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N-Oxide as an Intramolecular Oxidant in the Baeyer–Villiger Oxidation: Synthesis of 2-Alkyl-2*H*-indazol-3-yl Benzoates and 2-Alkyl-1,2-dihydro-3*H*-indazol-3-ones

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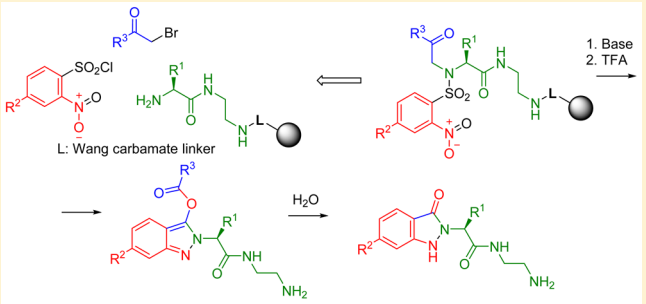
Supporting Information

ABSTRACT: In this study, we describe the intramolecular Baeyer–Villiger oxidation of ketones to esters using *N*-oxide. 2-Nitro-*N*-alkyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide compounds are known to undergo base-mediated C-arylation followed by N–N bond formation, producing unstable five-membered ring intermediates that spontaneously dehydrate to indazole oxides. We identified the reaction conditions under which the cyclic intermediate undergoes acid-mediated intramolecular Baeyer–Villiger oxidation of the ketone in which *N*-oxide serves as the intramolecular oxidizing agent. The solid-phase synthesis plays a critical role in the successful transformation, allowing rapid access to the unstable but Baeyer–Villiger oxidation-prone intermediate. This synthetic route provides practical access to 2-alkyl-2*H*-indazol-3-yl benzoates and 2-alkyl-1,2-dihydro-3*H*-indazol-3-ones, which are known privileged structures possessing remarkable diverse pharmacologically relevant activities.



INTRODUCTION

Our ongoing research has focused on developing new chemical routes for the expeditious solid-phase syntheses of combinatorial libraries of pharmacologically relevant heterocyclic compounds. We discovered that N-alkylated 2-nitrobenzenesulfonamides (Nos amides) undergo tandem carbon–carbon followed by nitrogen–nitrogen bond formation, leading to indazole oxides.[1] This finding inspired us to explore the C-arylation reaction for the preparation of various acyclic intermediates that can be converted into diverse nitrogenous heterocycles. Resin-bound acyclic N-alkylated 2-Nos amides with three points of diversification, referred to as advanced intermediates,[2] were applied to the syntheses of diverse classes of nitrogenous heterocycles, including indazoles,[3] quinazolines,[4] indoles,[5] benzothiadiazepinones,[6] and thiazines[7] (Scheme 1).

Because the synthesis of indazole oxides provided products with a high yield and purity and proceeded under mild conditions using commercially available starting materials, we further extended the synthetic potential of the tandem C–C followed by N–N bond formation. We reported the transformation of 3-benzoyl-2*H*-indazole 1-oxides via the Baeyer–Villiger oxidation of ketones to esters.[8,9] This oxidation provided straightforward access to 2-alkyl-2*H*-indazol-3-yl benzoates and their hydrolysis products, 2-alkyl-1,2-dihydro-3*H*-indazol-3-ones, an important class of privileged structures. To our delight, we found that N-oxide served as an intramolecular oxidant and provided indazolyl benzoates via the Baeyer–Villiger oxidation of ketones to esters. To the best of our knowledge, the transformation of ketones to esters using *N*-oxide as an intramolecular oxidant has not been previously reported.

The 2-alkyl-2*H*-indazol-3-yl benzoates have not been reported in the literature; their structural motif can be found only in polynuclear heterocycles.[10−12] However, their hydrolytic products, 1,2-dihydro-3*H*-indazol-3-ones, represent a true privileged structure known to exhibit remarkably diverse pharmacological activities, including anti-inflammatory activity,[13,14] TRPV1-antagonist activity,[15] inhibition of myeloperoxidase,[16] antichagasic activity,[17,18] glycogen synthase activator activity,[19] antioxidant activity,[20] neuroprotective activity,[21] phosphomannose isomerase inhibition,[22] TACE inhibition,[23] and antimalarial activity.[24] Therefore, not surprisingly, numerous synthetic routes leading to indazolones were described in the literature, as recently reviewed by Haddain et al.[25]

RESULTS AND DISCUSSION

Synthesis. By exploiting the specific advantages of solid-phase synthesis, polymer-supported *N*-2-oxo-2-phenylethyl Nos amides **4** were synthesized according to a published procedure[1] using amino acids attached to a carbamate linker[26] on a Wang

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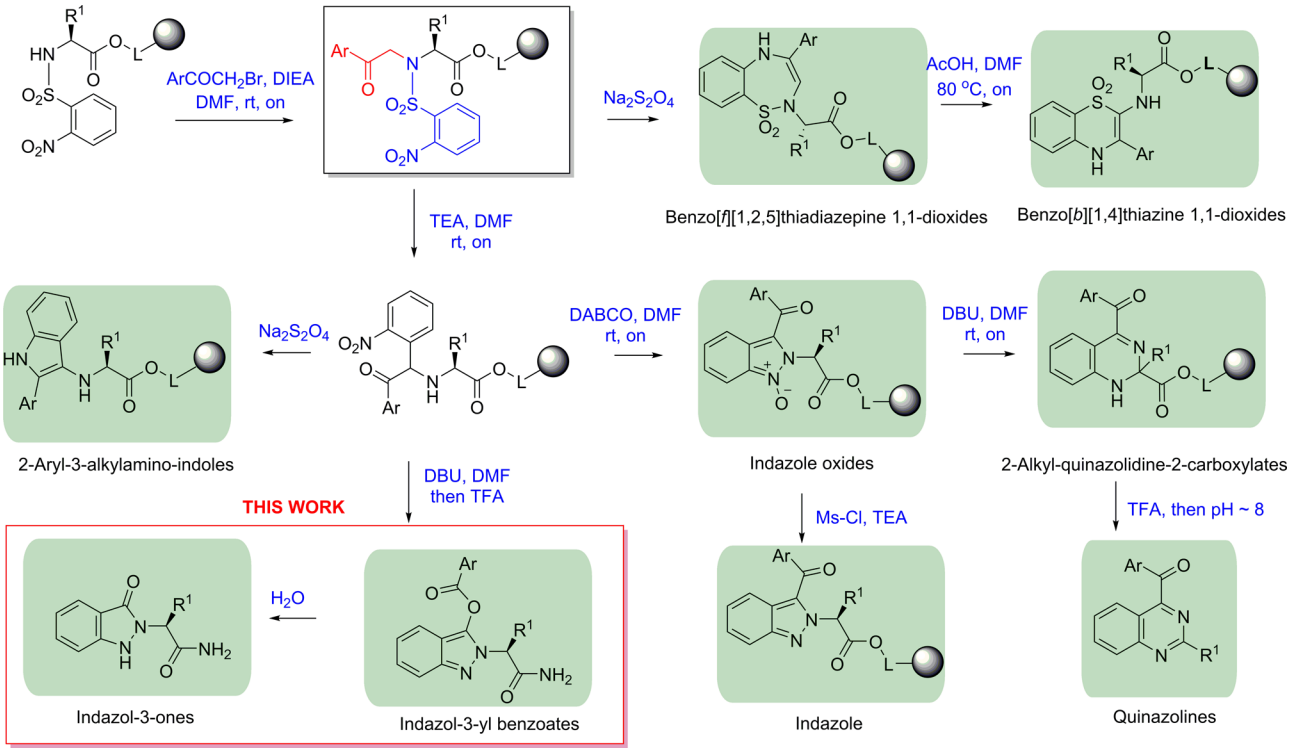
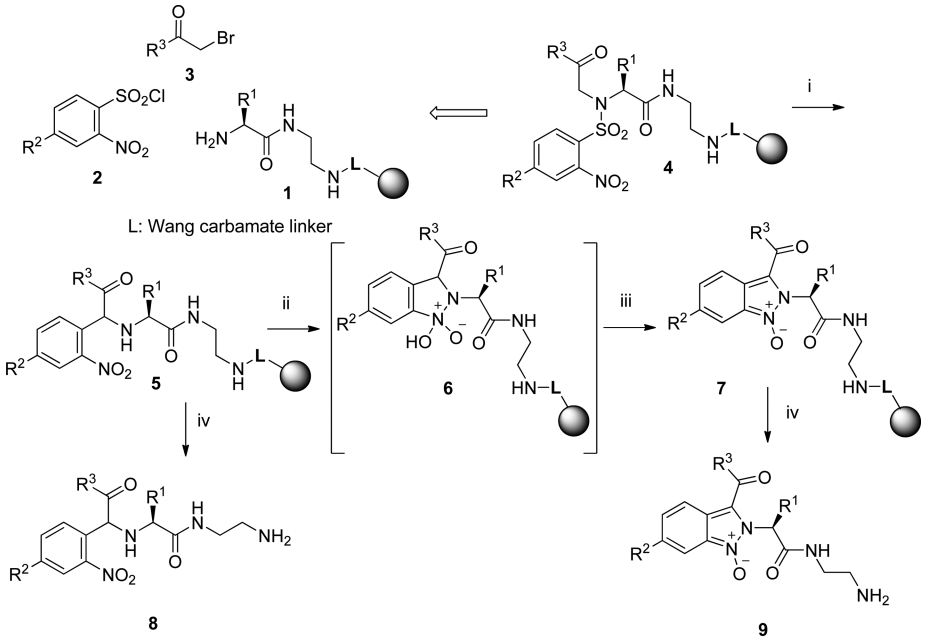
Scheme 1. Diversity of Nitrogenous Heterocycles Prepared from N-Alkylated 2-Nos Intermediates



