# Facile Synthesis of 3(2*H*)-Pyridazinones and 2(3*H*)-Furanones of Anticipated Biological Activities

J. M. Morsy
*Chemistry Department, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt*

3-Aroyl-2-arylpropionic acids **2a-e** were utilized to synthesize 3(2*H*)-pyridazinones **3a-e** and 2(3*H*)-furanones **6** through reaction with hydrazine hydrate and freshly distilled acetic anhydride, respectively, in the hope of obtaining new 3(2*H*)-pyridazinones with no ulcerogenic side effect or with negligible general side effects as those currently used $NSAID_S$ as well as biologically active 2(3*H*)-furanones.

**Keywords:** 3-Aroyl-2-arylpropionic acids; 4,6-Disubstituted-3(2*H*)-pyridazinones; 3,5-Disubstituted-2(3*H*)-furanones; $NSAID_S$.

## INTRODUCTION

3(2*H*)-Pyridazinones are important scaffolds in the drug industry, with many of their analogs being utilized in the treatment of different human pathological states. This class of heterocyclic compounds have been described as non-steroidal anti-inflammatory drugs,[1] agents for therapeutic intervention of renal-urologic,[2] cardiovascular,[3] respiratory,[4] dermatologic diseases.[5] They also have platelet inhibitory activity.[6-10] The majority of currently known non-steroidal anti-inflammatory and analgesic drugs [$NSAID_S$], i.e, aspirin and ibuprofen, mainly act peripherally by blocking the production of prostaglandins through inhibition of cyclooxygenase (COX) enzymes, COX-1 and COX-2.[11] These drugs tend to produce side effects such as gastrointestinal ulceration and suppression of renal function due to inhibition of the constitutive COX-1, which is responsible for the production of prostaglandins, which are responsible for gastroprotection and vascular hemeostasis.[12-14] As a result of the previously mentioned facts, the main trend nowadays in pain therapy focuses on improved non-steroidal analgesics which are effective as analgesics but devoid of the side effects which are inherent to traditional $NSAID_S$. Moreover, the 2(3*H*)-furanone fragment is present in a wide variety of biologically active natural products.[15] The importance of 2(3*H*)-furanones is due to facile ring cleavage by a variety of nucleophilic species to afford acyclic derivatives which may undergo ring closure to produce other synthetically and biologically important heterocyclic systems.[16]

