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Unprecedented reactivity of 3-amino-1*H*,3*H*-quinoline-2,4-diones with urea: an efficient synthesis of 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones

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Abstract—Substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones react with urea in acetic acid to give novel 2,6-dihydro-imidazo[1,5-*c*]-quinazoline-3,5-diones in high yields. The same compounds were obtained, albeit with small yields, from 3-chloro-1*H*,3*H*-quinoline-2,4-diones and urea. In the proposed reaction mechanism, a molecular rearrangement of the primarily formed mono-substituted urea takes place. The prepared 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones were characterized by their ^{1}H, ^{13}C, ^{15}N NMR and IR spectra and atmospheric pressure chemical ionisation mass spectra.

1. Introduction

More than 100 derivatives of imidazo[4,5-*c*]quinoline-2-ones (**1a**,**b**) are described in the literature, half of them with descriptions of biological activity in various respects. Nevertheless, no single substance with the imidazo[4,5-*c*]-quinolone skeleton is known to bear a substituent in position 3a (**2a** or **2b**), i.e. one being formally derived from 3-alkyl/aryl-1*H*,3*H*-quinoline-2,4-diones (Fig. 1).

In the scope of systematic research on 3,3-disubstituted 1*H*,3*H*-quinoline-2,4-diones, we decided to prepare new compounds of type **2a**. Suitable starting materials were considered to be 3-amino-1*H*,3*H*-quinoline-2,4-diones **4**, whose preparation from 3-chloroderivatives **3** or the corresponding 3-azidoderivatives we described recently.[1] In accordance with the generally well-known method of preparing substituted ureas, we assumed that addition of α-aminoketones **4** to isocyanic acid (arising by thermal breakdown of urea in boiling acetic acid) would produce compounds **5**. Urea derivatives **5** could then produce the desired products **6** through a subsequent cyclocondensation (Scheme 1) because preparation of analogous 1,3-dihydro-imidazol-2-ones from α-aminoketones and urea has been described.[2] We would like to demonstrate in this work that reaction of compounds **4** with urea does not proceed according to the stated assumption, but that molecular rearrangement occurs in its course producing new 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **7** (Scheme 1).

2. Results and discussion

Starting amines **4** boiled with urea in a solution of acetic acid produced in high yields, after subsequent processing, compounds for which results of elemental analyses were in accord with expected structure **6**. However, the experimental results of ^{13}C NMR spectra were in fundamental

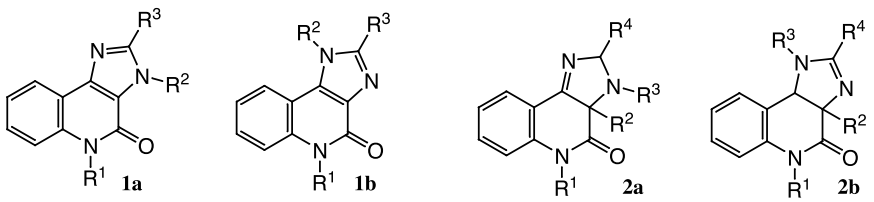

Figure 1.

Keywords: molecular rearrangement; urea derivatives; α-aminoketones; reaction mechanism; NMR; MS.
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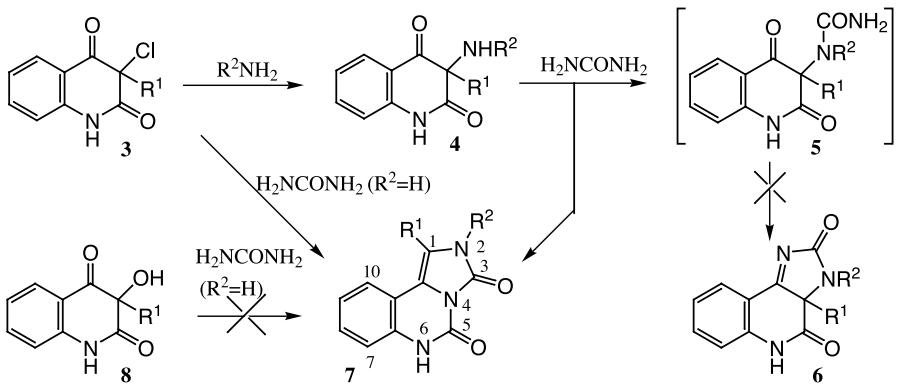