Scheme 2. Solid-Phase Synthesis of Indazole Oxides



(i) 0.5 M DIEA, DMF, rt, on; (ii) 0.2 M DBU, DMF, rt, 30 min; (iii) DMF, rt, on; (iv) reagent grade TFA, DCM, rt, 1 h

resin[27] via an ethylenediamine spacer (resin **1**, Scheme 2), followed by reaction with 2-Nos-Cl **2** and the subsequent alkylation with α-bromoacetophenones, **3**. The key step of the indazole synthesis was the base-mediated C-arylation of the methylene carbon to form resin **5**. C-Arylation occurred during the alkylation reaction, which was conducted in the presence of diisopropylethylamine (DIEA). This C-aryl derivative, **8**, was isolated after cleavage from the resin using trifluoroacetic acid (TFA) and was fully characterized by NMR and HRMS. The C-aryl derivative, **5**, underwent 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)-mediated ring closure by the formation of a N−N bond, resulting in intermediate **6**, which spontaneously dehydrated to indazole oxide **7**.

Baeyer−Villiger Oxidation. We performed the conventional Baeyer-Villiger oxidation using an external oxidant with resin-bound ketone **7**{*1,1,1*}, prepared from Fmoc-Ala-OH (R^1 = CH_3), 2-Nos-Cl (R^2 = H), and α-bromoacetophenone (R^3 = H), with 3-chloroperbenzoic acid (mCPBA) in

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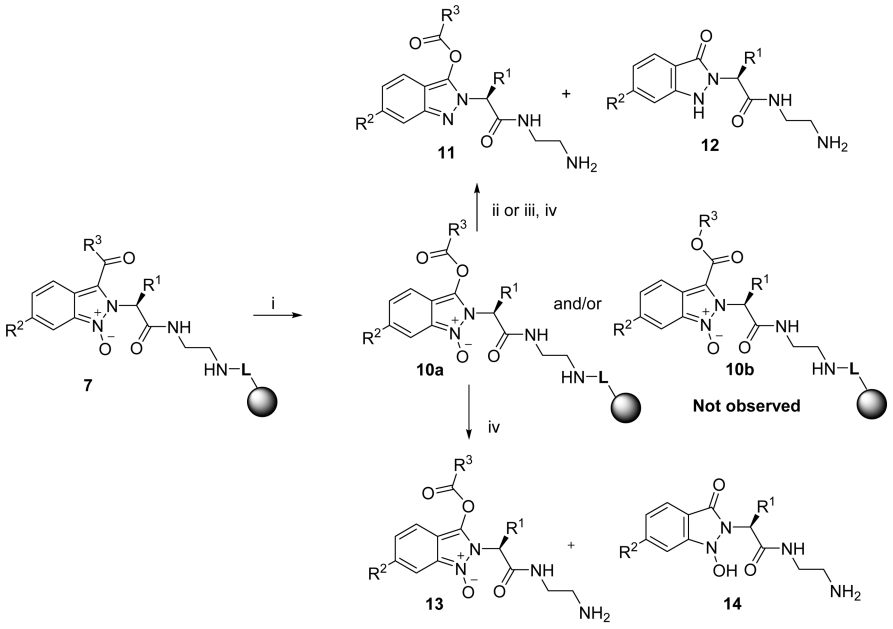
Scheme 3. Baeyer–Villiger Oxidation of Ketone 7 and Subsequent Reduction to Ester 11



(i) 0.5 M mCPBA, DCM, rt, 30 min - on; (ii) 0.7 M TEA in DCM, 0 °C, add 0.5 M Ms-Cl in DCM, rt, on; (iii) $Na_2S_2O_4$, K_2CO_3, tetrabutylammonium hydrogen sulfate, H_2O/DCM (1:1), rt, 2 h; (iv) TFA, DCM (1:1), rt, 1 h.

dichloromethane (DCM) to prepare ester **13**{*1,1,1*} (Scheme 3). The use of DCM as a solvent is beneficial for solid-phase synthesis because of resin swelling. We searched for the optimal reaction conditions with respect to the excess of reagent solution and reaction time (for details, see Supporting Information). Crude reaction mixtures were analyzed by liquid chromatography/mass spectrometry (LC/MS) after cleavage from the resin by TFA. Under the standard reaction conditions (60 mg of resin, 0.5 M mCPBA in 2 mL of DCM) only traces of the product **13**{*1,1,1*} were detected on LC/MS. Overnight reaction caused complete cleavage of compounds from the resin. When we performed the oxidation in a larger volume with the same concentration (20 mg resin, 5 mL of 0.5 M mCPBA solution in DCM) at rt for 30 min, indazole oxide ester **13**{*1,1,1*} was formed predominantly, although the reaction was not complete. Repeated treatment with the mCPBA solution yielded the expected product **13**{*1,1,1*} with an impressive crude purity (cf. Supporting Information).

The oxidation of *N*-oxide ketone **7** to *N*-oxide ester **10** using mCPBA can, in principle, lead to two different isomeric products, **10a** and **10b**, which have the same molecular mass.[9] The LC/MS analysis of the oxidized and cleaved model compound **7**{*1,1,1*} revealed that in addition to the expected product, the presence of a compound with molecular ion *m*/*z* 265 was found, corresponding to hydrolyzed ester **14**{*1,1,1*} (isolated and fully characterized), thus indicating that the oxygen insertion occurred between the carbonyl and the indazole carbon.

The use of a neutral buffer for the purification of indazole oxide ester **13**{*1,1,1*} led to immediate hydrolysis to form **14**{*1,1,1*}, which is expected for this type of ester. Using 0.1% TFA in water/MeCN as the mobile phases, we succeeded in isolating indazole oxide ester **13**{*1,1,1*}, as well as hydrolyzed ester **14**{*1,1,1*}. However, only compound **14**{*1,1,1*} was stable and was fully characterized. *N*-Oxide ester **13**{*1,1,1*} was prone to hydrolysis, and ^{1}H and ^{13}C NMR spectra indicated the presence of **14**{*1,1,1*} along with benzoic acid.

Because *N*-oxide ester **13**{*1,1,1*} was prone to hydrolysis, we reduced the *N*-oxide ester **10a**{*1,1,1*} on a solid support to obtain ester **11**{*1,1,1*}. The reduction of *N*-oxide was performed using two methods: deoxygenation with mesyl chloride[1] and reduction with sodium dithionite.[28] Both reduction routes led to the formation of expected product **11**{*1,1,1*} and indazolone **12**{*1,1,1*}, although in a complex mixture containing other unidentified components. In an attempt to improve the product purity, we performed the reduction of indazole oxide **7**{*1,1,1*} to indazole prior to oxidation using the same reagents used above (Scheme 4). We obtained clean indazoles; however, we were unable to oxidize the ketone even under the substantially harsher conditions typically used for the Baeyer–Villiger oxidation (50 °C overnight (on) and using microwave irradiation at 150 °C, 300 W, 1 h).

Baeyer–Villiger Oxidation with an Intramolecular Oxidant. Following the unsuccessful attempts to develop the Baeyer–Villiger oxidation of 3-benzoyl-2*H*-indazole 1-oxides in a useful manner, we attempted to cleave the unstable intermediate **6**{*1,1,1*} from the resin. Numerous C-arylation and cleavage conditions were evaluated to prevent spontaneous transformation to indazole oxides. The treatment of the resin by DBU in DMF was immediately followed by washing with dichloromethane (DCM) and cleavage of the product from the resin by 50% TFA in DCM (Scheme 5). To our delight, we succeeded in isolating a new product. The product was isolated and purified by reverse phase HPLC in 0.1% aqueous TFA/acetonitrile. Its structure was determined by 1D and 2D ^{1}H and ^{13}C NMR spectrometry as indazole ester **11**{*1,1,1*}, formed by the intramolecular oxidation of the ketone by the *N*-oxide. Encouraged by this unanticipated result, we focused on the scope and limitation of this unexpected but very interesting and practical transformation. This transformation was possible on a solid support because of the rapid removal of the DMF solution of DBU followed by exposure to TFA.

