Cyclic Carboxylic Anhydrides as New Reagents for Formation of Chromone Ring

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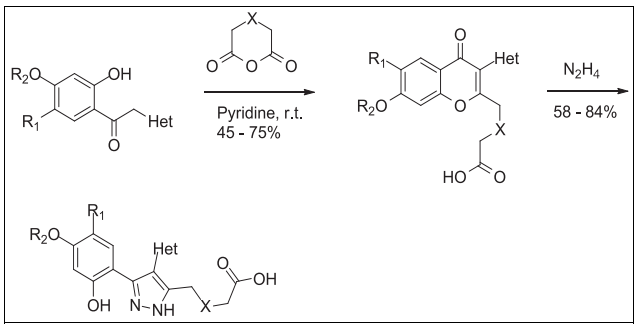

The propensity of cyclic carboxylic anhydrides to undergo ring-opening was exploited in a reaction with 2'-hydroxy-α-heteroarylacetophenones leading to the formation of chromones. New simple method was developed for the synthesis of 2-(ω-carboxyalkyl)-3-heteroarylchromones without protecting either the phenolic or the carboxylic groups. Treatment with hydrazine led to the formation of 3(5)-(ω-carboxyalkyl)-5(3)-(2,4-dihydroxyphenyl)-4-heteroarylpyrazoles.

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INTRODUCTION

The 4*H*-[1]-benzopyran-4-one (chromone) system is a part of the heterocyclic skeleton of widely distributed natural compounds. The best known are the flavones and isoflavones, which contain aryl substituents in position 2 or 3, respectively [1]. Several minor groups of natural compounds with chromone ring are represented by polyketides, chromone alkaloids, and antibiotics [2], which also contain nitrogen atoms in their structures. Typically, these compounds possess saturated (un)fused piperidine or pyrrolidine rings at position 6 or 8 of chromone ring. Also, imidazole [3], pyrrole [4], isoquinoline [5], and benzoxazole [6] moieties are found in the molecules of chromone alkaloids. Moreover, synthesis of mimics of these compounds is widely used for making different modifications in the flavonoids. Various nitrogen-containing flavonoid derivatives were synthesized using alkaloid rohitukine as a starting model. Some of them have shown potential activity against cyclin-dependent kinases [7], including cyclin-dependent kinase inhibitor *Flavopiridol*, which is under clinical development [8].

Replacement of carbon and/or oxygen atoms in natural flavonoids with nitrogen atoms usually leads to the retention of biological activity and sometimes the appearance of new biological properties. Thus, 3-arylquinazolinones (**1**, X = Y = N) as well as the initial genistein structure (**1**, X = O, Y = C) possess estrogenic properties [9], and 3-(5-tetrazolyl) chromones show high antihistamine activity, which is atypical for flavonoids [10] (see Fig. 1). Additionally, the introduction of an azaheterocycle into flavonoids increases their conjugation with DNA through stacking interactions and formation of hydrogen bonds. In this article, we report the chemical modification of chromone skeletons necessary to secure new heterocycles for biological evaluation.

RESULTS AND DISCUSSION

One of the important pathways for obtaining isoflavones and 3-hetarylchromones involves derivatives substituted in position 2 of the chromone ring. In most cases, this method includes cyclization of 2'-hydroxy-2-(hetero)arylacetophenones with formic, acetic, and oxalic acids derivatives. High molecular weight carboxylic acid derivatives have limited applicability in this method. Some synthetic procedures were reported previously for the synthesis of isoflavones **2**, carrying carboxyalkyl attachment in position 2 of chromone ring. These compounds were developed for immunoassay techniques for the epidemiological screening of the isoflavonoid plant phytoestrogens such as daidzein and genistein [11,12] and were utilized as haptens for coupling with proteins in the development and validation of immunological tests [13]. Thus, 2-(ω-carboxyalkyl)isoflavones **2** were obtained in multistep reactions of particularly O-methylated deoxybenzoins with

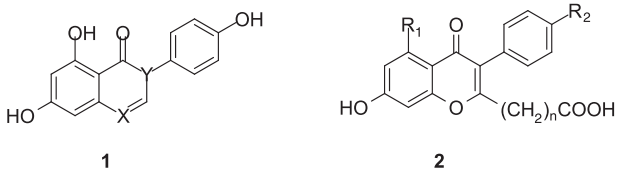


Figure 1. General structures of (aza)isoflavonoid estrogens.

ethoxycarbonyl alkyl carbonyl chlorides followed by the intramolecular formation of chromone ring and subsequent deprotection of phenolic and carboxylic groups [11]. A further improvement of this method was the use of acetone as a solvent for the one-pot exhaustive acylation and cyclization of (un)protected deoxybenzoins into chromone ring with subsequent deblocking of carboxylic group [12,13]. An alternative method for the 2-carboxymethyl isoflavones synthesis was developed starting from 2-bromomethyl isoflavones [14].

In many cases, replacement of 3-aryl with 3-heteroaryl substituent in isoflavones requires a different synthetic approach for obtaining the target 3-heteroarylchromones. The nature of heterocyclic substituent in position 3 of chromone ring places some limitations on the use of standard methods for the synthesis of isoflavones, whereas other procedures are applicable only for synthesis of 3-heteroarylchromones. Although ethyl oxalyl chloride reacts normally with 2,4-dihydroxy-α-heteroarylacetophenones in pyridine [15], the use of ethoxycarbonylalkylcarbonyl chlorides was not previously reported. From this point of view, the development of facile method for the synthesis of 2-carboxyalkyl-3-heteroarylchromones is of current importance for biological screening and is the subject of this report.

Science α-heteroaryl-2',4'-dihydroxyacetophenones **3a–g** contain an activated methylene group, we hoped to develop a one-step synthesis of 2-(ω-carboxyalkyl)-3-azaheteroaryl isoflavones **4–6** using anhydrides of aliphatic α,ω-dicarboxylic acids.

The starting α-heteroaryl-2,4-dihydroxyacetophenone derivatives **4a–g** were obtained by Hoesh reaction of (un) substituted resorcinol with 2-azaheteroaryl acetonitriles such as 2-cyanomethylbenzimidazole, its 1-methyl derivative, 2-benzothiazoleacetonitrile, and 4-methylthiazoleacetonitrile [16].

The optimal conditions for obtaining acids **4–6** is to treat the compounds **3a–g** for extended period with large excess of commercially available succinic or glutaric anhydride in pyridine at room temperature. This method does not require the protection of phenolic and carboxylic groups or the activation of carboxylic group as their acid chlorides. The reaction was quenched with water to afford the ω-(3-heteroaryl-7-hydroxy-4-oxochromen-2-yl)propionic acids **4a–g** or the ω-(3-heteroaryl-7-hydroxy-4-oxochromen-2-yl) butyric acids **4c–g**. The reaction was also effected using diglycolic anhydride, leading to {(3-heteroaryl-7-hydroxy-4-oxochromen-2-yl)methoxy}acetic acids **6d–g**. The acylation of the 4-hydroxy group of ketones **3a–g** and/or the 7-hydroxy group of chromone ring does not occur under these conditions.