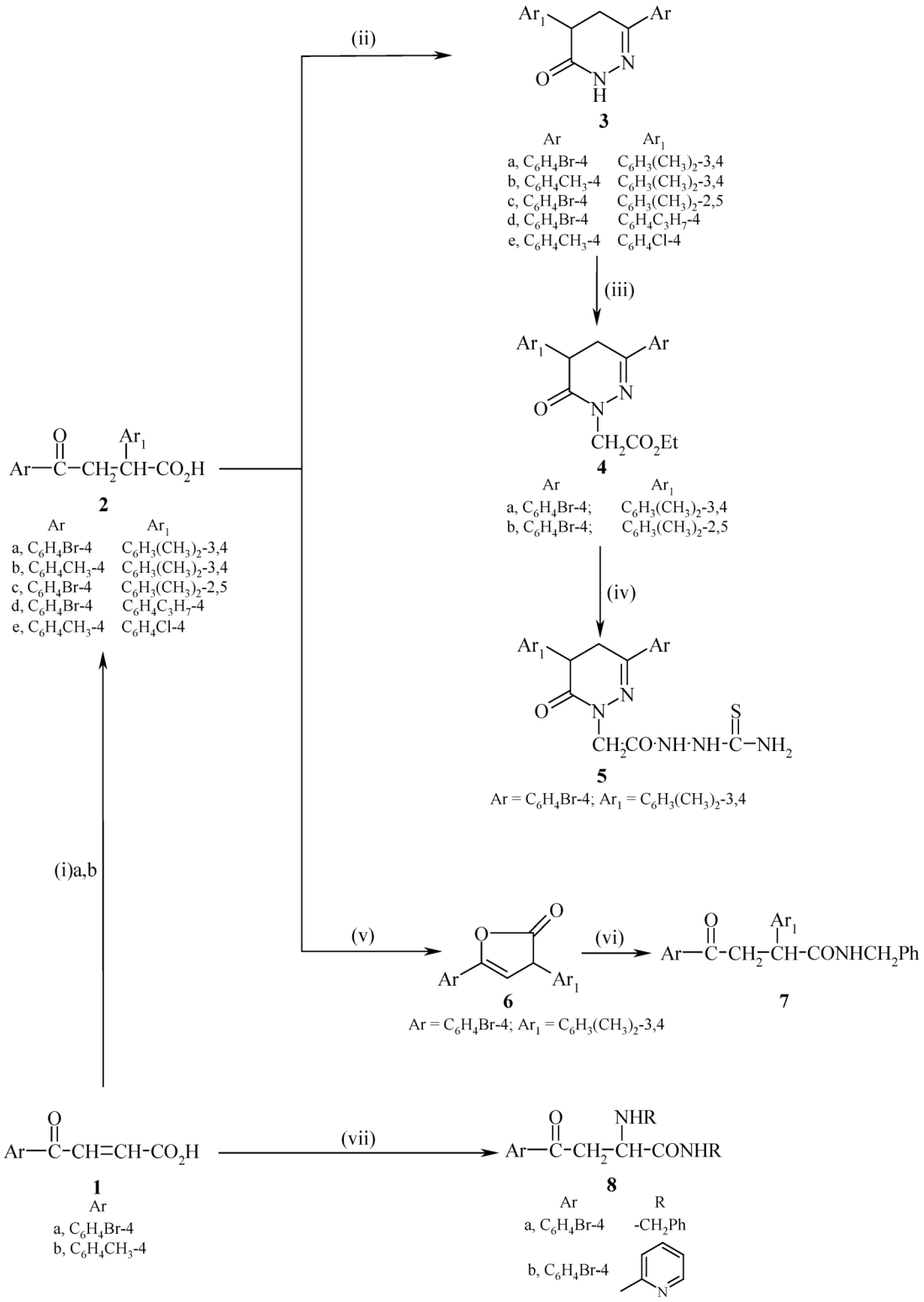
## RESULTS AND DISCUSSION

Taking into account all the aforementioned facts and to achieve facile synthetic routes of new 3(2*H*)-pyridazinones and 2(3*H*)-furanones, the author decided to carry out the present study aiming that the new 3(2*H*)-pyridazinones will be with no ulcerogenic side effects or with negligible general side effects as those of currently used $NSAID_S$. Herein, the author reports a convenient and versatile synthetic approach to novel 3(2*H*)-pyridazinones from readily obtainable simple compounds *viz* 3-aroylprop-2-enoic acids **1**.[17,18] The methodology adopted by the author consists of treatment of 3-aroylprop-2-enoic acids **1** by active aromatic hydrocarbons under Friedel-Crafts reaction conditions followed by reaction of the product with hydrazine hydrate. Thus, when acids **1** were allowed to react with *o*-xylene, *p*-xylene, cumene and/or chlorobenzene in the presence of anhydrous aluminium chloride, it afforded 3-aroyl-2-arylpropionic acids **2a-e** (cf. Scheme I).

The interesting pharmacological activity displayed by pyridazinones has been demonstrated in recent years. They have initially received special attention in the search of drugs acting on the cardiovascular system,[19] but more recent publications have dealt with the wide range of biological activities of this class of compounds.[20] Despite the usefulness of 3(2*H*)-pyridazinones, few methods for the introduction of a range of substituents into this six-member heterocyclic system to get good analgesic and anti-inflammatory activities have been presented.[21-25] For this reason, new advances in this area continue to be of interest and this

* Corresponding author. E-mail: jmmorsy@yahoo.com

**Scheme I**




prompted the author to synthesize 4,6-disubstituted-3(2*H*)-pyridazinones through interaction of acids **2** with hydrazine hydrate in the hope of obtaining new biologically active pyridazinones.

Thus, when acids **2** reacted with hydrazine hydrate in boiling ethanol and/or n-butanol, it gave 4,6-diaryl-2,3,4,5-tetrahydro-3(2*H*)-pyridazinones **3a-e** (cf. Scheme I).

It has been found that the heterocyclic ring substitutions at the six-position, and the presence of acetamide side chain that is linked to the lactam nitrogen of pyridazinone ring at the two-position, improved the analgesic and anti-inflammatory activities along with nil or very low ulcerogenicity.[26] Accordingly, in the present study, the author has synthesized the structurally-like amide derivative, i.e, 2-thiocarbamoylaminocarbamoylmethyl pyridazinone derivative (**5**) through the effect of thiosemicarbazide upon 2-ethoxycarbonylmethyl derivative (**4**) in pyridine heated to reflux temperature. Thus, when compounds **3a** and/or **3c** were allowed to react with ethyl chloroacetate in dry acetone heated to refluxing temperature in the presence of anhydrous potassium carbonate as a basic catalyst, it afforded 2-ethoxycarbonylmethyl-4,6-disubstituted-3(2*H*)-pyridazinones **4a** and **4b** respectively.

To the best of my knowledge, the reaction of 4,6-diaryl-3(2*H*)-pyridazinones with ethyl chloroacetate under the same conditions leads to access of a state of structure-conflict. In some studies,[27-28] it has been reported that the product is 3-ethoxycarbonylmethoxy pyradizinone derivative and that means that *O*-alkylation takes place on the carbonyl-oxygen atom. On the other hand, other publications reported that the product is 2-ethoxycarbonylmethyl pyridazinone derivative which refers to an *N*-alkylation product.[29]

In the present study, the infra-red spectra of **4a** and **4b** showed strong absorption bands at 1672 and 1683 $cm^{-1}$ ($\upsilon_{C=O}$ pyridazine) as well as 1738 and 1741 $cm^{-1}$ ($\upsilon_{C=O}$ ester). The $^1$H-NMR and IR spectra of **4a** and **4b** are devoid of any bands for the NH group. When compound **4a** was allowed to react with thiosemicarbazide in pyridine heated to refluxing temperature, it gave the target compound, 2-thiocarbamoylaminocarbamoylmethyl derivative (**5**) through a tetrahedral mechanism in which the C-N bond formation precedes the C-O bond breaking and consequently a lot of energy is accumulated in the reaction medium, and the system receives much of its energy payback from the formation of the newly formed C-N bond before having to return this energy amount for the C-O bond breaking.[30]

**Reagents and Reaction Conditions**

(i) a, an aromatic hydrocarbon solution of acid **1** (10 mmol/50 mL) is saturated with dry HCl at rt in the presence of anhydrous $AlCl_3$ (40 mmol).

b, heating a mixture of acid **1** (10 mmol), dry aromatic hydrocarbon (50 mL) and anhydrous $AlCl_3$ (40 mmol) on a water bath, 10 h.