Because of the inherent instability of intermediate **6**, which is prone to spontaneous dehydration to indazole oxide **7**, the cleavage/rearrangement reaction conditions were critical for the successful preparation of indazole ester **11**. To develop a

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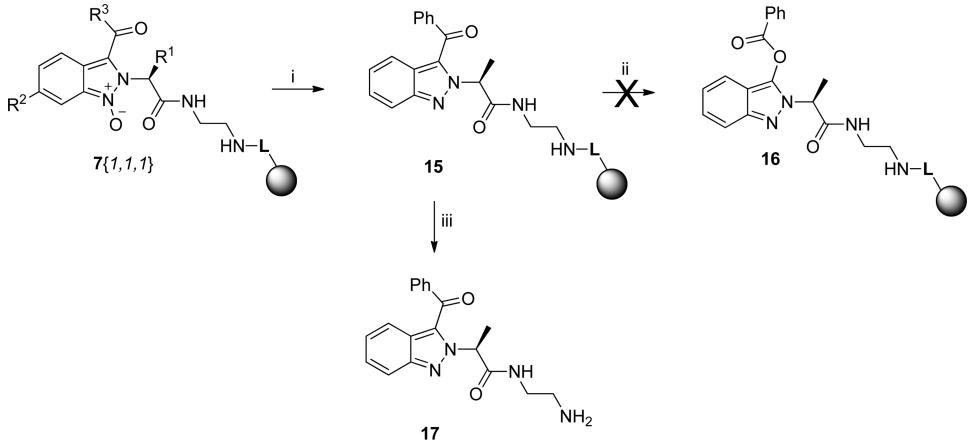
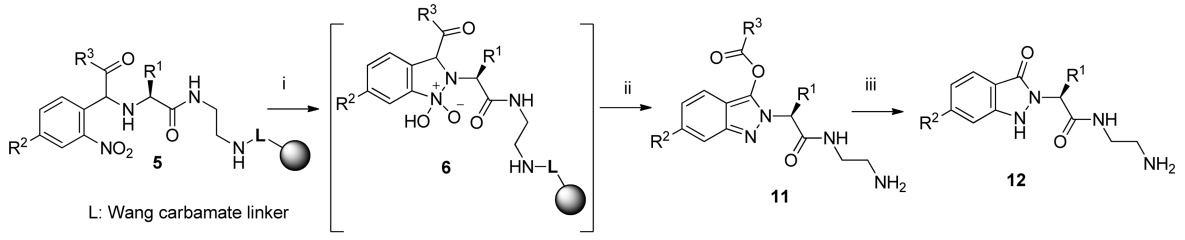
Scheme 4. Swapping Reaction Steps: Deoxygenation of Indazole Oxide 7 to Indazole 15 and Subsequent Baeyer–Villiger Oxidation to Ester 16



(i) 0.7 M TEA in DCM, 0 °C, add 0.5 M Ms-Cl in DCM, rt, on; (ii) 0.5 M mCPBA, DCM, rt (or 50 °C, or MW), 30 min - on; (iii) TFA, DCM (1:1), rt, 1 h.

Scheme 5. Baeyer–Villiger Oxidation with Internal *N*-Oxide



(i) 0.2 M DBU, DMF, rt, 30 min; (ii) redistilled TFA, anhydrous DCM, rt, 1 h, (iii) H_2O, MeOH, rt, on

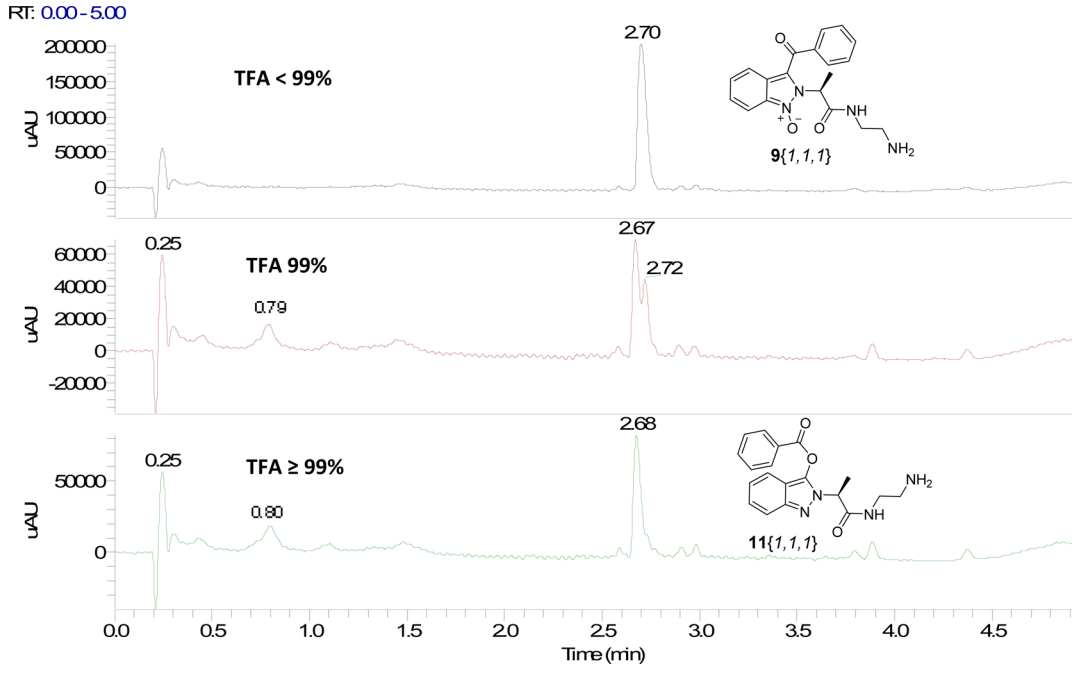


Figure 1. Crude LC traces of **9**{*1,1,1*} and **11**{*1,1,1*}.

practically useful protocol, we tested a variety of reaction conditions and analyzed crude samples by LC/MS. Although the ketone **9**{*1,1,1*} (t_R 2.70 min, first LC traces and 2.72 min, second LC traces, Figure 1) and the ester **11**{*1,1,1*} (t_R 2.67 min, second LC traces and 2.68 min, third LC traces, Figure 1) eluted with similar retention times, their UV spectra differed significantly (Figure 2). The λ_{max} values for indazole oxide ketone **9**{*1,1,1*} and indazole ester **11**{*1,1,1*} were

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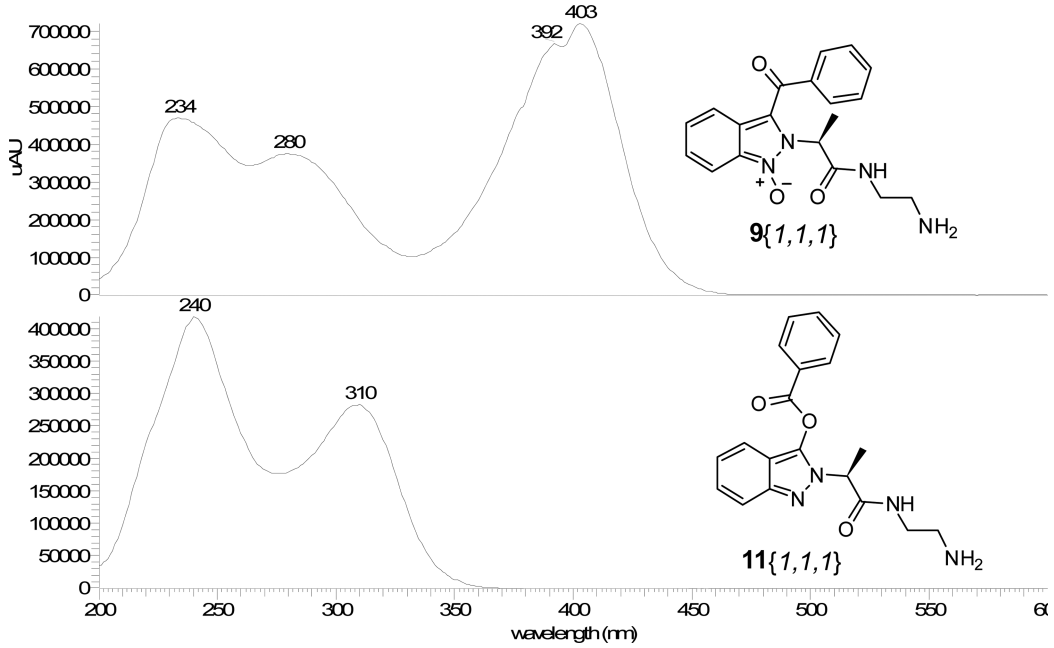

Figure 2. UV spectra of **9**{*1,1,1*} and **11**{*1,1,1*}.

403 and 310 nm, respectively, allowing for the unequivocal detection of both compounds. The LC traces of ketone **9**{*1,1,1*} showed a single major peak, and the cleavage of ester **11**{*1,1,1*} revealed the presence of one early eluting compound (t_R 0.79 min, second LC traces and 0.80 min, third LC traces, Figure 1) corresponding to the hydrolyzed ester **12**{*1,1,1*} (Scheme 5).

