170, 177 (C=O amide), 19(CH_3), 23$(CH_3)_2$, 31(C-H aliphatic tertiary), 46(CH_2), 46(C-H aliphatic). 127,130(C=C, Ar), 137,139(=C-Ar for ibuprofen ring), 59(C-H aliphatic of five membered ring), 25, 22, 42 (CH_2 aliphatic of five membered ring), 16(CH_3 in captopril), 40(C-H aliphatic in captopril).

Synthesis of 2-[2-(4-Isobutyl-phenyl)-propionyloxy]-benzoic acid 6:

A mixture of an equimolar ratio of **3** and salicylic acid in 25ml of K_2CO_3 solution in acetone was refluxed for 5hr. The mixture was cooled and poured onto crushed ice. The colorless oily layer was extracted by ether and dried over $MgSO_4$ [24]. Excess ether has been evaporated under vacuum to deposit the target product **6** in a pure form. IR(KBr cm^{-1}): (C=O carboxylic 1721), (C=O ester 1739), (C-H aliphatic 2846-2954). ^{1}H-NMR: ($CDCl_3$) δ at 0.9(d,$(CH_3)_2$), 1.4(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.6(q, 1H), 7.1(dd, Ar, J=1.83), 10.7(s ,OH carboxylic), 7.2(d, Ar,2H), 6.9(t, Ar, 2H), 7.0(t,Ar,1H).^{13}C-NMR**:**170, 163(C=O ester, carboxylic), 18(CH_3), 22$(CH_3)_2$, 30(C-H aliphatic tertiary), 45(CH_2), 52(C-H aliphatic). 127,129(C=C, Ar), 137,140(=C-Ar for Ibuprofen ring), 125, 126, 132, 119, 152, 122(C=C , Ar for salicylic ring).

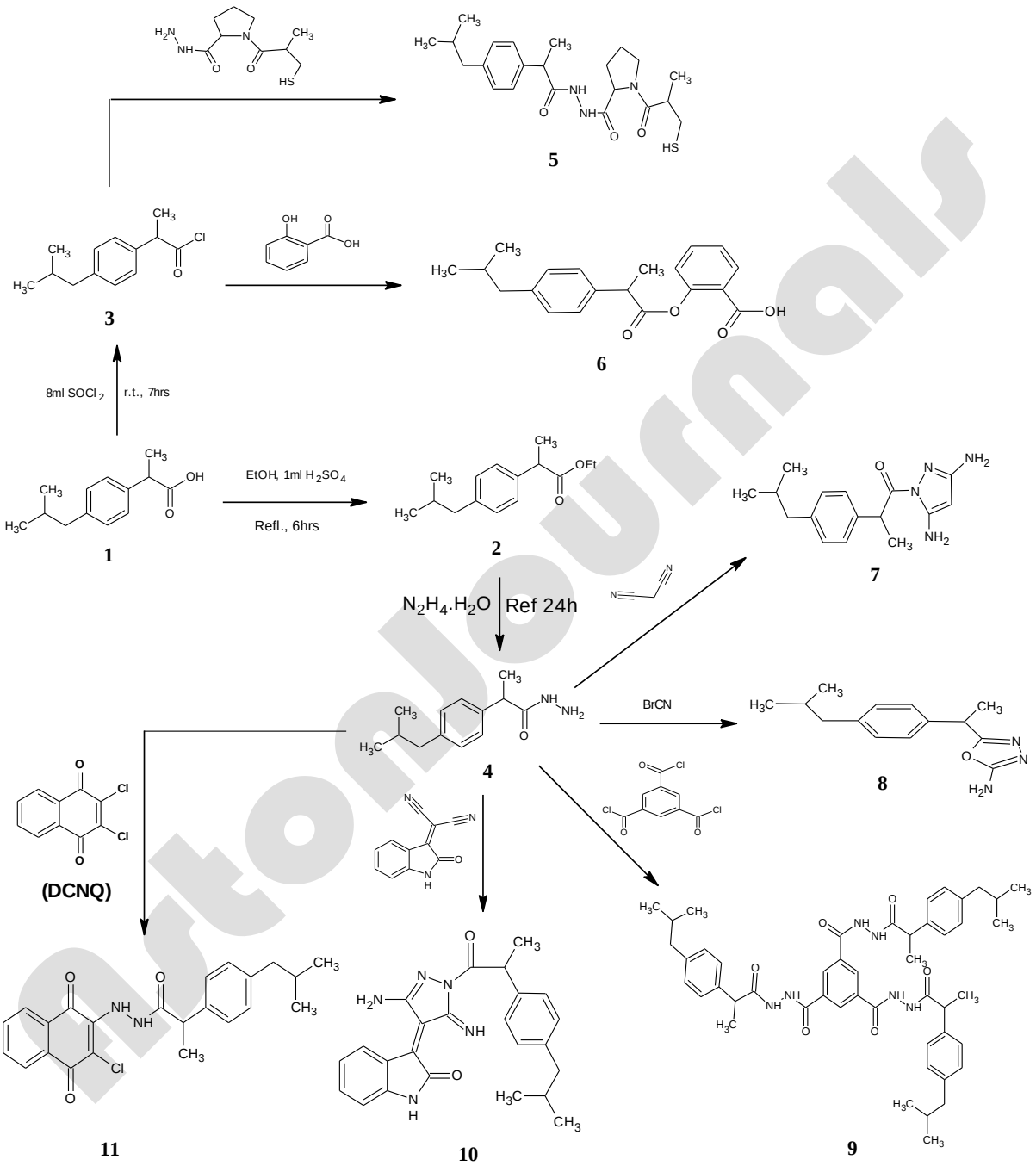
Synthesis of 1-(3,5-Diamino-pyrazol-1-yl)-2-(4-isobutyl-phenyl)-propan-1-one 7:

