Synthesis of Indolin-2-one, Isoindolin-1-one, and Indole Derivatives from Homophthalic Acid

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Abstract: We hereby report the preparation of indolin-2-one and isoindolin-1-one and their derivatives starting from 2-(carboxymethyl)benzoic acid, which was first regiospecifically converted into the isomeric half esters. Transformation of the acid functionalities to the acyl azides followed by Curtius rearrangement gave the regioisomeric isocyanates. Reaction of the isocyanates with aniline produced urethane derivatives. Intramolecular cyclization provided the target compounds.

Key words: amides, azides, fused-ring systems, heterocycles, indoles

Figure 1

The indole scaffold is a core nucleus for many biologically active molecules.[1,2] Accordingly, after 100 years of intensive research, a variety of methods for elaborating and functionalizing indoles have been established.[3] Substituted indoles have been referred to as 'privileged structures' since they are capable of binding to many receptors with high affinity.[3a] Key factors, including starting material availability and functional group tolerance, often dictate the most convenient indole synthesis.

Indolin-2-one (**2**), an oxidation product of 1*H*-indole (**1**) (Figure 1), and its derivatives have been designed as a novel class of tyrosine kinase inhibitors, which exhibit selectivity towards different receptor tyrosine kinases (RTKs).[4–8] Various indolin-2-ones have been identified as pharmacologically active compounds in extracts of the traditional anti-inflammatory herb, *Isatis tinctoria*.[7] Furthermore, it has been shown that they inhibit compound 48/80-induced mast cell degranulation in vitro. Since in-
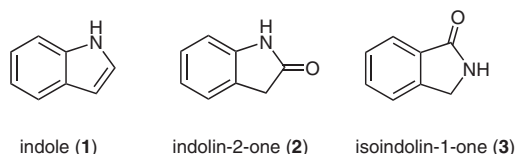
dolinone systems are useful and important in the field of medicinal chemistry, the development of simple, convenient, and high-yielding protocols is desirable.

Isoindolinone (**3**) derivatives also show a wide range of important biological activity. A series of isoindolinone derivatives have recently been synthesized[9] and screened. Some substituted isoindolinone derivatives show potent metabotropic glutamate receptor 1 antagonist activity.[10] Moreover, it has been demonstrated that some derivatives exhibit antipsychotic-like effects in animal models. Among others, N-substituted isoindolin-1-ones were selected for further evaluation in the treatment of schizophrenia with neuroleptic drugs.[11,12] Several methods have been developed for the synthesis of isoindolinone derivatives.[13–19] In this paper we describe a new route for the synthesis of the indolinone and isoindolinone skeletons based upon Curtius rearrangement of the azides derived from isomeric [2-(methoxycarbonyl)phenyl]acetic acid (**4**) and 2-(2-methoxy-2-oxoethyl)benzoic acid (**5**). As the starting material, homophthalic acid **6** and its derivatives were used. Our plan for the construction of the desired heterocyclic ring systems **2** and **3** involved an intramolec-
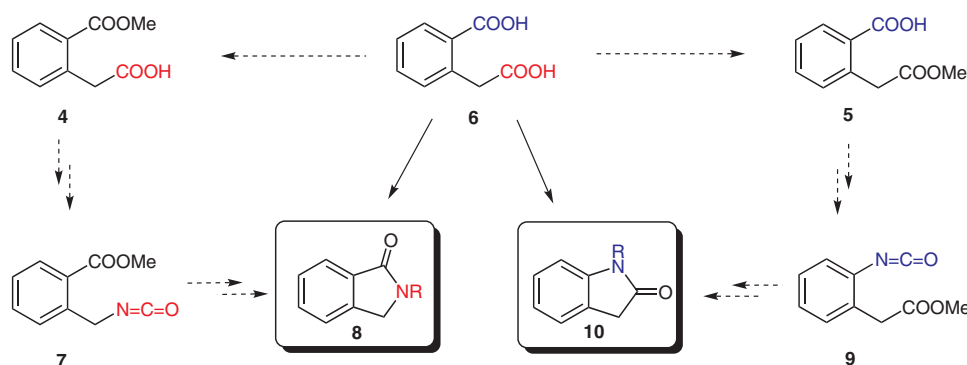

Scheme 1 Retrosynthetic analysis of indolinone and isoindolinone derivatives

ular cyclization reaction of the isocyanates **7** and **9**, which can be generated by Curtius rearrangement[20] of the corresponding acyl azides. Retrosynthetic analysis, following the sequences outlined in Scheme 1, led us to plan to synthesize the regioisomeric half esters **4** and **5** starting from diacid **6**.

The starting materials **4a–c** were synthesized as described in the literature.[21,22] The esterification of homophthalic acid derivatives **6a–c** was carried out in refluxing methanol in the presence of thionyl chloride to give the diesters **11a–c**. Recently, we reported that the reactivity of the ester carbonyl groups in similar systems are different.[23] The ester functionality adjacent to the CH₂ group is more reactive than the other. Therefore, the regiospecific hydrolysis of the ester functionalities in **11a–c** was possible. Reaction of **11a–c** with potassium carbonate in refluxing methanol–water (1:1) gave the half esters **4a–c** in 60–74% yields (Scheme 2).

The most general and versatile synthesis of acyl azides involves the reaction of acyl chlorides with sodium azide in aqueous medium. The half esters **4** were treated with oxalyl chloride in dichloromethane in the presence of a catalytic amount of *N,N*-dimethylformamide to give acyl