Analysis of the experimental data (cf. Supporting Information) indicated that the purity of the TFA used in the cleavage cocktail was critical for successful conversion to indazole ester **11**{*1,1,1*}. We analyzed crude samples prepared by cleavage using commercial TFAs of three different qualities: synthesis grade TFA (<99%), reagent grade TFA (99%), and TFA purified by redistillation for protein sequencing (purity ≥99%). The analytical results unequivocally demonstrated the strong effect of the TFA quality on the reaction outcome. Exclusive formation of ketone **9**{*1,1,1*} was observed with the lower-quality synthesis grade TFA (purity <99%, Figure 1, first traces). The use of reagent grade TFA led to a mixture of ketone **9**{*1,1,1*} and ester **11**{*1,1,1*} (purity 99%, Figure 1, second traces), whereas the clean conversion to indazole ester **11**{*1,1,1*} was observed only with redistilled TFA (purity ≥99%, Figure 1, third LC traces). TFA is prepared industrially by the electrofluorination of acetyl chloride and acetic anhydride, followed by the hydrolysis of the resulting trifluoroacetyl fluoride.[29] Thus, reagent grade TFA may be contaminated with water and/or anhydride. To investigate the effect of this potential contamination on the reaction outcome, we spiked the high purity TFA with water and trifluoroacetic anhydride and used this reagent for the cleavage of the products from resin **6**{*1,1,1*}. The results indicated that as little as 0.5% water led exclusively to ketone **9**{*1,1,1*} (cf. Supporting Information). Reactions performed using different acids, 36% aqueous HCl in dioxane (1:10) at room temperature and formic acid at elevated temperature (70 °C), led to the formation of indazole oxides, confirming that the use of redistilled TFA was critical.

Structure Determination. The ^{1}H and ^{13}C NMR spectra of purified model compound **11**{*1,1,1*} exhibited resonances analogous to those of indazole oxide **9**{*1,1,1*}; however, several proton and carbon resonances were shifted downfield relative to the corresponding resonances for ester **11**. The ^{1}H NMR spectrum of a mixture of **9**{*1,1,1*} and **11**{*1,1,1*} (Figure 3) showed an unambiguous difference in the chemical shifts of the protons on the sp^2 carbons ($\Delta\delta$ = 0.39 ppm between H3 and H6) of benzene fused to a heterocycle and the amino acid side chains. The most noticeable difference was observed in the quartet of Ala ($\Delta\delta$ = 1.29 ppm between H1 and H4) and the methyl doublet of Ala ($\Delta\delta$ = 0.17 ppm between H2 and H5). In the ^{13}C NMR spectrum, the difference was most evident in the carbonyl resonances (182.0 ppm for the ketone and 170.1 ppm for the ester).

The structure of **11**{*1,1,1*} was confirmed from its 1D and 2D ^{1}H and ^{13}C NMR spectra. Proton connectivities were assigned by examination of the COSY spectrum. The signals of all carbons with directly attached protons were derived using the HSQC spectrum. Finally, the HMBC spectrum was used to determine the quaternary carbons. The spectroscopic data for **11**{*1,1,1*} are presented in the Supporting Information.

Rearrangement Mechanism. To investigate the putative mechanism of this rearrangement, we performed the following experiments. First, we treated indazole oxide ketone **9**{*1,1,1*} with TFA to show that the ester was not formed from indazole oxide. None of the reaction conditions tested (different TFA concentrations, temperatures, and durations) yielded any indication of the transformation of indazole oxide ketone **9**{*1,1,1*} to indazole ester **11**{*1,1,1*}. We also treated the ester with TFA, and no indazole oxide traces were observed.

Next, we exposed the DBU-treated resins to ethanolamine to determine whether the ester was formed by the DBU and was present on the resin or whether it was produced by TFA (Scheme 6). The *N*-(2-hydroxyethyl)benzamide product of potential ester cleavage **19** was not detected in the solution. After treatment with ethanolamine, the resin was treated with the TFA solution. A significant increase of indazole oxide **9** was observed at the expense of the ester due to spontaneous dehydration. Interestingly, when the resin was treated with DBU followed by

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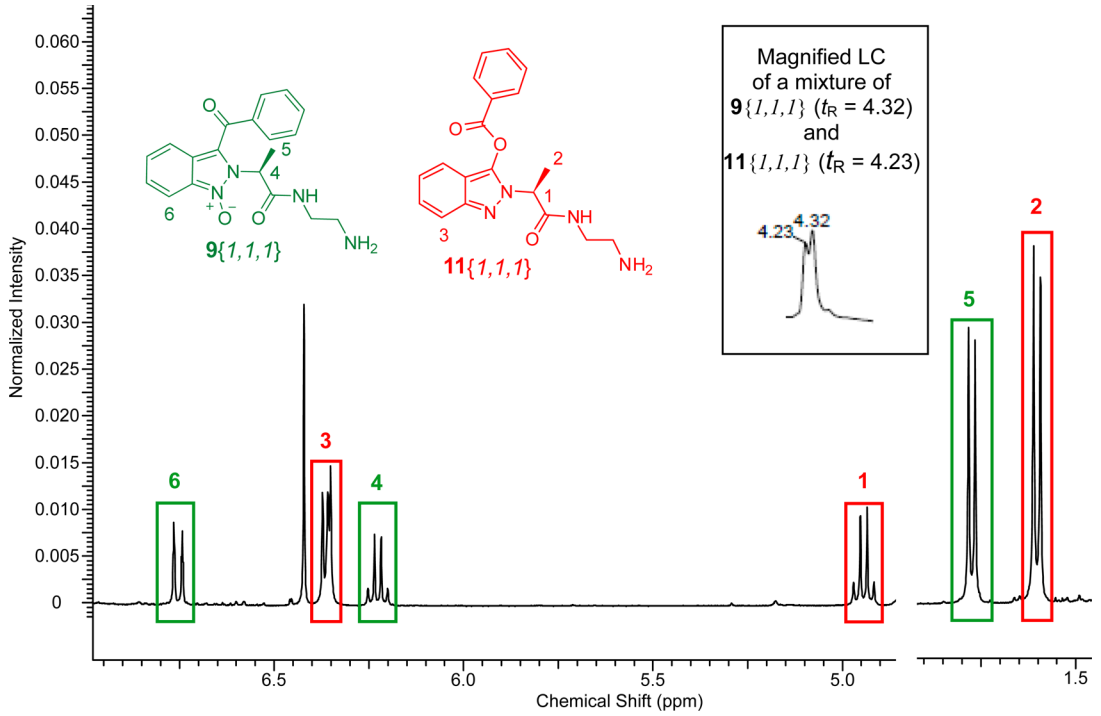
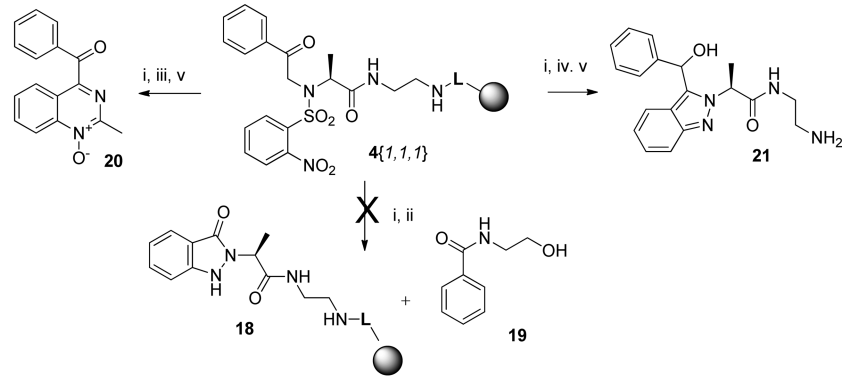


Figure 3. Zoomed ^{1}H NMR spectrum of a mixture of **9**{*1,1,1*} and **11**{*1,1,1*} diagnostic signals.

Scheme 6. Model Transformation Experiments of Resin 4{*1,1,1*}



(i) 0.2 M DBU, DMF, rt, 0.5 h; (ii) 0.5 M ethanolamine, DMF, rt, 0.5 h; (iii) NaOH, THF/MeOH (1:1), rt, 30 min; (iv) $Na_2S_2O_4$, K_2CO_3, tetrabutylammonium hydrogen sulfate, H_2O/DCM (1:1), rt, 16 h; (v) TFA, DCM, rt, 1 h

exposure to a solution of sodium hydroxide in MeOH/THF (Scheme 6), we isolated quinazoline **20** from the solution (characterized by NMR and HRMS). Subsequent treatment of the resin with TFA did not release any product from the resin, indicating the complete cleavage to **20** by the NaOH solution.

An independent experiment excluding the presence of an ester on the resin was based on the different reactivities of the ester and ketone upon reduction with tetrabutylammonium hydrogen sulfate (Scheme 6). LC/MS analysis detected a compound with reduced carbonyl and *N*-oxide (**21**) signals but no ester cleavage.