A mixture of an equimolar amounts of **4** and malononitrile in ethanol with few drops of TEA was refluxed for 5hr. The solvent was removed under reduced pressure. The solid that deposited has been collected, dried under vacuum and recrystallized from ethanol to afford **7** as a pure brown powder. IR(KBr cm^{-1}) :(C=O amide 1655), (NH_2, 3113,3292), (C-H aliphatic 2867-2952), (Ar, 3024). ^{1}H-NMR: (Acetone-d6) δ at 0.0.85(d,$(CH_3)_2$), 1.3(d, 3H aliphatic), 1.9(m, 1H aliphatic), 2.3(d, -CH_2-), 3.6(q, 1H), 7.1(dd, Ar, J=5.04), 6.4(s, 1H of pyrazole ring), 2.81(s, 4H, of 2NH_2). ^{13}C-NMR:171(C=O amide),18(CH_3), 21$(CH_3)_2$, 31(C-H aliphatic tertiary), 43.6(C-H aliphatic) ,44.7(CH_2). 127,129(C=C, Ar), 138,139(=C-Ar for ibuprofen ring), 156, 156, 161(3C in pyrazole ring).

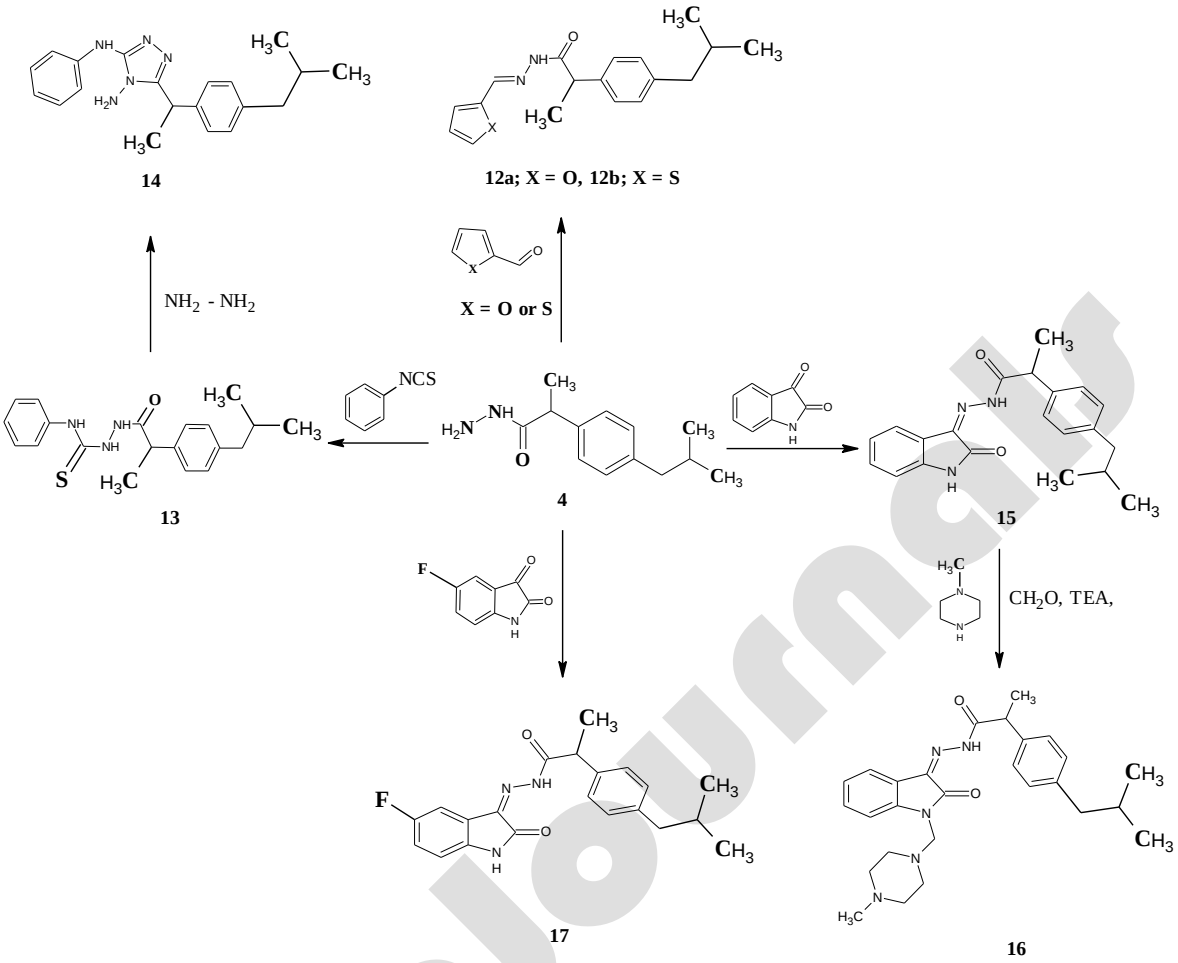
Synthesis of 5-{1-[4-(2-methylpropyl)phenyl]ethyl}-1,3,4-oxadiazol-2-amine 8:

A mixture of (0.005mole) of **4** and (0.0075mole) of bromocyanogene in 25ml of methanol was refluxed for 10hr. The mixture was cooled and poured onto crushed ice and neutralized with sodium bicarbonate. The precipitate then collected and recrystallized from ethanol to get **8** as a white crystal [25]. IR(KBr cm^{-1}): (C=N of oxadiazole ring1655), (NH_2, 3113, 3292), (C-H aliphatic 2866-2953). MS (EI, 70 eV), m/z (Irel, %): a molecular ion peak (M^+) at m/z =246.1, 100% which is the base peak. ^{1}H-NMR: (Aceton-d6) δ at 0.0.85(d,$(CH_3)_2$), 1.5(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 4.1(q, 1H), 7.1(dd, Ar, J=8.24), 6.0(s, 2H,NH_2). ^{13}C-NMR:162,143(C=N of oxadiazole ring),

19(CH_3), 22(CH_3)$_2$, 29(C-H aliphatic tertiary), 44(CH_2), 36(C-H aliphatic). 129,1130(C=C, Ar), 137,140(=C-Ar for ibuprofen ring).



(Scheme 1)



(Scheme 2)

Table 1: Physical properties of synthesized compounds.

No.	M.F.	M. Wt.	Solvent	Yield%	M.P. or B.P. (^{0}C)
5	$C_{20}H_{22}O_4$	326.38	Ether	77	240-243 Oily
6	$C_{23}H_{35}N_3O_22S$	417.6	Ethanol	71	177-179
7	$C_{16}H_{22}N_4O$	286.18	Ethanol	65	173-176
8	$C_{14}H_{19}N_3O$	245.15	Ethanol	75	198-199
9	$C_{48}H_{60}N_6O_6$	816.46	Ethanol	81	164-166
10	$C_{24}H_{27}N_5O_2$	417.22	Ethanol	72	170-171
11	$C_{23}H_{23}ClN_2O_3$	410.14	Dioxan/ethanol	69	214-216
12a	$C_{18}H_{22}N_2OS$	314.15	Ethanol	85	140-142
12b	$C_{18}H_{22}N_2O_2$	298.17	Ethanol	87	153-155
13	$C_{20}H_{25}N_3OS$	355.17	Ethanol	81	176-178
14	$C_{20}H_{25}N_5$	335.21	Ethanol	74	147-149
15	$C_{21}H_2N_3O$	349.18	Ethanol	86	166-164
16	$C_{27}H_{35}N_5O_2$	461.28	Ethanol	64	93-95
17	$C_{21}H_{22}FN_3O_2$	367.17	Ethanol	87	169-171

Synthesis of 1,3,5-tricarbohydrazide-tris-N'-[2-(4-isobutyl-phenyl)-propionyl]-hydrazide 9:
A mixture of (0.03mole) of **4** 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 to give **9** as a white powder. IR(KBr cm^{-1}): (C=O amide 1662), (NH, 3254), (C-H aliphatic 2868-2954), (Ar, 3022). MS (EI, 70 eV), m/z (%): a molecular ion peak (M^+) at m/z =817,100% which is the base peak. ^{1}H-NMR:(Aceton-d6) δ at 0.85(d,$(CH_3)_2$), 1.4(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.8(q, 1H), 7.2(dd, Ar, J=8.24), 8.4(s,3H,Ar, in the benzene ring), 9.3,9.8(s, 2H, NH-NH). ^{13}C-NMR: 164,173(C=O of amide), 18(CH_3,3C), 21($(CH_3)_2$,6C), 30(C-H aliphatic tertiary,3C), 45(CH_2,3C), 43(C-H aliphatic,3C). 129,1130(C=C, Ar,12C), 137,140(=C-Ar for ibuprofen ring,6C), 129(C=C in benzene ring, 3C), 133(C=C in benzene ring, 3C).

