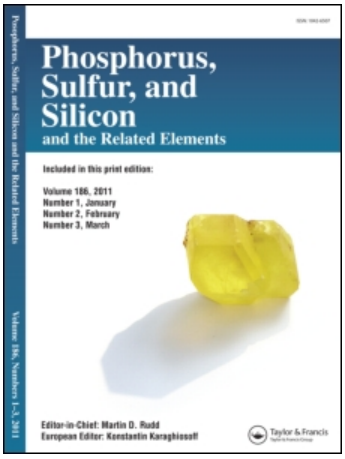

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SYNTHESIS OF 15*H*-ISOQUINO[2',3':3,4]IMIDAZO[2,1-*B*]QUINAZOLINE-7,13,15-TRIONES AND 14*H*-ISOQUINO[2',3':3,4]IMIDAZO[2,1-*B*]BENZO[*G*]QUINAZOLINE-8,14,16-TRIONE AS NEW POLYCYCLIC FUSED-RING SYSTEMS

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SYNTHESIS OF 15*H*-ISOQUINO[2′,3′:3,4]IMIDAZO[2,1-*B*]QUINAZOLINE-7,13,15-TRIONES AND 14*H*-ISOQUINO[2′,3′:3,4]IMIDAZO[2,1-*B*]BENZO[*G*]QUINAZOLINE-8,14,16-TRIONE AS NEW POLYCYCLIC FUSED-RING SYSTEMS

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*3-Thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (**3**) and 2-substituted 3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-diones (**4a–l**) were prepared from the reaction of 2-thiohydantoin (**2**) and 3-substituted 2-thiohydantoin (**5a–l**) with 2-formyl benzoic acid (**1**). Alkylation of **3** under an anhydrous basic conditions afforded **4a–i**. The alkylation of **3** in aqueous basic solution afforded 3-(alkylmercapto)imidazo[1,5-*b*]isoquinoline-1,5-diones (**7a,b**). Reactions of the aromatic amino acids **9a,b** and **12** with **7a** afforded 2-(2*H*-1,5-dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)benzoic acids (**10a, b**) and 3-(2*H*-1,5-dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)-2-naphthalenecarboxylic acid (**13**), which were then cyclyzed by heating in acetic anhydride to afford 15*H*-isoquino[2′,3′:3,4]-imidazo[2,1-*b*]quinazoline-7,13,15-triones (**11a,b**) and 14*H*-isoquino-[2′,3′:3,4]imidazo[2,1-*b*]benzo[*g*]quinazoline-8,14,16-trione (**14**). Some of the new compounds were tested for their antitumor activities.*

Keywords: 3-Thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-diones; 14*H*-isoquino[2′,3′:3,4]imidazo[2,1-*b*]benzo[*g*]quinazoline-8,14,16-trione; 15*H*-isoquino[2′,3′:3,4]imidazo[2,1-*b*]quinazoline-7,13,15-triones; antitumor agents; polycyclic fused-ring systems

We thank ADIR (Groupe Servier, Paris) for carrying out the antitumor testing of the prepared compounds and Prof. Dr. J. Jochims, (Fachbereich Chemie, Universität Konstanz, Konstanz, Germany), for valuable discussions.

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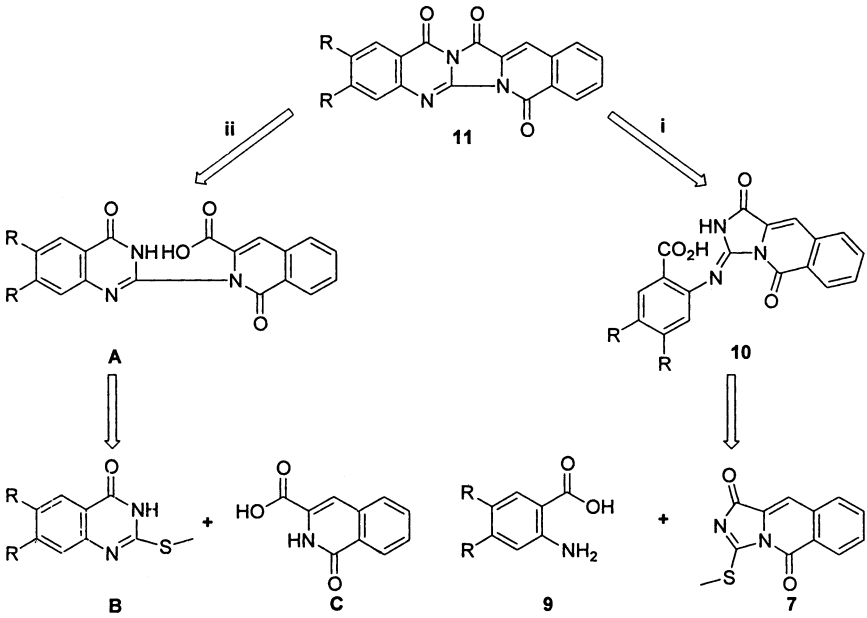
INTRODUCTION