7a: $R^1 = C_4H_9$, R^2 = H (63%) **7d**: $R^1 = Ph$, $R^2 = C_4H_9$ (76%) **7g**: $R^1 = CH_2Ph$, $R^2 = C_4H_9$ (87%)
7b: $R^1 = CH_2Ph$, R^2 = H (71%) **7e**: $R^1 = R^2 = C_4H_9$ (95%) **7h**: $R^1 = R^2 = CH_2Ph$ (66%)
7c: $R^1 = Ph$, R^2 = H (90%) **7f**: $R^1 = C_4H_9$, $R^2 = CH_2Ph$ (93%)

Scheme 1.

disagreement with the anticipated structure. Except for signals pertaining to substituents (butyl, benzyl), all other signals were located in a region of approx. 112–149 ppm. This fact rules out structure **6** because a signal for the amide group in the region of 165–170 ppm would have to appear in the ^{13}C NMR spectra of **6**, and a signal for the quaternary carbon atom C-3a would have to be present in the region around 60–80 ppm. Signals occurring at lowest field values (around 148 and 145 ppm) must belong to two carbonyl groups present in the molecule. These carbonyl groups, however, cannot belong to carboxamide type but according to the position of pertinent signals must be of a urea type. From the results of 1D and 2D NMR experiments (Table 1), simultaneously taking into account theoretical possibilities of starting materials **4** transforming their structure, it followed that the isolated substances are derivatives of 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (**7**). According to the best of our knowledge, there is only one

Table 1. ^1H and ^{13}C NMR shifts (δ, ppm) of compounds **7c–h** (in DMSO-d_6)

Position	7c		7d		7e		7f		7g	7h	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_H	δ_C
1	–	116.75	–	117.95	–	118.77	–	118.92	–	–	116.10
2	10.20	–	–	–	–	–	–	–	–	–	–
3	–	149.07	–	148.07	–	148.30	–	148.67	–	–	148.77
5	–	145.46	–	145.03	–	145.19	–	145.00	–	–	145.08
6	10.68	–	10.75	–	10.63	–	10.67	–	10.69	10.78	–
6a	–	134.62	–	134.38	–	134.12	–	134.23	–	–	134.55
7	7.02	115.32	7.01	115.26	7.01	115.17	7.04	115.14	7.04	7.07	115.23
8	7.20	128.31	7.15	128.10	7.20	127.28	7.24	127.50	7.22	7.23	128.02
9	6.87	122.52	6.77	122.59	7.09	123.06	7.11	123.12	7.00	6.97	123.09
10	7.25	120.83	6.71	121.12	7.50	121.80	7.52	122.04	7.52	7.47	122.11
10a	–	113.41	–	113.00	–	113.69	–	113.54	–	–	113.27
10b	–	112.93	–	113.00	–	112.00	–	112.32	–	–	114.35
1′(1)	–	–	–	–	2.80	23.27	2.72	23.43	–	–	–
2′(1)	–	–	–	–	1.55	30.30	1.28	29.78	–	–	–
3′(1)	–	–	–	–	1.50	22.01	1.37	21.79	–	–	–
4′(1)	–	–	–	–	0.98	13.78	0.82	13.65	–	–	–
1′(2)	–	–	3.45	40.26	3.67	39.98	–	–	3.60	–	–
2′(2)	–	–	1.35	30.37	1.61	31.12	–	–	1.31	–	–
3′(2)	–	–	1.12	19.14	1.37	19.52	–	–	1.19	–	–
4′(2)	–	–	0.72	13.39	0.96	13.71	–	–	0.79	–	–
CH_2(1)	–	–	–	–	–	–	–	–	4.35	4.21	29.20
CH_2(2)	–	–	–	–	–	–	4.99	43.19	–	4.84	43.45
i-Ph(1)	–	129.45	–	128.44	–	–	–	–	–	–	136.34
o-Ph(1)	7.5–7.6	129.45	7.58	131.02	–	–	–	–	7.26	~7.2	127.69
m-Ph(1)	7.5–7.6	129.16	7.66	129.64	–	–	–	–	7.36	~7.3	[a]
p-Ph(1)	7.5–7.6	129.41	7.66	130.16	–	–	–	–	7.29	~7.25	[b]
i-Ph(2)	–	–	–	–	–	–	–	137.49	–	–	136.99
o-Ph(2)	–	–	–	–	–	–	7.33	126.74	–	~7.2	126.73
m-Ph(2)	–	–	–	–	–	–	7.40	128.76	–	~7.3	[a]
p-Ph(2)	–	–	–	–	–	–	7.35	127.50	–	~7.25	[b]