Synthesis of 3-{3-Amino-5-imino-1-[2-(4-isobutyl-phenyl)-propionyl]-1,5-dihydro-pyrazol-4-ylidene}-1,3-dihydro-indol-2-one 10:
A mixture of an equimolar ratio of **4** 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 recrystallized from ethanol to give **10** as yellow crystals. IR(KBr cm^{-1}): (C=N in pyrazolre ring 1619), (C=O amide 1692), (C=O cyclic amide in indole ring 1717), (NH, 3184,3210), (C-H aliphatic 2868-2954), (Ar, 3029). ^{1}H-NMR: (Chloroform-D) δ at 0.9(d,$(CH_3)_2$), 1.5(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.8(q, 1H), 7.1(dd, Ar, 4H,J=7.7), 6.8(d,Ar,,1H), 6.9(s,NH,1H), 5.7(s,NH_2,2H), 7.5(s,NH,1H),7.3(d,Ar,1H), 7.5(d,Ar,1H), 7.6(d,Ar,1H). ^{13}C-NMR: 164,173(C=O amide, cyclic amide), 18(CH_3), 22($(CH_3)_2$, 30(C-H aliphatic tertiary), 45(CH_2), 40(C-H aliphatic). 127,129(C=C, Ar, 4C), 137,140(=C-Ar for ibuprofen ring, 2C), 157, 159, 126(3C in pyrazole ring), 106,107,110,120,123,124(C=C,Ar,6C in benzene ring).

Synthesis of 2-(4-Isobutyl-phenyl)-propionic acid N'-(3-chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-hydrazide 11:
A mixture of an equimolar quantities of **4** and 2,3-dichloronaphthalene-1,4-dione (DCNQ) in 25ml of ethanol and few drops of TEA was refluxed for 4hr. The obtained precipitate was collected and recrystallized from ethanol to give **11** as a yellow powder. IR(KBr cm^{-1}): (C=O amide 1648, C=O of ketone 1707),(NH, 3112), (C-H aliphatic 2868-2954), (Ar, 3029)**.** ^{1}H-NMR**:**(Acetone-D_6)δ at0.95(d,$(CH_3)_2$), 1.5(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.8(q, 1H), 7.0(dd, Ar, 4H,J=7.7),7.8(tt,Ar,2H,J=15.11)**,** 8.1(dd, Ar,2H,J=9.1), 4.3(s, NH, 1H). ^{13}C-NMR**:** 185(2C=O ketone),173(C=O amide),19(CH_3), 23($(CH_3)_2$, 29(C-H aliphatic tertiary), 44(CH_2), 41(C-H aliphatic) . 127,129(C=C, Ar,4C), 137,140(=C-Ar for ibuprofen ring,2C), 131, 136, 138(C=C, Ar, 6C of benzene ring), 158(C-NH), 122(C-Cl).

Synthesis of 2-[4-(2-methylpropyl)phenyl]-N'-[(E)-arylmethylidene]propanehydrazides 12a-b:
A mixture of an equimolar ratio of **4** and furan-2-carbaldehyde or thiophene-2-carbaldehyde in 25ml of absolute ethanol and few drops of glacial acetic acid was refluxed for 4hr. The solvent was evaporated under vacuum and the precipitate that formed was collected and recrystallized from ethanol to afford N'-[(E)-furan-2-ylmethylidene]-2-[4-(2-methylpropyl)phenyl]propanehydrazide**12a** and N-[(E)-thiophen-2-ylmethylidene]-2-[4-(2-methylpropyl)phenyl]propanehydrazide**12b** respectively [26].

N-[(E)-furan-2-ylmethylidene]-2-[4-(2-methylpropyl)phenyl]propanehydrazide 12a:
This product was obtained as a yellow powder. IR(KBr cm^{-1}): (C=O amide 1666), (C=N 1607), (NH3178), (C-H aliphatic 2867-2952), (Ar, 3029). ^{1}H-NMR**:** (Chloroform-D)δ at0.85(d,$(CH_3)_2$), 1.5(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.7(q, 1H), 7.1(dd, Ar, 4H,J= 8.24), 7.6(s, -CH=N,1H), 8.0(s,-NH, 1H), 6.8(d,Ar,1H in furan ring), 6.9(t,Ar, 1H in furan ring), 7.6(d,Ar,1H in furan). ^{13}C-NMR: 176(C=O amide), 19(CH_3), 22($(CH_3)_2$, 30(C-H aliphatic tertiary), 42.6(C-H aliphatic), 45.7(CH_2), 127,129(C=C, Ar,4C), 138, 139(=C-Ar,2C, for ibuprofen ring), 149(-C=N), 149, 144(C-O, of furan ring,2C), 128(C-C, in furan ring,2C).

N-[(E)-thiophen-2-ylmethylidene]-2-[4-(2-methylpropyl)phenyl]propanehydrazide 12b:
This product was obtained as a brown powder. IR(KBr cm^{-1}): (C=O amide 1667), (C=N 1597), (NH 3190), (C-H aliphatic 2868-2951), (Ar, 3045). ^{1}H-NMR**:** (Chloroform-D)δ at0.9(d,$(CH_3)_2$), 1.45(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.5(d, -CH_2-), 3.8(q, 1H), 7.0(dd, Ar, 4H,J= 8.1), 7.7(s, -CH=N,1H), 8.1(s,-NH, 1H), 6.3(d,Ar,2H in thiophene ring), 6.9(t,Ar, 1H in thiophene ring). ^{13}C-NMR: 174(C=O amide), 18(CH_3), 23($(CH_3)_2$, 31(C-H aliphatic tertiary), 43(C-

H aliphatic), 47(CH_2). 128,129(C=C, Ar,4C), 137,140(=C-Ar,2C, for ibuprofen ring), 159(-C=N), 131,147(C-S, of thiophene ring,2C), 129(C-C, in thiophene ring,2C).