chlorides **12** followed by the addition of a solution of sodium azide in water. The azide formation was successful and provided acyl azides **13a–c** in 80–85% yields. When the acyl azides **13a–c** were refluxed in methanol for 12 hours, the desired urethane derivatives **15a–c** were obtained in 48–86% yields. Alternately, acyl azides **13a–c** were refluxed in benzene to form isocyanates **14a–c**, which were reacted with aniline in dichloromethane to give the urea derivatives **16a–c**. After satisfactory synthesis of urea and urethanes, we focused on the ring-closure reactions. When urethanes **15a–c** were treated with potassium carbonate in acetonitrile, they cyclized smoothly to give the isoindolinone derivatives **17** in high yields. Analysis of ¹H and ¹³C NMR and elemental analysis data suggested that the desired isoindolinones **17a–c** were formed. Accordingly, the reaction of urea derivatives **16a–c** with potassium carbonate afforded isoindolinonecarboxamides **18a–c** in 83–85% yields. In the cyclization reaction of **16**, two cyclization products **18** and **19** were expected as a result of the attack of the two different amide functionalities on the ester carbonyl group. The formation of five-membered ring **18** was preferred over the seven-membered ring **19** (Figure 2).
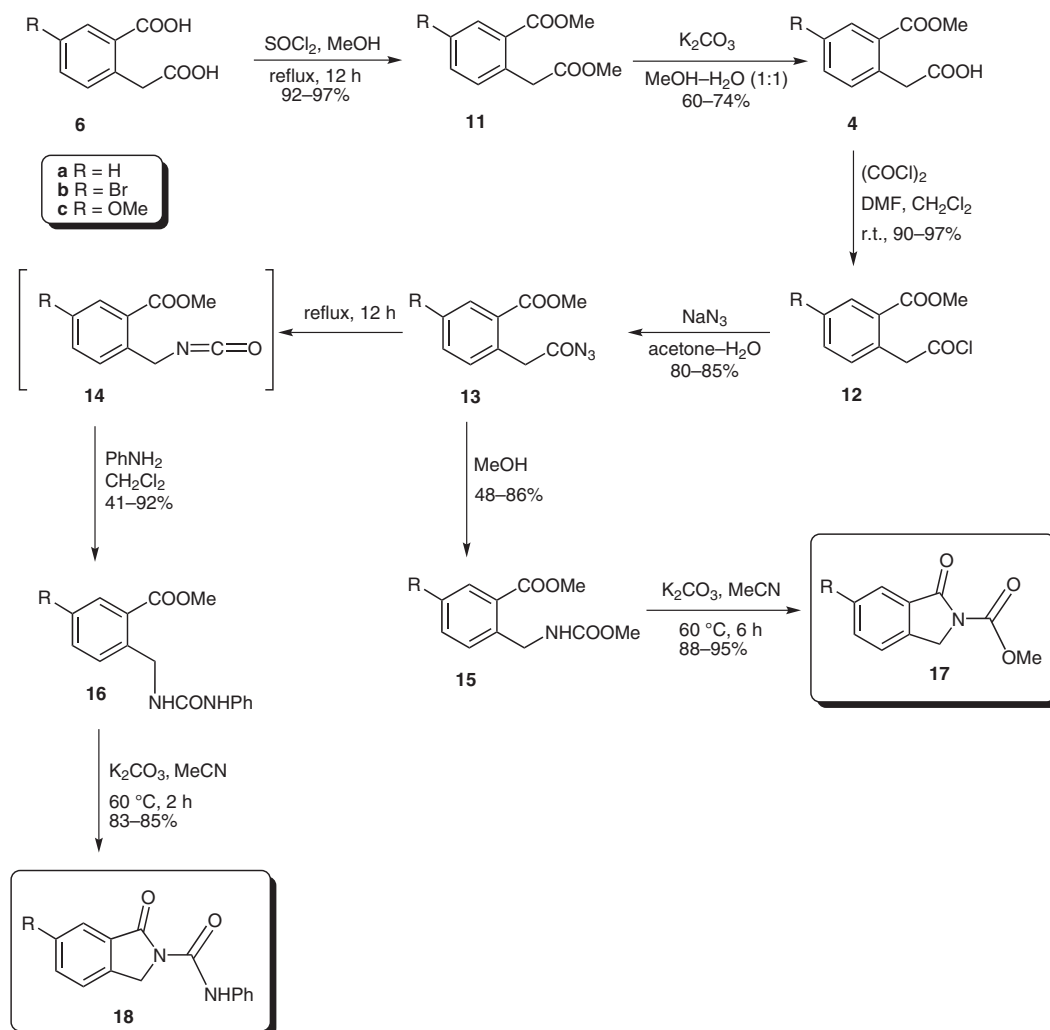
Scheme 2 Synthesis of isoindolin-1-one derivatives **17a–c** and **18a–c** starting from substituted homophthalic acids **4a–c**
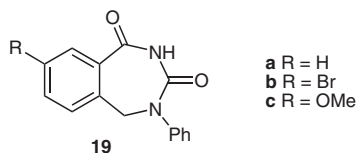
Figure 2

After successful completion of the synthesis of isoindolinones **17** and **18**, we turned our attention to the synthesis of indolinone derivatives **2**. Recently, we synthesized the half ester **5** and studied its ring-closure reactions. As an extension of this work we have searched the general applicability of this methodology to substituted homophthalic acid derivatives.[24] Synthesis of half esters **5a,b** was achieved through the reaction of methanol at reflux temperature with anhydrides **20a,b**,[21b,25–27] which were obtained by reaction of the diacids **6** with thionyl chloride (Scheme 3). Methanol regioselectively attacks the more reactive carbonyl group which is attached to the methylene group. The reactivity of the other carbonyl group is decreased due to conjugation with the benzene ring.

The half esters **5a,b** were reacted with ethyl chloroformate in the presence of triethylamine followed by addition of a solution of sodium azide in water. Azide formation was successful and provided acyl azides **21a,b** in 92% yield. Curtius rearrangement of acyl azides **21a,b** in refluxing benzene furnished isocyanates **22a,b**, which were easily transformed to urea derivatives **23a,b** upon treatment with aniline. Finally, we focused our effort on the ring-closure reaction of **23** already bearing the necessary

functionalities as shown in Scheme 3. The ring-closure reaction of **23** was accomplished by treatment with potassium carbonate in acetonitrile. The NMR spectral studies indicated the formation of two major products, the intermolecular condensation products **24** and the fragmentation products **25**. In the case of methoxy derivative **23b**, additionally two minor products **26b** and **27** were isolated.

The expected products **28** were not found in the isolated products. However, we assume that the ring-cyclization products **28** are generated as intermediates by an intramolecular cyclization reaction of **23** to form a five-membered ring. Since the methylene protons in **28** are more acidic than the methylene protons in **18**, the reaction proceeds further and base abstracts an α-proton to form the carbanion **29**, which can undergo an intermolecular reaction with indolinone derivatives **28** to form **30** followed by a fragmentation reaction to furnish the products **24** and **25** (Scheme 4).
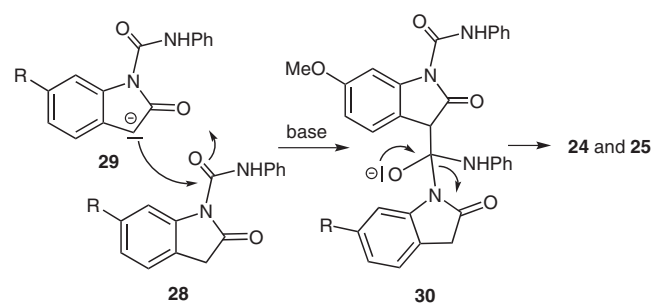
Scheme 4 Formation mechanism of the products **24** and **25**
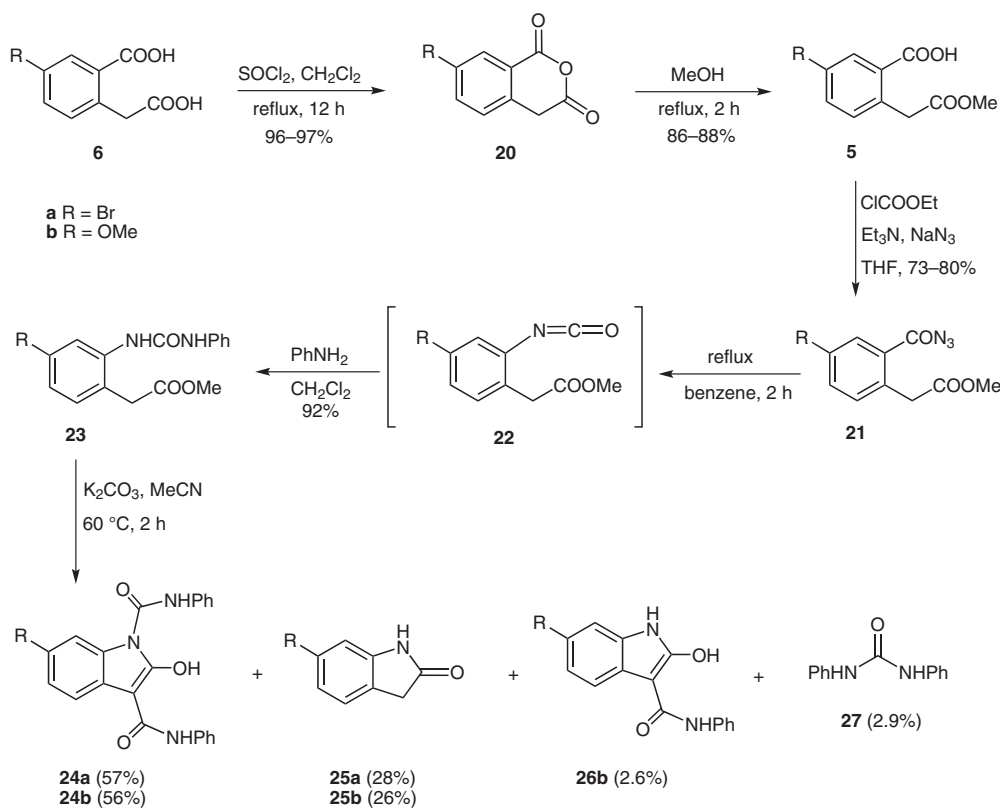
Scheme 3 Synthesis of indolin-2-one and some indole derivatives starting from substituted homophthalic acids **4a,b**
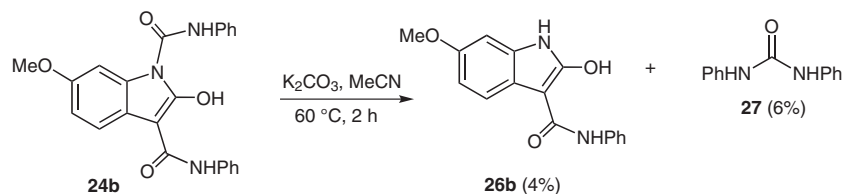
Scheme 5   Reaction of cyclization product **24b** with potassium carbonate
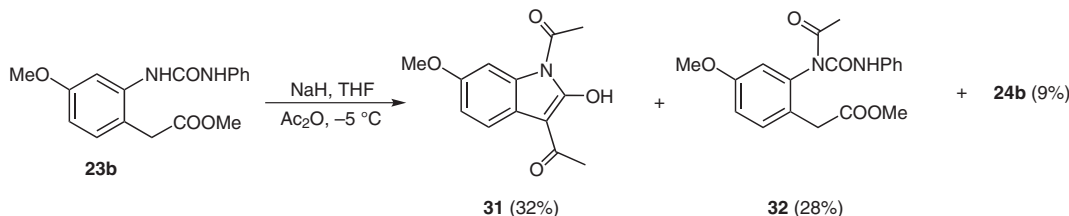
Scheme 6   Cyclization of urea derivative **23b** in the presence of acetic anhydride