[a] 128.89 or 128.53.
[b] 127.69 or 126.83.

report in the literature describing a substance with the imidazo[1,5-*c*]quinazoline skeleton, namely 5-cyanoimino-5,6-dihydroimidazo[1,5-*c*]quinazoline, which was prepared[3] through reaction of 5-methyl-4(2-aminophenyl)imidazole with *N*-cyano-dithiocarbonimidic acid dimethyl ester.

All the signals in ^{1}H and ^{13}C NMR spectra were assigned on the basis of COSY, HMBC and HMQC experiments to the corresponding atoms (Table 1); their positions are in accord with the proposed structure **7**. Assignment of signals to the corresponding atoms is supported by following interactions: **7c**: C-10b with H-10, C-1 with protons *o*-Ph(1) (HMBC) and H-6 with H-7 (NOESY); **7d**: carbon *i*-Ph(1) with protons *m*-Ph(1) and C-3 with H-1′(1) (HMBC), H-6 with H-7, and H-1′(1) with protons *o*-Ph(1) (NOESY); **7f**: C-3 with PhCH_2(1); **7h**: C-3 with PhCH_2(2), PhCH_2(1) with carbons *i*-Ph(1) and *o*-Ph(1). Data in Table 1 for proton and also carbon atoms in positions 2′ and 3′ of the butyl group in compound **7f** are admittedly surprising but, according to COSY and HSQC, correct. Signals of carbons *m*-Ph(1), *p*-Ph(1), *m*-Ph(2) and *p*-Ph(2) cannot be unambiguously assigned.

The fact that a molecular rearrangement takes place during the reaction of compounds **4** with urea producing 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **7** is also in full accordance with the result of analysis of the gs-^{1}H, ^{15}N-HMBC spectrum of compound **7f** (Fig. 2). The signal, which resonates at −264.6 ppm, splits into a doublet ($^{1}J(^{15}N, ^{1}H)$=93.6 Hz) and simultaneously interacts with proton H-7. This signifies that it belongs to nitrogen N-6 and thereby unambiguously confirms an –NHCO– group. In addition, the proton of NH group interacts by means of $^{3}J(^{15}N, ^{1}H)$ with nitrogen in position N-4 ($\delta(^{15}N)$=−232.0). The same effect was noticed in Ref. 4 with fragment –NHCON– in 2-phenyl-2-hydroxymethyl-4-oxo-1,2,3,4-tetrahydroquinazoline. Nitrogen atom N-2 ($\delta(^{15}N)$=−241.8) may be positively assigned on the basis of interaction with methylene protons of butyl and benzyl groups. Values of ^{15}N chemical shifts in substance **7d** are as follows: $\delta(^{15}N\text{-}2)$=−241.0, $\delta(^{15}N\text{-}4)$=−231.4, and $\delta(^{15}N\text{-}6)$=−264.5 ppm.