Next, we followed the reaction of the *C*-aryl derivative with DBU in solution by NMR. *C*-Aryl compound **8**{*1,1,1*} was dissolved in DMSO-d_6, and ^{1}H NMR spectra were collected before and after addition of the base. After DBU addition, we immediately observed the conversion of *C*-aryl compound **8**{*1,1,1*} (s, 6.36 ppm) into an intermediate (6.00 ppm, 5.98 ppm), which was further transformed into ketone **9**{*1,1,1*}, as revealed by the characteristic quartet of the Ala CH proton at 6.14 ppm over 30 min (Figure 4). The addition of a weaker base, TEA, slowed the conversion, and we were able to capture the intermediate only for diagnostic resonances before the formation of ketone **9**{*1,1,1*}. However, attempts to purify the intermediate were unsuccessful due to its rapid conversion to indazole oxide.

The above-described experiments indicated that the ester was formed during TFA treatment rather than on the resin. In addition, we showed that the indazole oxide ketone could not be transformed to the ester and vice versa. On the basis of these findings, we proposed the following putative mechanism of the formation of the ester **11′** (structural simplification of the pertinent intermediate **11**) from the unstable intermediate **6′** (Scheme 7), which is analogous to the Baeyer−Villiger oxidation mechanism.

Scope and Limitations. Because the transformation proceeded smoothly under mild conditions and because the derivatives of 2-alkyl-2*H*-indazol-3-yl benzoates are pharmacologically relevant, we synthesized a set of compounds with different R groups to address the scope and limitations of the ester formation. To efficiently isolate and characterize both

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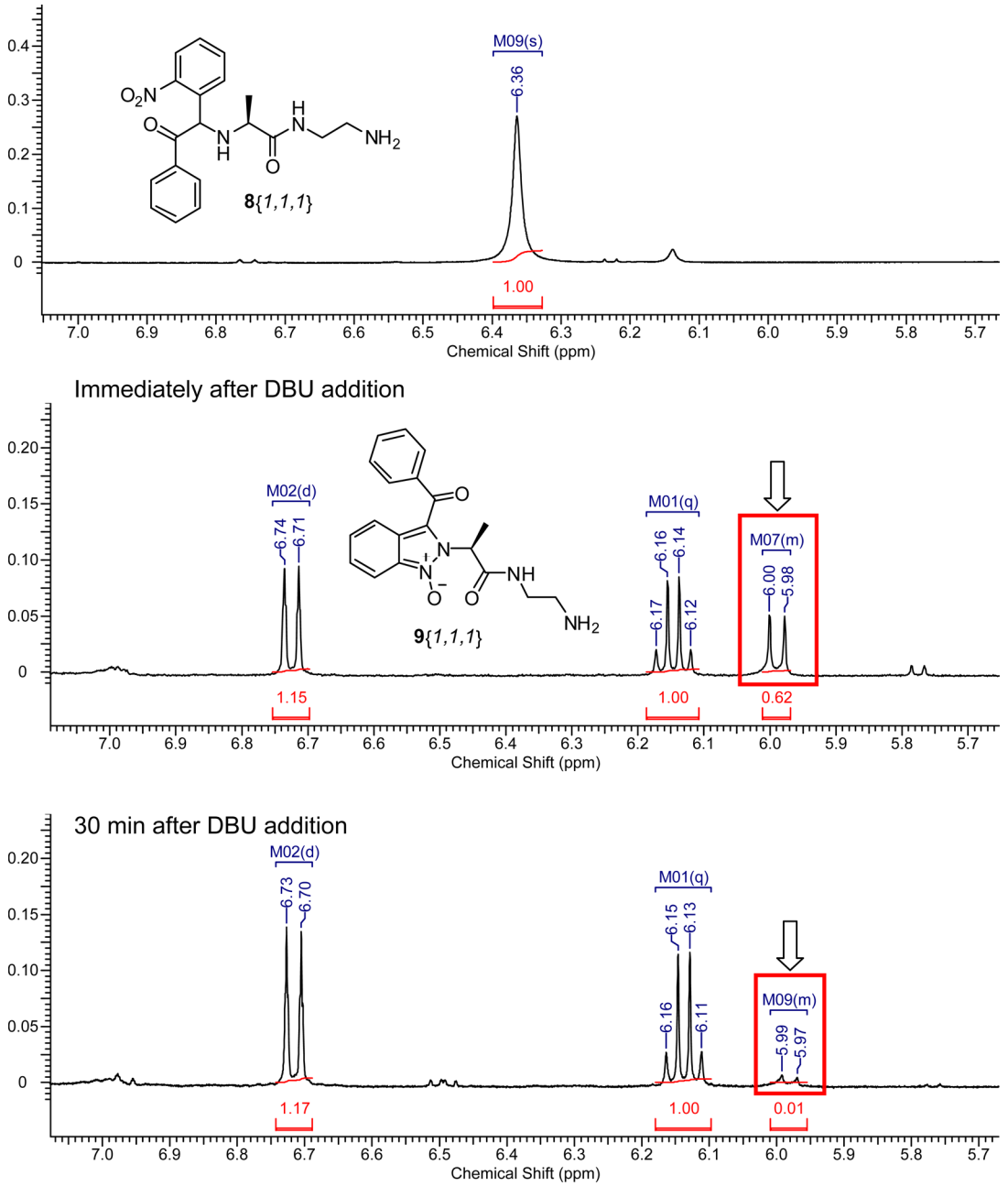
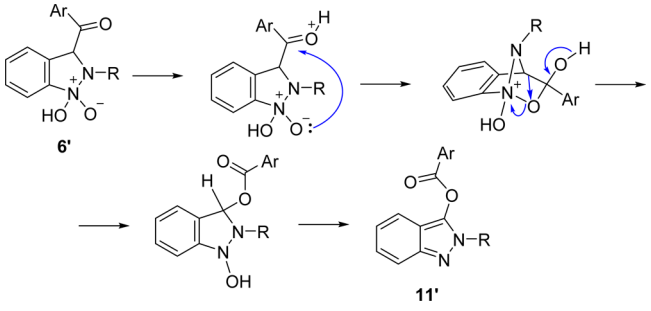


Figure 4. Zoomed ^{1}H NMR spectra of *C*-aryl **8**{*1,1,1*} and the eventual formation of ketone **9**{*1,1,1*} after the addition of DBU.

Scheme 7. Putative Mechanism of Ester 11′ Formation



the 2-alkyl-2*H*-indazol-3-yl benzoates, **11**, and their hydrolytic products, **12**, we subjected partially hydrolyzed crude samples to reverse-phase HPLC purification and isolated both compounds. Table 1 lists the prepared compounds and demonstrates the versatility of this chemical transformation.

The presence of an α-amino acid (Ala, Phe, Lys, or Ser) was crucial for the formation of ester **11** (Table 1) because the β-amino acid (β-Ala) led exclusively to ketone **9** (Table 2). The synthesis was compatible with electron-withdrawing groups (CF_3, CN, and Cl) on either of the two aromatic rings (R^2 and R^3 substituents). An electron-donating substituent (OCH_3, for entry 5 in Table 1) at the R^2, or at R^3 position combined with an electron-withdrawing group at R^2 position (CF_3, for entry 4 in Table 1), led to the formation of ester **11**.

■ CONCLUSION

The unstable cyclic intermediate **6**, formed by the base-mediated C-arylation of 2-nitro-*N*-alkyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamides and the subsequent N−N bond formation, was

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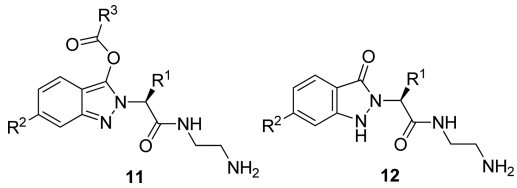
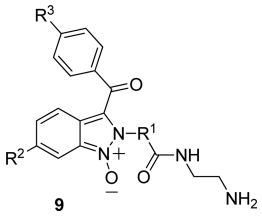
Table 1. Summary of the Synthesized Compounds: Esters (11) and Debenzoylated Products (12)



entry	resin	R^1	R^2	R^3	**11**[a]	**12**[a]
1	**6**{*1,1,1*}	Me	H	Ph	62/33	27/22
2	**6**{*1,1,4*}	Me	H	4-Cl-Ph	38/17	24/NI
3	**6**{*1,2,1*}	Me	CF_3	Ph	45/26	42/52
4	**6**{*1,2,5*}	Me	CF_3	OCH_3-Ph	36/16	51/44
5	**6**{*1,3,1*}	Me	OCH_3	Ph	45/21	25/22
6	**6**{*2,1,1*}	Ph	H	Ph	40/16	43/36
7	**6**{*3,1,1*}	$(CH_2)_4NH_2$	H	Ph	38/16	40/39
8	**6**{*4,1,1*}	CH_2O-*t*Bu	H	Ph	57/21	7/NI

[a]The purity is estimated from LC traces at 210−400 nm. The yields are calculated from ^{1}H NMR spectra;[30] NI, not isolated.