The presence of the carboxylic group and azaheterocyclic moiety in compounds **4–6** discourages the acylation of the phenol hydroxylic group during on treatment with acyl chlorides in pyridine. To synthesize 7-O-acyl derivatives **4h**, **5h**, and **6h**, we used 4-O-pivaloyl derivative of ketone **3h**, which was obtained by acylation of **3d** with an equivalent quantity of pivaloyl chloride in pyridine. It was interesting that the compound **3h** in DMSO-d_6 exists as one isomer in contrast to compounds **3a–g**, which exist as keto-enolic tautomers. We studied the NOE spectra of compound **3h** in various solvents for confirm its structure. In $CDCl_3$ solution, we observed only 5–7% of ketone form. The observed NOE established that the conformation of **3h** is predominantly enolic. Although the existence of the enaminoketone form was not contradicted by NOE. When a mixture of DMSO-d_6 and C_6D_6 was used as solvent, NOE spectra confirmed the enaminoketone form because of the presence of NH interaction with neighboring H-4 proton of benzimidazole ring (Fig. 2).

Isoflavone derivatives are useful intermediates for the synthesis of various 2-hydroxyphenyl substituted pyrazoles [15,17], pyrimidines [15,18,19], pyrazolo[1,5-*a*]pyrimidines [20], and isoxazoles [15,21], which can be obtained by

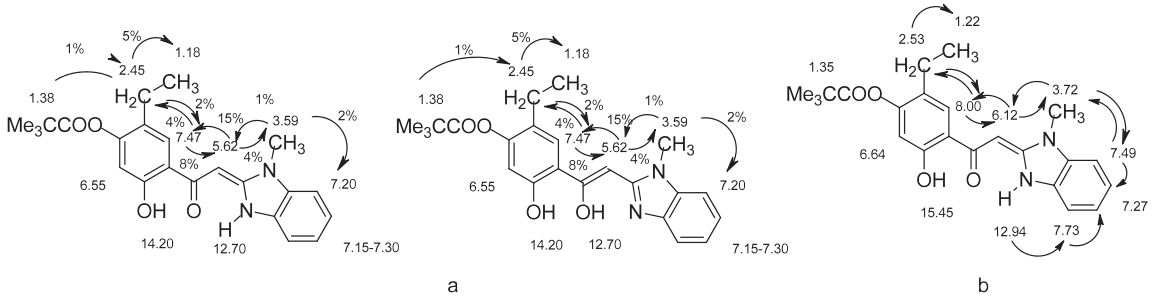


Figure 2. Observed NOE interactions in tautomers (compound **3h**) in $CDCl_3$ solution (**a**) and in DMSO-d_6/C_6D_6 mixture (**b**).

cleavage of chromone ring with binucleophiles. These compounds are interesting targets because of their biological activity. For example, 4-aryl and 4-heteroaryl derivatives of pyrazole and isoxazole possess heat shock protein 90 (Hsp90) inhibitor activity [17].

We studied the reaction of acids **4–6** with hydrazine to obtain pyrazole derivatives with a carboxyalkyl substituent. Heating these compounds with hydrazine hydrate in ethanol led to the formation of 3(5)-(ω-carboxyalkyl)-4-heteroaryl-5(3)-(2,4-dihydroxyphenyl)pyrazoles **7a,c,d** and **8c,d,h** and 3(5)-carboxymethoxymethyl-4-heteroaryl-5(3)-(2,4-dihydroxyphenyl)pyrazole derivatives **9g,h** (Scheme 1). Structures were confirmed by ^{13}C and ^{1}H NMR spectroscopy. In contrast to ^{1}H NMR spectra of pyrazoles **7–9**, assignment of ^{13}C NMR peaks was complicated by the presence of both tautomeric forms, which leads to broadening of carbon atom peaks, nearest to pyrazole nitrogen atoms. All assignments were carried out using HMQC, HMBC, and NOESY methods.

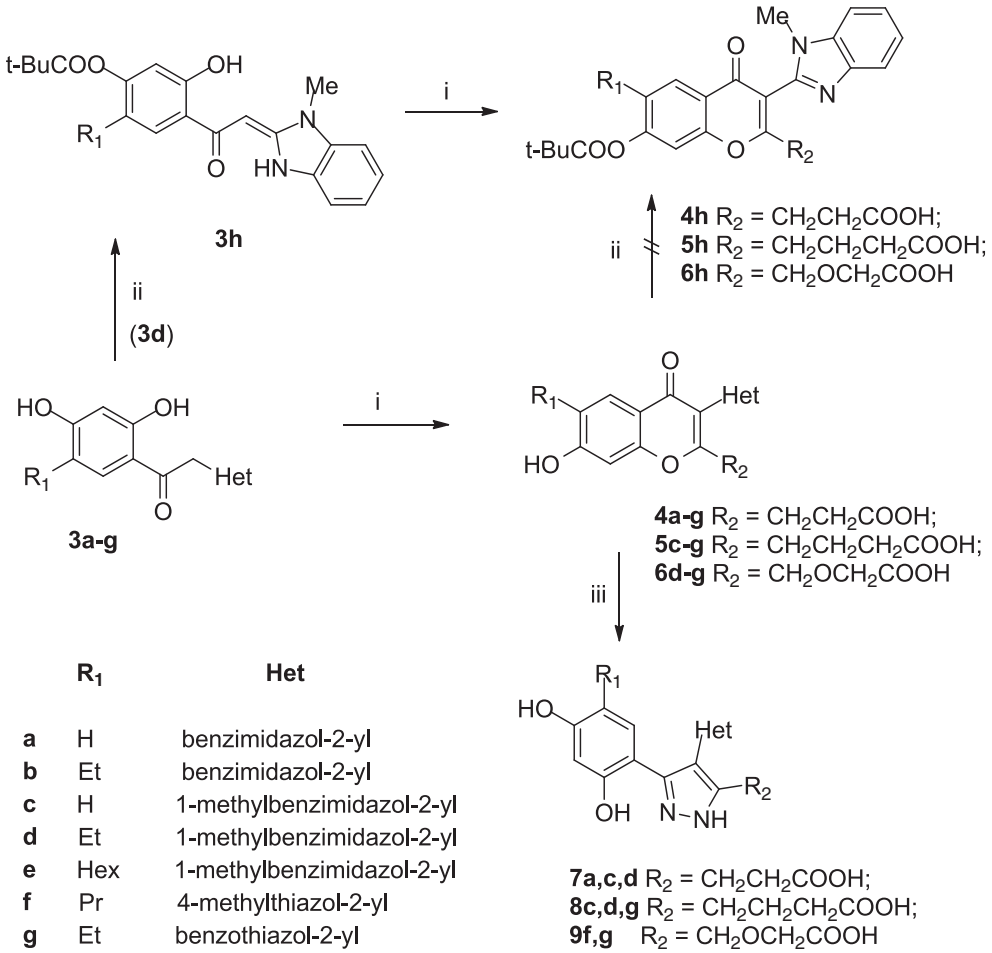
CONCLUSION

In addition to well-known reagents for the formation chromone ring (Vilsmeier–Haack reagent, acetic and trifluoroacetic anhydrides, ethyl oxalyl chloride, etc.), we developed a method that utilizes commercially available anhydrides of aliphatic α,ω-dicarboxylic acids. We demonstrated that 2-carboxyalkyl-3-hetaryl chromones were synthesized by this procedure without any protection of phenolic and carboxylic groups. In addition, the interaction of these compounds with hydrazine leads to the formation of carboxyalkyl substituted 4-hetaryl-3(5)-(2,4-dihydroxyphenyl)pyrazoles.