A number of 5*H*,10*H*-imidazo[1,5-*b*]isoquinazoline-1,3-diones has been synthesized[1,2] for pharmacological evaluation, and some of these compounds have been found to exhibit a higher positive isotropic activity in guinea pig isolated atria, in comparison to (−)-isoprenaline.[3] These results indicated that there was merit in continuing further the investigations of these potentially useful compounds by introducing functional groups to the tetrahydroisoquinoline ring, in order to initiate exploration of the exoreceptor environment. Furthermore, the biological activities of polycyclic fused-ring systems[4] stimulated our interest in the syntheses and the chemistry of this class of compounds. Moreover, Polycyclic quinazolines display a wide range of biological activities including antihypertensive,[5,6] antiinflammatory,[7] antifungal,[8] antimelanoma,[9] anticarcinoma,[9] and inhibiting platelet properties antiplatelet.[10] Polycyclic quinazolines are antimetabolites[11] and α_1-adrenoceptor antagonists.[12–15] This article describes simple and efficient procedures for the synthesis of 2-substituted 3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-diones (**4a–l**), 15*H*-isoquino[2′,3′:3,4]-imidazo[2,1-*b*]quinazoline-7,13,15-triones (**11a,b**), and 14*H*-isoquino[2′,3′:3,4]-imidazo[2,1-*b*]benzo-[*g*]quinazoline-8,14,16-trione (**14**) as novel polycyclic fused-ring systems. Furthermore, some tests for the biological effectiveness of the hitherto unreported compounds are presented.

Retrosynthetic analysis of the target heterocyclic compounds of type **11** revealed two possible disconnections i–ii. The disconnection i can lead to **10**, whose synthesis can be achieved from the nucleophilic displacement of a leaving group in **7** by amino group of anthranilic acid and its derivatives **9**. The alternative disconnection ii requires A, which could panel from the reaction of B with C. The first approach seems to be the most reliable one for the synthesis of the leaner condensed heterocyclic system and its analogues (Scheme 1).

RESULTS AND DISCUSSION

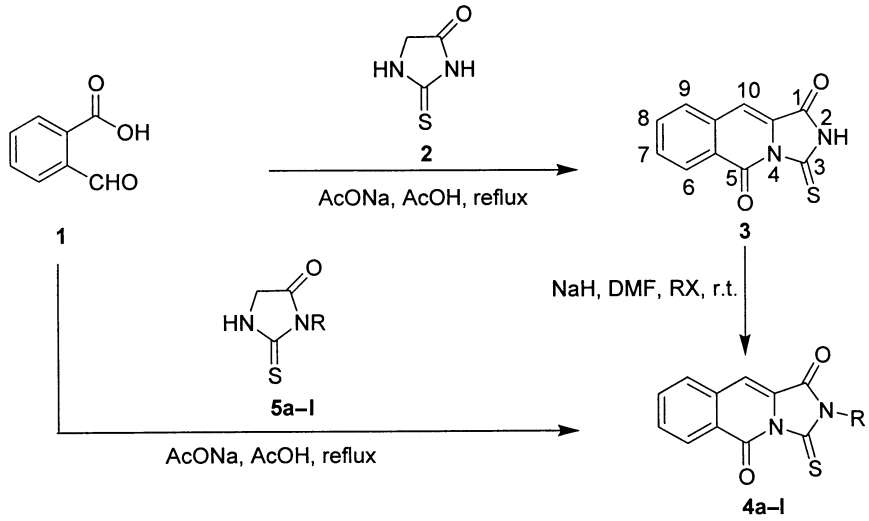
The condensation of 2-formyl benzoic acid (**1**) with 2-thiohydantoin (**2**) in boiling acetic acid containing sodium acetate afforded the 3-thioxoisoquinoline **3**.[16] This compound could be alkylated with alkyl halides in the presence of NaH in anhydrous dimethylformamide (DMF) to furnish the products **4a–i** of *N*-alkylation exclusively. Correspondingly, reaction of 3-substituted 2-thiohydantoins (**5a–l**) with **1** in the presence of sodium acetate in refluxing acetic acid gave compounds **4a–l**



SCHEME 1

(Scheme 2). The structures of **4a–l** were assigned on the basis of elemental analyses and spectral data (IR, NMR, and MS). For instance, the IR absorption spectrum of compound **4a** did not show a signal for NH around 3180 cm^{-1}. Signals at 1738 and 1691 cm^{-1} were assigned to the carbonyl groups. Analytical data for compound **4a** revealed a molecular formula $C_{12}H_8N_2O_2S$ (*m/z* 244). The ^1H NMR spectrum of compound **4a** showed a singlet at $\delta = 3.27$ ppm assigned to the methyl protons. Signals for the protons of the isoquinoline ring were found at 7.65, 7.80, 7.90, 8.00, and 8.38 ppm, respectively. The ^{13}C NMR spectrum of compound **4a** showed a methyl signal at $\delta = 27.65$ ppm. Signals for the carbons of the imidazoisoquinoline ring were found at 108.87, 127.65, 129.01, 129.05, 130.15, 130.91, 133.62, 134.56, 157.48, 161.05, and 174.19 ppm, respectively (Scheme 2).