The major product **24b** was proposed as an intermediate for the formation of the side products **26b** and **27** due to a resemblance between their structures. Then the major product **24b** was reacted under identical conditions to clarify these suspicions (Scheme 5). Treatment of the indole derivative **24b** with potassium carbonate in acetonitrile for two hours yielded the same products **26b** and **27**. It was proven that these compounds are secondary compounds and that they were formed by a hydrolysis reaction.

We assume that first carboxamide unit attached to nitrogen atom slowly undergoes hydrolysis with potassium carbonate to form the indole derivative **26b** and aniline. The formed aniline attacks the carboxamide unit in **24b** attached to nitrogen atom to form **26b** and *N,N′*-diphenyl-urea **27**.

To prevent the intermolecular condensation shown in Scheme 5 and as a further support for the formation mechanism of **24** and **25**, the proposed intermediate **29** shown in Scheme 4 was trapped with acetic anhydride. For this purpose, the urea derivative **23b** was treated with sodium hydride in the presence of acetic anhydride in tetrahydrofuran (Scheme 6). Interestingly, the formation of three products was observed: an acetylated urea derivative **32**, diacetylated indole **31**, along the intermolecular condensation product **24b**, which was the major product of the potassium carbonate based cyclization process.

The presented results establish that cyclization of acyl azides is a valuable method for the synthesis of heterocyclic compounds. In conclusion, we have developed a new synthetic methodology for construction of N-substituted isoindolin-1-one derivatives. Furthermore, by starting from benzene ring substituted diesters, further substituted isoindolin-1-one derivatives can be synthesized. By application of the same methodology to half esters **5**, isoindolin-2-one derivatives **28** are formed as the intermediates. Due to the acidic methylene protons in **28**, they undergo further condensation reactions. However, if the intermediate is trapped with electrophiles, various indole derivatives substituted at the benzene ring as well as at the five-membered ring can be synthesized.

Melting points are uncorrected. Infrared spectra were obtained from a soln (CHCl₃) in 0.1-mm cells or KBr pellets on an FT-IR Bruker Vertex 70 instrument. ¹H and ¹³C NMR spectra were recorded on a Bruker-Biospin (DPX-400) instrument. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck), TLC was carried out on Merck 0.2 mm silica gel 60 F₂₅₄ analytical aluminum plates. Elemental analyses were carried out on a Leco-932 model CHNS analyzer.

Diesters 11a–c; General Procedure

To a soln of homophthalic acid **6a–c** (10.0 mmol) in MeOH (50 mL) was added SOCl₂ (3.57 g, 30.0 mmol) dropwise at r.t.; the mixture was refluxed for 12 h. After completion of the reaction, the solvent was evaporated to give diester **11a–c**. Chromatography of the residue over a short column (silica gel, CH₂Cl₂) gave pure diester.

Methyl 2-(2-Methoxy-2-oxoethyl)benzoate (11a)

Colorless oil; yield: 1.93 g (93%).[21b,28]

Methyl 5-Bromo-2-(2-methoxy-2-oxoethyl)benzoate (11b)

White powder; yield: 2.63 g (92%); mp 101–103 °C.

IR (KBr): 2991, 2951, 1723, 1591, 1288, 1254, 1167 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.06 (d, $J_{6,4}$ = 2.1 Hz, 1 H, H6), 7.51 (dd, $J_{4,3}$ = 8.1 Hz, $J_{4,6}$ = 2.1 Hz, 1 H, H4), 7.05 (d, $J_{3,4}$ = 8.2 Hz, 1 H, H3), 3.88 (s, 2 H, CH₂), 3.79 (s, 3 H, OCH₃), 3.61 (s, 3 H, OCH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 171.3, 166.1, 135.2, 134.9, 133.9, 133.8, 131.3, 121.1, 52.3, 52.0, 39.8.

Anal. Calcd for C₁₁H₁₁BrO₄: C, 46.02; H, 3.86. Found: C, 46.23; H, 3.75.

Methyl 5-Methoxy-2-(2-methoxy-2-oxoethyl)benzoate (11c)

Colorless oil; yield: 2.31 g (97%). The analytical data are in accord with literature values.[29]

2-(Methoxycarbonyl)phenylacetic Acid (4a); Typical Procedure

To a soln of diester **11a** (4.0 g, 19.2 mmol) in MeOH–H₂O (1:1, 50 mL) was added K₂CO₃ (3.98 g, 28.8 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H₂O was added. To remove the unreacted diester **12a**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M

HCl and extracted with EtOAc. Evaporation of the solvent gave pure **4a** as a white solid; yield: 2.4 g (64%); mp 147–148 °C (Lit.[30] 146–148 °C). The analytical data are in accord with literature values.

[4-Bromo-2-(methoxycarbonyl)phenyl]acetic Acid (4b)

Following the typical procedure for **4a** using diester **11b** (2.82 g, 9.82 mmol) gave **4b** as a colorless viscous liquid; yield: 1.75 g (73%, based on reacted diester **11b**); mp 161–163 °C.

IR (KBr): 3500, 2953, 1706, 1435, 1288, 1255, 1080 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.00–10.20 (br s, 1 H, OH), 8.07 (d, $J_{3,5}$ = 2.2 Hz, 1 H, H3), 7.52 (dd, $J_{5,6}$ = 8.2 Hz, $J_{5,3}$ = 2.2 Hz, 1 H, H5), 7.05 (d, $J_{6,5}$ = 8.2 Hz, 1 H, H6), 3.90 (s, 2 H, CH$_2$), 3.80 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 175.5, 165.4, 134.5, 133.3, 133.0, 132.9, 130.1, 120.5, 51.5, 39.0.