EXPERIMENTAL

NMR spectra were recorded on a Varian VXR 300 (300 MHz) or a Varian Mercury 400 (400 MHz) spectrometers (Varian Inc., Palo Alto, CA). TMS (^{1}H, δ = 0.00) was used as an internal standard, and chemical shifts are given in δ (ppm) and *J* values in

Scheme 1. Reagents and conditions: (1) α,ω-dicarboxylic acid anhydride (5–6 equiv), anhydrous pyridine, 25°C, 72 h, then H_2O; (2) pivaloyl choride (1.2 equiv), pyridine, 25°C, 24 h, then H_2O, 0°C, 5 h; (3) N_2H_4, ethanol, reflux, 4 h.



	R_1	Het
a	H	benzimidazol-2-yl
b	Et	benzimidazol-2-yl
c	H	1-methylbenzimidazol-2-yl
d	Et	1-methylbenzimidazol-2-yl
e	Hex	1-methylbenzimidazol-2-yl
f	Pr	4-methylthiazol-2-yl
g	Et	benzothiazol-2-yl

hertz. ^{13}C NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer using mixture 1:1 of DMSO-d_6 and CCl_4 as solvent. Solvent DMSO-d_6 (^{13}C, δ = 39.5) was used as an internal reference. IR spectra were recorded on a Nicolet Nexus 470 ESP FT/IR spectrometer (Thermo Nicolet, Madison, WI). Melting points were determined in open capillarity tubes with an Buchi B-535 apparatus and uncorrected (Agilent Technologies, Santa Clara, CA). Mass spectra were obtained with a Agillent 1100 using chemical ionization (Merck KGaA, Darmstadt, Germany). TLC was conducted on Merck silica gel 60F_{254} plates (Lachema, Brno, Czech Republic). All compounds were homogenous on TLC. Pyridine was redistilled from CaH_2.

2-Ethyl-5-hydroxy-4-[2-(1-methyl-1,3-dihydro-2*H*-benzimidazol-2-ylidene)acetyl]phenyl pivalate (3h). Pivaloyl chloride (2.71 mL, 22 mmol) was added dropwise to a stirred solution of 6.2 g (20 mmol) compound **3d** in 25 mL of dry pyridine at 0°C and stirred at room temperature for 24 h. The reaction mixture was poured into 500 mL of cool water, and the formed precipitate was filtered off, washed with cold water to give crude product, which was crystallized from methanol to give compound **3h** (5.9 g, 75%) as yellow-green solid, mp 196–198°C; IR (KBr): 2969, 1742, 1566, 1536, 1479, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$-2'), 1.38 (s, 9H, (C*H*$_3$)$_3$CCOO) 2.48 (q, 2H, J = 7.6 Hz, CH$_3$C*H*$_2$-2'), 3.61 (s, 3H, NC*H*$_3$), 5.69 (s, 1H, C*H*C = O) 6.56 (s, 1H, *H*-6'), 7.16–7.34 (m, 4H, *benzimidazole ring*), 7.47 (s, 1H, *H*-3'), 12.79 (s, 1H, O*H*-5'), 14.20 (s, 1H, NH); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 15.0, 22.5, 26.7, 29.1, 38.6, 71.5, 108.6, 110.5, 111.8, 118.5, 122.1, 122.4, 124.5, 127.8, 130.3, 131.7, 151.3, 152.2, 160.9, 175.4, 182.9; MS (CI) *m/z* (%): 395.3 (100, MH$^+$). *Anal*. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.30; H, 6.42; N, 7.18.

General procedure for synthesis of chromones 4–6. Acid anhydride (10 mmol for succinic or 12 mmol for glutaric and diglycolic) was added to a stirred solution of substituted ketone **3a–h** (2 mmol) in 10 mL of dry pyridine at room temperature. After standing for 72 h at room temperature, the reaction mixture was poured out into 100 mL of cool water, and the formed precipitate was filtered off, washed with cold water, and crystallized from methanol.

3-[3-(1H-Benzimidazol-2-yl)-7-hydroxy-4-oxo-4H-chromen-2-yl]propanoic acid (4a). This compound was obtained as colorless solid (336 mg, 48% yield); mp 271–272°C; IR (KBr): 3060, 2913, 1657, 1630, 1556, 1460 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.79 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 3.45 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 6.92 (d, 1H, *J* = 2.3 Hz, *H*-8'), 7.00 (dd, 1H, *J* = 2.3, 8.8 Hz, *H*-6'), 7.21 (m, 2H, *H*-5'' and *H*-6''), 7.64 (m, 2H, *H*-4'' and *H*-7''), 8.01(d, 1H, *J* = 8.8 Hz, *H*-5'), 11.02 (s, 1H, O*H*-7'), 12.63 (s, 2H, COO*H* and N*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 28.8, 30.8, 101.9, 112.0, 115.1, 115.4, 121.5, 126.9, 145.7, 156.7, 163.1, 169.1, 173.0, 174.7; MS (CI) *m/z* (%): 351.2 (100, MH$^+$). *Anal*. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.24; H, 4.18; N, 8.22.

3-[3-(1H-Benzimidazol-2-yl)-6-ethyl-7-hydroxy-4-oxo-4H-chromen-2-yl]propanoic acid (4b). This compound was obtained as colorless solid (431 mg, 57% yield); mp 273–274°C; IR (KBr): 3556, 2963, 1644, 1626, 1560, 1418, 1305 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.18 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$-6'), 2.63 (q, 2H, *J* = 7.6 Hz, C*H*$_2$-6'), 2.76 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 3.45 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 6.93 (s, 1H, *H*-8'), 7.22 (m, 2H, *H*-5'' and *H*-6''), 7.65 (m, 2H, *H*-4'' and *H*-7''), 7.85 (s, 1H, *H*-5'), 11.10 (s, 1H, O*H*-7'), 12.50 (s, 2H, COO*H* and N*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.7, 22.5, 28.7, 30.8, 101.2, 111.8, 114.7, 121.4, 124.6, 130.4, 145.9, 155.0, 161.1, 168.7, 172.9, 174.7; MS (CI) *m/z* (%): 379.1 (100, MH$^+$). *Anal*. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.45; H, 4.98; N, 7.13.