Compound **3** was condensed with formaldehyde in the presence of morpholine to afford 2-(4-morpholinomethyl)-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (**6**). On the other hand, compound **3** was reacted with alkyl halides in aqueous NaOH in methanol to give 3-(alkylmercapto)imidazo[1,5-*b*]isoquinoline-1,5-diones (**7a,b**). Reaction of **7a** with 12 M HCl in refluxing ethanol resulted in the formation of 2*H*-imidazo[1,5-*b*]isoquinoline-1,3,5-trione (**8**).[16] The IR absorption spectrum of compound **8** showed signals at 3065, 1786, 1735, and



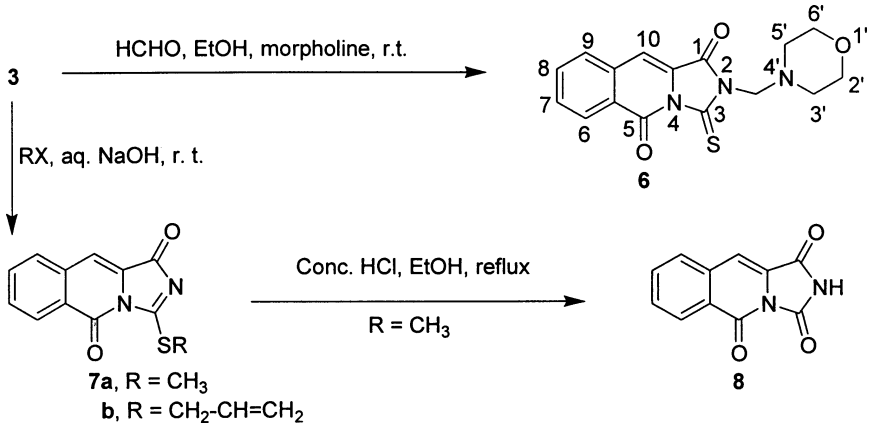
4,5a, R = CH_3
b, R = CH_3CH_2
c, R = $CH_3(CH_2)_5$
d, R = CH_2=$CHCH_2$
e, R = 4-morpholinoethyl
f, R = 4-morpholinopropyl

4,5g, R = $(CH_3)_2NCH_2(CH_2)_2$
h, R = $C_6H_5CH_2$
i, R = $C_6H_5CH_2CH_2$
j, R = C_6H_5
k, R = 2-ClC_6H_4
l, R = 4-$CH_3C_6H_4$

SCHEME 2

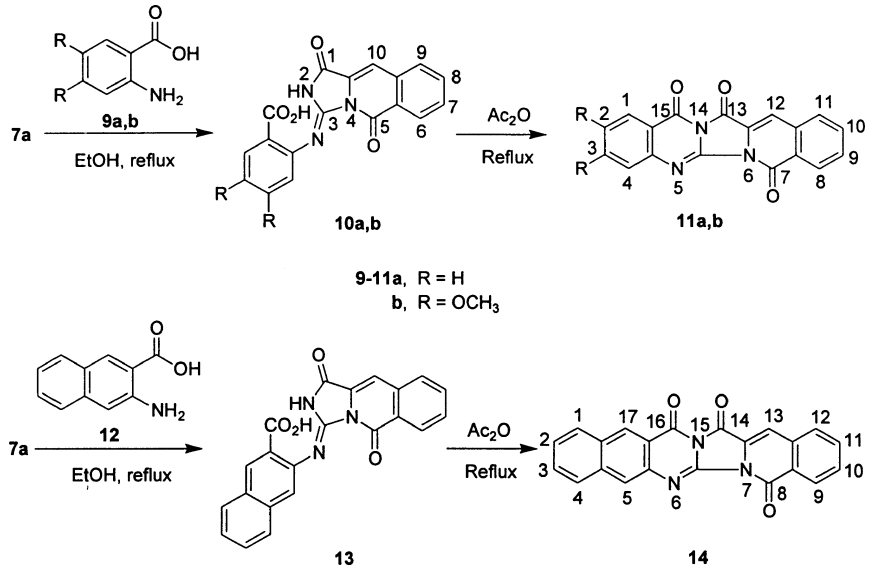
1672 cm^{-1} assigned to NH and the carbonyl groups, respectively. A singlet at $\delta = 10.52$ ppm in the ^1H NMR spectrum of compound **8** can be assigned to the NH. The ^{13}C NMR spectrum of compound **8** showed a singlet at $\delta = 136.52$ ppm assigned to C-3 (Scheme 3).

When **7a** was treated with anthranilic acid derivatives (**9a,b**) in refluxing ethanol, 2-(2*H*-1,5-dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)benzoic acids (**10a,b**) were produced, which could be cyclyzed by heating in acetic anhydride to afford 15*H*-isoquino[2′,3′:3,4]imidazo[2,1-*b*]quinazoline-7,13,15-triones (**11a,b**). Correspondingly, 3-(2*H*-1,5-dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)-2-naphthalenecarboxylic acid (**13**) was prepared from the reaction of **7a** with 3-amino-2-naphthoic acid (**12**) in refluxing ethanol, which could be cyclyzed in the same manner described above, and the corresponding 14*H*-isoquino[2′,3′:3,4]-imidazo[2,1-*b*]benzo[*g*]quinazoline-8,14,16-trione (**14**) was obtained. The structure of **11a** was supported by its mass spectrum, which showed a molecular ion peak at *m/z* 315. In its IR absorption spectrum signals at 1779, 1717, and 1691 cm^{-1} assigned to the carbonyl groups. The ^1H NMR spectrum of compound **11a** did



SCHEME 3

not show signals for NH and COOH around 13.31 and 13.68 ppm, respectively. Signals for nine aromatic protons were observed at δ 7.79–8.59 ppm. In the ^{13}C NMR spectrum the resonance of C-12 was found at δ 110.90 ppm (Scheme 4).