[4-Methoxy-2-(methoxycarbonyl)phenyl]acetic Acid (4c)

Following the typical procedure for **4a** using diester **11c** (1.45 g, 6.09 mmol) gave **4c** as a white solid; yield: 0.82 g (60%, based on reacted diester **13c**); mp 136–137 °C (Lit.[30] 79–81 °C). The analytical data are in accord with literature values.[30,31]

Methyl 2-(2-Chloro-2-oxoethyl)benzoate (12a); Typical Procedure

To a stirred suspension of half ester **4a** (2.0 g, 10.2 mmol) in CH$_2$Cl$_2$ (25 mL) was added oxalyl chloride (1.57 g, 12.2 mmol) and DMF (2 drops) as catalyst. The resulting soln was stirred at r.t. for 1 h. After completion of the reaction, the solvent was evaporated to give **12a** (1.97 g, 90%) as a colorless viscous oil. The analytical data are in accord with literature values.[25]

Methyl 5-Bromo-2-(2-chloro-2-oxoethyl)benzoate (12b)

Following the typical procedure for **12a** using half ester **4b** (0.82 g, 3.0 mmol) gave **12b** as a yellowish oil (0.85 g, 97%).

IR (KBr): 2953, 1799, 1721, 1259, 963, 752 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.15 (d, $J_{6,4}$ = 2.2 Hz, 1 H, H6), 7.58 (dd, $J_{4,3}$ = 8.1 Hz, $J_{4,6}$ = 2.2 Hz, 1 H, H4), 7.06 (d, $J_{3,4}$ = 8.2 Hz, 1 H, H3), 4.42 (s, 2 H, CH$_2$), 3.84 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.3, 165.7, 135.8, 134.4, 133.7, 132.9, 130.7, 122.5, 52.6, 51.9.

Methyl 2-(2-Chloro-2-oxoethyl)-5-methoxybenzoate (12c)

Following the typical procedure for **12a** using half ester **4c** (0.79 g, 3.52 mmol) gave **12c** as yellowish oil (0.81 g, 95%).

IR (KBr): 2954, 1799, 1716, 1287, 904 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.61 (d, $J_{6,4}$ = 2.8 Hz, 1 H, H6), 7.16 (d, $J_{3,4}$ = 8.5 Hz, 1 H, H3), 7.06 (dd, $J_{3,4}$ = 8.5 Hz, $J_{6,4}$ = 2.8 Hz, 1 H, H4), 4.46 (s, 2 H, CH$_2$), 3.91 (s, 3 H, OMe), 3.85 (s, 3 H, OMe).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.2, 166.8, 159.4, 133.3, 130.1, 126.0, 118.7, 116.3, 55.6, 52.4, 51.9.

Methyl 2-(2-Azido-2-oxoethyl)benzoate (13a); Typical Procedure

To a soln of acyl chloride **12a** (1.8 g, 8.25 mmol) in acetone (30 mL) was added a soln of NaN$_3$ (1.66 g, 25.5 mmol) in H$_2$O (10 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. After the addition of H$_2$O (25 mL) the mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts were washed with sat. NaHCO$_3$ and H$_2$O, and dried (MgSO$_4$). After concentration of the solvent, acyl azide **13a** (1.58 g, 85%), unstable at r.t., was obtained as a pale-yellow solid, which was used for the next step without purification.

IR (KBr): 3002, 2953, 2265, 2139, 1716, 1579, 1435, 1270 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.95 (d, $J_{5,6}$ = 7.8, $J_{4,6}$ = 1.4 Hz, 1 H, H6), 7.43 (dt, $J_{5,6}$ = 7.5 Hz, J = 1.4 Hz, 1 H, H4), 7.32 (d, J = 7.6, 1.2 Hz, 1 H, H5), 7.17 (br d, J = 7.6 Hz, 1 H, H3), 3.96 (s, 2 H, CH$_2$), 3.81 (s, 3 H, OCH$_3$).

Methyl 2-(2-Azido-2-oxoethyl)-5-bromobenzoate (13b)

Following the typical procedure for **13a** using acyl chloride **12b** (1.54 g, 5.28 mmol) gave **13b** (1.34 g, 85%) as a yellowish oil.

IR (KBr): 2952, 2316, 1716, 1640, 1289, 1254, 1064, 833 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.12 (d, $J_{3,5}$ = 2.2 Hz, 1 H, H3), 7.56 (dd, $J_{5,6}$ = 8.1 Hz, $J_{5,3}$ = 2.2 Hz, 1 H, H5), 7.05 (d, $J_{6,5}$ = 8.2 Hz, 1 H, H6), 3.92 (s, 2 H, CH$_2$), 3.83 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 176.7, 164.9, 134.5, 133.1, 133.0, 132.9, 130.0, 120.7, 51.4, 41.3.

Methyl 2-(2-Azido-2-oxoethyl)-5-methoxybenzoate (13c)

Following the typical procedure for **13a** using acyl chloride **12c** (1.51 g, 6.22 mmol) gave **13c** (1.39 g, 89%) as a yellowish oil.

IR (KBr): 2953, 2254, 2138, 1716, 1610, 1504, 1275, 905, 728 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.57 (d, $J_{3,5}$ = 2.6 Hz, 1 H, H3), 7.16 (d, $J_{6,5}$ = 8.4 Hz, 1 H, H6), 7.05 (dd, $J_{5,6}$ = 8.4 Hz, $J_{5,3}$ = 2.6 Hz, 1 H, H5), 3.96 (s, 2 H, CH$_2$), 3.89 (s, 3 H, OCH$_3$), 3.85 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 178.7, 167.1, 158.9, 133.5, 130.2, 127.1, 118.6, 116.1, 55.5, 52.2, 42.2.

Methyl 2-{[(Methoxycarbonyl)amino]methyl}benzoate (15a); Typical Procedure

A soln of acyl azide **13a** (2.0 g, 9.13 mmol) in MeOH (150 mL) was refluxed for 12 h with TLC monitoring. After completion of reaction, the solvent was removed under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc–hexane–CH$_2$Cl$_2$, 1:1:2) afforded **15a** (163 g, 86%) as a pale-yellow solid.

IR (KBr): 3349, 2952, 1704, 1650, 1508, 1434, 1252 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.91 (br d, $J_{6,5}$ = 7.8 Hz, 1 H, H6), 7.43 (m, 2 H, H4, H3), 7.28 (br d, $J_{5,6}$ = 7.8 Hz, 1 H, H5), 5.75 (br s, 1 H, NH), 4.48 (d, $J_{1(NH)}$ = 6.6 Hz, 2 H, CH$_2$), 3.87 (s, 3 H, OCH$_3$), 3.56 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.7, 157.0, 140.5, 132.9, 131.3, 131.0, 128.7, 127.7, 52.2, 51.0, 42.3.

Methyl 5-Bromo-2-{[(methoxycarbonyl)amino]methyl}benzoate (15b)

Following the typical procedure for **15a** using acyl azide **13b** (1.54 g, 5.17 mmol) gave **15b** as colorless solid (0.75 g, 48%); mp 82–83 °C.

IR (KBr): 3442, 2952, 1708, 1497, 1447, 1246, 996 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.05 (d, $J_{6,4}$ = 1.9 Hz, 1 H, H6), 7.55 (dd, $J_{4,3}$ = 8.2 Hz, $J_{4,6}$ = 2.2 Hz, 1 H, H4), 7.35 (d, $J_{3,4}$ = 8.2 Hz, 1 H, H3), 5.73 (br s, 1 H, NH), 4.43 (d, $J_{1(NH)}$ = 6.8 Hz, 2 H, CH$_2$), 3.85 (s, 3 H, OCH$_3$), 3.56 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.4, 157.0, 139.5, 135.7, 133.9, 132.8, 130.2, 121.4, 52.5, 52.1, 43.6.

HRMS: m/z [M + Na]$^+$ calcd for C$_{11}$H$_{12}$NO$_4$Na: 323.9842; found: 323.9842.