(ii) 10 mmol of acid **2**, EtOH or $Bu^n$-OH (30 mL), $N_2H_4.H_2O$ (10 mL), reflux 3 h.

(iii) 10 mmol of **3**, dry acetone (100 mL), $ClCH_2CO_2Et$ (20 mmol), anhydrous $K_2CO_3$ (40 mmol), reflux 20 h.

(iv) equimolar mixture of **4** and $NH_2NHCSNH_2$ (10 mmol), pyridine (30 mL), reflux 5 h.

(v) acid **2** (10 mmol), $Ac_2O$ (10 mL), reflux 2 h.

(vi) compound **6** (10 mmol), $PhCH_2NH_2$ (10 mmol), EtOH (40 mL), reflux 4 h.

(vii) a mixture of acid **1** (10 mmol), appropriate amine (10 mmol), absolute EtOH (50 mL) is left at rt for 5 days or heated to reflux temperature 6 h in dry benzene (40 mL).

Oxygen containing heterocycles are frequent and important targets in synthetic organic chemistry due to their common occurrence in nature as well as that some 2(3*H*)-furanones exhibit appreciable photochemical properties.[31] Thus, the author intended to extend the present work through the reaction of 3-(4-bromobenzoyl)-2-(3,4-dimethylphenyl)propionic acid **2a** with freshly distilled acetic anhydride to yield 5-(4-bromophenyl)-3-(3,4-dimethylphenyl)-2(3*H*)-furanone **6** *via* an intramolecular cyclization process. The latter underwent hetero ring cleavage at C-2 on treatment with a nitrogen nucleophile, namely benzyl amine to afford 3-(4-bromobenzoyl)-2-(3,4-dimethylphenyl)-*N*-benzoylpropionamide **7**.

Recently,[32] it has been reported that 3-(4-bromobenzoyl)prop-2-enoic acid has antibacterial activity towards *Staphilococus aureus*, *Escherichia coli* and *Kllebsiella*. This activity was ascribed to the presence of the highly conjugated aroylacrylic system which may react with biologically essential –SH groups. Herein, the author sought the behaviour of this acid towards compounds containing the –NH groups which might react with the toxophoric system in the benzoylacrylic system C=C-C=O. Thus, when acid **1a** was allowed to react with aralkyl and heteroaromatic amines, namely benzyl amine and/or 2-aminopyridine, it gave 3-(4-bromobenzoyl)-2-benzylamino-N-benzylpropionamide and 3-(4-bromobenzoyl)-2-(2-pyridylamino)-N-(2-pyridyl)propionamide **8a** and **8b**, respectively (cf. Scheme I).

**EXPERIMENTAL**

All melting points are uncorrected and were deter-

mined on a Gallenkamp electric melting point apparatus. The IR spectra were recorded on a Shimadzu FTIR 8101 PC as KBr discs. The $^1$H-NMR and $^{13}$C-NMR spectra were measured on a Varian Gemini 200 MHz instrument in DMSO-$d_6$ as a solvent with chemical shifts (δ) expressed in ppm from downfield to upfield from TMS as internal standard. TLC was run using TLC aluminium sheets silica gel $F_{254}$ (Merck) to check the purity of all synthesized compounds. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000 Ex instrument operating at 70 eV.

**Reaction of 3-aroylprop-2-enoic acids 1a,b with active aromatic hydrocarbons-Formation of 2a-e**

**Method (A)**

A solution of acid **1a** and/or **1b** (10 mmol; 2.54 g and 1.90 g, respectively) in aromatic hydracarbon namely, *o*-xylene, *p*-xylene, cumene and/or chlorobenzene (50 mL) was saturated with dry HCl. Anhydrous $AlCl_3$ (40 mmol; 5.33 g) was then added portionwise with efficient stirring. A yellow paste was formed with vigorous evolution of HCl gas. The reaction mixture was stirred for an additional 15 h at room temperature and left overnight, treated with ice/HCl. The organic layer was washed with cold water and the excess solvent was removed by steam distillation. The organic material was extracted by ether and the ethereal solution was treated throroughly with $Na_2CO_3$ solution (10%). The alkaline solution was acidified by cold diluted HCl to afford the crude product which was recrystallized from a suitable solvent to yield the corresponding propionic acid derivatives **2a-e**.

**Method (B)**

To a solution of acid **1a** and/or **1b** (10 mmol; 2.54 g and 1.90, respectively) in aromatic hydrocarbons, namely *o*-xylene, *p*-xylene, cumene and/or chlorobenzene (50 mL), anhydrous $AlCl_3$ (40 mmol; 5.33 g) was added at room temperature then the reaction mixture was heated on a boiling water bath for 10 h followed by treatment as described in method (A).

**3-Aroyl-2-arylpropionic acids 2a-e**

**2a:** Yield: 72%; white crystals, mp 160-61°C (Toluene). IR (cm$^{-1}$): 1675 (CO aroyl ketone), 1697 (CO acid), 2919 and 2980 (CH aliph) and 3395 (OH).$^1$H-NMR, (DMSO-$d_6$) δ: 11.59 (s, 1H, COOH, exchangeable), 7.28-6.90 (m, 7H, ArH), 4.29 (dd, 1H, C<u>H</u>CH$_2$-), 3.21 (octet, 2H, CO<u>CH$_2$</u>-, diastereotropic non-equivalent methylene protons). MS *m/z* (%): 361 (M$^{\cdot+}$, 7.20), 316 (52.00), 184 (100.00), 156 (37.00), 76 (26.00), 45 (36.00). Anal. Calcd. for $C_{18}H_{17}BrO_3$ (%): C 59.83, H 4.71, Br 22.16; Found: C 59.55, H 4.37, Br 21.94. $^{13}$C-NMR (DMSO-$d_6$): δ = 18.81, 19.13, 40.74, 48.88, 126.60, 127.51, 129.82, 130.58, 131.43, 131.50, 132.34, 135.63, 135.73, 137.18, 177.34, 200.10.