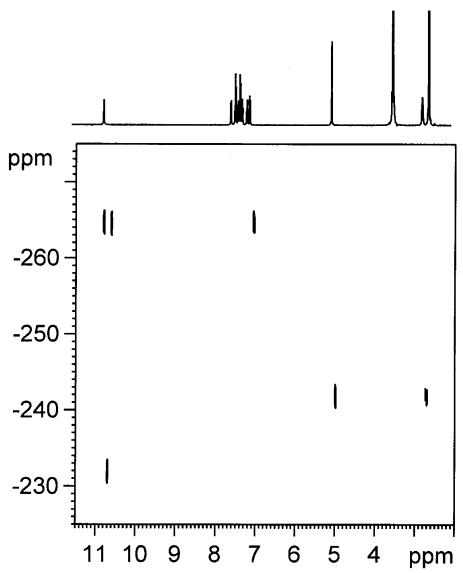


Figure 2. Gradient selected ^{1}H, ^{15}N-HMBC spectrum of compound **7f** (in DMSO-d_6).

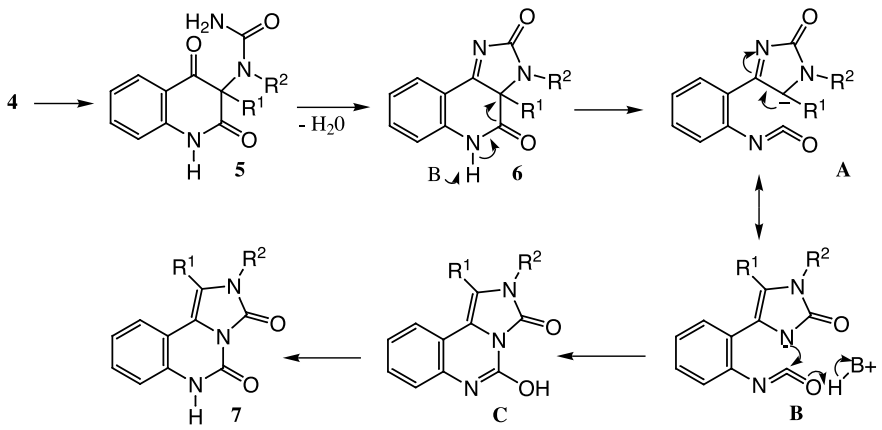
Coupling constants $^{1}J(^{15}N\text{-}6, ^{1}H)$ were measured for compounds **7c** (93.3 Hz), **7d** (92.8 Hz), **7e** (92.8 Hz) and **7f** (93.6 Hz) employing 1D gs-^{1}H, ^{15}N-HMBC spectra and digital resolution ±0.3 Hz.

NMR spectra of compounds **7a** and **7b** are not presented in Table 1. Their ^{1}H NMR spectra, due to very low solubility in dimethyl sulfoxide, were measured in trifluoroacetic acid-*d* and are shown in Section 3, ^{13}C NMR spectra were not measured owing to low solubility. Measurement of the ^{13}C NMR spectrum of compound **7g** was also unsuccessful due to low solubility.

IR spectra of compounds **7** indicate that with compounds bearing both nitrogen atoms in positions 2 and 6 secondary (**7a**–**c**), a characteristic wide split band may be found in the region of 2800–3300 cm^{-1}. Further characteristic absorption bands appear in regions of 1637–1660 and 1585–1611 cm^{-1}. Compounds **7d**–**h** having merely the nitrogen atom of the quinolone system as secondary, exhibit three characteristic absorption bands of similar pattern in regions of 3000–3200 cm^{-1}. Further characteristic absorption bands are in regions of 1754–1758, 1670–1673 and 1606–1610 cm^{-1}. An absorption band around 1490 cm^{-1} occurs in IR spectra of all compounds **7**, however, it cannot be safely assigned.