3-[7-Hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]propanoic acid (4c). This compound was obtained as colorless solid (539 mg, 74% yield); mp 278–280°C; IR (KBr): 3067, 2929, 1643, 1639, 1457, 1394 cm^{-1}; ^{1}H NMR (300 MHz): δ 2.68 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 2.85 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 3.63 (s, 3H, NC*H*$_3$), 6.94 (d, 1H, *J* = 2.3 Hz, *H*-8'), 6.98 (dd, 1H, *J* = 2.3, 8.8 Hz, *H*-6'), 7.25 (1H, m, *H*-5''), 7.31 (1H, m, *H*-6''), 7.62 (1H, m, *H*-7''), 7.68 (1H, m, *H*-4''), 7.94 (d, 1H, *J* = 8.8 Hz, *H*-5'), 10.96 (s, 1H, O*H*-7'), 12.25 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): 27.8, 30.3, 30.4, 102.1, 109.9, 113.2, 115.0, 115.3, 118.9, 121.4, 122.1, 126.8, 135.5, 142.2, 147.1, 157.2, 163.1, 168.5, 172.6, 173.9; MS (CI) *m/z* (%) = 365.1 (100, MH$^+$). *Anal*. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.88; H, 4.27; N, 7.43.

3-[6-Ethyl-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]propanoic acid (4d). This compound was obtained as colorless solid (377 mg, 48% yield); mp >300°C; IR (KBr): 3067, 2928, 1642, 1470 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.19 (t, 3H, *J* = 7.6Hz, C*H*$_3$CH$_2$-6'), 2.63 (q, 2H, *J* = 7.6 Hz, C*H*$_2$-6'), 2.67 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 2.85 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 3.63 (s, 3H, NC*H*$_3$), 6.95 (s, 1H, *H*-8'), 7.23 (1H, m, *H*-5''), 7.30 (1H, m, *H*-6''), 7.59 (1H, m, *H*-7''), 7.66 (1H, m, *H*-4''), 7.80 (s, 1H, *H*-5'), 11.03 (s, 1H, O*H*-7'), 12.56 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.8, 22.4, 27.9, 30.3, 30.5, 101.6, 110.3, 113.3, 114.7, 119.0, 121.6, 122.3, 124.7, 130.6, 135.7, 142.5, 147.6, 155.6, 161.2, 168.6, 173.0, 174.2; MS (CI) *m/z* (%): 393.1 (100, MH$^+$). *Anal*. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.56; H, 5.32; N, 7.38.

3-[6-Hexyl-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]propanoic acid (4e). This compound was obtained as colorless solid (673 mg, 75% yield); mp 150–152°C; IR (KBr): 3060, 2928, 1737, 1631, 1583, 1470 cm^{-1}; ^{1}H NMR (400 MHz): δ 0.86, 1.32, 1.58, 2.63, (4 m, 3H, 6H, 2H, 4H, *Hex*-6' and C*H*$_2$COOH), 2.85 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 3.62 (s, 3H, NC*H*$_3$), 6.94 (s, 1H, *H*-8'), 7.21 (1H, m, *H*-5''), 7.27 (1H, m, *H*-6''), 7.52 (1H, m, *H*-7''), 7.63 (1H, m, *H*-4''), 7.75 (s, 1H, *H*-5'), 10.94 (s, 1H, O*H*-7'), 12.03 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): 13.9, 22.1, 27.8, 28.6, 29.0, 29.3, 30.2, 30.5, 31.2, 101.4, 109.8, 113.2, 114.6, 118.9, 121.2, 121.9, 125.4, 128.9, 135.6, 142.4, 147.3, 155.5, 161.1, 168.0, 172.6, 173.9; MS (CI) *m/z* (%): 449.1 (100, MH$^+$). *Anal*. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.39; H, 6.18; N, 6.48.

3-[6-Ethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-4H-chromen-2-yl]propanoic acid (4f). This compound was obtained as colorless solid (532 mg, 74% yield); mp 275–276°C; IR (KBr): 3231, 2976, 1700, 1617, 1578, 1249 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.19 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$-6'), 2.43 (s, 3H, C*H*$_3$-4''), 2.63 (q, 2H, *J* = 7.6 Hz, C*H*$_2$-6'), 2.76 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 3.56 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 6.89 (s, 1H, *H*-8'), 7.34 (s, 1H, *H*-5''), 7.83 (s, 1H, *H*-5'), 11.00 (s, 1H, O*H*-7'), 12.31 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.6, 16.9, 22.4, 29.2, 30.7, 101.0, 114.1, 114.2, 115.2, 124.6, 130.3, 150.0, 154.7, 157.0, 160.8, 167.2, 173.0, 173.4; MS (CI) *m/z* (%): 360.2 (100, MH$^+$). *Anal*. Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90; S, 8.92. Found: C, 60.16; H, 4.77; N, 3.90; S, 8.92.

3-[3-(1,3-Benzothiazol-2-yl)-7-hydroxy-4-oxo-6-propyl-4H-chromen-2-yl]propanoic acid (4g). This compound was obtained as colorless solid (540 mg, 66% yield); mp 227–229°C;

IR (KBr): 3118, 2960, 1698, 1614, 1574, 1374 cm^{-1}; ^1H NMR (300 MHz): δ 0.92 (m, 3H, $CH_3CH_2CH_2$-6'), 1.63 (m, 2H, $CH_3CH_2CH_2$-6'), 2.62 (m, 2H, $CH_3CH_2CH_2$-6'), 2.82 (t, 2H, J = 7.6 Hz, CH_2COOH), 3.65 (t, 2H, J = 7.6 Hz, CH_2-3), 6.94 (s, 1H, *H*-8'), 7.46 (1H, m, *H*-5''), 7.53 (1H, m, H-6''), 7.83 (s, 1H, *H*-5'), 8.01 (1H, m, *H*-7''), 8.15 (1H, m, *H*-4''), 11.13 (s, 1H, O*H*-7'), 12.20 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.7, 22.1, 29.6, 30.8, 31.4, 101.2, 114.1, 114.3, 121.0, 122.3, 124.4, 125.4, 125.6, 129.0, 135.2, 151.0, 154.8, 159.5, 161.4, 169.4, 173.1, 173.6; MS (CI) *m/z* (%): 410.1 (100, MH^+). *Anal*. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42; S, 7.83. Found: C, 64.45; H, 4.39; N, 3.24; S, 7.66.