**2b:** Yield: 67%; white crystals, mp 150-52 °C (Benzene), IR (cm$^{-1}$): 1678 (CO aroyl ketone), 1699 (CO acid), 2922 and 2984 (CH aliph) and 3405 (OH). $^1$H-NMR, (DMSO-$d_6$) δ: 11.58 (s, 1H, COOH, exchangeable), 7.27-6.85 (m, 7H, ArH), 4.24 (dd, 1H, C<u>H</u>CH$_2$-), 3.13 (octet, 2H, CO<u>CH$_2$</u>-, diastereotropic non-equivalent methylene protons), 2.17 (s, 6H, 2CH$_3$). MS *m/z* (%): 296 (M$^{\cdot+}$, 6.80), 251 (57.00), 119 (100.00), 91 (69.00), 65 (38.00), 45 (41.00). Anal. Calcd. for $C_{19}H_{20}O_3$ (%): C 77.03, H 6.76; Found: C 76.89, H 6.46. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.75, 19.06, 21.26, 40.68, 48.92, 126.63, 128.66, 128.94, 130.64, 131.48, 132.33, 133.72, 135.61, 137.24, 142.81, 177.29, 200.12.

**2c:** Yield: 71%; white crystals, mp 164-65 °C (Toluene). IR (cm$^{-1}$): 1681 (CO aroyl ketone), 1700 (CO acid), 2925 and 2987 (CH aliph) and 3412 (OH). $^1$H-NMR, (DMSO-$d_6$) δ: 11.55 (s, 1H, COOH, exchangeable), 7.20-6.95 (m, 7H, ArH), 4.30 (dd, 1H, C<u>H</u>CH$_2$-), 3.18 (octet, 2H, CO<u>CH$_2$</u>-, diastereotropic non-equivalent methylene protons), 2.12 (s, 6H, 2CH$_3$). Anal. Calcd. for $C_{18}H_{17}BrO_3$ (%): C 59.83, H 4.71, Br 22.16; Found: C 59.65, H 4.43, Br 21.83. $^{13}$C-NMR, (DMSO-$d_6$) δ = 19.14, 21.58, 41.04, 46.37, 127.48, 127.72, 129.77, 130.55, 131.46, 132.73, 133.68, 135.68, 135.76, 136.37, 177.33, 200.14.

**2d:** Yield: 53%; white crystals, mp 140-42 °C (Benzene). IR (cm$^{-1}$): 1683 (CO aroyl ketone), 1702 (CO acid), 2928 and 2990 (CH aliph) and 3418 (OH).$^1$H-NMR, (DMSO-$d_6$) δ: 11.49 (s, 1H, COOH, exchangeable), 7.26-7.10 (m, 8H, ArH), 4.32 (dd, 1H, C<u>H</u>CH$_2$-), 3.55 (s, 1H, methine proton of isopropyl group), 3.19 (octet, 2H, CO<u>CH$_2$</u>-, diastereotropic non-equivalent methylene protons). MS *m/z* (%): 375 (M$^{\cdot+}$, 4.90), 330 (49.00), 184 (100.00), 156 (31.00), 76 (29.00), 45 (43.00). Anal. Calcd. for $C_{19}H_{19}BrO_3$ (%): C 60.80, H 5.07, Br 21.33; Found: C 60.49, H 4.81, Br 21.19. $^{13}$C-NMR, (DMSO-$d_6$) δ = 23.25, 33.17, 40.73, 48.55, 126.46, 127.53, 129.42, 129.75, 131.46, 135.03, 135.67, 147.24, 177.26, 200.07.

**2e:** Yield: 68%; white crystals, mp 189-90 °C (Ethanol). IR (cm$^{-1}$): 1685 (CO aroyl ketone), 1705 (CO acid), 2930 and 2994 (CH aliph) and 3421 (OH). $^1$H-NMR, (DMSO-$d_6$) δ: 11.61 (s, 1H, COOH, exchangeable), 7.18-6.92 (m, 8H, ArH), 4.20 (dd, 1H, C<u>H</u>CH$_2$-), 3.50 (octet, 2H, CO<u>CH$_2$</u>-, diastereotropic non-equivalent methylene

protons), 2.36 (s, 3H, $CH_3$). MS *m/z* (%): 302.5 ($M^{\cdot+}$, 5.20), 257.5 (55.00), 119 (100.00), 91 (62.00), 65 (36.00), 45 (37.0). Anal. Calcd. for $C_{17}H_{15}ClO_3$ (%): C 67.44, H 4.96, Cl 11.74; Found: C 67.19, H 4.72, Cl 11.34. $^{13}$C-NMR, (DMSO-$d_6$) δ = 21.29, 40.67, 48.55, 128.66, 128.85, 129.16, 131.14, 133.13, 133.72, 135.86, 142.78, 177.29, 200.08.

**Reaction of 3-aroyl-2-arylpropionic acids 2a-e with hydrazine hydrate-Formation of 3a-e**

To a solution of acid **2a-e** (10 mmol) in absolute ethanol and/or dry n-butanol (30 mL), 100% hydrazine hydrate (10 mmol; 0.5 mL) was added, and the solution was heated under reflux for 3 h. The solid that separated out after concentrating and cooling the reaction solution, was filtered off by suction and recrystallized from a suitable solvent to give the pyridazinones **3a-e**.