The positive-ion atmospheric pressure chemical ionisation (APCI) mass spectra of all eight compounds studied show the protonated molecules $[M+H]^{+}$ as the only ions in the spectra, which confirms unambiguously the expected molecular weights. The fragment ions observed in MS/MS spectra are in accordance with the suggested structures. The primary cleavage usually leading to the base peak of MS/MS spectrum is the neutral loss of the side alkyl chain or aromatic substituent, such as the losses of butene (*m*/*z* 56) and propane (*m*/*z* 44) for R=butyl, the losses of benzene (*m*/*z* 78) and toluene (*m*/*z* 92) for R=benzyl. If both R^1 and R^2 groups are present, then the loss from the position R^2 is preferred. Other fragment ions have significantly lower intensity in comparison to discussed ions.

Even though the structure of compounds **7** is at the first glance very far from the structure of the starting materials **4**, their origin may be explained through a reaction mechanism proposed in Scheme 2. The proposal proceeds from assuming the primary reaction is addition of the amino group of **4** to isocyanic acid H–N=C=O (which originates through thermal breakdown of urea). Intermediate **5** subsequently cyclizes with formation of the initially expected reaction product **6**. This compound is obviously not stable under the reaction conditions and further alters through a mechanism formally similar to the mechanism of the rearrangement of 3a*H*,5*H*-furo[2,3-*c*]quinoline-2,4-diones to isomeric 1*H*,5*H*-furo[3,4-*c*]quinoline-3,4-diones.[5] A base-catalysed ring opening takes place giving rise to anion **A**, which is in tautomeric equilibrium with intermediate **B**. Ammonia from urea breakdown can act as basic catalyst and/or even urea itself can despite being a weak base. Intramolecular addition of imide anion to the



Scheme 2.

isocyanate group in intermediate **B** and subsequent protonation produces tautomeric form **C** changing through a 1,3-hydrogen shift to product **7**.

To support the proposed reaction mechanism, we also performed a reaction of urea with 3-chloro-1*H*,3*H*-quinoline-2,4-diones **3a** and **3b** in a solution of ethylene glycol during which alkylation of urea to give **5** must primarily take place. The sole products to be isolated, though in low yields, were again substances **7a** and **7b**. It is interesting that under these conditions, i.e. in ethylene glycol solution, compounds **4** do not react with urea even after several hours at a temperature of 170°C. According to our observation, 3-hydroxy-1*H*,3*H*-quinoline-2,4-diones (**8**) also do not react with urea even in boiling acetic acid although preparation of substituted ureas from tertiary alcohols and urea belongs to generally well-known reactions, and reactions of α-hydroxyketones with urea producing 3,4-dihydro-2*H*-imidazol-2-ones are also described in literature.[6–8]

We would finally like to emphasize that the described reaction of 3-amino-1*H*,3*H*-quinoline-2,4-diones **4** with urea is not merely interesting from a theoretical point of view but owing to simple reaction protocol presents an easy path to preparing hitherto undescribed 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones (**7**). As a whole number of imidazoquinazoline derivatives display significant biological activity,[9] compounds **7** could also be interesting structures for study in this line.

The proposed isocyanate mechanism of **4** changing into **7** can naturally proceed only with those compounds **4** possessing a secondary lactam group in the quinoline ring. As we found in preliminary experiments, compounds **4** possessing a tertiary lactam group do not give compounds of type **7** through a reaction with urea but react in a different manner. We are working on the problem at present and results of investigation into these reactions will be the subject of a subsequent paper.