SCHEME 4

In conclusion, we have described the successful synthesis of 3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-diones (**4a–l**), 15*H*-isoquino[2′,3′:3,

TABLE I Antitumor Activity of 2-[2-(4-morpholino)ethyl]-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (**4e**), 15*H*-isoquino[2′,3′:3,4] imidazo[2,1-*b*]quinazoline-7,13,15-triones (**11a**,**b**), and 14*H*-isoquino-[2′,3′:3,4]-imidazo[2,1-*b*]-benzo[*g*]-quinazoline-8,14,16-trione (**14**) Against Leukemia-1210

Compound	IC_{50}[a] (μM) cellules L-1210
4e	4.90
11a	>10
11b	Insoluble
14	22.40
Doxorubicin	0.02

[a]50% Inhibitory concentration: molar concentration of compound that causes 50% inhibition for cell growth.

4]-imidazo[2,1-*b*]quinazoline-7,13,15-triones (**11a**,**b**) and 14*H*-isoquino[2′,3′:3,4]imidazo[2,1-*b*]benzo[*g*]quinazoline-8,14,16-trione (**14**) via simple and efficient methods. These compounds were submitted to antitumor tests. Compounds **4e**, **11a**,**b**, and **14** were screened against leukemia-1210; however, they were found to be considerably less active than doxorubicin (Table I). The antiviral and further antitumor activities of the new prepared compounds are under investigation and will be reported in the due time.

EXPERIMENTAL

Aluminum sheets coated with silica gel 60 F_{254} (Merk) were used for thin layer chromatography (TLC). Detection was effected by viewing under a short wavelength UV lamp. IR spectra (KBr discs, cm^{-1}) were obtained on a Pye Unicam Spectrometer 1000. ^1H NMR spectra were measured on a Bruker Advance DPX 300 MHz spectrometers in dimethylsolfoxide (DMSO)-d_6 and $CDCl_3$ using tetramethylsilane (TMS) as internal standard, δ values, couplings J in Hz. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Service Central de Microanalyse (CNRS, Lyon). The 3-substituted 2-thiohydantoins **5a–l** were prepared according to the published method[15] for the preparation of 3-phenyl-2-thiohydantoin.

3-Thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (3)

A mixture of **1** (1.50 g, 10 mmol), anhydrous sodium acetate (2.80 g, 34 mmol), and **2** (1.16 g, 10 mmol) in glacial acetic acid (14 ml) was boiled under reflux for 4 h (TLC). After cooling to room temperature,

the reaction mixture was poured into cold water. The separated crystals were collected by filtration and recrystallization from ethanol to give 1.80 g (78%) of orange **3**, m.p. 325–327°C (Lit.[16] m.p. 278–279°C). IR: ν 3176 (NH), 1739, 1690 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 7.50 (s, 1H, 10-H), 7.75, 7.85 (2t, $J = 7.8$ Hz, 2-H, 7-H, 8-H), 7.96, 8.36 (2d, $J = 7.8$ Hz, 2H, 6-H, 9-H). 13.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 107.92, 128.92, 128.85, 129.10, 130.10, 130.68, 134.03, 134.43, 157.80 (C-Ar), 162.27 (C-1), 175.45 (C-3); MS, $m/z = 230$ (M^+).

General Procedures for the Preparation of 2-substituted 3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-diones 4a–l

Method A

A mixture of **1** (0.15 g, 1 mmol), anhydrous sodium acetate (0.28 g, 3.40 mmol) and **5a–l** (1 mmol) in glacial acetic acid (3 ml) was boiled under reflux for 4 h (TLC). After cooling to room temperature, the reaction mixture was poured into cold water. The separated crystals were collected by filtration and recrystallization from ethanol to give the pure products **4a–l** (Scheme 2).

Method B

At room temperature compound **3** (230 mg, 1 mmol) was suspended in anhydrous DMF (3 ml). NaH (60%, 45 mg, 1 mmol) was added and the mixture was stirred for 30 min. Alkyl halide (1 mmol) was added to the clear solution, and the mixture was stirred at 50–60°C for 12 h until the starting materials were consumed (TLC). Filtration and evaporation of the filtrate under reduced pressure afforded a residue, which was purified by flash chromatography (eluent: diethyl ether/petroleum ether, 40–60°C) (1:1) and gave the pure products **4a–i** (Scheme 2).

*2-Methyl-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4a)*

Yield 220 mg (90%; method A), 166 mg (72%; method B) of yellow crystals, m.p. 240–242°C (Lit.[16] m.p. 242°C). IR: ν 1738, 1691 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 3.27 (s, 3H, CH_3), 7.65 (s, 1H, 10-H), 7.80, 7.90 (2t, $J = 7.8$ Hz, 2-H, 7-H, 8-H), 8.00, 8.38 (2d, $J = 7.8$ Hz, 2H, 6-H, 9-H). ^{13}C NMR (DMSO-d_6): δ 27.65 (CH_3), 108.87 (C-10), 127.65, 129.01, 129.05, 130.15, 130.91, 133.62, 134.56 (C-Ar), 157.48 (C-5), 161.05 (C-1), 174.19 (C-3); MS, $m/z = 244$ (M^+).