**4,6-Disubstituted-3(2*H*)-pyridazinones 3a-e**

**3a:** Yield: 81%; pale yellow crystals, mp 129-30 °C (Ethanol). IR ($cm^{-1}$): 1658 (CO), 1616 (C=N), 3200 (NH). $^1$H-NMR, (DMSO-$d_6$) δ: 11.17 (s, 1H, NH, exchangeable), 7.22-6.92 (m, 7H, ArH), 3.99 (dd, methine C-4 proton of pyridazinone moiety), 3.07 (octet, 2H, CO$\underline{CH_2}$-, diastereotropic non-equivalent methylene protons of pyridazinone moiety), 2.15 (s, 6H, $2CH_3$). MS *m/z* (%): 357 ($M^{\cdot+}$, 2.10), 251 ($M^{\cdot+}$-$C_6H_3(CH_3)_2$-2,5), 201 ($M^{\cdot+}$-$C_6H_4$Br.4, 4.6), 95 ($M^{\cdot+}$-$C_6H_3(CH_3)_2$-2,5 + $C_6H_4$Br.4, 76.50), 76 ($C_6H_4^{\cdot+}$, 58.00), 50 (100.00). Anal. Calcd. for $C_{18}H_{17}BrN_2O$ (%): C 60.50, H 4.76, N 7.84, Br 22.41; Found: C 60.31, H 4.50, N 7.62, Br 22.22. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.76, 19.12, 33.86, 52.57, 125.41, 126.53, 128.56, 130.73, 131.38, 131.71, 133.24, 135.42, 135.65, 137.28, 146.53, 177.07.

**3b:** Yield: 59%; pale yellow crystals, mp 125-26 °C (Ethanol). IR ($cm^{-1}$): 1662 (CO), 1618 (C=N), 3235 (NH). $^1$H-NMR, (DMSO-$d_6$) δ: 11.16 (s, 1H, NH, exchangeable), 7.14-688 (m, 7H, ArH), 3.96 (dd, methine C-4 proton of pyridazinone moiety), 3.08 (octet, 2H, CO$\underline{CH_2}$-, diastereotropic non-equivalent methylene protons of pyridazinone moiety), 2.34 (s, 3H, $CH_3$), 2.15 (s, 6H, $2CH_3$). MS *m/z* (%): 292 ($M^{\cdot+}$, 4.60), 201 ($M^{\cdot+}$-$C_6H_4$.$CH_3$.4, 3.8), 187 (54.00), 186 ($M^{\cdot+}$-$C_6H_3(CH_3)_2$-3,4, 42.00), 92 (66.00), 91 (tropylium ion, 86.00), 65 ($C_5H_5^+$, 100.00). Anal. Calcd. for $C_{19}H_{20}N_2O$ (%): C 78.80, H 6.85, N 9.59; Found: C 77.91, H 6.60, N 9.28. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.77, 19.11, 21.27, 33.86, 52.55, 126.49, 127.03, 129.06, 130.71, 131.43, 133.17, 133.42, 135.66, 137.31, 140.72, 146.48, 177.02.

**3c:** Yield: 74%, pale yellow crystals, mp 180-82 °C (Ethanol). IR ($cm^{-1}$): 1670 (CO), 1617 (C=N), 3244 (NH). $^1$H-NMR (DMSO-$d_6$) δ: 11.15 (s, 1H, NH, exchangeable), 7.20-6.90 (m, 7H, ArH), 4.00 (dd, methine proton, C-4 proton of pyridazinone moiety), 3.10 (octet, 2H, $COCH_2$ diastereotropic non-equivalent methylene protons at C-5 of pyridazinone moiety), 2.10 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{18}H_{17}BrN_2O$ (%): C 60.50, H 4.76, N 7.84, Br 22.41; Found: C 60.28, H 4.39, N 7.65, Br 21.27. $^{13}$C-NMR, (DMSO-$d_6$) δ = 19.13, 21.57, 34.16, 50.12, 125.38, 127.77, 128.62, 130.73, 131.65, 132.64, 134.61, 135.43, 135.94, 136.26, 146.48, 177.03.

**3d:** Yield: 62%, pale yellow crystals, mp 170-71 °C (Dioxan). IR ($cm^{-1}$): 1674 (CO), 1619 (C=N), 3259 (NH). $^1$H-NMR (DMSO-$d_6$) δ: 11.14 (s, 1H, NH, exchangeable), 7.22-6.93 (m, 8H, ArH), 3.98 (dd, methine proton, C-4 proton of pyridazinone moiety), 3.60 (m, 1H, methine proton of isopropyl group), 3.11 (octet, 2H, $COCH_2$, diastereotropic non-equivalent methylene protons at C-5 of pyridazinone moiety), 1.41 (d, 6H, $2CH_3$ of isopropyl group). MS *m/z* (%): 371 ($M^{\cdot+}$, 2.5), 253 (M-$C_6H_4$.$C_3H_7$.4]$^+$, 7.5), 215 (M-$C_6H_4$Br.4, 2.5), 119 ($C_6H_4$.$C_3H_7$.4]$^+$, 6.8), 93 ($MC_6H_4$.$C_3H_7$.4+$C_6H_4$.Br.4]$^{\cdot+}$, 86.30), 77 ($C_6H5^{\cdot+}$, 15.60), 61 (100.00), 51 (10.00). Anal. Calcd. for $C_{19}H_{19}BrN_2O$ (%): C 61.46, H 5.12, N 7.55, Br 21.56; Found: C 61.61, H 5.45, N 7.69, Br 21.72. $^{13}$C-NMR, (DMSO-$d_6$) δ = 23.31, 33.15, 33.87, 52.26, 125.39, 126.61. 128.55, 129.26, 131.66, 133.52, 135.37, 146.58, 147.33, 177.10.