3. Experimental

Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N) in the respective solvents. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. ^{15}N chemical shifts were referred to external neat nitromethane in co-axial capillary (δ=0.0). All 2D experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton spectra were assigned using gs-COSY. Benzene ring protons were assigned according to their characteristic multiplet pattern. Protonated carbons were assigned by gs-HMQC. Quaternary carbons were assigned by gs-HMBC. The positive-ion APCI mass spectra were measured on an ion trap analyser Esquire 3000 (Bruker Daltonics, Bremen, Germany) within the mass range m/z=50–500. Samples were dissolved in acetonitrile and analysed by direct infusion at the flow rate of 40 μL/min. The ion source temperature was 300EC, the APCI probe temperature was 350EC, the flow rate and the pressure of nitrogen were 3 L/min and 25 psi, respectively. For MS/MS measurements, the collision amplitude was 0.9 V and the isolation width of precursor ions was 4 m/z. The course of reaction and also the purity of substances were monitored by TLC (elution systems benzene-ethyl acetate, 4:1, and chloroform-ethanol, 9:1 and/or 19:1) on Alugram® SIL G/UV$_{254}$ foils (Macherey-Nagel). Elemental analyses (C, H, N) were performed with a Perkin–Elmer 2400 CHN Analyser and EA 1108 Elemental Analyzer (Fisons Instrument).

3-Chloro-1*H*,3*H*-quinoline-2,4-diones (**3a**–**h**) and 3-amino-1*H*,3*H*-quinoline-2,4-diones (**4a**–**h**) were prepared according to the general procedure described in Ref. 1.

3.1. General procedure for the preparation of 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones (7a–h)

Method A. A mixture of appropriate 3-amino-1*H*,3*H*-quinoline-2,4 dione (**4a**–**h**) (2.5 mmol) and urea (0.9 g, 15 mmol) in acetic acid (5 mL) was refluxed for 5–120 min and the course of the reaction was monitored by TLC. After cooling, the reaction mixture was diluted with water (80 mL). The precipitated product **7a**–**h** was filtered off with suction and recrystallized.

Method B. A mixture of appropriate 3-chloro-1*H*,3*H*-quinoline-2,4-dione (**3a**,**b**) (2.5 mmol) and urea (0.37 g, 6.2 mmol) in ethylene glycol (2.5 mL) was stirred at 170°C for 2 h. After cooling, the reaction mixture was diluted with water (30 mL). The precipitated product **7a**,**b** was filtered off with suction and recrystallized.

3.1.1. 1-Butyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7a). Yield 63% (Method A, 90 min) or 24% (Method B). Colourless crystals, mp 341–344°C (acetic acid), IR: 3199, 3140, 3081, 3063, 2995, 2969, 2930, 2873, 1770, 1667, 1637, 1613, 1601, 1587, 1492, 1380, 1336, 1307, 1120, 1040, 950, 928, 803, 747, 655, 593, 538 cm^{-1}. δ_H (TFA-*d*): 1.06 (t, *J*=7.3 Hz, 3H, CH_3 of butyl), 1.48–1.65 (m, 2H, H-3 of butyl), 1.74–1.88 (m, 2H, H-2 of butyl), 3.00 (t, *J*=7.4 Hz, 2H, H-1 of butyl), 7.19 (d, *J*=7.2 Hz, 1H, H-7), 7.32–7.490 (m, 2H, H-8 and H-9), 7.78 (d, *J*=7.5 Hz, H-10), 11.29 (s, 2H, two NH). APCI-MS: *m/z* 258 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 258: *m/z* 228 $[M+H-H_2CO]^+$, 214 $[M+H-CH_3CH_2CH_3]^+$ (100%), 202 $[M+H-CH_3CH_2CH{=}CH_2]^+$, 173, 161. Anal. calcd (found) for $C_{14}H_{15}N_3O_2$: C 65.35 (65.19); H 5.88 (5.91); N 16.33 (16.13).