3-[7-[(2,2-Dimethylpropanoyl)oxy]-6-ethyl-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]propanoic acid (4h). This compound was obtained as colorless solid (639 mg, 67% yield); mp 225–226°C; IR (KBr): 3471, 2973, 1747, 1653, 1472, 1109 cm^{-1}; ^1H NMR (300 MHz): δ 1.18 (t, 3H, J = 7.6 Hz, CH_3CH_2-6'), 1.38 (s, 9H, $(CH_3)_3CCOO$-7'), 2.63 (q, 2H, J = 7.6 Hz, CH_2-6'), 2.70 (t, 2H, J = 7.6 Hz, CH_2COOH), 2.89 (t, 2H, J = 7.6 Hz, CH_2-3), 3.66 (s, 3H, NCH_3), 7.27 (1H, m, *H*-5''), 7.34 (1H, m, H-6''), 7.62 (s, 1H, *H*-8'), 7.64 (1H, m, *H*-7''), 7.70 (1H, m, *H*-4''), 8.02 (s, 1H, *H*-5'), 12.35 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.9, 22.4, 26.6, 27.9, 30.1, 30.2, 38.8, 109.8, 111.7, 113.8, 119.0, 120.3, 121.3, 122.1, 125.4, 134.2, 135.6, 142.4, 146.7, 153.1, 154.1, 169.5, 172.5, 174.1, 175.2; MS (CI) *m/z* (%): 477.2 (100, MH^+). *Anal*. Calcd for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92; N, 5.88. Found: C, 67.82; H, 6.17; N, 5.84.

4-[7-Hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]butanoic acid (5c). This compound was obtained as colorless solid (446 mg, 59% yield); mp 240–241°C; IR (KBr): 3436, 3025, 1714, 1635, 1625, 1391 cm^{-1}; ^1H NMR (300 MHz): δ 1.88 (m, 2H, CH_2-3), 2.25 (m, 2H, CH_2COOH), 2.63 (m, 2H, CH_2-4), 3.63 (s, 3H, NCH_3), 6.94 (d, 1H, J = 2.3 Hz, *H*-8'), 6.97 (dd, 1H, J = 2.3, 8.8 Hz, *H*-6'), 7.23 (1H, m, *H*-5''), 7.30 (1H, m, *H*-6''), 7.60 (1H, m, *H*-7''), 7.67 (1H, m, *H*-4''), 7.94 (d, 1H, J = 8.8 Hz, *H*-5'), 10.91 (s, 1H, O*H*-7'), 12.00 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 22.0, 30.2, 31.4, 32.5, 102.1, 109.8, 113.3, 115.0, 115.2, 119.0, 121.3, 122.0, 126.8, 135.6, 142.4, 147.1, 157.3, 163.1, 169.3, 173.4, 174.1; MS (CI) *m/z* (%): 379.2 (100, MH^+). *Anal*. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.43; H, 4.99; N, 7.26.

4-[6-Ethyl-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]butanoic acid (5d). This compound was obtained as colorless solid (585 mg, 72% yield); mp 257–259°C; IR (KBr): 3226, 2965, 1641, 1632, 1471, 1258 cm^{-1}; ^1H NMR (400 MHz): δ 1.23 (t, 3H, J = 7.6 Hz, CH_3CH_2-6'), 1.93 (m, 2H, CH_2-3), 2.23 (m, 2H, CH_2COOH), 2.67 (m, 4H, CH_2-4 and CH_2-6'), 3.66 (s, 3H, NCH_3), 6.91 (s, 1H, *H*-8'), 7.25 (1H, m, *H*-5''), 7.28 (1H, m, *H*-6''), 7.55 (1H, m, *H*-7''), 7.65 (1H, m, *H*-4''), 7.76 (s, 1H, *H*-5'), 10.80 (s, 1H, O*H*-7'), 12.15 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.6, 22.0, 22.4, 30.2, 31.4, 32.5, 101.4, 109.7, 113.2, 114.7, 118.9, 121.2, 121.9, 124.6, 130.2, 135.5, 142.4, 147.3, 155.6, 161.0, 168.9, 173.3, 174.0;. MS (CI) *m/z* (%): 407.1 (100, MH^+). *Anal*. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.88; H, 5.18; N, 7.10.

4-[6-Hexyl-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]butanoic acid (5e). This compound was obtained as colorless solid (583 mg, 63% yield); mp 125–127°C; IR (KBr): 3061, 2928, 1713, 1627, 1586, 1470 cm^{-1}; ^1H NMR (300 MHz): δ 0.86, 1.29, 1.57, 1.86, 2.38, 2.63 (6 m, 3H, 6H, 2H, 2H, 2H, 4H, *Hex*-6' and $CH_2CH_2CH_2COOH$), 3.63 (s, 3H, NCH_3), 6.95 (s, 1H, *H*-8'), 7.24 (1H, m, *H*-5''), 7.31 (1H, m, *H*-6''), 7.60 (1H, m, *H*-7''), 7.67 (1H, m, *H*-4''),7.76 (s, 1H, *H*-5'), 10.95 (s, 1H, O*H*-7'), 12.06 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.9, 22.0, 22.1, 28.6, 29.0, 29.3, 30.2, 31.2, 31.4, 32.5, 101.5, 109.8, 113.2, 114.6, 119.0, 121.2, 121.9, 125.3, 125.4, 128.9, 135.5, 142.4, 155.5, 161.1, 168.9, 173.3, 174.0; MS (CI) *m/z* (%): 463.3 (100, MH^+). *Anal*. Calcd for $C_{27}H_{30}N_2O_5$: C, 70.11; H, 6.54; N, 6.06. Found: C, 70.32; H, 6.48; N, 6.28.

4-[6-Ethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-4H-chromen-2-yl]butanoic acid (5f). This compound was obtained as colorless solid (500 mg, 67% yield); mp 196–198°C; IR (KBr): 3101, 2964, 1708, 1616, 1573, 1365 cm^{-1}; ^1H NMR (400 MHz): δ 1.20 (t, 3H, J = 7.6 Hz, CH_3CH_2-6'), 2.02 (m, 2H, CH_2-3), 2.37 (m, 2H, CH_2COOH), 2.46 (s, 3H, CH_3-4''), 2.64 (q, 2H, J = 7.6 Hz, CH_2-6'), 3.34 (m, 2H, CH_2-4), 6.91 (s, 1H, *H*-8'), 7.31 (s, 1H, *H*-5''), 7.83 (s, 1H, *H*-5'), 10.95 (s, 1H, O*H*-7'), 12.05 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.6, 16.9, 22.4, 22.5, 32.4, 33.1, 101.1, 114.2, 114.3, 115.2, 124.6, 130.2, 150.0, 154.8, 157.1, 160.9, 161.0, 168.4, 173.5; MS (CI) *m/z* (%): 374.1 (100, MH^+). *Anal*. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75; S, 8.59. Found: C, 61.33; H, 5.35; N, 3.59; S, 8.86.