**3e:** Yield: 64%, pale yellow crystals, mp 204-06 °C (Ethanol). IR ($cm^{-1}$): 1679 (CO), 1621 (C=N), 3255 (NH). $^1$H-NMR (DMSO-$d_6$) δ: 11.16 (s, 1H, NH, exchangeable), 7.15-6.86 (m, 8H, ArH), 4.11 (dd, methine proton, C-4 proton of pyridazinone moiety), 3.14 (octet, 2H, $COCH_2$, diastereotropic non-equivalent methylene protons at C-5 of pyridazinone moiety), 2.39 (s, 3H, $CH_3$). MS *m/z* (%): 298.5 ($M^{\cdot+}$, 3.89), 207.5 ($M^{\cdot+}$-$C_6H_4$.$CH_3$.4,-2,9), 187 ($M^{\cdot+}$-$C_6H_4$Cl.4, 7.20), 111.5 ($C_6H_4Cl^{\cdot+}$, 8.4), 96 ($MC_6H_4$Cl.4 + $C_6H_4CH_3$.4, 3.5), 91 (tropylium ion, 84.00), 77 (23.00), 76 (18.50). Anal. Calcd. for $C_{17}H_{15}ClN_2O$ (%): C 68.34, H 5.03, N 9.38, Cl 11.89.41; Found: C 68.66, H 5.19, N 9.53, Cl 12.19. $^{13}$C-NMR, (DMSO-$d_6$) δ = 21.34, 33.92, 52.27, 127.04, 129.13, 129.34, 131.03, 133.22, 133.38, 134.42, 140.66, 146.48, 177.06.

**Reaction of 6-(4-bromophenyl)-4-(3,4- and/or 2,5-dimethylphenyl)-3(2*H*)-pyridazinone 3a and/or 3c with ethyl chloroacetate-Formation of 4a and 4b**

To a solution of **3a** and/or **3c** (10 mmol; 3.57 g), ethyl cloroacetate (10 mmol; 1.1 mL) in dry acetone (60 mL), an-

hydrous potassium carbonate (40 mmol; 5.52 g) was added, then the reaction mixture was heated to refluxing temperature on a boiling water bath for 24 h. Most of the solvent was distilled off and the residue was left to cool and then poured, with stirring, onto ice-cold water after being cold. The solid that separated out was collected by suction filtration, dried and recrystallized from light petroleum (80-100 °C) to afford **4a** and **4b**, respectively.

**6-(4-Bromophenyl)-4-(3,4- and/or 2,5-dimethylphenyl)-2-ethoxycarbonylmethyl-2,3,4,5-tetrahydropyridazin-3(2*H*)-one 4a and 4b**

**4a:** Yield: 66%; pale yellow crystals, mp 109-10 °C (Light petrol). IR ($cm^{-1}$): 1672 (CO pyridazinone) and 1738 (CO ester). The spectrum is devoid of any band for NH. $^1$H-NMR (DMSO-$d_6$) δ: 7.20-6.94 (m, 7H, ArH), 3.96 (dd, methine C-4 proton of pyridazinone moiety), 3.92 (s, 2H, $CH_2$COO-), 3.28 (q, 2H, $\underline{CH_2}CH_3$, $J$ = 6.98 Hz), 3.08 (octet, 2H, CO$\underline{CH_2}$-2$CH_3$), 1.25 (t, 3H, $CH_2\underline{CH_3}$, $J$ = 6.98 Hz). MS *m/z* (%): 443 ($M^{\cdot+}$, 3.70), 417 (6.20), 373 (29.00), 370 (100.00), 287 (23,30), 156 (18.60), 105 (9.80), 104 (11.40), 92 (28.20), 91 (71.00), 65 (34.00). Anal. Calcd. for $C_{22}H_{23}BrN_2O_3$ (%): C 59.59, H 5.19, N 6.32, Br 18.06; Found: C 59.88, H 5.41, N 6.64, Br 18.29. $^{13}$C-NMR, (DMSO-$d_6$) δ = 14.14, 18.76, 19.13, 34.24, 50.06, 61.03, 125.37, 126.52, 128.55, 130.68, 131.41, 131.73, 133.24, 135.38, 135.73, 137.28, 146.51, 169.52, 176.04.

**4b:** Yield: 69%; pale yellow crystals, mp 118-19 °C (Light petrol). IR ($cm^{-1}$): 1683 (CO pyridazinone) and 1741 (CO ester). The spectrum is devoid of any band for NH. $^1$H-NMR (DMSO-$d_6$) δ: 7.27-6.90 (m, 7H, ArH), 3.99 (dd, methine C-4 proton of pyridazinone moiety), 3.90 (s, 2H, $CH_2$COO-), 3.16 (q, 2H, $\underline{CH_2}CH_3$, $J$ = 7.10 Hz), 3.09 (octet, 2H, CO$\underline{CH_2}$-, diastereotropic non-equivalent methylene protons of pyridazinone moiety), 2.12 (s, 6H, 2$CH_3$), 1.29 (t, 3H, $CH_2\underline{CH_3}$, $J$ = 7.10 Hz). Anal. Calcd. for $C_{22}H_{23}BrN_2O_3$ (%): C 59.59, H 5.19, N 6.32, Br 18.06; Found: C 59.79, H 5.38, N 6.59, Br 18.31.