3.1.2. 1-Benzyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7b). Yield 71% (Method A, 20 min) or 14% (Method B). Colourless crystals, mp 340–346°C (DMF), IR: 3207, 3141, 3099, 3058, 2992, 2922, 2861, 1754, 1668, 1637, 1585, 1490, 1455, 1424, 1378, 1334, 1307, 1157, 1116, 1074, 1004, 994, 918, 881, 853, 761, 745, 701, 636, 552, 532 cm^{-1}. δ_H (TFA-*d*): 4.34 (s, 2H, $PhCH_2$), 7.20 (d, *J*=7.9 Hz, 1H, H-7), 7.26–7.49 (m, 6H, H-8, H-9 and Ph), 7.81 (d, *J*=7.7 Hz, H-10), 11.32 (s, 2H, two NH). APCI-MS: *m/z* 292 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 292: *m/z* 262 $[M+H-H_2CO]^+$, 247, 214 $[M+H-C_6H_6]^+$ (100%), 186, 171, 91 $[C_6H_5CH_2]^+$. Anal. calcd (found) for $C_{17}H_{13}N_3O_2$: C 70.09 (69.88); H 4.50 (4.32); N 14.42 (14.19).

3.1.3. 1-Phenyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7c). Yield 90% (Method A, 5 min). Colourless crystals, mp>360°C (DMF), IR: 3208, 3152, 3054, 2864, 2830, 1776, 1758, 1660, 1612, 1486, 1375, 1328, 1312, 1270, 1244, 1156, 1127, 960, 848, 752, 699, 666, 595, 537 cm^{-1}. APCI-MS: *m/z* 278 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 278: *m/z* 250 $[M+H-CO]^+$, 235 $[M+H-NHCO]^+$ (100%), 167, 146, 118. Anal. calcd (found) for $C_{16}H_{11}N_3O_2$: C 69.31 (69.11); H 4.00 (3.96); N 15.15 (14.87).

3.1.4. 2-Butyl-1-phenyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7d). Yield 76% (Method A, 30 min). Colourless crystals, mp 293–296°C (ethanol), IR: 3204, 3153, 3100, 3058, 2953, 2933, 2867, 1756, 1681, 1611, 1587, 1484, 1443, 1368, 1330, 1315, 1272, 1178, 923, 886, 799, 753, 697, 600 cm^{-1}. APCI-MS: *m/z* 334 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 334: *m/z* 316 $[M+H-H_2O]^+$, 290, 278 $[M+H-CH_3CH_2CH{=}CH_2]^+$ (100%), 235. Anal. calcd (found) for $C_{20}H_{19}N_3O_2$: C 72.05 (72.29); H 5.74 (5.57); N 12.60 (12.64).

3.1.5. 1,2-Dibutyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7e). Yield 95% (Method A, 30 min). Colourless crystals, mp 282–284°C (acetic acid), IR: 3138, 3098, 3059, 2988, 2951, 2927, 2878, 1757, 1671, 1610, 1588, 1491, 1463, 1435, 1401, 1376, 1362, 1331, 1316, 1265, 1232, 1162, 1080, 938, 896, 862, 794, 750, 684, 661, 644, 579, 548, 524 cm^{-1}. APCI-MS, *m/z* 314 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 314: *m/z* 296 $[M+H-H_2O]^+$, 284 $[M+H-H_2CO]^+$, 270, 258 $[M+H-CH_3CH_2CH{=}CH_2]^+$ (100%), 230, 215, 202 $[M+H-2^*CH_3CH_2CH{=}CH_2]^+$. Anal. calcd (found) for $C_{18}H_{23}N_3O_2$: C 68.98 (68.75); H 7.40 (7.65); N 13.41 (13.22).

3.1.6. 2-Benzyl-1-butyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7f). Yield 93% (Method A, 30 min). Colourless crystals, mp 281–284°C (acetic acid), IR: 3150, 3098, 3057, 3003, 2985, 2954, 2927, 2869, 1754, 1673, 1610, 1588, 1491, 1464, 1437, 1370, 1357, 1332, 1312, 1264, 1235, 1215, 1103, 973, 939, 895, 849, 747, 700, 634, 574, 519 cm^{-1}. APCI-MS, *m/z* 348 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 348: *m/z* 330 $[M+H-H_2O]^+$, 304 $[M+H-CH_3CH_2CH_3]^+$, 256 $[M+H-C_6H_5CH_2]^+$ (100%), 230, 214, 202. Anal. calcd (found) for $C_{21}H_{21}N_3O_2$: C 72.60 (72.41); H 6.09 (6.28); N 12.10 (12.04).