Methyl 5-Methoxy-2-{[(methoxycarbonyl)amino]methyl}benzoate (15c)

Following the typical procedure for **15a** using acyl azide **13c** (1.15 g, 4.61 mmol) gave **15c** (0.88 g, 75%) as a colorless oil.

IR (KBr): 3349, 2952, 1707, 1608, 1500, 1217, 1074, 1036 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, $J_{4,6}$ = 2.7 Hz, 1 H, H6), 7.45 (d, $J_{3,4}$ = 8.5 Hz, 1 H, H3), 7.03 (dd, $J_{3,4}$ = 8.5 Hz, $J_{4,6}$ = 2.7 Hz, 1 H, H4), 5.82 (br s, 1 H, NH), 4.47 (br d, J = 6.6 Hz, 2 H, CH$_2$), 3.91 (s, 3 H, OCH$_3$), 3.83 (s, 3 H, OCH$_3$), 3.62 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.5, 158.8, 157.00, 132.8, 129.6, 118.4, 116.1, 55.5, 52.3, 51.9, 43.6.

HRMS: m/z [M + Na]$^+$ calcd for C$_{12}$H$_{15}$NO$_5$Na: 276.0842; found: 276.0843.

Methyl 2-{[(Anilinocarbonyl)amino]methyl}benzoate (16a); Typical Procedure

A soln of acyl azide **13a** (1.4 g, 6.4 mmol) in anhyd benzene (50 mL) was refluxed for 1 h. After completion of the reaction, the mixture was cooled to r.t. and the solvent was removed under vacuum. The formed isocyanate **14a** was dissolved in CH$_2$Cl$_2$ (50 mL). A soln of aniline (700 mg, 7.5 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise at r.t. The resulting mixture was stirred at r.t. for 2 h. The organic phase was extracted with 10% HCl soln and H$_2$O. Evaporation of the solvent gave urea derivative **16a** (1.67 g, 92%). Crystallization (EtOAc–n-hexane, 10:2) gave analytical pure **16a**; mp 136–137 °C.

IR (KBr): 3367, 1718, 1650, 1600, 1552, 1440, 1270, 1084 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.83 (br d, $J_{6,5}$ = 7.7 Hz, 1 H, H6), 7.43 (br d, $J_{3,4}$ = 7.5 Hz, 1 H, H3), 7.32 (dd, $J_{4,5}$ = 7.4 Hz, $J_{4,3}$ = 7.5 Hz, 1 H, H4), 7.09–7.22 (m, 6 H, H$_{arom}$, NH), 6.90 (dd, J_{4a3a} = 7.1 Hz, J_{4a5a} = 7.0 Hz, 1 H, H4a), 6.22 (br d, 1 H, NH), 4.53 (d, J = 6.2 Hz, 2 H, CH$_2$), 3.73 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.9, 156.2, 141.0, 139.0, 132.8, 130.9, 130.5, 128.9, (2 C), 128.6, 127.3, 123.1, 120.4 (2 C), 52.1, 42.9.

Anal. Calcd for C$_{16}$H$_{16}$N$_2$O$_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.33; H, 5.75; N, 10.04.

Methyl 2-{[(Anilinocarbonyl)amino]methyl}-5-bromobenzoate (16b)

Following the typical procedure for **16a** using acyl azide **13b** (1.5 g, 13.44 mmol) gave **16b** (0.840 g, 46%) as a colorless solid; mp 170–172 °C.

IR (KBr): 3303, 1709, 1626, 1557, 1247, 1073 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.01 (d, $J_{6,4}$ = 2.1 Hz, 1 H, H6), 7.52 (dd, $J_{3,4}$ = 8.2 Hz, $J_{6,4}$ = 2.1 Hz, 1 H, H4), 7.39 (d, $J_{3,4}$ = 8.2 Hz, 1 H, H3), 7.30–7.10 (m, 4 H), 7.05–6.90 (m, 1 H), 6.51 (br s, 1 H, NH), 5.94 (br t, J = 6.3 Hz, 1 H, NH), 4.50 (d, J = 6.5 Hz, 2 H, CH$_2$), 3.81 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.7, 155.8, 139.9, 138.6, 135.7, 133.8, 133.7, 130.2, 129.2, 123.6, 121.5, 121.2, 120.7, 52.5, 42.6.

HRMS: m/z [M + Na]$^+$ calcd for C$_{16}$H$_{15}$BrN$_2$O$_3$Na: 385.0164; found: 385.0168.

Methyl 2-{[(Anilinocarbonyl)amino]methyl}-5-methoxybenzoate (16c)

Following the typical procedure for **16a** using acyl azide **13c** (0.65 mg, 2.6 mmol) gave **16c** (0.336 g, 41%) as colorless solid; mp 142–144 °C.

IR (KBr): 3310, 3056, 1718, 1627, 1597, 1357, 1177, 1066, 784 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, $J_{3,4}$ = 8.5 Hz, 1 H, H3), 7.46 (d, $J_{4,6}$ = 2.8 Hz, 1 H, H6), 7.40–7.20 (m, 4 H), 7.10–6.90 (m, 2 H), 6.58 (br s, 1 H, NH), 6.03 (br s, 1 H, NH), 4.55 (br d, J = 5.62 Hz, 2 H, CH$_2$), 3.87 (s, 3 H, OCH$_3$), 3.81 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.9, 158.7, 155.4, 138.7, 133.1, 133.0, 129.7, 129.1, 123.5, 120.7, 118.4, 116.1, 55.5, 52.3, 42.7.

HRMS: m/z [M + Na]$^+$ calcd for C$_{17}$H$_{18}$N$_2$O$_4$Na: 337.1159; found: 337.1141.

Methyl 1-Oxo-1,3-dihydro-2*H*-isoindole-2-carboxylate (17a); Typical Procedure

To a soln of urethane **15a** (1.8 g, 8 mmol) in MeCN (40 mL) was added excess K$_2$CO$_3$ (1.8 g, 13 mmol) and the resulting mixture was stirred at 60 °C for 6 h. After completion of the reaction, excess K$_2$CO$_3$ was filtered off and washed with MeCN (10 mL). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, 20 g, EtOAc–hexane, 8:2) to give **17a** (1.35 g, 88%) as a white solid; mp 135–136 °C (Lit.[26] 136–138 °C).The analytical data are in accord with literature values.[26]

Methyl 6-Bromo-1-oxo-1,3-dihydro-2*H*-isoindole-2-carboxylate (17b)

Following the typical procedure for **17a** using urethane **15b** (0.48 mg, 1.59 mmol) gave **17b** (0.41 g, 95%) as a colorless solid; mp 164–165 °C (EtOAc–n-hexane).

IR (KBr): 2949, 1767, 1695, 1438, 1363, 1320, 1208, 842 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.06 (d, $J_{7,5}$ = 1.7 Hz, 1 H, H7), 7.77 (dd, $J_{5,4}$ = 8.1 Hz, $J_{7,5}$ = 1.7 Hz, 1 H, H5), 7.39 (d, $J_{5,4}$ = 8.1 Hz, 1 H, H4), 4.78 (s, 2 H, CH$_2$), 3.97 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.7, 152.3, 139.4, 136.8, 133.0, 128.2, 124.8, 122.7, 53.9, 48.9.

HRMS: m/z [M + Na]$^+$ calcd for C$_{10}$H$_8$NO$_3$Na: 291.9585; found: 291.9587.

Methyl 6-Methoxy-1-oxo-1,3-dihydro-2*H*isoindole-2-carboxylate (17c)

Following the typical procedure for **17a** using urethane **15c** (0.42 g, 1.66 mmol) gave **17c** (0.34 g, 92%) as a white solid; mp 161–163 °C (EtOAc–n-hexane).