**Reaction of 6-(4-bromophenyl)-4-(3,4-dimethylphenyl)-2-ethoxycarbonylmethyl-2,3,4,5-tetrahydropyridazin-3(2*H*)-one 4a with thiosemicarbazide-Formation of 5**

A solution of **4a** (10 mmol; 4.42 g) in pyridine (30 mL) thiosemicarbazide (10 mmol; 0.91 g) was added and the mixture was heated under reflux for 5 h. The reaction solution was concentrated, left to cool, poured onto ice/HCl with stirring. The solid that deposited was collected by suction filtration, washed thoroughly with cold water, dried and recrystallized from ethanol to give **5**.

**6-(4-Bromophenyl)-4-(3,4-dimethylphenyl)-2-thiocarbamoylaminocarbamoylmethyl-2,3,4,5-tetrahydropyridazin-3(2*H*)-one 5**

Yield: 55%; yellow crystals, mp 178-79 °C (Ethanol). IR ($cm^{-1}$): 3409, 3306, 3205 (NH) 1674 (CO pyridazinone), 1665 (CO). $^1$H-NMR (DMSO-$d_6$): δ: 7.21-6.90 (m, 7H, ArH), 6.48 (s, 2H, 2NH, exchangeable), 5.00 (s, 2H, $NH_2$, exchangeable), 4.68 (s, 2H, $CH_2$CO), 3.98 (dd, methine C-4 proton of pyridazinone moiety), 3.15 (octet, 2H, CO$\underline{CH_2}$-, diastereotropic non-equivalent methylene protons of pyridazinone moiety), 2.18 (s, 6H, 2$CH_3$), MS *m/z* (%): 488 ($M^{\cdot+}$, 5.00), 398 (17.50), 370 (100.00), 156 (14.50), 105 (12.20), 104 (16.50), 91 (88.00), 65 (53.00). Anal. Calcd. for $C_{21}H_{22}BrN_2O_5S$ (%): C 51.64, H 4.51, N 14.34, Br 16.39, S 6.56; Found: C 51.36, H 4 .36, N 14.20, Br 16.18, S 6.41. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.76, 19.13, 34.16, 50.13, 55.44, 125.37, 126.52, 128.63, 130.71, 131.42, 131.65, 133.23, 135.42, 135.68, 137.27, 146.54, 170.27, 176.04, 182.53.

**Reaction of 3-(4-bromobenzoyl)-2-(3,4-dimethylphenyl)propionic acid 2a with acetic anhydride-Formation of 6**

Propionic acid derivative **2a** (10 mmol; 3.61 g) was added to freshly distilled acetic anhydride (10 mL) and the reaction mixture was heated under reflux on a boiling water bath for 1 h and then left to cool. The solid that deposited down was filtered off, washed with cold ethanol and recrystallized from n-butanol to give **6**.

**5-(4-Bromophenyl)-3-(3,4-dimethylphenyl)-2(3*H*)-furanone 6**

Yield: 60%; pale yellow crystals, mp 260-62 °C (Butanol). IR ($cm^{-1}$): exhibits a strong absorption band at 1789 attributable to lactonic CO. $^1$H-NMR (DMSO-$d_6$): δ: 7.60-7.40 (m, 7H, ArH), 6.00 (s, 1H, olefinic), 3.15 (s, 1H, methine proton), 2.10 (s, 6H, 2$CH_3$). MS *m/z* (%): 284 ($M^{\cdot+}$[$CO_2$+$CH_3$], 15.40), 224 (68.00), 223 (100.00), 144 (75.00), 92 (11.00), 91 (12.00), 89 (74.00). Anal. Calcd. for $C_{18}H_{15}BrO_2$ (%): C 62.97, H 4.37, Br 23.32; Found: C 63.23, H 4.61, Br 23.69. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.76, 19.13, 50.02, 95.04, 122.31, 126.55, 128.62, 129.33, 130.57, 131.46, 135.57, 136.39, 137.22, 147.23, 169.04.

**Reaction of 5-(4-bromophenyl)-2-(3,4-dimethylphenyl)-2(3*H*)-furanone 6 with benzylamine-Formation of 7**

Equimolar amounts of **6** (10 mmol; 3.43 g) and benzylamine (10 mmol; 1.1 mL) are added to ethanol (50 mL)

and the reaction mixture was heated under reflux for 4 h, concentrated and left to cool at room temperature. The solid that separated out was filtered off and recrystallized from ethanol to yield **7**.