3.1.7. 1-Benzyl-2-butyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7g). Yield 87% (Method A, 120 min). Colourless crystals, mp 353–360°C (acetic acid), IR: 3139, 3098, 3057, 2963, 2928, 2872, 1756, 1671, 1608, 1588, 1489, 1455, 1430, 1364, 1331, 1315, 1267, 1223, 1158, 1135, 1075, 1030, 952, 902, 864, 783, 761, 751, 711, 644, 583, 566, 524 cm^{-1}. APCI-MS: *m/z* 348 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 348: *m/z* 330 $[M+H-H_2O]^+$, 292 $[M+H-CH_3CH_2CH{=}CH_2]^+$ (100%), 256 $[M+H-C_6H_5CH_2]^+$, 248, 214 $[M+H-CH_3CH_2CH{=}CH_2-C_6H_6]^+$. Anal. calcd (found) for $C_{21}H_{21}N_3O_2$: C 72.60 (72.44); H 6.09 (6.24); N 12.10 (11.84).

3.1.8. 1,2-Dibenzyl-2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-dione (7h). Yield 66% (Method A, 120 min). Colourless crystals, mp 293–301°C (acetic acid), IR: 3485, 3204, 3166, 3098, 3061, 3030, 3002, 2929, 2863, 1757, 1743, 1673, 1607, 1588, 1488, 1453, 1425, 1383, 1364, 1354, 1323, 1311, 1262, 1231, 1218, 1152, 1074, 1030, 981, 952, 895, 865, 851, 774, 754, 705, 637, 614, 574, 563, 516 cm^{-1}. APCI-MS: *m/z* 382 $[M+H]^+$ (100%). APCI-MS/MS of precursor ion *m/z* 382: *m/z* 304 $[M+H-C_6H_6]^+$, 290 $[M+H-C_6H_5CH_2]^+$, 264, 247, 214 $[M+H-C_6H_5CH_2-C_6H_4]^+$ (100%), 202, 181, 166. Anal. calcd (found) for $C_{24}H_{19}N_3O_2$: C 75.57 (75.25); H 5.02 (4.94); N 11.02 (10.78).

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References

1. Kafka, S.; Klásek, A.; Polis, J.; Košmrlj, J. *Heterocycles* **2002**, *57*, 1659–1682.
2. Zavyalov, S. I.; Sitkareva, I. V.; Ezhova, G. I.; Dorofeeva, O. V.; Zavozin, A. G.; Rumyantseva, E. E. *Izv. Akad. Nauk SSSR Ser. Khim.* **1990**, *8*, 1435–1437.
3. Hoffman, J. M.; Pietruszkiewicz, A. M.; Habecker, C. N.; Phillips, B. T.; Bolhofer, W. A.; Cragoe, E. J.; Torchiana, M. L.; Lumma, W. C.; Baldwin, J. J. *J. Med. Chem.* **1983**, *26*, 140–144.
4. Hradil, P.; Kvapil, L.; Hlaváč, J.; Weidlich, T.; Lyčka, A.; Lemr, K. *J. Heterocycl. Chem.* **2000**, *37*, 831–837.
5. Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. *Heterocycles* **1998**, *48*, 2309–2326.
6. Zaher, H. A.; Ibrahim, Y. A.; Sherif, O.; Mohammady, R. *Indian J. Chem.* **1983**, *22B*, 559–561.
7. Boehme, H.; Schneider, H. *Chem. Ber.* **1958**, *91*, 988–996.
8. Sasaki, T.; Eguchi, S.; Okano, T. *Synthesis* **1980**, *6*, 472–475.
9. Shaban, M.; Taha, M.; Sharshira, E. M. *Adv. Heterocycl. Chem.* **1991**, *52*, 1–153.