Table 2. Summary of the Synthesized Compounds: Ketones (9)



entry	resin	R^1	R^2	R^3	**9**[a]
1	7{*3,1,1*}	*β*-Ala	H	Ph	97/95
2	7{*3,2,1*}	*β*-Ala	CF_3	Ph	98/78
3	7{*3,2,2*}	*β*-Ala	CF_3	4-CF_3-Ph	96/71
4	7{*3,2,3*}	*β*-Ala	CF_3	4-CN-Ph	85/26
5	7{*3,3,1*}	*β*-Ala	OCH_3	Ph	96/37

[a]The purity is estimated from LC traces at 210−400 nm. The yields are calculated from ^{1}H NMR spectra.

converted to 2-alkyl-2*H*-indazol-3-yl benzoates. The transformation occurred via the acid-mediated intramolecular Baeyer−Villiger oxidation of a ketone to an ester in the absence of an external oxidizing agent in which *N*-oxide served as the internal oxidant. Solid-phase synthesis played a crucial role in the expeditious transformation of the unstable intermediate. The 2-alkyl-2*H*-indazol-3-yl benzoates **11** and their hydrolytic products, 2-alkyl-1,2-dihydro-3*H*-indazol-3-ones **12**, represent privileged structures with remarkable diversity of pharmacologically relevant activities. Thus, the reported synthesis provides an expeditious, convenient, and practical route to arrays of target molecules for high throughput screening.

EXPERIMENTAL SECTION

The solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disc). The volume of the wash solvent was 10 mL per 1 g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before the solvent was changed. All of the reactions were performed at ambient temperature, unless otherwise stated. Commercially available Wang resin (100−200 mesh, 1.0 mmol/g) was used. The yields of the crude products were calculated with respect to the loading of the initial starting material. The reaction conditions for the individual steps of the syntheses were analogous to those reported in our previous communication.[1]

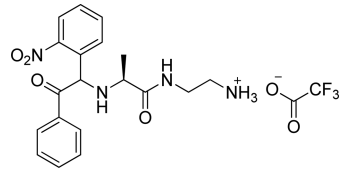
Alkylation with Bromoacetophenone (resins 4 and 5). After reaction with Nos-Cl (1 g), the resin was washed three times with DCM and then three times with DMF. A solution of 0.5 M bromoacetophenone (5 mmol) and 0.5 M DIEA (5 mmol, 870 μL) in 10 mL of DMF was added, and the syringe was shaken at ambient temperature overnight. The resin was washed five times with DMF and three times with DCM. If the conversion to resin **4** was not complete, then the reaction with bromoacetophenone was repeated.

Reaction with DBU (resin 6). Resin **5** (250 mg) was washed three times with DCM and then three times with DMF. A solution of 0.2 M DBU (1 mmol, 150 μL) in 5 mL of DMF was added, and the resin slurry was shaken at ambient temperature for 30 min. The resin was washed three times with DMF and three times with DCM.

Cleavage and Isolation. (a) Reagent grade TFA < 99% (compounds **8**, **9**, **14** and **17**). (b) Redistilled TFA ≥ 99% (compounds **11** and **12**). Resin **5** (or **6** or **7** or **15**) (250 mg) was treated with 50% TFA (reagent grade for compounds **8**, **9**, and **17** and redistilled TFA ≥ 99% for compounds **11** and **12**) in DCM (3 mL) for 1 h. The TFA solution was collected, and the resin was washed three times with 3 mL of 50% TFA in DCM. The extracts were combined and evaporated under a nitrogen stream. The oily products were dissolved in methanol (3 mL) and purified by semipreparative reverse phase HPLC on C18 with mobile phases CH_3CN/H_2O−0.01% TFA (for compounds **8**, **9**, **11**, **12**, **14**) and CH_3CN/H_2O−NH_4AcO (10 mM) (for compounds **17**, **20**).

Baeyer−Villiger Oxidation (resin 10a). Resin **7** (250 mg) was divided into three portions, and each portion was placed in a 20 mL syringe. Each portion was washed three times with DCM, and then, a solution of 0.5 M mCPBA (5 mmol, 860 mg) in 10 mL of DCM was added. The resin slurry was shaken at ambient temperature for 30 min, and the resin was washed three times with DCM. Then, all three portions were combined.

Analytical Data of Synthetic Compounds. *2-((2S)-2-((1-(2-Nitrophenyl)-2-oxo-2-phenylethyl)amino)propanamido)ethanaminium 2,2,2-trifluoroacetate* ***8****{1,1,1}.*



Yield 13.3 mg (34%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 1H), 8.09 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.93 (m, 5 H), 7.78−7.71 (m, 1H), 7.67−7.58 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.52−7.46 (m, 2H), 6.36 (s, 1H), 3.63 (q, *J* = 6.5 Hz, 1H), 3.31−3.15 (m, 2H), 2.88−2.75 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.3, 171.9, 158.4 (q, *J* = 33.2 Hz), 148.2, 134.4, 134.1, 133.9, 131.3, 130.4, 128.9, 128.7, 125.5, 60.6, 56.2,

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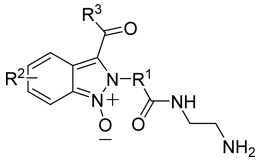
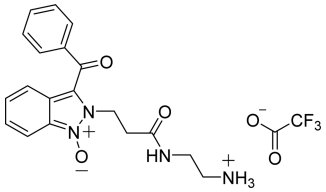
38.3, 36.5, 17.6. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{22}N_4O_4$ $[M + H]^+$ 371.1714, found 371.1693.

Analytical Data of Synthetic Compounds: 2*H*-Indazole 1-Oxides 9{*R*^{1},*R*^{2},*R*^{3}}.

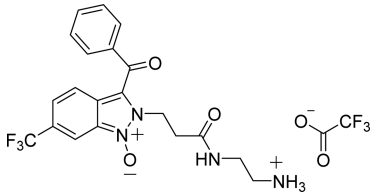


*2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate **9**{3,1,1}.*



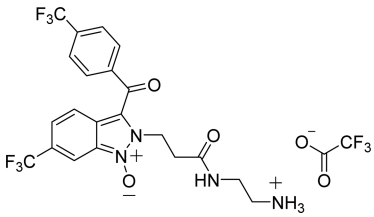
Yield 88.0 mg (95%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (t, J = 5.7 Hz, 1H), 8.02 (br s, 3H), 7.77−7.71 (m, 3H), 7.71−7.67 (m, 1H), 7.61−7.55 (m, 2H), 7.31 (ddd, J = 8.7, 6.8, 0.8 Hz, 1H), 7.18 (ddd, J = 8.7, 6.8, 0.9 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 5.03 (t, J = 7.1 Hz, 2H), 3.28 (m, 2H), 2.88 (m, 2H), 2.81 (t, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.9, 170.0, 158.9 (q, J = 32.5 Hz, 1C), 139.3, 132.7, 129.0, 128.8, 128.7, 127.7, 126.4, 120.1, 120.0, 117.1, 116.9 (q, J = 295.9 Hz, 1C), 113.4, 42.2, 38.7, 36.5, 33.3. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_4O_3$ $[M + H]^+$ 353.1608, found 353.1608.

*2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-6-(trifluoromethyl)-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate **9**{3,2,1}.*



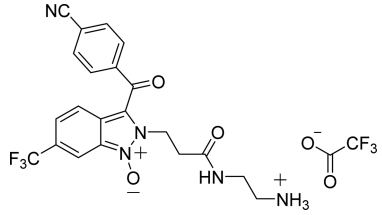
Yield 75.0 mg (78%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (t, J = 5.7 Hz, 1H), 8.14−8.08 (m, 1H), 7.97 (br s, 3H), 7.81−7.77 (m, 2H), 7.77−7.71 (m, 1H), 7.64−7.56 (m, 2H), 7.44 (dd, J = 9.2, 1.6 Hz, 1H), 6.95 (dt, J = 9.0, 0.8 Hz, 1H), 5.04 (t, J = 7.0 Hz, 2H), 3.32−3.20 (m, 2H), 2.92−2.76 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.9, 169.9, 158.8 (q, J = 32.5 Hz, 1C), 138.7, 133.2, 129.2, 128.9, 127.2, 126.4 (q, J = 32.7 Hz, 1C), 123.7 (q, J = 272.1 Hz, 1C), 122.8, 122.2, 120.3, 117.6, 116.9 (q, J = 297.0 Hz, 1C), 112.1 (q, J = 4.8 Hz, 1C), 42.6, 38.7, 36.5, 33.0. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}F_3N_4O_3$ $[M + H]^+$ 421.1482, found 421.1482.