IR (KBr): 1771, 1690, 1494, 1423, 1272, 1250, 1002, 779 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37 (d, $J_{4,5}$ = 8.3 Hz, 1 H, H4), 7.36 (d, $J_{7,5}$ = 2.5 Hz, 1 H, H7), 7.22 (dd, $J_{5,4}$ = 8.3 Hz, $J_{5,7}$ = 2.5 Hz, 1 H, H5), 4.75 (s, 2 H, CH$_2$), 3.97 (s, 3 H, OCH$_3$), 3.88 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.3, 160.3, 152.5, 133.2, 132.2, 124.0, 122.8, 107.1, 55.7, 53.7, 48.7.

HRMS: m/z [M + Na]$^+$ calcd for C$_{11}$H$_{11}$NO$_4$Na: 244.0580; found: 244.0580.

1-Oxo-*N*-phenyl-1,3-dihydro-2*H*-isoindole-2-carboxamide (18a); Typical Procedure

To a soln urea derivative **16a** (3.0 g, 11 mmol) in MeCN (150 mL) was added K$_2$CO$_3$ (3.0 g, 22 mmol). The resulting mixture was stirred at 60 °C for 2 h. After completion of the reaction, excess K$_2$CO$_3$ was filtered and washed with MeCN (10 mL). The solvent was evaporated and the residue was chromatographed (silica gel, EtOAc–hexane, 1:1) to give **18a** (2.23 g, 84%) as a white crystalline compound; mp 178–179 °C.

IR (KBr): 3390, 1711, 1604, 1440, 1305, 1242 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.66 (br s, 1 H, NH), 7.86 (br d, $J_{7,6}$ = 7.7 Hz, 1 H, H7), 7.61 (dd, $J_{6,5}$ = 7.4 Hz, $J_{6,7}$ = 7.6 Hz, 1 H, H6), 7.54–7.45 (m, 4 H, H$_{arom}$), 7.28 (m, 2 H, H3a, H5a), 7.04 (m, 1 H, H4a), 4.85 (s, 2 H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.5, 150.3, 141.1, 137.6, 134.0, 131.0, 129.1 (2 C), 128.7, 124.9, 124.1, 123.4, 120.1 (2 C), 48.6.

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.44; H, 5.04; N, 10.82.

6-Bromo-1-oxo-*N*-phenyl-1,3-dihydro-2*H*-isoindole-2-carboxamide (18b)
Following the typical procedure for **18a** using urea **16b** (0.60 g, 1.65 mmol) gave **18b** (0.47 g, 85%) as a white powder; mp 241–243 °C (EtOAc–*n*-hexane).

IR (KBr): 1702, 1678, 1444, 1368, 1311 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.55 (br s, 1 H, NH), 8.00 (d, $J_{7,5}$ = 1.7 Hz, 1 H, H7), 7.74 (dd, $J_{5,4}$ = 8.1 Hz, $J_{5,7}$ = 1.7 Hz, 1 H, H5), 7.53 (d, J = 7.6 Hz, 2 H), 7.40 (d, $J_{4,5}$ = 8.1 Hz, 1 H), 7.29 (t, J = 7.4 Hz, 2 H), 7.07 (t, J = 7.4 Hz, 1 H), 4.83 (s, 2 H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.0, 149.9, 139.7, 137.3, 137.0, 133.0, 129.1, 127.9, 125.0, 124.3, 122.7, 120.2, 48.4.

Anal. Calcd for $C_{15}H_{11}BrN_2O_2$: C, 54.40; H, 3.35; N 8.46. Found: C, 54.09; H, 3.41; N, 8.35.

6-Methoxy-1-oxo-*N*-phenyl-1,3-dihydro-2*H*-isoindole-2-carboxamide (18c)
Following the typical procedure for **18a** using urea **16c** (0.32 g, 1.02 mmol) gave **18c** (0.24 g, 83%) as a white powder; mp 193–195 °C (EtOAc–*n*-hexane).

IR (KBr): 3242, 3220, 3034, 1710, 1674, 1339, 1257, 1145, 749 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.7 (br s, 1 H, NH), 7.53 (d, J = 7.6 Hz, 2 H), 7.38 (br d, $J_{4,5}$ = 8.3 Hz, 1 H, H4), 7.33–7.25 (m, 3 H), 7.18 (dd, $J_{5,4}$ = 8.4, $J_{5,7}$ = 2.5 Hz, 1 H, H5), 7.05 (br t, J = 7.4 Hz, 1 H), 4.79 (s, 2 H, CH$_2$), 3.82 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.5, 159.3, 149.3, 136.5, 132.5, 131.1, 128.1, 123.3, 123.1, 121.8, 119.1, 105.9, 54.7, 47.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_3Na$: 305.0902; found: 305.0926.

7-Bromo-1*H*-isochromene-1,3(4*H*)-dione (20a); Typical Procedure
To a suspension of bromohomophthalic acid **6b** (5.0 g, 19 mmol) in CH$_2$Cl$_2$ (100 mL), excess SOCl$_2$ (5 mL, 68 mmol) was added at r.t. and the mixture was refluxed overnight. After completion of the reaction (observation of a clear soln), solvent and excess SOCl$_2$ were removed under vacuum pressure to give **20a** (4.5 g, 97%) as a light-yellow solid; mp 171–173 °C (CH$_2$Cl$_2$). The analytical data are in accord with literature values.[32–34]

7-Methoxy-1*H*-isochromene-1,3(4*H*)-dione (20b)
Following the typical procedure for **20a** using methoxyhomophthalic acid **6c** (5.0 g, 23.8 mmol) gave **20b** (4.4 g, 96%) as a colorless liquid. The analytical data are in accord with literature values.[32]

5-Bromo-2-(2-methoxy-2-oxoethyl)benzoic Acid (5a); Typical Procedure
The anhydride **20a** (4.5 g, 18.7 mmol) was dissolved in MeOH (100 mL) and refluxed for 2 h. After evaporation of the solvent, **5a** (4.41 g, 86%) was obtained as a light-yellow solid; mp 135–138 °C (EtOAc–hexane, 4:1).

IR (KBr): 2923, 1728, 1685, 1591, 1437, 1259, 1213 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.77 (br s, 1 H, OH), 8.26 (d, $J_{6,2}$ = 2.4 Hz, 1 H, H6), 7.65 (br dd, $J_{2,3}$ = 8.0 Hz, $J_{2,6}$ = 2.4 Hz, 1 H, H2), 7.16 (br d, $J_{3,2}$ = 8.0 Hz, 1 H, H3), 4.01 (s, 2 H, CH$_2$), 3.70 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.5, 170.8, 136.1, 135.6, 134.7, 133.9, 130.3, 121.3, 52.1, 39.9.

Anal. Calcd for $C_{10}H_9BrO_4$; C, 43.98; H, 3.32. Found: C, 43.66; H, 3.29.

5-Methoxy-2-(2-methoxy-2-oxoethyl)benzoic Acid (5b)
Following the typical procedure for **5a** using anhydride **20b** (4.4 g, 22.8 mmol) gave **20b** (4.50 g, 20.1 mmol, 88%) as a light-yellow solid; mp 112–113 °C (EtOAc–hexane, 3:1). The analytical data are in accord with literature values.[35]

Methyl [2-(Azidocarbonyl)-4-bromophenyl]acetate (21a); Typical Procedure
To a soln of half ester **5a** (2.0 g, 7.3 mmol) in freshly distilled THF (10 mL) at –5 °C was added a soln of Et$_3$N (1.22 mL, 8.7 mmol) in THF (6 mL) dropwise and the resulting mixture was stirred for 30 min. This was followed by slow addition of a soln of ethyl chloroformate (0.82 mL, 8.7 mmol) in THF (10 mL) to the mixture, which was continuously stirred for 30 min at this temperature. Then, NaN$_3$ (0.56 g, 8.7 mmol) dissolved in H$_2$O (10 mL) was added dropwise and the mixture was stirred at this temperature overnight. After removal of the solvent under reduced pressure, H$_2$O was added and the mixture was extracted with EtOAc (2 × 30 mL) and the organic phase was washed with sat. NaHCO$_3$ and dried (MgSO$_4$). Evaporation of the solvent gave azide **21a** (1.59 g, 73%) as a viscous liquid.