Synthesis of 2-{2-[4-(2-methylpropyl)phenyl]propanoyl}-N- phenylhydrazinecarbothioamide 13:
A mixture of an equimolar ratio of **4** and phenylisothiocyanate in 25ml of ethanol was refluxed for 4hr. The solvent was evaporated and the precipitate that formed was collected and recrystallized from ethanol to give **13** as a white powder. IR(KBr cm^{-1}): (C=O amide 1677), (C=S 1172), (C-H aliphatic 2866-2949), (3138, 3247, 3345 –NH), (Ar, 3049). ^{1}H-NMR**:** (Chloroform-D)δ at 0.9(d,(CH_3)$_2$), 1.5(d, 3H aliphatic), 1.8(m, 1H aliphatic), 2.4(d, -CH_2-), 3.6(q, 1H), 7.0(dd, Ar, 4H), 6.9(d, -NH, 1H), 9.0(d,-NH,1H), 8.3(s,-NH,1H)**,** 6.8(d,Ar,2H in benzene ring), 6.9(t,Ar,1H in benzene ring), 7.2(t,Ar,2H in benzene ring). ^{13}C-NMR: 173(C=O amide), 179 (C=S), 19(CH_3), 24(CH_3)$_2$, 32(C-H aliphatic tertiary), 44(C-H aliphatic), 46(CH_2). 127,129(C=C, Ar,4C), 137,140(=C-Ar,2C, for ibuprofen ring), 146, 118, 129, 127, 130, 118(C-C, Ar , 6C in benzene ring).

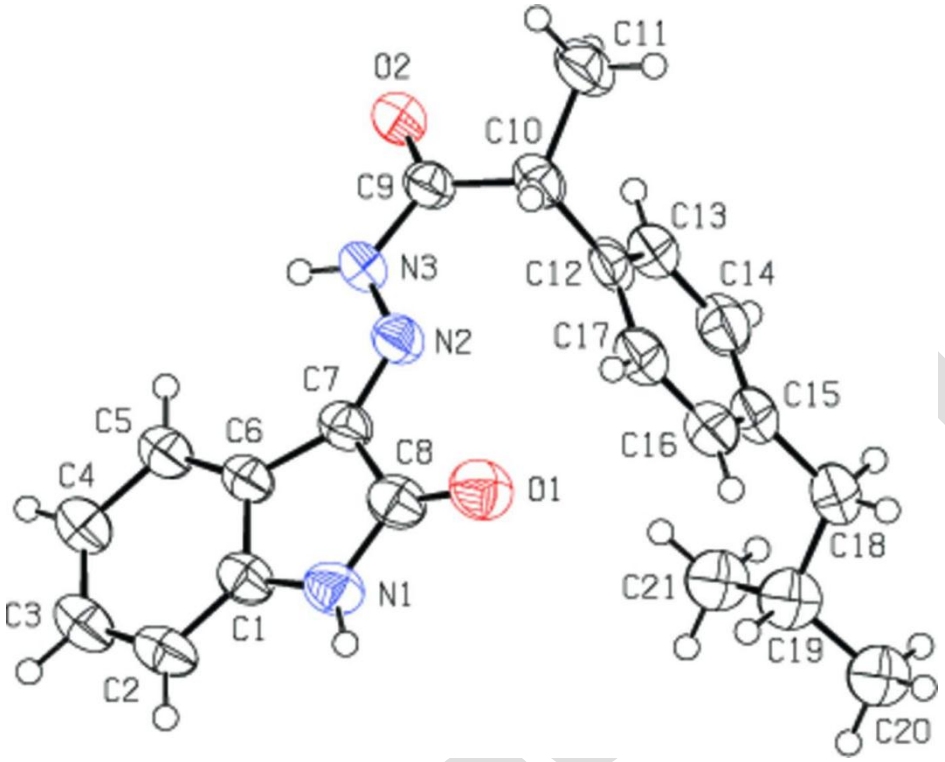
Synthesis of 5-{1-[4-(2-methylpropyl)phenyl]ethyl}-N3-phenyl-4H-1,2,4-triazole-3,4-diamine 14:
A mixture of (0.001mol) of compound **13** and excess of hydrazine hydrate in 25ml of ethanol was refluxed for 5hr. The mixture was cooled and poured onto crushed ice. The obtained precipitate was collected and recrystallized from ethanol to give **14** as a white powder [27]. IR(KBr cm^{-1})**:** (C=N 1597), (NH 3100, 3115), (C-H aliphatic 2866-2952), (Ar, 3048). ^{1}H-NMR: (Chloroform-D) δ at 0.85(d,(2CH_3), 1.6(d, 3H aliphatic), 1.85(m, 1H aliphatic), 2.5(d, -CH_2-), 3.5(q, 1H), 6.8(dd, J=7.7, Ar, 4H), 4.0(s,NH_2, 2H), 7.3(t,Ar,2H), 7.5(d,Ar,2H), 7.1(t,Ar,1H). ^{13}C-NMR: 168, 155 (C=N of triazole ring), 19(CH_3), 22(CH_3)$_2$, 29(C-H aliphatic tertiary), 44(CH_2), 36(C-H aliphatic). 129,130(C=C, Ar), 137,140(=C-Ar for ibuprofen ring). 117(C=C, Ar,2C in benzene ring), 131(C=C, Ar,2C in benzene ring), 117(C=C,Ar, 1C in benzene ring).