**3-(4-Bromobenzoyl)-2-(3,4-dimethylphenyl)-*N*-benzyl-propionamide 7**

Yield: 52%; pale yellow crystals, mp 190-91 °C (Ethanol). IR ($cm^{-1}$): 3400 (NH), 1622 (CONH), 1693 (CO ketone). $^1$H-NMR (DMSO-$d_6$): δ: 7.57-7.36 (m, 12H, ArH), 6.36 (s, 1H, NH, exchangeable), 4.53 (dd, methine proton, C-4 proton of pyridazinone moiety), 4.53 (s, 2H, $\underline{CH_2}$Ph), 3.22 (octet, 2H, CO$\underline{CH_2}$-, diastereotropic non-equivalent methylene protons of pyridazinone), 2.14 (s, 6H, $2CH_3$). MS *m/z* (%): 343 ($M.^+$-$C_6H_5CH_2NH_2$, 29.00), 184 ($Br.C_6H_4.CO]^+$, 100.00), 156 (46.00), 134 (59.00), 107 (61.00), 91 (92.00), 65 (74.00), 50 (69.00). Anal. Calcd. for $C_{25}H_{24}BrNO_2$ (%): C 66.67, H 5.33, N 3.11, Br 17.78; Found: C 66.39, H 5.12, N 3.33, Br 17.38. $^{13}$C-NMR, (DMSO-$d_6$) δ = 18.75, 19.13, 40.76, 41.63, 43.86. 126.46, 126.66, 126.85, 127.51, 128.49, 129.78, 130.72, 131.36, 131.54, 133.23, 135.68, 137.34, 137.92, 171.39, 200.14.

**Reaction of 3-(4-bromobenzoyl)prop-2-enoic acid 1a with benzylamine and/or 2-aminopyridine-Formation of 8a and 8b**

**Method (A)**

An equimolar mixture of acid **1a** (10 mmol; 2.54 g) and benzylamine (10 mmol; 1.1 mL) and/or 2-aminopyridine (10 mmol; 0.94 g) was kept at room temperature for 5 days with occasional shaking. The reaction mixture was filtered off, washed with light petrol and recrystallized from ethanol to afford **8a** and/or **8b**, respectively.

**Method (B)**

7.80-7.30 (m, 14H, ArH), an equimolar mixture of acid **1a** (10 mmol; 2.54 g) and benzylamine (10 mmol; 1.1 mL) and/or 2-aminopyridine (10 mmol ; 0.94 g) was heated under reflux in dry benzene (40 mL) for 6 h. The reaction solution was concentrated, left to cool, and the solid that deposited was filtered off and recrystallized from ethanol to yield **8a** and/or **8b**, respectively.

**3-(4-Bromobenzoyl)-2-benzylamino-*N*-benzylpropion-amide 8a and 3-(4-bromobenzoyl)-2-(2-pyridylamino)-*N*-(2-pyridyl)propionamide 8b**

**8a:** Yield: 85%, pale yellow crystals, mp 162-63 °C (Ethanol). IR ($cm^{-1}$): 1677 (CO ketonic), 1650 (CO carboxamide). $^1$H-NMR (DMSO-$d_6$) δ: 7.80-7.30 (m, 14H, ArH), 6.40 (s, 2H, 2NH, exchangeable), 4.60 (dd, methine proton, C-4 proton of pyridazinone moiety), 4.00 (s, 4H, 2 $CH_2$Ph), 3.20 (octet, 2H, $COCH_2$ diastereotropic non-equivalent methylene protons at C-5 of pyridazinone). MS *m/z* (%): 299 (M-[benzylamine+isocyanic acid+$H_2$], 16.20), 184 ($BrC_6H_4CO]^+$, 100.00), 156 ($C_6H_4Br]^+$, 49.00), 107 (benzylamine]$^+$, 87.00), 91 (tropyliumion, 29.00), 76 ($C_6H_4]^+$, 81.00), 65 ($C_5H_5]^+$, 31.00), 50 (79.00). Anal. Calcd. for $C_{24}H_{23}BrN_2O_2$ (%): C 63.86, H 5.10, N 6.21, Br 17.74; Found: C 63.65, H 4.87, N 6.52, Br 17.56. $^{13}$C-NMR, (DMSO-$d_6$) δ = 43.55, 46.57, 50.85, 56.13, 126.65, 126.94, 127.03, 127.46, 127.88, 128.52, 129.75, 131.47, 135.71, 137.86, 140.23, 172.04, 197.37.

**8b:** Yield: 75%, pale yellow crystals, mp 183-84 °C (Ethanol). IR ($cm^{-1}$): 1682 (CO ketonic), 1656 (CO carboxamide). $^1$H-NMR (DMSO-$d_6$) δ: 8.55-7.72 (m, 12H, ArH), 6.46 (s, 1H, NH, exchangeable), 6.28 (s, 1H, NH, exchangeable), 4.62 (dd, methine proton, C-4 proton of pyridazinone moiety), 3.24 (octet, 2H, $COCH_2$ diastereotropic non-equivalent methylene protons at C-5 of pyridazinone). MS *m/z* (%): 286 (M-[2-aminopyridine + isocyanicacid + $H_2$], 12.00), 184 ($BrC_6H_4CO]^+$, 100.00), 156 ($C_6H_4Br]^+$, 45.0) 94 (2-aminopyridine].$^+$, 82.00), 93 (diazatropyliumion, 20.00), 76 ($C_6H_4]^+$, 85.00), 50 (80.00). Anal. Calcd. for $C_{20}H_{17}BrN_4O_2$ (%): C 56.47, H 4.00, N 13.18, Br 18.82; Found: C 56.22, H 3.92, N 12.96, Br 18.74. $^{13}$C-NMR, (DMSO-$d_6$) δ = 46.24, 58.15, 106.48, 115.76, 117.86, 124.35, 127.53, 129.75, 131.46, 135.67, 138.26, 138.65, 146.72, 148.13, 151.77, 154.18, 172.65, 197.27.

## CONCLUSION

The present research aims to synthesize some new 3(2*H*)-pyridazinones of anticipated biological activity as non-steroidal anti-infalmmatory and analgesic drugs [NSAIDs] devoid of the undesired side effects which are inherent to traditional NSAIDs like aspirin and ibuprofen.

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