IR (KBr): 2952, 2273, 2141, 1740, 1691, 1230, 1169 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.06 (d, $J_{6,2}$ = 1.9 Hz, 1 H, H6), 7.57 (br dd, $J_{2,3}$ = 8.0 Hz, $J_{2,6}$ = 1.9 Hz, 1 H, H2), 7.07 (br d, $J_{3,2}$ = 8.1 Hz, 1 H, H3), 3.91 (s, 2 H, CH$_2$), 3.62 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.0, 171.0, 136.4, 135.5, 134.1, 133.7, 131.2, 121.2, 52.0, 39.7.

Methyl [2-(Azidocarbonyl)-4-methoxyphenyl]acetate (21b)
Following the typical procedure for **21a** using half ester **5b** (2.0 g, 8.9 mmol) gave **23b** (1.77 g, 80%) as an oily product.

IR (KBr): 2887, 2278, 2144, 1740, 1691, 1270, 1209, 913, 743 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, $J_{6,2}$ = 2.8 Hz, 1 H, H6), 7.19 (br d, $J_{3,2}$ = 8.4 Hz, 1 H, H3), 7.09 (br dd, $J_{2,3}$ = 8.4 Hz, $J_{2,6}$ = 2.8 Hz, 1 H, H2), 3.97 (s, 2 H, CH$_2$), 3.84 (s, 3 H, OCH$_3$), 3.71 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.9, 171.9, 158.6, 133.7, 130.3, 128.7, 119.5, 116.1, 55.5, 55.4, 39.5.

Methyl {2-[(Anilinocarbonyl)amino]-4-bromophenyl}acetate (23a); Typical Procedure
The acyl azide **21a** (1.59 g, 5.3 mmol) was dissolved in anhyd benzene and refluxed for 1 h. Evaporation of solvent gave isocyanate **22a** (1.41 g, 5.2 mmol, 98%), which was used for further reactions. The residue was dissolved in CH$_2$Cl$_2$ and aniline (0.56 mL, 6.2 mmol) was added and the soln was stirred at r.t. for 2 h. Filtration of the precipitate yielded the urea derivative **23a** (1.77 g, 92%) as a white solid; mp 179–181 °C (EtOAc).

IR (KBr): 3277, 1733, 1640, 1597, 1578, 1533, 1445, 1236, 1154 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.83 (d, $J_{5,3}$ = 1.6 Hz, 1 H, H5), 7.74 (br s, 1 H, NH), 7.32 (br s, 1 H, NH), 7.32–7.19 (m, 4 H, H$_{arom}$), 7.19 (br dd, $J_{3,2}$ = 8.0 Hz, $J_{3,5}$ = 1.6 Hz, 1 H, H3), 7.06 (br t, J = 6.8 Hz, 1 H, H$_{arom}$), 7.02 (br d, $J_{3,2}$ = 8.0 Hz, 1 H, H3), 3.60 (s, 3 H, OCH$_3$), 3.54 (s, 2 H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.4, 153.8, 138.1, 138.0, 132.0, 129.1, 128.4, 128.2, 126.2, 124.0, 121.7, 120.9, 52.5, 37.6.

Anal. Calcd for $C_{16}H_{15}BrN_2O_3$; C, 52.91; H, 4.16; N, 7.71. Found: C, 52.49; H, 4.12; N, 7.66.

Methyl {2-[(Anilinocarbonyl)amino]-4-methoxyphenyl}acetate (23b)

Following the typical procedure for **23a** using acyl azide **21b** (1.77 g, 7.1 mmol) gave **23b** (2.05 g, 92%) as a white solid; mp 168–170 °C (EtOAc).

IR (KBr): 3265, 2896, 1723, 1618, 1553, 1462, 1260, 1243, 1150, 989 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.45 (br s, 1 H, NH), 7.30 (br d, J = 7.6 Hz, 2 H, H$_{arom}$), 7.22 (m, 3 H, H$_{arom}$), 7.04 (br d, $J_{2,3}$ = 8.4 Hz, 1 H, H2), 7.00 (br t, J = 7.6 Hz, 1 H, H$_{arom}$), 6.71 (br s, 1 H, NH), 6.63 (br dd, $J_{3,2}$ = 8.4 Hz, $J_{3,5}$ = 2.4 Hz, 1 H, H3), 3.72 (s, 3 H, OCH$_3$), 3.56 (s, 3 H, OCH$_3$), 3.52 (s, 2 H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.1, 159.7, 153.9, 138.2, 137.7, 131.7, 129.1, 123.9, 120.7, 119.5, 111.9, 110.7, 55.4, 52.4, 37.3.

Anal. Calcd for C$_{17}$H$_{18}$N$_2$O$_4$; C, 62.96; H, 5.77; N, 8.91. Found: C, 63.29; H, 5.56; N, 8.62.

6-Bromo-2-hydroxy-N^1,N^3-diphenyl-1*H*-indole-1,3-dicarboxamide (24a) and 6-Bromo-1,3-dihydro-2*H*-indol-2-one (25a); Typical Procedure

To a soln of urea derivative **23a** (1.5 g, 4.13 mmol) in MeCN (50 mL) at 60 °C was added excess K$_2$CO$_3$ (5.0 g, 36 mmol). After stirring for 1.5 h, excess K$_2$CO$_3$ was filtered and solvent was evaporated under reduced pressure. The formed products were separated by treatment of the mixture with CHCl$_3$. The major product **24a** was insoluble in CHCl$_3$ and was separated by filtration (0.51 g, 57%). The solvent was removed and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 7:3) to give the minor product **25a** (0.25 g, 28%).

6-Bromo-2-hydroxy-N^1,N^3-diphenyl-1*H*-indole-1,3-dicarboxamide (24a)

Purple solid; mp >320 °C.

IR (KBr): 3604, 3289, 1679, 1594, 1583, 1559, 1445, 1403 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.8 (br s, 1 H, NH), 10.74 (br s, 1 H, NH), 8.4 (d, $J_{6,8}$ = 1.4 Hz, 1 H, H6), 8.02 (br d, $J_{9,8}$ = 8.1 Hz, 1 H, H9), 7.78 (br d, J = 7.9 Hz, 2 H, H$_{arom}$), 7.72 (br d, J = 7.8 Hz, 2 H, H$_{arom}$), 7.35 (br t, J = 7.8 Hz, 2 H, H$_{arom}$), 7.24 (br t, J = 7.8 Hz, 2 H, H$_{arom}$), 7.10 (br dd, $J_{8,9}$ = 8.1 Hz, $J_{8,6}$ = 1.6 Hz, 1 H, H8), 7.05 (br t, J = 7.3 Hz, 1 H, H$_{arom}$), 6.89 (br t, J = 7.3 Hz, 1 H, H$_{arom}$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 165.9, 152.9, 142.4, 140.3, 132.3, 130.3, 129.7, 129.4, 125.3, 123.5, 121.6, 120.4, 119.3, 119.1, 117.3, 111.1, 86.6.

HRMS: *m/z* [M]$^+$ calcd for C$_{22}$H$_{16}$BrN$_3$O$_3$: 448.0296; found: 448.0309.

6-Bromo-1,3-dihydro-2*H*-indol-2-one (25a)

Orange solid; mp 208–212 °C (Lit.[36] 214–215 °C). The analytical data are in accord with literature values.