Synthesis of 2-[4-(2-methylpropyl)phenyl]-N'-[(3Z)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]propanehydrazide 15:
A mixture of **4** (0.01mol) and isatin (0.01mol) was transferred to beaker along with few drops of glacial acetic acid as a catalyst. The mixture has been irradiated under microwave for 2 minutes with intervals every 5 seconds then left to cool at room temperature. The product that obtained was collected and recrystallized from ethanol to furnish **15** as yellow crystals [28]. IR(KBr cm^{-1})**:** (C=O amide 1691), (C=O cyclic 1733), (C=N, 1616), (NH 3224), (C-H aliphatic 2866-2953), (C-H Ar3044). ^{1}H-NMR**:** (Chloroform-D)δ at 0.85(d, (2CH_3), 2.0(m, 1H aliphatic), 2.4(d, -CH_2-), 1.6(d, 3H aliphatic), 3.7(q, 1H), 7.1(dd, Ar, J=8.24), 8.2(s, NH), 7.9(s, NH of cyclic amide), 7.5(d, 1H, Ar), 7.6(d, 1H,Ar, 7.6), 7.4(triplet, 2H, Ar). ^{13}C-NMR**:** 177, 160(2C, C=O), 19(CH_3), 23(2CH_3), 44(CH_2 aliphatic), 43(C-H aliphatic), 31(C-H aliphatic tertiary), 127, 129(C=C Ar), 140, 135(=C- Ar), 151(C=N), 117, 129, 121, 127, 122, 140 (6C for benzene ring). X-ray analysis of **15** showed the indolin-2-one group is essentially planar, with a maximum deviation of 0.016 (2) A ° for the N atom, and makes a dihedral angle of 84.38 (14) with the benzene ring. The N-N(H)-C(O)-C- torsion angle is 0.9 (3). In the crystal, molecules are linked into a three-dimensional network via N-H---O and C-H---O hydrogen bonds. In addition, a C-H--π interaction was observed. The crystal structure of the single crystal of **15** is shown below in Figure 1.

Synthesis of 2-(4-Isobutyl-phenyl)-propionic acid [1-(4-methyl-piperazin-1-ylmethyl)-2-oxo-1,2-dihydro-indol-3-ylidene]-hydrazide 16:
A mixture of 0.01 mol of **15**, 0.01 mol of N-methyl piperazine and excess of formaldehyde solution along with few drops of TEA in 25ml of ethanol was refluxed for 8hr. The solvent was removed and the mass solid product was collected and recrystallized from ethanol to give **16** as yellow crystals. IR(KBr cm^{-1}): (C=O amide1680, 1630), (C=N 1612), (NH 3207), (C-H aliphatic 2868-2953), (Ar, 3053).

^{1}H-NMR**:** (Chloroform-D)δ at 0.85(d, (2CH_3), 1.8(m, 1H aliphatic), 2.4(d, -CH_2), 1.5(d, 3H aliphatic), 3.8(q, 1H), 7.0(dd, Ar, J=7.3), 2.7(s, 3H aliphatic), 4.4(s, 2H aliphatic), 2.3(t, 8H, aliphatic in piperazine ring), 7.1(t, Ar,1H), 7.3(t,Ar,1H), 7.5, 7.6(d,d, Ar,2H). ^{13}C-NMR: 176, 165(C=O amide and cyclic amide), 153(C=N), 19(CH_3), 21(2CH_3), 31(C-H aliphatic tertiary), 44(CH_2), 46(C-H aliphatic), 62(CH_2, 1C of formaldehyde), 53(CH_2, 2C of piperazine ring), 58(CH_2, 2C of piperazine ring), 39(CH_3, 1C). 127, 129(C=C, Ar), 137, 140(=C-Ar for ibuprofen ring), 131, 125, 132, 120, 138 ,123(C=C, 6C in benzene ring of isatin).

Figure 1: Crystal structure of 15.