*2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-6-(trifluoromethyl)-3-(4-(trifluoromethyl)benzoyl)-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate **9**{3,2,2}.*



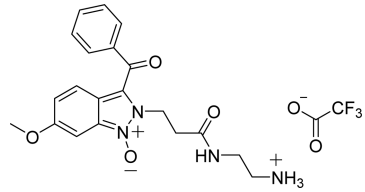
Yield 92.0 mg (71%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (t, J = 5.7 Hz, 1H), 8.17−8.12 (m, 1H), 8.03−7.93 (m, 7H), 7.48 (dd, J = 9.2, 1.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 5.05 (t, J = 6.9 Hz, 2H), 3.32−3.20 (m, 2H), 2.94−2.77 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.6, 169.9, 158.9 (q, J = 32.1 Hz, 1C), 142.3, 132.5 (q, J = 32.1 Hz, 1C), 130.0, 127.4, 126.5 (q, J = 32.8 Hz, 1C), 126.0 (q, J = 3.6 Hz, 1C), 123.9 (q, J = 272.7 Hz, 1C), 123.7 (q, J = 272.7 Hz, 1C), 123.3 (q, J = 2.5 Hz, 1C), 122.1, 120.7, 117.2, 117.0 (q, J = 297.8 Hz, 1C), 112.2 (q, J = 4.7 Hz, 1C), 42.7, 38.7, 36.5, 32.8. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{18}F_6N_4O_3$ $[M + H]^+$ 489.1356, found 489.1354.

*2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-3-(4-cyanobenzoyl)-6-(trifluoromethyl)-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate **9**{3,2,3}.*



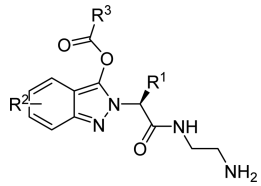
Yield 26.0 mg (26%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (t, J = 5.7 Hz, 1H), 8.21−8.16 (m, 1H), 8.13−8.08 (m, 2H), 7.96−7.91 (m, 2H), 7.85 (br s, 3H), 7.50 (dd, J = 9.2, 1.5 Hz, 1H), 6.96 (dt, J = 9.0, 0.7 Hz, 1H), 5.04 (t, J = 7.0 Hz, 2H), 3.24 (q, J = 6.1 Hz, 2H), 2.88−2.77 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.4, 169.9, 158.4 (q, J = 32.4 Hz, 1C), 142.5, 133.0, 129.7, 127.5, 126.5 (q, J = 32.7 Hz, 1C), 123.7 (q, J = 272.2 Hz, 1C), 123.4 (q, J = 2.8 Hz, 1C), 122.2, 120.8, 118.3, 117.0, 116.9 (q, J = 292.4 Hz, 1C), 115.0, 112.2 (q, J = 4.9 Hz, 1C), 42.7, 38.7, 36.5, 32.7. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{18}F_3N_5O_3$ $[M + H]^+$ 446.1435, found 446.1433.

*2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-6-methoxy-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate **9**{3,3,1}.*

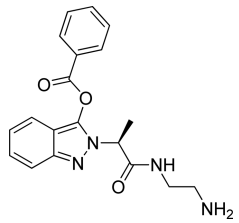


Yield 63.0 mg (37%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (t, J = 5.6 Hz, 1H), 7.93 (br s, 3H), 7.77−7.69 (m, 3H), 7.58 (t, J = 7.6 Hz, 2H), 6.99 (d, J = 2.2 Hz, 1H), 6.88 (dd, J = 9.3, 2.2 Hz, 1H), 6.62 (d, J = 9.3 Hz, 1H), 5.01−4.93 (m, 2H), 3.84 (s, 3H), 3.31−3.21 (m, 2H), 2.91−2.80 (m, 2H), 2.80−2.73 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.8, 170.1, 158.7 (q, J = 34.0 Hz, 1C), 158.5, 139.2, 132.8, 129.4, 129.0, 128.8, 122.1, 121.3, 117.7, 116.5 (q, J = 294.9 Hz, 1C), 115.7, 90.9, 55.8, 42.0, 38.8, 36.5, 33.6. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{22}N_4O_4$ $[M + H]^+$ 383.1714, found 383.1716.

Analytical Data of Synthetic Compounds: 2*H*-Indazol-3-yl Benzoates 11{*R*^{1},*R*^{2},*R*^{3}}.



*(S)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-2H-indazol-3-yl Benzoate **11**{1,1,1}.*



Yield 13.2 mg (33%) of amorphous solid^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (t, J = 5.8 Hz, 1H), 7.87−7.84 (m, 2H), 7.83−7.78 (m, 2H), 7.75 (br s, 2H), 7.69−7.64 (m, 2H), 7.47 (ddd, J = 8.6, 7.3, 1.3 Hz, 1H), 7.34 (ddd, J = 7.9, 7.2, 0.7 Hz, 1H), 6.34 (d, J = 8.6 Hz, 1H), 4.93 (q, J = 7.2 Hz, 1H), 3.47 (dq, J = 13.3, 6.5 Hz, 1H),

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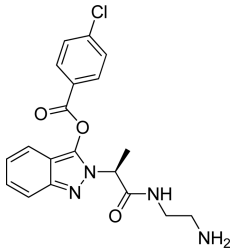
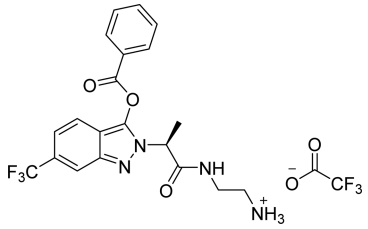
3.26−3.18 (m, 1H), 2.93−2.85 (m, 2H), 1.58 (d, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.0, 167.1, 164.6, 143.0, 133.81, 133.78, 133.5, 129.4, 129.3, 124.9, 123.7, 118.5, 113.0, 56.7, 38.6, 36.8, 14.3. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_4O_3$ $[M + H]^+$ 353.1608, found 353.1618.

(S)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-2H-indazol-3-yl 4-Chlorobenzoate ***11****{1,1,4}.*



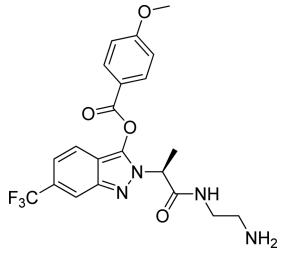
Yield 6.5 mg (17%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (t, J = 5.8 Hz, 1H), 7.92−7.88 (m, 2H), 7.83 (dq, J = 7.7, 0.7 Hz, 1H), 7.76 (d, J = 8.8 Hz, 4H), 7.54 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 7.37 (ddd, J = 7.9, 7.1, 0.8 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 4.92 (q, J = 7.3 Hz, 1H), 3.52−3.40 (m, 1H), 3.28−3.18 (m, 1H), 2.96−2.82 (m, 2H), 1.60 (d, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 166.0, 164.8, 142.9, 138.6, 133.7, 132.4, 131.3, 129.6, 125.0, 123.8, 118.6, 113.2, 56.9, 38.6, 36.8, 14.3. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{19}ClN_4O_3$ $[M + H]^+$ 387.1218, found 387.1230.

(S)-2-(2-(3-(Benzoyloxy)-6-(trifluoromethyl)-2H-indazol-2-yl)-propanamido)ethanaminium 2,2,2-Trifluoroacetate ***11****{1,2,1}.*



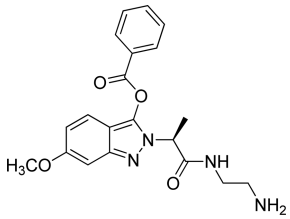
Yield 36.0 mg (26%) of amorphous solid. Slightly contaminated by benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (t, J = 5.8 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.91−7.79 (m, 5H), 7.73−7.65 (m, 3H), 6.59 (s, 1H), 4.97 (q, J = 7.2 Hz, 1H), 3.54−3.42 (m, 1H), 3.33−3.20 (m, 1H), 2.91 (d, J = 5.6 Hz, 2H), 1.68 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 166.5, 163.9, 158.6 (q, J = 32.2 Hz, 1C), 142.6, 133.8, 133.4, 132.8 (q, J = 32.2 Hz, 1C), 129.5, 129.4, 128.2, 125.3, 123.3 (q, J = 273.0 Hz, 1C), 122.0, 121.4 (q, J = 3.4 Hz, 1C), 110.3 (q, J = 4.2 Hz, 1C), 57.9, 38.5, 37.0, 14.6. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}F_3N_4O_3$ $[M + H]^+$ 421.1482, found 421.1480.

(S)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-6-(trifluoromethyl)-2H-indazol-3-yl 4-Methoxybenzoate ***11****{1,2,5}.*



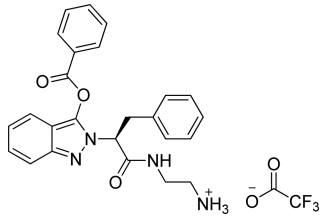
Yield 14.0 mg (16%) of amorphous solid. Slightly contaminated by 4-methoxybenzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13−8.02 (m, 2H), 7.93−7.89 (m, 2H), 7.79 (br s, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.26−7.20 (m, 2H), 6.82 (s, 1H), 4.91 (q, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.50−3.39 (m, 1H), 3.30−3.19 (m, 1H), 2.95−2.84 (m, 2H), 1.65 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 166.2, 164.0, 163.6, 142.9, 132.7 (q, J = 31.8 Hz, 1C), 132.2, 125.3, 124.9, 123.3 (q, J = 273.0 Hz, 1C), 121.8 (q, J = 1.0 Hz, 1C), 121.1 (q, J = 3.2 Hz, 1C), 114.8, 110.1 (q, J = 4.6 Hz, 1C), 57.5, 55.9, 38.5, 36.9, 14.6. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{21}F_3N_4O_4$ $[M + H]^+$ 451.1588, found 451.1588.