2-Hydroxy-6-methoxy-N^1,N^3-diphenyl-1*H*-indole-1,3-dicarboxamide (24b), 6-Methoxy-1,3-dihydro-2*H*-indol-2-one (25b), 2-Hydroxy-6-methoxy-N-phenyl-1*H*-indole-3-carboxamide (26b), and 1,3-Diphenylurea (27)

Following the typical procedure for **24a** and **25a** using **23b** (3.0 g, 9.55 mmol) with K$_2$CO$_3$ (5.0 g, 36 mmol). The major product **24b** was precipitated from CHCl$_3$ (1.06 g, 56%). The residue was submitted to column chromatography (silica gel, EtOAc–CH$_2$Cl$_2$, 4:6). The compounds were isolated in the following order: **25b** (0.4 g, 26%), **26b** (0.07 g, 2.6%), and **27** (0.06 g, 0.28 mmol, 2.9%).

2-Hydroxy-6-methoxy-N^1,N^3-diphenyl-1*H*-indole-1,3-dicarboxamide (24b)

Purple solid; mp 199–201 °C.

IR (KBr): 3629, 3201, 3033, 1678, 1596, 1583, 1550, 1443, 1414 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.69 (br s, 1 H, NH), 10.58 (br s, 1 H, NH), 7.87 (d, $J_{6,8}$ = 2.4 Hz, 1 H, H6), 7.80 (br d, $J_{9,8}$ = 8.4 Hz, 1 H, H9), 7.67 (br d, J = 7.6 Hz, 2 H, H$_{arom}$), 7.65 (br d, J = 7.6 Hz, 2 H, H$_{arom}$), 7.37 (br t, J = 7.6 Hz, 2 H, H$_{arom}$), 7.27 (br t, J = 7.6 Hz, 2 H, H$_{arom}$), 7.08 (br t, J = 7.2 Hz, 1 H, H$_{arom}$), 6.9 (br t, J = 7.2 Hz, 1 H, H$_{arom}$), 6.65 (br dd, $J_{8,9}$ = 8.4 Hz, $J_{8,6}$ = 2.4 Hz, 1 H, H8), 3.74 (s, 3 H, -OCH$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.3, 164.1, 153.2, 151.8, 140.9, 138.6, 130.5, 129.0, 128.6, 122.9, 122.8, 120.7, 119.4, 118.1, 116.8, 108.5, 100.7, 84.6, 55.3.

HRMS: *m/z* [M + K]$^+$ calcd for C$_{23}$H$_{19}$N$_3$O$_4$K: 440.1012; found: 410.1007.

6-Methoxy-1,3-dihydro-2*H*-indol-2-one (25b)

Light-red solid; mp 157–159 °C (Lit.[37] 162 °C). The analytical data are in accord with literature values.

2-Hydroxy-6-methoxy-N-phenyl-1*H*-indole-3-carboxamide (26b)

White crystalline solid; mp 250–252 °C.

IR (KBr): 3446, 3268, 3006, 1715, 1668, 1626, 1598, 1217, 1162, 1005 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.98 (br s, 1 H, NH), 11.47 (br s, 1 H, NH), 7.44 (m, 3 H, H$_{arom}$), 7.30 (br t, J = 7.6 Hz, 2 H, H$_{arom}$), 7.08 (br t, J = 7.6 Hz, 1 H, H$_{arom}$), 6.58 (br dd, $J_{8,9}$ = 8.4 Hz, $J_{8,6}$ = 2.4 Hz, 1 H, H8), 6.33 (d, $J_{6,8}$ = 2.4 Hz, 1 H, H6), 3.69 (s, 3 H, OCH$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5, 165.4, 160.7, 143.7, 138.0, 129.0, 128.8, 126.0, 124.3, 120.2, 119.7, 116.6, 108.1, 97.1, 63.9, 55.3.

Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_3$; C, 68.07; H, 5.00; N, 9.92; O, 17.00. Found: C, 68.19; H, 4.74; N, 9.93.

1,3-Diphenylurea (27)

White crystals; mp 238–240 °C (Lit.[38] 231–235 °C).

Reaction of Indole Derivative 24b with Potassium Carbonate

Following the typical procedure for **24a** and **25a** using **24b** (0.3 g, 4.13 mmol), MeCN (20 mL), and K$_2$CO$_3$ for 2 h. Analysis of the product mixture by NMR spectroscopy indicated the formation of **26b** and **27** in 4 and 6% yields, respectively, where the most of the starting material remained unreacted.

1,1′-(2-Hydroxy-6-methoxy-1*H*-indole-1,3-diyl)diethanone (31), Methyl {4-Methoxy-2-[N-(anilinocarbonyl)acetamido]phenyl}acetate (32), and 2-Hydroxy-6-methoxy-N^1,N^3-diphenyl-1*H*-indole-1,3-dicarboxamide (24b)

The urea derivative **23b** (1.2 g, 3.81 mmol) was dissolved in freshly distilled THF (20 mL) and the mixture was cooled to –5 °C. At this temperature NaH (0.175 g, 7.63 mmol) was added and the mixture was stirred for 30 min. Then Ac$_2$O (0.8 g, 7.84 mmol) added to the soln which was further stirred overnight at r.t. After removal of solvent, H$_2$O was added and extracted with EtOAc (2 × 30 mL) and the organic phase was dried (MgSO$_4$). After removal of solvent the residue was submitted to column chromatography (silica gel, EtOAc–hexane, 3:2) to give in the following order the products **32** (0.38 g, 28%), **31** (0.27 g, 32%), and **24b** (0.07 g, 9%).

1,1′-(2-Hydroxy-6-methoxy-1*H*-indole-1,3-diyl)diethanone (31)

Purple solid; mp 158–160 °C (EtOAc).

IR (KBr): 3019, 1711, 1623, 1214, 711 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 13.00 (br s, 1 H, OH), 7.93 (d, $J_{5,7}$ = 2.4 Hz, 1 H, H7), 7.18 (br d, $J_{4,5}$ = 8.8 Hz, 1 H, H4), 7.56 (dd, $J_{4,5}$ = 8.8 Hz, $J_{5,7}$ = 2.4 Hz, 1 H, H5), 3.77 (s, 3 H, OCH$_3$), 2.68 (s, 3 H, CH$_3$), 2.38 (s, 3 H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.0, 172.4, 170.8, 158.4, 136.4, 119.8, 115.5, 111.1, 103.0, 101.5, 55.7, 26.9, 20.7.

HRMS: m/z [M]$^+$ calcd for C$_{13}$H$_{13}$NO$_4$: 248.0922; found: 248.0917.

Methyl {4-Methoxy-2-[*N*-(anilinocarbonyl)acetamido]phenyl}acetate (32)

Brown solid; mp 107–109 °C (EtOAc).

IR (KBr): 3341, 3019, 2953, 1713, 1660, 1447, 1372, 1305, 1215 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.80 (d, $J_{2,6}$ = 2.4 Hz, 1 H, H2), 7.30 (br d, J = 7.6 Hz, 2 H, H$_{arom}$), 7.22 (br t, J = 7.6 Hz, 2 H, H$_{arom}$), 7.05 (br d, J = 8.4 Hz, 1 H, H5), 6.98 (br t, J = 7.6 Hz, 1 H, H$_{arom}$), 6.65–6.63 (m, 2 H, NH, H6), 3.74 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, OCH$_3$), 3.55 (s, 2 H, CH$_2$), 2.58 (s, 3 H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 176.0, 171.0, 159.7, 154.0, 137.9, 129.0, 124.4, 123.4, 118.7, 115.1, 110.8, 102.5, 110.7, 55.6, 52.3, 36.1, 26.7.

Anal. Calcd for C$_{19}$H$_{20}$N$_2$O$_5$; C, 64.04; H, 5.66; N, 7.86. Found: C, 63.69; H, 5.43; N, 7.98.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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