4-[3-(1,3-Benzothiazol-2-yl)-7-hydroxy-4-oxo-6-propyl-4H-chromen-2-yl]butanoic acid (5g). This compound was obtained as colorless solid (381 mg, 45% yield); mp 242–244°C; IR (KBr): 3421, 2961, 1704, 1614, 1571, 1373 cm^{-1}; ^1H NMR (400 MHz): δ 0.93 (m, 3H, $CH_3CH_2CH_2$-6'), 1.61 (m, 2H, CH_2CH_2-6'), 2.08 (m, 2H, CH_2-3), 2.36 (m, 2H, CH_2COOH), 2.61 (m, 2H, CH_2-6'), 3.40 (m, 2H, CH_2-4), 7.00 (s, 1H, *H*-8'), 7.44 (1H, m, *H*-5''), 7.51 (1H, m, *H*-6''), 7.79 (s, 1H, *H*-5'), 8.05 (1H, m, *H*-7''), 8.12 (1H, m, *H*-4''), 10.96 (s, 1H, O*H*-7'), 12.02 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.8, 22.1, 23.2, 31.5, 33.0, 34.6, 101.3, 113.5, 114.1, 121.0, 122.4, 124.4, 125.3, 125.4, 129.2, 135.3, 151.1, 155.1, 159.7, 162.7, 170.6, 173.8, 175.1; MS (CI) *m/z* (%): 424.1 (100, MH^+). *Anal*. Calcd for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00; N, 3.31; S, 7.57. Found: C, 64.98; H, 5.26; N, 3.25; S, 7.68.

4-[7-[(2,2-Dimethylpropanoyl)oxy]-6-ethyl-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]butanoic acid (5h). This compound was obtained as colorless solid (569 mg, 58% yield); mp 207–208°C; IR (KBr): 3443, 2972, 1759, 1652, 1471, 1096 cm^{-1}; ^1H NMR (300 MHz): δ 1.18 (t, 3H, J = 7.6 Hz, CH_3CH_2-6'), 1.38 (s, 9H, $(CH_3)_3CCOO$-7'), 1.91 (m, 2H, CH_2-3), 2.27 (m, 2H, CH_2COOH), 2.65 (m, 4H, CH_2-4 and CH_2-6'), 3.65 (s, 3H, NCH_3), 7.25 (1H, m, *H*-5''), 7.32 (1H, m, *H*-6''), 7.62 (1H, m, *H*-7''), 7.63 (1H, s, *H*-8'), 7.69 (1H, m, *H*-4''), 8.02 (s, 1H, *H*-5'), 12.07 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.9, 21.8, 22.4, 26.6, 30.2, 31.5, 32.5, 38.8, 109.8, 111.7, 113.8, 119.0, 120.3, 121.3, 122.0, 125.4, 134.1, 135.6, 142.5, 146.6, 153.1, 154.2, 170.2, 173.3, 174.2, 175.2; MS (CI) *m/z* (%): 491.1 (100, MH^+). *Anal*. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.34; H, 6.28; N, 5.66.

{[6-Ethyl-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]methoxy}acetic acid (6d). This compound was obtained as colorless solid (466 mg, 57% yield); mp 272–273°C; IR (KBr): 3430, 2965, 1649, 1589, 1487, 1400 cm^{-1}; ^1H NMR (300 MHz): δ 1.20 (t, 3H, J = 7.6 Hz, CH_3CH_2-6'), 2.66 (q, 2H, J = 7.6 Hz, CH_2-6'), 3.64 (s, 3H, NCH_3), 4.11 (s 2H, CH_2COOH), 4.51 (s 2H, CH_2-2'), 7.00 (s, 1H, *H*-8'), 7.26 (1H, m, *H*-5''), 7.32 (1H, m, *H*-6''), 7.62 (1H, m, *H*-7''), 7.68 (1H, m, *H*-4''), 7.82

(s, 1H, *H*-5'), 11.12 (s, 1H, O*H*-7'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.7, 22.5, 30.3, 67.1, 67.4, 101.7, 110.0, 114.3, 114.9, 118.9, 121.5, 122.3, 124.7, 130.7, 135.7, 142.1, 146.4, 155.7, 161.5, 163.9, 170.7, 174.0; MS (CI) *m/z* (%): 409.2 (100, MH^+). *Anal*. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.56; H, 4.78; N, 7.11.

{[6-Ethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-4H-chromen-2-yl]methoxy}acetic acid (6f). This compound was obtained as colorless solid (383 mg, 51% yield); mp 182–184°C; IR (KBr): 3428, 3105, 2965, 1738, 1614, 1574, 1247 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.21 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$-6'), 2.46 (s, 3H, C*H*$_3$-4''), 2.64 (q, 2H, *J* = 7.6 Hz, C*H*$_2$-6'), 4.24 (s 2H, C*H*$_2$COOH), 5.23 (s 2H, C*H*$_2$-2'), 6.96 (s, 1H, *H*-8'), 7.34 (s, 1H, *H*-5''), 7.85 (s, 1H, *H*-5'), 10.95 (s, 1H, O*H*-7'), 12.02 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.6, 16.8, 22.4, 67.4, 68.1, 101.3, 114.4, 115.1, 115.9, 124.6, 130.6, 150.3, 154.8, 156.4, 161.2, 162.8, 171.0, 173.4; MS (CI) *m/z* (%): 376.1 (100, MH^+). *Anal*. Calcd for $C_{18}H_{17}NO_6S$: C, 57.59; H, 4.56; N, 3.73; S, 8.54. Found: C, 57.68; H, 4.36; N, 3.66; S, 8.56.

{[3-(1,3-Benzothiazol-2-yl)-7-hydroxy-4-oxo-6-propyl-4H-chromen-2-yl]methoxy}acetic acid (6g). This compound was obtained as colorless solid (545 mg, 64% yield); mp 302–303°C; IR (KBr): 3118, 2960, 1698, 1614, 1574, 1374 cm^{-1}; ^{1}H NMR (400 MHz): δ 0.91 (m, 3H, C*H*$_3$CH$_2$CH$_2$-6'), 1.57 (m, 2H, CH$_2$C*H*$_2$-6'), 2.57 (m, 2H, C*H*$_2$-6'), 4.00 (s 2H, C*H*$_2$COOH), 5.31 (s 2H, C*H*$_2$-2'), 7.26 (s, 1H, *H*-8'), 7.45 (1H, m, *H*-5''), 7.55 (1H, m, *H*-6''), 7.77 (s, 1H, *H*-5'), 8.08 (1H, m, *H*-7''), 8.16 (1H, m, *H*-4''), 11.08 (s, 1H, O*H*-7'), 12.08 (s, 1H, COO*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.7, 21.9, 31.3, 68.6, 69.6, 101.6, 114.0, 114.4, 121.2, 122.4, 124.6, 125.5, 125.6, 129.5, 135.4, 151.1, 155.1, 159.3, 162.2, 166.0, 173.7, 173.8; MS (CI) *m/z* (%): 426.0 (100, MH^+). *Anal*. Calcd for $C_{22}H_{19}NO_6S$: C, 62.11; H, 4.50; N, 3.29; S, 7.54. Found: C, 62.28; H, 4.39; N, 3.18; S, 7.48.