Synthesis of 2-(4-Isobutyl-phenyl)-propionic acid (5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide 17:
A homogenous solid mixture of an equimolar ratio of **4** and 5-flouro isatin was transferred to a beaker along with few drops of glacial acetic acid as a catalyst. The mixture has been irradiated under microwave for 2 minutes then left to cool at room temperature. The product that was obtained was collected and recrystallized from ethanol to furnish **17** as a yellow powder [29]. IR(KBr cm^{-1}): (C=O amide 1699, 1718), (C=N 1628), (NH 3234), (C-H aliphatic 2867-2950), (Ar, 3048). ^{1}H-NMR: (Chloroform-D)δ at 0.9(d, ($2CH_3$), 2.1(m, 1H aliphatic), 2.5(d, -CH_2-), 1.6(d, 3H aliphatic), 3.6(q, 1H), 7.1(dd, Ar, J=8.24), 8.1(s, NH), 7.8(s, NH of cyclic amide), 7.5(d, 1H, Ar), 7.6(d, 1H,Ar, 7.6), 7.3(triplet, 2H, Ar). ^{13}C-NMR: 177, 164(2C, C=O), 19(CH_3), 23(CH_3)2, 44(CH_2 aliphatic), 43(C-H aliphatic), 31(C-H aliphatic tertiary), 127, 129(C=C Ar), 140, 135(=C- Ar), 151(C=N), 155(C-F, 1C), 128, 131, 121, 139, 123 (5C for benzene ring).

3. Results and Discussion

Compound **5** was confirmed by IR which showed three carbonyl amide bands at (C=O amide 1630, 1642, 1675). ^{1}H-NMR of **5** showed a significant signal (t at 2.0ppm) which belongs to SH in captopril moiety. In addition, there are many signals in the range of 0.85-3.5ppm which are more than those of ibuprofen moiety confirming that these signals belong to captopril and ibuprofen aliphatic protons which have been incorporated together. ^{13}C-NMR of **5** showed three characteristic signals at 171, 170, 177ppm belonging to three amide carbonyls which disappeared in DEPT confirming that these signals belong to amide because they are not attached to H atom. Also, the DEPT showed that there are three signals at 25, 22, 42 ppm oriented down belonging to the CH_2 at five membered ring and there are two signals at 46ppm and 29ppm oriented down belonging to CH_2 in ibuprofen and captopril respectively. Compound **6** was proofed by ^{1}H-NMR which showed a significant signal (s at 10.7) which belongs to carboxylic OH of salicylic acid. In addition, the signals of the aromatic protons of benzene ring appeared at 7.2(d, Ar,2H), 6.9(t, Ar, 2H), 7.0(t,Ar,1H). ^{13}C-NMR of **6** showed two signals at 163 and 170ppm belonging to the ester and

acid carbonyl groups, respectively. The methylene group (-CH_2-) in ibuprofen moiety was confirmed since it appeared at 45ppm and disappeared in DEPT confirming that the ibuprofen is inserted with salicylic acid.