*2-Ethyl-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4b)*

Yield 245 mg (95%; method A), 202 mg (78%; method B) of yellow crystals, m.p. 211–213°C. IR: ν 1736, 1691 (2 × CO). ^{1}H NMR ($CDCl_3$):

δ 1.24 (t, $J = 7.2$ Hz, 3H, 2′-H), 3.88 (q, $J = 7.2$ Hz, 2H, 1′-H), 7.26 (s, 1H, H-10), 7.65–8.56 (m, 4H, 6-H, 7-H, 8-H, 9-H). MS, $m/z = 258$ (M^+). Calcd. for $C_{13}H_{10}N_2O_2S$ (258.29): C, 60.45; H, 3.90; N, 10.84. Found: C, 60.28; H, 4.12; N, 10.63.

*2-Hexyl-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4c)*

Yield 250 mg (80%; method A), 192 mg (61%; method B) of yellow crystals, m.p. 176–178°C. IR: ν 1730, 1692 (2 × CO). ^{1}H NMR ($CDCl_3$): δ0.88 (t, $J = 7.5$ Hz, 3H, 6′-H), 1.30 (m, 6H, 5′-H, 4′-H, 3′-H), 1.72 (m, 2H, 2′-H), 3.82 (t, $J = 7.5$ Hz, 2H, 1′-H), 7.27 (s, 1H, 10-H), 7.64–8.54 (m, 4H, 6-H, 7-H, 8-H, 9-H). ^{13}C NMR ($CDCl_3$): δ 13.88 (C-6′), 22.39 (C-5′), 26.34 (C-4′), 27.04 (C-3′), 3.19 (C-2′), 41.19 (C-1′), 108.72 (C-10), 126.92, 128.05, 129.51, 129.84, 130.65, 133.02, 134.06 (C-Ar), 157.75 (C-5), 160.75 (C-1), 172.37 (C-3). MS, $m/z = 314$ (M^+). Calcd. for $C_{17}H_{18}N_2O_2S$ (314.40): C, 64.94; H, 5.77; N, 8.91. Found: C, 65.06; H, 5.82; N, 8.66.

*2-Allyl-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4d)*

Yield 225 mg (87%; method A), 180 mg (70%; method B) of yellow crystals, m.p. 198–200°C (Lit.[16] m.p. 204°C). IR: ν 1729, 1694 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 4.60 (dd, $J = 1.31, 5.6$ Hz, 2H, 3′-H), 5.25 (m, 2H, 1′-H), 5.87 (m, 1H, 2′-H), 7.50 (s, 1H, 10-H), 7.73–8.48 (m, 4H, 6-H, 7-H, 8-H, 9-H). ^{13}C NMR (DMSO-d_6): δ 42.75 (C-3′), 118.56 (C-2′), 109.31, 125.68, 126.78, 129.24, 129.79, 130.72, 133.15, 134.23 (C-Ar), 157.61 (C-5), 160.17 (C-1), 172.27 (C-3). MS, $m/z = 270$ (M^+).

*2-[2-(4-Morpholino)ethyl]-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4e)*

Yield 302 mg (88%; method A), 257 mg (75%; method B) of yellow crystals, m.p. 189–191°C. IR: ν 1738, 1690 (2 × CO). ^{1}H NMR ($CDCl_3$): δ 2.54 (t, $J = 4.5$ Hz, 4H, 2″-H, 6″-H), 2.72 (t, $J = 6.0$ Hz, 2H, 2′-H), 3.64 (t, $J = 4.5$ Hz, 4H, 3″-H, 5″-H), 4.16 (t, $J = 6.0$ Hz, 2H, 1′-H), 7.33 (s, 1H, H-10), 7.69-8.60 (m, 4H, 6-H, 7-H, 8-H, 9-H). ^{13}C NMR ($CDCl_3$): δ 38.12 (C-2′), 53.69 (C-2″, C-6″), 54.85 (C-1′), 66.95 (C-3″, C-5″), 109.12 (C-10), 126.98, 129.43, 129.67, 130.06, 130.88, 133.18, 134.28 (C-Ar), 158.01 (C-5), 160.97 (C-1), 172.60 (C-3). MS, $m/z = 343$ (M^+). Calcd. for $C_{17}H_{17}N_3O_3S$ (343.41): C, 59.46; H, 4.99; N, 12.24. Found: C, 59.21; H, 5.30; N, 12.46.