{[7-[(2,2-Dimethylpropanoyl)oxy]-6-ethyl-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-2-yl]methoxy}acetic acid (6h). This compound was obtained as colorless solid (768 mg, 78% yield); mp 237–238°C; IR (KBr): 2973, 1758, 1647, 1620, 1474, 1104 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.19 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$-6'), 1.38 (s, 9H, (C*H*$_3$)$_3$CCOO-7'), 2.66 (q, 2H, *J* = 7.6 Hz, C*H*$_2$-6'), 3.66 (s, 3H, NC*H*$_3$), 4.14 (s 2H, C*H*$_2$COOH), 4.55 (s 2H, C*H*$_2$-2'), 7.27 (1H, m, *H*-5''), 7.33 (1H, m, *H*-6''), 7.63 (1H, m, *H*-7''), 7.68 (1H, m, *H*-4''), 7.69 (s, 1H, *H*-8'), 8.05 (s, 1H, *H*-5'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.9, 22.4, 26.7, 30.4, 38.8, 67.1, 67.3, 110.0, 112.1, 114.8, 119.1, 120.5, 121.4, 122.2, 125.4, 134.5, 135.7, 142.3, 145.8, 153.5, 154.3, 165.2, 170.7, 174.3, 175.2; MS (CI) *m/z* (%): 493.2 (100, MH^+). *Anal*. Calcd for $C_{27}H_{28}N_2O_7$: C, 65.84; H, 5.73; N, 5.69. Found: C, 65.68; H, 5.92; N, 5.58.

General procedure for synthesis compounds 7–9. The hydrazine hydrate (8 mmol) was added to a stirred solution of 1 mmol chromone **4–6** in 10 mL of ethanol. The reaction mixture was refluxed for 4 h, neutralized by acetic acid to pH 7 and diluted by water. The precipitate was filtered off, washed with cold water, and crystallized from mixture ethanol–water.

3-[4-(1H-Benzimidazol-2-yl)-3-(2,4-dihydroxy–phenyl)-1H-pyrazol-5-yl]propanoic acid (7a). This compound was obtained as colorless solid (211 mg, 58% yield); mp 199–201°C; IR (KBr): 3172, 3106, 1622, 1605, 1550, 1401 cm^{-1}; ^{1}H NMR (300 MHz): 2.63 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 3.04 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 6.23 (dd, 1H, *J* = 2.4, 8.4 Hz, *H*-5'), 6.37 (d, 1H, *J* = 2.4 Hz, *H*-3'), 6.95 (d, 1H, *J* = 8.4 Hz, *H*-6'), 7.19 (m, 2H, *H*-5'' and *H*-6''), 7.54 (m, 2H, *H*-4'' and *H*-7''), 9.51 (br. s, 1H, O*H*-4'), 12.00 (br. s, 3H, COO*H*, N*H* and O*H*-2'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 21.4, 32.4, 104.6, 104.7, 107.0, 109.4, 109.5, 121.5, 130.4, 138.2, 143.6, 147.0, 147.3, 156.9, 159.0, 173.8; MS (CI) *m/z* (%): 365.1 (100, MH^+). *Anal*. Calcd for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38. Found: C, 62.47; H, 4.56; N, 15.11.

3-[3-(2,4-Dihydroxyphenyl)-4-(1-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]propanoic acid (7c). This compound was obtained as colorless solid (295 mg, 78% yield); mp 284–285°C; IR (KBr): 3086, 2945, 1638, 1488, 1164 cm^{-1}; ^{1}H NMR (300 MHz): δ 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 2.85 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 3.32 (s, 3H, NC*H*$_3$), 6.09 (dd, 1H, *J* = 2.4, 8.4 Hz, *H*-5'), 6.33 (d, 1H, *J* = 2.4 Hz, *H*-3'), 6.60 (d, 1H, *J* = 8.4 Hz, *H*-6'), 7.23 (m, 2H, *H*-5'' and *H*-7''), 7.50 (m, 1H, *H*-7''), 7.66 (m, 1H, *H*-4''), 9.53 (br. s, 1H, O*H*-4'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 20.7, 30.0, 32.5, 103.0, 104.9, 106.8, 108.1, 109.8, 118.7, 121.3, 121.7, 127.9, 135.4, 142.8, 145.1, 146.5, 148.2, 156.6, 158.6, 173.2; MS (CI) *m/z* (%): 379.2 (100, MH^+). *Anal*. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.49; H, 4.80; N, 14.81. Found: C, 63.46; H, 4.56; N, 15.08.

3-[3-(5-Ethyl-2,4-dihydroxyphenyl)-4-(1-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]propanoic acid (7d). This compound was obtained as colorless solid (236 mg, 58% yield); mp 166–168°C; IR (KBr): 3180, 2963, 1710, 1620, 1459, 1403 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.63 (t, 3H, *J* = 7.6, C*H*$_3$CH$_2$-5'), 2.14 (q, 2H, *J* = 7.6, C*H*$_2$-5'), 2.56 (t, 2H, *J* = 7.6 Hz, C*H*$_2$COOH), 2.86 (t, 2H, *J* = 7.6 Hz, C*H*$_2$-3), 3.31 (s, 3H, NC*H*$_3$), 6.37 (s, 1H, *H*-3'), 6.40 (s, 1H, *H*-6'), 7.23 (m, 2H, *H*-5'' and *H*-6''), 7.50 (m, 1H, *H*-7''), 7.66 (m, 1H, *H*-4''), 9.42 (s, 1H, O*H*-4'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.4, 20.7, 21,3, 30.0, 32.6, 102.6, 104.8, 107.5, 109.6, 118.6, 120.9, 121.3, 121.7, 126.9, 135.4, 142.6, 145.4, 146.3, 148.2, 154.2, 155.9, 173.2; MS (CI) *m/z* (%): 407.1 (100, MH^+). *Anal*. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 64.84; H, 5.56; N, 13.66.

4-[3-(2,4-Dihydroxyphenyl)-4-(1-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]butanoic acid (8c). This compound was obtained as colorless solid (247 mg, 63% yield); mp 267–268°C; IR (KBr): 3379, 3116, 2945, 1618, 1412, 1242 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.76 (m, 2H, C*H*$_2$-3), 2.18 (m, 2H, C*H*$_2$COOH), 2.64 (m, 2H, C*H*$_2$-4), 3.34 (s, 3H, NC*H*$_3$), 6.07 (dd, 1H, *J* = 2.4, 8.4 Hz, *H*-5'), 6.31 (d, 1H, *J* = 2.4 Hz, *H*-3'), 6.57 (d, 1H, *J* = 8.4 Hz, *H*-6'), 7.23 (m, 2H, *H*-5'' and *H*-6''), 7.50 (m, 1H, *H*-7''), 7.66 (m, 1H, *H*-4''), 9.53 (s, 1H, O*H*-4'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 23.7, 24.1, 30.1, 32.9, 103.0, 104.8, 106.9, 108.3, 109.9, 118.7, 121.4, 121.8, 127.7, 135.4, 142.7, 146.0, 146.7, 148.1, 156.7, 158.6, 173.8; MS (CI) *m/z* (%): 393.2 (100, MH^+). *Anal*. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.42; H, 5.00; N, 14.07.