Compound **7** was proofed by ^{1}H-NMR which showed significant two signals (s at 2.8ppm) belonging to 4H of NH_2. ^{13}C-NMR of **7** showed the amide carbonyl at 171ppm. The signal of carbon atoms in pyrazole ring which is not attached to H atom appeared at 155ppm and disappeared in DEPT while the signal of the carbon atom in pyrazole ring which is attached to H atom appeared at 76ppm and didn't disappear in DEPT. Compound **8** was proofed by ^{1}H-NMR which showed a very significant signal (s at 6.0) which belongs to NH_2, in addition to the ordinary signals of aliphatic protons in ibuprofen core structure. ^{13}C-NMR of **8** showed two significant signals at 156 and 109 belonging to C-O in oxadiazole ring which disappeared in DEPT. The mass spectrum of **8** showed the molecular ion peak (M^+) at m/z 246.16, 100% which is the base peak also confirming the structure. Compound **9** was proofed by IR spectrum which showed vCH aromatic at 3022, vCH aliphatic in the region of (2868-2954), vC=O of amide at 1662 and vNH at 3254 and by mass spectrum which showed the molecular ion peak at (M^+)at m/z=817, 100% which is also the base peak. ^{1}H-NMR of **9** showed a significant signal (s at 8.4) which belongs to three protons in benzene ring. The signals of –NH-NH- protons appeared as (s at 9.3, 9.8). In addition, the aromatic protons in ibuprofen moiety showed one signal (dd at 7.2, J=8.2). ^{13}C-NMR of **9** showed two signals at 164, 173 which belong to the amide carbonyl atoms and these two signals disappeared in DEPT. Compound **10** was proofed by IR which showed vC=N of pyrazole ring at 1619 and vC=O amide carbonyls at 1692 and 1717 which belongs to the cyclic amide in indole ring and vCH aromatic at 3029, vCH aliphatic in the region of 2868-2954. ^{1}H-NMR of **10** showed three signals (s at 5.7) belonging to –NH_2, (s at 6.9) C=NH in pyrazole ring and (s at 7.5) belonging to –NH in the indole ring. On the other hand, the signals of all the aromatic protons appeared in the range of 6.8-7.7ppm, but no singlet signals are in this range which confirms that such singlet signals belong to –NH and –NH_2. ^{13}C-NMR of **10** showed two significant signals at 164 and 173 belonging to amide carbonyl atoms and these two signals disappeared in DEPT because they are not attached to H atom. Compound **11** was proofed by IR which showed vC=O of two carbonyl groups at 1648 belonging to amide and at 1709 belonging to ketone, vCH aromatic at 3029, vCH aliphatic in the region of 2868-2954 and vNH at 3112. ^{1}H-NMR of **11** showed significant signals in the aromatic region (tt at 7.8 J=15.11 for two protons in benzene ring), (dd, at 8.1 J=9.1) and (dd, at 7.0, J=7.7 for four protons in ibuprofen core). ^{13}C-NMR of **11** showed two signals for three carbonyl atoms at 185ppm for two ketonic carbonyl groups and at 173ppm for amide carbonyl. These two signals disappeared in DEPT confirming its existence. Another significant signal appeared at 122ppm belonging to C-Cl and the second one at 158ppm belonging to C-NH in benzene ring and these two signals disappeared in DEPT. Compound **12a** was proofed by IR which showed vC=O of amide at 1666, vC=N at 1607 and vNH at 3178. ^{1}H-NMR of **12a** showed two significant signals, the first one (s, at 7.6) which belongs to CH=N proton and the second one (s, at 8.0) which belongs to –NH of amide. The aromatic protons of furan ring appeared in the range of 6.8-7.6ppm as t, d and d signals in addition to aromatic protons of ibuprofen which appeared as dd at 7.0. ^{13}C-NMR of **12a** showed the signal C=O amide at 176ppm which disappeared in DEPT while the signal of CH=N- appeared at 149 and didn't disappear in DEPT. There are additional four signals at 128, 128, 144 and 149, the one at 149ppm disappeared in DEPT confirming that this carbon atom is not attached to H atom in furan ring. Compound **12b** was proofed in the same manner and it showed approximately same bands in IR and same signals in NMR. Compound **13** was proofed by IR which showed vC=O at 1677 and vC=S at 1172 vN-H at 3138, 3247 and 3345. ^{1}H-NMR of **13** showed a significant signal (s, at 8.3) belonging to Ar-HN-C=S proton, (d, at 9.0ppm) belonging to HN-C=S proton and (d at 6.9) belonging to –HN-C=O proton. In addition, ibuprofen aliphatic protons appeared in their ordinary positions in the range 0.8-3.7ppm and the aromatic protons of ibuprofen appeared, as expected, (dd, 7.0 J=8.1). The aromatic protons of benzene ring appeared in the range of 6.8-7.3ppm as t, t and d signals. ^{13}C-NMR of **13** showed two significant signals, the first one at 179ppm belonging to C=S and the second one at 173ppm belonging to C=O, both signals disappeared in DEPT confirming the structure of the compound. Compound **14** was proofed by IR which showed, on comparison with **13** IR, the disappearance of vC=O band at 1677 and vC=S band at 1172 and the appearance of vC=N band at 1597 vNH at 3100, 3115. ^{1}H-NMR of **14** showed the significant signals (s, at 4.0) which belong to –NH_2 protons. The aromatic protons of ibuprofen moiety appeared (dd, at 6.8 J=7.7), and the aromatic protons of benzene ring appeared (t, at 7.3), (t, 7.1), (d, at 7.5). ^{13}C-NMR of **14** showed significant signals at 168 and 155 which belong to two carbon atoms in triazole ring, these two signals disappeared in DEPT confirming that they are not attached to H atom. Compound **15** was proofed by X-ray which confirmed the structure of mono crystal of this compound (Figure 1) in addition to IR and NMR spectral data. Compound **16** was proofed by IR which showed two vC=O amide at 1680 (cyclic amide in indole ring) and at 1630. In addition, vC=N band appeared at 1612 and vNH at 3207. Also,

νC-H aliphatic appeared in the region of 2868-2953 confirming existence of the hydrazone moiety. ^{1}H-NMR of **16** showed very significant signals (s at 2.7) belonging to CH_3 protons of N-methyl piperazine, (s, at 4.4) belonging to $–CH_2$- protons of formaldehyde which is linking the indole core with N-methyl piperazine ring. The aliphatic protons 4(CH_2) of piperazine ring appeared (t, at 2.3) confirming that the two cores have been incorporated. The aromatic protons of benzene ring of indole appeared in the range 7.1-7.6 as d and t signals. The aromatic protons of ibuprofen appeared (dd, at 7.0, J=7.3). ^{13}C-NMR of **16** was very helpful in characterization of this compound, as it showed clearly the 9 signals of the aliphatic carbon atoms which are in the range 18-59, four of them are $–CH_2$-. So, there are four signals at 44,53,58,62 that appeared in ^{13}C-NMR and disappeared in DEPT confirming that signals belong to four methylene groups. In addition, there are two signals at 176 and 165 belonging to C=O amide which disappeared in DEPT. Compound **17** was proofed by IR which showed two νC=O for amide at 1718, 1699, νC=N at 1628, νNH at 3234 in addition to νC-H aliphatic in the region of 2867-2950. ^{1}H-NMR of **17** showed a significant signal (s, at 7.8) belonging to NH in indole ring and (s, at 8.1) belonging to NH of ibuprofen hydrazide. ^{13}C-NMR of **17** showed two signals for C=O amide at 177 and 164ppm which disappeared in DEPT.

Competing Interests

The authors have no competing interests with anyone.

Authors' Contributions

All authors are in equal contribution in different forms.

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