*2-[3-(4-Morpholino)propyl]-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4f)*

Yield 300 mg (84%; method A), 260 mg (73%; method B) of yellow crystals, m.p. 192–194°C. IR: ν 1730, 1693 (2 × CO). ^{1}H NMR ($CDCl_3$): δ 1.94 (m, 2H, 2′-H), 2.38 (t, $J = 4.5$ Hz, 4H, 2″-H, 6″-H), 2.46 (t, $J = 6.4$ Hz, 2H, 3′-H), 3.57 (t, $J = 4.5$ Hz, 4H, 3″-H, 5″-H), 4.13 (t, $J = 6.5$ Hz, 2H, 1′-H), 7.31 (s, 1H, H-10), 7.68–8.60 (m, 4H, 6-H, 7-H, 8-H, 9-H). ^{13}C NMR ($CDCl_3$): δ 23.20 (C-2′), 39.89 (C-3′), 53.65 (C-2″, C-6″), 56.23 (C-1′), 66.95 (C-3″, C-5″), 108.78 (C-10), 127.11, 129.42, 129.50, 129.98, 130.84, 133.07, 134.27 (C-Ar), 157.85 (C-5), 161.04 (C-1), 172.60 (C-3). MS, $m/z = 357$ (M^+). Calcd. for $C_{18}H_{19}N_3O_3S$ (357.42): C, 60.49; H, 5.36; N, 11.75. Found: C, 60.28; H, 5.48; N, 11.57.

*2-(3-Dimethylaminopropyl)-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4g)*

Yield 250 mg (79%; method A), 233 mg (74%; method B) of yellow crystals, m.p. 199–201°C. IR: ν 1739, 1691 (2 × CO). ^{1}H NMR ($CDCl_3$): δ 2.33 (m, 2H, H-2′), 3.00 (s, 6H, NMe_2), 3.34 (m, 2H, H-3′), 4.21 (m, 2H, H-1′), 7.60 (s, 1H, H-10), 7.82–8.61 (m, 4H, 6-H, 7-H, 8-H, 9-H). ^{13}C NMR ($CDCl_3$): δ 23.49 (C-2′), 38.58 (C-3′), 44.37 (CH_3), 56.76 (C-1′), 113.30 (C-10), 126.37, 129.24, 130.83, 130.99, 132.96, 133.77, 136.37 (C-Ar), 158.85 (C-5), 163.26 (C-1), 172.37 (C-3). MS, $m/z = 315$ (M^+). Calcd. for $C_{16}H_{17}N_3O_2S$ (315.39): C, 60.93; H, 5.43; N, 13.32. Found: C, 60.78; H, 5.60; N, 13.56.

*2-Benzyl-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4h)*

Yield 300 mg (94%; method A), 282 mg (88%; method B) of yellow crystals, m.p. 216–218°C. IR: ν 1737, 1694 (2 × CO). ^{1}H NMR ($CDCl_3$): d5.22 (s, 2H, H-1′), 7.29–8.56 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H, C_6H_5). MS, $m/z = 320$ (M^+). Calcd. for $C_{18}H_{12}N_2O_2S$ (320.37): C, 67.48; H, 3.78; N, 8.74. Found: C, 67.25; H, 4.00; N, 8.62.

*2-(2-Phenylethyl)-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (4i)*

Yield 284 mg (85%; method A), 242 mg (72%; method B) of yellow crystals, m.p. 210–212°C. IR: ν 1730, 1691 (2 × CO). ^{1}H NMR ($CDCl_3$): δ 3.05 (t, $J = 7.60$ Hz, 3H, 2′-H), 4.28 (s, 2H, 1′-H), 7.55 (s, 1H, 10-H), 7.26–8.63 (m, 9H, 6-H, 7-H, 8-H, 9-H, C_6H_5). Dept-135 NMR ($CDCl_3$): δ 33.26 (C-2′), 43.23 (C-1′), 111.99 (C-10), 127.40, 129.07, 129.14, 130.43, 130.58, 132.22, 135.68 (Ar-H_C). MS, $m/z = 334$ (M^+). Calcd. for $C_{19}H_{14}N_2O_2S$ (334.39): C, 68.25; H, 4.22; N, 8.38. Found: C, 68.12; H, 4.45; N, 8.03.

*2-Phenyl-3-thioxo-2*H-*imidazo[1,5-*b*]isoquinoline-1,5-dione (4j)*

Yield 300 mg (98%; method A) of yellow crystals, m.p. 343–345°C (Lit.[16] m.p. 342°C and Lit.[17] m.p. 300°C). IR: ν 1739, 1694 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 7.67 (s, 1H, H-10), 7.38–8.45 (m, 9H, 6-H, 7-H, 8-H, 9-H, C_6H_5). MS, $m/z = 306$ (M^+).

*2-(2-Chlorophenyl)-3-thioxo-2*H-*imidazo[1,5-*b*]isoquinoline-1,5-dione (4k)*

Yield 224 mg (66%; method A) of yellow crystals, m.p. 289–291°C. IR: ν 1738, 1694 (2 × C). ^{1}H NMR (DMSO-d_6): δ 7.43–8.50 (m, 9H, 6-H, 7-H, 8-H, 9-H, 10-H, C_6H_4). MS, $m/z = 340$ (M^+). Calcd. for $C_{17}H_9ClN_2O_2S$ (340.78): C, 59.92; H, 2.66; N, 8.22. Found: C, 59.76; H, 2.58; N, 8.15.

*2-(4-Methylphenyl)-3-thioxo-2*H-*imidazo[1,5-*b*]isoquinoline-1,5-dione (4l)*

Yield 300 mg (94%; method A) of yellow crystals, m.p. 310–312°C. IR: ν 1734, 1691 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.27–8.43 (m, 9H, 6-H, 7-H, 8-H, 9-H, 10-H, C_6H_4). MS, $m/z = 320$ (M^+). Calcd. for $C_{18}H_{12}N_2O_2S$ (320.37): C, 67.48; H, 3.78; N, 8.74. Found: C, 67.62; H, 3.98; N, 8.54.