4-[3-(5-Ethyl-2,4-dihydroxyphenyl)-4-(1-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]butanoic acid (8d). This compound was obtained as colorless solid (269 mg, 64% yield); mp 214–216°C; IR (KBr): 3218, 2963, 1616, 1473, 1407, 1238 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.60 (t, 3H, *J* = 7.6, C*H*$_3$CH$_2$-5'), 1.78 (m, 2H, C*H*$_2$-3), 2.12 (q, 2H, *J* = 7.6, C*H*$_2$-5'), 2.18 (m, 2H, C*H*$_2$COOH), 2.65 (m, 2H, C*H*$_2$-4), 3.32 (s, 3H, NC*H*$_3$), 6.36 (m, 1H, *H*-3'), 6.39 (s, 1H, *H*-6'), 7.23 (m, 2H, *H*-5'' and *H*-6''), 7.49 (m, 1H, *H*-7''), 7.65 (m, 1H, *H*-4''), 9.35 (s, 1H, O*H*-4'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.4, 21.3, 23,8, 24.1, 30.0, 32.9, 102.6, 104.7, 107.6, 109.7, 118.7, 120.9, 121.4, 121.9, 126.6, 135.4, 142.6, 146.4, 146.5, 148.2, 154.3, 155.9, 173.8; MS (CI) *m/z* (%): 421.3 (100, MH^+). *Anal*. Calcd for $C_{23}H_{24}N_4O_4$: C, 65.70; H, 5.75; N, 13.32. Found: C, 65.98; H, 5.56; N, 13.21.

4-[4-(1,3-Benzothiazol-2-yl)-3-(2,4-dihydroxy-5-propylphenyl)-1H-pyrazol-5-yl]butanoic acid (8g). This compound was obtained as colorless solid (341 mg, 78% yield); mp 182–184°C; IR (KBr): 3234, 2957, 1705, 1621, 1525, 1453 cm^{-1}; ^1H NMR (300 MHz): δ 0.84 (m, 3H, $CH_3CH_2CH_2$-5'), 1.49 (m, 2H, CH_2CH_2-5'), 1.95 (m, 2H, CH_2-3), 2.34 (m, 2H, CH_2-5''), 2.40 (m, 2H, CH_2COOH), 3.05 (m, 2H, CH_2-4), 6.47 (s, 1H, *H*-3'), 6.87 (s, 1H, *H*-6'), 7.29 (1H, m, *H*-5''), 7.42 (1H, m, *H*-6''), 7.88 (2H, m, *H*-7''), 7.92 (1H, m, *H*-4''), 9.31 (s, 1H, O*H*-4'), 9.45 (s, 1H, O*H*-2'), 12.45 (br. s, 2H, COO*H* and N*H*); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.8, 22.6, 23.6, 26.2, 31.0, 33.4, 102.7, 107.1, 111.6, 119.3, 120.9, 121.7, 123.7, 125.2, 131.9, 134.2, 143.7, 148.3, 152.7, 154.6, 157.0, 161.8, 174.1; MS (CI) *m/z* (%): 438.2 (100, MH^+). *Anal*. Calcd for $C_{23}H_{23}N_3O_4S$: C, 63.14; H, 5.30; N, 9.60; S, 7.33. Found: C, 63.37; H, 5.11; N, 9.46; S, 7.48.

{[3-(5-Ethyl-2,4-dihydroxyphenyl)-4-(4-methyl-1,3-thiazol-2-yl)-1H-pyrazol-5-yl]methoxy}acetic acid (9f). This compound was obtained as colorless solid (288 mg, 74% yield); mp 134–135°C; IR (KBr): 3205, 2963, 1714, 1619, 1522, 1418 cm^{-1}; ^1H NMR (300 MHz): δ 1.06 (t, 3H, J = 7.6, CH_3CH_2-5'), 2.33 (s, 3H, CH_3-4''), 2.42 (q, 2H, J = 7.6, CH_2-5''), 4.10 (s, 2H, CH_2COOH), 4.85 (s, 2H, CH_2O), 6.45 (s, 1H, *H*-3'), 6.85 (s, 1H, *H*-6'), 7.00 (s, 1H, *H*-5''), 9.25 (s, 2H, O*H*-2' and O*H*-4'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 14.3, 16.7, 21.9, 64.4, 66.7, 103.1, 107.2, 112.4, 112.5, 121.0, 131.0, 141.9, 144.1, 150.7, 154.5, 156.8, 160.1, 171.3; MS (CI) *m/z* (%): 390.2 (100, MH^+). *Anal*. Calcd for $C_{18}H_{19}N_3O_5S$: C, 55.52; H, 4.92; N, 10.79; S, 8.23. Found: C, 55.28; H, 4.76; N, 10.95; S, 8.42.

{[4-(1,3-Benzothiazol-2-yl)-3-(2,4-dihydroxy-5-propylphenyl)-1H-pyrazol-5-yl]methoxy}acetic acid (9g). This compound was obtained as colorless solid (369 mg, 84% yield); mp 241–243°C; IR (KBr): 3229, 2958, 1731, 1623, 1530, 1351 cm^{-1}; ^1H NMR (300 MHz): δ 0.86 (m, 3H, $CH_3CH_2CH_2$-5'), 1.51 (m, 2H, CH_2CH_2-5'), 2.42 (m, 2H, CH_2-5''), 4.19 (s, 2H, CH_2COOH), 5.00 (s, 2H, CH_2O), 6.50 (s, 1H, *H*-3'), 6.90 (s, 1H, *H*-6'), 7.30 (1H, m, *H*-5''), 7.44 (1H, m, *H*-6''), 7.90 (1H, m, *H*-7''), 7.94 (1H, m, *H*-4''), 9.35 (s, 1H, O*H*-4'), 9.47 (br. s, O*H*-2'); ^{13}C NMR (100 MHz, CCl_4 + DMSO-d_6): δ 13.8 22.6, 31.0, 64.8, 66.8, 102.8, 106.3, 112.4, 119.5, 121.0, 121.7, 123.9, 125.3, 132.0, 134.1, 143.1, 145.3, 152.5, 154.6, 157.4, 161.3, 171.4; MS (CI) *m/z* (%): 440.1 (100, MH^+). *Anal*. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56; S, 7.30. Found: C, 60.33; H, 4.68; N, 9.54; S, 7.45.

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