2-(4-Morpholinomethyl)-3-thioxo-2*H*-imidazo[1,5-*b*]isoquinoline-1,5-dione (6)

A mixture of **3** (230 mg, 1 mmol) and morpholine (87 mg, 1 mmol mole) in EtOH (3 ml) was added to 36% aqueous formaldehyde (0.1 ml, 1 mmol). After stirring at temperature for 12 h the precipitate was collected by filtration. Recrystallization from EtOH gave the product **6**, yield 299 mg (91%) of orange crystals, m.p. 226–228°C. IR: ν 1737, 1693 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 2.30 (m, 4H, 2′-H, 6′-H), 3.50 (m, 4H, 3′-H, 5′-H), 4.57 (s, 2H, CH_2), 7.25 (s, 1H, 10-H), 7.45, 7.65 (2t, $J = 7.70$ Hz, 2H, 7-H, 8-H), 7.76, 8.15 (2d, $J = 7.8$ Hz, 2H, 6-H, H-9). ^{13}C NMR (DMSO-d_6): δ 51.13 (C-2′, C-6′), 65.86 (CH_2), 66.28 65.96 (C-3′, C-5′), 107.65 (C-10), 128.87, 128.24, 129.10, 130.01, 130.56, 134.02, 134.34 (C-Ar), 157.71 (C-5), 162.63 (C-1), 175.82 (C-3). MS, $m/z = 329$ (M^+). Calcd. for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.34; H, 4.59; N, 12.76. Found: C, 58.24; H, 4.58; N, 12.60.

3-(Alkylmercapto)imidazo[1,5-*b*]isoquinoline-1,5-diones (7a,b)

Aqueous NaOH (2.2%, 10 ml) was added to a suspension of **3** (1.15 g, 5 mmol) in MeOH (20 ml). After addition of MeI (0.35 g, 5 mmol) or

allyl iodide (0.84 g, 5 mmol), the reaction mixture was stirred at room temperature for 12 h. Filtration and recrystallization of the residue from MeOH afforded the products **7a,b**, respectively.

*3-(Methylmercapto)imidazo[1,5-*b*]isoquinoline-1,5-dione (7a)*

Yield 212 mg (87%) of red crystals, m.p. 294–296°C. IR: ν 1718, 1675 (2 × CO). ^{1}H NMR (DMSO-d_6): δ 2.68 (s, 3H, SCH_3), 7.56 (s, 1H, H-10), 7.70, 7.82 (2t, J = 8.1 Hz, 2H, 7-H, 8-H), 7.90, 8.36 (2d, J = 7.1 Hz, 2H, 6-H, 9-H). MS, m/z = 244 (M^+). Calcd. for $C_{12}H_8N_2O_2S$ (244.26): C, 59.01; H, 3.30; N, 11.47. Found: C, 59.23; H, 3.58; N, 11.34.

*3-(Allylmercapto)imidazo[1,5-*b*]isoquinoline-1,5-dione (7b)*

Yield 201 mg (74%) of orange crystals, m.p. 222–224°C. IR: ν 1718, 1676 (2 × CO). ^{1}H NMR ($CDCl_3$): δ 4.04 (d, J = 7.00 Hz, 2H, 3′-H), 5.40 (m, 2H, 1′-H), 6.06 (m, 1H, 2′-H), 7.42 (s, 1H, 10-H), 7.75–8.5 (m, 4H, 6-H, 8-H, 7-H, H-9). ^{13}C NMR ($CDCl_3$): δ 35.93 (C-3′), 111.73 (C-10), 120.54 (C-2′), 127.66 (C-1′), 125.90, 129.46, 129.99, 130.84, 134.69, 134.89 (C-Ar), 157.45 (C-5), 172.60 (C-1), 179.11 (C-3). MS, m/z = 270 (M^+). Calcd. for $C_{14}H_{10}N_2O_2S$ (270.31): C, 62.21; H, 3.73; N, 10.36. Found: C, 62.00; H, 3.84; N, 10.32.

2*H*-Imidazo[1,5-*b*]isoquinoline-1,3,5-trione (8)

A solution of **7a** (0.24 g, 1 mmol) in EtOH (10 ml) containing 12M HCl (1 ml) was refluxed for 2 h. After cooling to room temperature, the precipitate was filtered off and crystallized from AcOH to give product **8**, yield 167 mg (78%) of pale yellow crystals, m.p. 286–288°C (Lit.[16] m.p. 278°C). IR: ν 3065 (N—H), 1786, 1735, 1672 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 7.34 (s, 1H, 10-H), 7.57–8.24 (m, 4H, 6-H, H-7, H-8, H-9), 10.52 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 106.31 (C-10), 127.08, 127.10, 127.18, 127.93, 128.46, 132.12, 134.43 (C-Ar), 136.52 (C-3), 161.33 (C-5), 162.93 (C-1). MS, m/z = 214 (M^+).

2-(2*H*-1,5-Dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)benzoic Acid (10a)

A mixture of **7a** (460 mg, 2 mmol) and anthranilic acid (300 mg, 2 mmol), respectively 4,5-dimethoxy-2-aminobenzoic acid (400 mg, 2 mmol), respectively 3-amino-2-naphthoic acid (374 mg, 2 mmol) in EtOH (10 ml) was heated under reflux for 24 h. After cooling to room temperature the precipitate was collected by filtration and recrystallized from DMF to

give the product **10a**: Yield 500 mg (75%) of yellow crystals, m.p. 258–260°C. IR: ν 3064 (NH), 1780, 1720, 1670 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 7.52 (s, 1H, 10-H), 7.33–8.77 (m, 8H, Ar-H), 13.31 (s, 1H, NH), 13.68 (br. s, 1H, COOH). MS, $m/z = 333$ (M^+). Calcd. for $C_{18}H_{11}N_3O_4$ (333.31): C, 64.86; H, 3.33; N, 12.60. Found: C, 64.62; H, 3.50; N, 12.49.

4,5-Dimethoxy-2-(2*H*-1,5-dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)benzoic Acid (10b)

From 400 mg (2 mmol) of 4,5-dimethoxy-2-aminobenzoic acid in the manner described for **10a**. Recrystallization from DMF afforded **10b**, yield 495 mg (62%) of yellow crystals, m.p. >300°C. IR: ν 3067 (NH), 1776, 1718, 1674 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 3.81, 3.91 (2s, 6H, 3 CH_3), 7.37–8.61 (m, 7H, H-Ar), 13.57 (s, 1H, NH). MS, $m/z = 393$ (M^+). Calcd. for $C_{20}H_{15}N_3O_6$ (393.34): C, 61.07; H, 3.84; N, 10.68. Found: C, 60.85; H, 3.66; N, 10.52.

3-(2*H*-1,5-Dioxoimidazo[1,5-*b*]isoquinazolin-3-ylideneamino)-2-naphthalenecarboxylic Acid (13)

From 374 mg (2 mmol) of 3-amino-2-naphthoic acid in the manner described for **10a**. Recrystallization from DMF afforded **13**, yield 520 mg (68%) of yellow crystals, m.p. >300°C. IR: ν 3068 (NH), 1779, 1719, 1672 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 7.51–9.68 (m, 11H, Ar-H), 12.30 (s, 1H, NH). MS, $m/z = 383$ (M^+). Calcd. for $C_{22}H_{13}N_3O_4$ (383.37): C, 68.93; H, 3.42; N, 10.96. Found: C, 68.78; H, 3.64; N, 10.71.

15*H*-Isoquino[2′,3′:3,4]imidazo[2,1-*b*]quinazoline-7,13,15-trione (11a)

A mixture of **10a** (333 mg, 1 mmol) and Ac_2O (3 ml) was heated under reflux for 2 h. The reaction mixture was poured into ice water. The precipitate was collected by filtration and recrystallized from DMF to give the product **11a**, yield 299 mg (95%) of orange crystals, m.p. >350°C. IR: ν 1779, 1717, 1691 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 7.79–8.59 (m, 9H, H-Ar). ^{13}C NMR (DMSO-d_6): δ 110.90 (C-12), 120.16, 122.18, 122.18, 122.84, 123.40, 127.86, 131.39, 131.76, 132.53, 133.94, 135.53, 135.77, 136.09, 136.65, 139.29, 140.48 (C-Ar), 149.42, 154.81, 156.35 (C-7, C-13, C-15). (MS, $m/z = 315$ (M^+). Calcd. for $C_{18}H_9N_3O_3$ (315.29): C, 68.57; H, 2.88; N, 13.32. Found: C, 68.36; H, 3.09; N, 13.18.

2,3-Dimethoxy-15*H*-isoquino[2′,3′:3,4]imidazo[2,1-*b*]-quinazoline-7,13,15-trione (11b)

From 393 mg (1 mmol) of **10b** in the manner described for **11a**. Recrystallization from DMF afforded **11b**, yield 337 mg (90%) of yellow crystals, m.p. >300°C. IR: ν 1779, 1718, 1691 (3 × CO). ^{1}H NMR (DMSO-d_6): δ 3.66, 3.82 (2s, 6H, 3 CH_3), 7.19–8.20 (m, 7H, H-Ar). MS, $m/z = 375$ (M^+). Calcd. for $C_{20}H_{13}N_3O_5$ (375.34): C, 64.00; H, 3.49; N, 11.19. Found: C, 63.83; H, 3.68; N, 10.90.

14*H*-Isoquino[2′,3′:3,4]imidazo[2,1-*b*]benzo[*g*]quinazoline-8,14,16-trione (14)

From 383 mg (1 mmol) of **13** in the manner described for **11a**. Recrystallization from DMF afforded **14**, yield 314 mg (86%) of orange crystals, m.p. >350°C. IR: ν 1780, 1716, 1694 cm^{-1} (3 × CO). ^{1}H NMR (DMSO-d_6): δ 7.76–8.60 (m, 11H, H—Ar); (MS, $m/z = 365$ (M^+). Calcd. for $C_{22}H_{11}N_3O_3$ (365.35): C, 72.33; H, 3.03; N, 11.50. Found: C, 72.06; H, 3.18; N, 11.28.

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