(S)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-6-methoxy-2H-indazol-3-yl Benzoate ***11****{1,3,1}.*



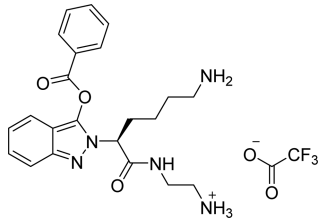
Yield 8.1 mg (21%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (t, J = 5.8 Hz, 1H), 7.87−7.81 (m, 2H), 7.81−7.76 (m, 3H), 7.73 (d, J = 8.7 Hz, 1H), 7.71−7.65 (m, 2H), 6.95 (dd, J = 8.7, 2.1 Hz, 1H), 5.74 (d, J = 2.1 Hz, 1H), 4.88 (q, J = 7.2 Hz, 1H), 3.51 (s, 3H), 3.50−3.43 (m, 1H), 3.29−3.18 (m, 1H), 2.95−2.86 (m, 2H), 1.56 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 166.9, 165.0, 163.4, 144.9, 133.9, 133.5, 129.5, 129.2, 125.2, 112.7, 111.6, 97.8, 57.0, 55.5, 38.6, 36.8, 14.3. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{22}N_4O_4$ $[M + H]^+$ 383.1714, found 383.1721.

(S)-2-(2-(3-(Benzoyloxy)-2H-indazol-2-yl)-3-phenylpropanamido)-ethanaminium 2,2,2-Trifluoroacetate ***11****{2,1,1}.*



Yield 7.1 mg (16%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (t, J = 5.9 Hz, 1H), 7.84−7.74 (m, 4H), 7.60 (t, J = 7.9 Hz, 2H), 7.38 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 7.34−7.27 (m, 3H), 7.19−7.14 (m, 1H), 7.13−7.07 (m, 3H), 6.01 (d, J = 8.4 Hz, 1H), 5.22 (dd, J = 11.4, 4.3 Hz, 1H), 3.59 (dq, J = 13.5, 6.6 Hz, 1H), 3.52 (d, J = 4.3 Hz, 1H), 3.35−3.23 (m, 2H), 3.00−2.89 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 166.5, 163.8, 158.2 (q, J = 33.3 Hz, 1C), 142.2, 137.7, 133.9, 133.44, 133.43, 129.4, 129.1, 128.8, 128.8 (q, J = 35.0 Hz, 1C), 128.3, 126.5, 125.0, 123.6, 118.3, 112.5, 62.2, 38.6, 36.8, 33.2. HRMS (ESI-TOF) m/z calcd for $C_{25}H_{24}N_4O_3$ $[M + H]^+$ 429.1921, found 429.1920.

(S)-2-(6-Amino-2-(3-(benzoyloxy)-2H-indazol-2-yl)hexanamido)-ethanaminium 2,2,2-Trifluoroacetate ***11****{3,1,1}.*



Yield 6.8 mg (16%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (t, J = 5.8 Hz, 1H), 7.87−7.72 (m, 8H), 7.72−7.66 (m, 2H), 7.49 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 7.36 (ddd, J = 7.9, 7.3, 0.7 Hz, 1H), 6.27 (d, J = 8.6 Hz, 1H), 4.93 (dd, J = 10.4, 4.9 Hz, 1H), 3.49−3.43 (m, 1H, overlap with the water), 3.29−3.19 (m, 1H), 2.95−2.85 (m, 2H), 2.82−2.72 (m, 2H), 2.24−2.02 (m, 2H), 1.57 (dq, J = 13.9, 6.9 Hz, 2H), 1.45−1.24 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.7, 166.9, 164.5, 158.2 (q, J = 31.9 Hz, 1C), 142.7, 133.9, 133.8, 133.6, 129.6, 129.3, 125.0, 124.0, 118.3, 117.0 (q, J = 297.9 Hz, 1C), 113.0, 60.8, 38.6, 38.4, 36.8, 27.9, 26.8, 23.0. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{27}N_5O_3$ $[M + H]^+$ 410.2187, found 410.2186.

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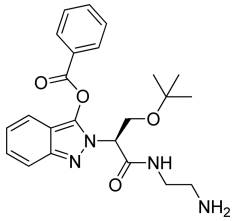
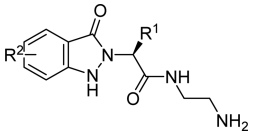
(S)-2-(1-((2-Aminoethyl)amino)-3-(tert-butoxy)-1-oxopropan-2-yl)-2H-indazol-3-yl Benzoate ***11****{4,1,1}.*

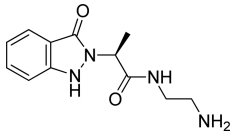


Yield 9.6 mg (21%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (t, J = 5.9 Hz, 1H), 7.87−7.81 (m, 1H), 7.81−7.74 (m, 5H), 7.73−7.67 (m, 2H), 7.50 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.38−7.33 (m, 1H), 6.30 (d, J = 8.6 Hz, 1H), 5.02 (dd, J = 9.4, 5.3 Hz, 1H), 3.94−4.02 (m, 1H), 3.94−3.85 (m, 1H), 3.51 (dq, J = 13.5, 6.6 Hz, 1H), 3.33−3.21 (m, 1H), 2.97−2.85 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 166.4, 165.1, 143.0, 133.9, 133.7, 129.6, 129.0, 123.9, 118.2, 73.3, 73.0, 61.2, 61.0, 58.4, 38.6, 36.6, 27.1. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{28}N_4O_4$ $[M + H]^+$ 425.2183, found 425.2181.

Analytical Data of Synthetic Compounds: 2-Alkyl-1,2-dihydro-3*H*-indazol-3-ones 12.

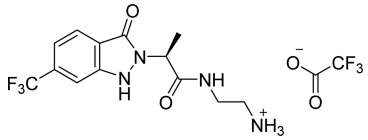


(S)-N-(2-Aminoethyl)-2-(3-oxo-1H-indazol-2(3H)-yl)propanamide ***12****{1,1}.*



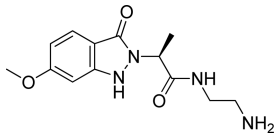
Yield 6.3 mg (22%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (br s, 1H), 8.27 (t, J = 5.6 Hz, 1H), 7.83 (br s, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.52 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 5.03 (q, J = 7.2 Hz, 1H), 3.33 (quin, J = 5.8 Hz, 2H), 2.89 (q, J = 5.9 Hz, 2H), 1.47 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) 170.6, 161.4, 147.0, 131.7, 123.0, 121.0, 117.0, 112.7, 52.3, 38.5, 36.8, 15.9 pm. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}N_4O_2$ $[M + H]^+$ 249.1346, found 249.1348.

(S)-2-(2-(3-Oxo-6-(trifluoromethyl)-1H-indazol-2(3H)-yl)-propanamido)ethanaminium 2,2,2-Trifluoroacetate ***12****{1,2}.*



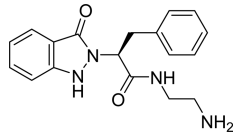
Yield 55.0 mg (72%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (br s, 1H), 8.39 (t, J = 5.6 Hz, 1H), 7.96 (br s, 2H), 7.87 (d, J = 8.2 Hz, 1H), 7.65 (s, 1H), 7.36 (dd, J = 8.2, 0.8 Hz, 1H), 5.11 (q, J = 7.2 Hz, 1H), 3.43−3.27 (m, 2H), 2.91 (t, J = 6.3 Hz, 2H), 1.51 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 159.8, 158.9 (q, J = 32.0 Hz, 1C), 145.6, 131.6 (q, J = 31.7 Hz, 1C), 124.6, 124.1 (q, J = 272.8 Hz, 1C), 119.3, 117.1 (q, J = 298.2 Hz, 1C), 116.7 (q, J = 3.0 Hz, 1C), 110.0 (q, J = 4.0 Hz, 1C), 52.3, 38.4, 36.8, 16.1. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{15}F_3N_4O_2$ $[M + H]^+$ 317.1220, found 317.1228.

(S)-N-(2-Aminoethyl)-2-(6-methoxy-3-oxo-1H-indazol-2(3H)-yl)-propanamide ***12****{1,3}.*



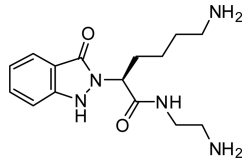
Yield 6.1 mg (22%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (br s, 1H), 8.24 (t, J = 5.7 Hz, 1H), 7.81 (br s, 2H), 7.52 (d, J = 9.1 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.69 (dd, J = 8.6, 2.1 Hz, 1H), 4.95 (q, J = 7.1 Hz, 1H), 3.81 (s, 3H), 3.38−3.28 (m, 2H), 2.94−2.85 (m, 2H), 1.42 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.7, 162.9, 161.7, 149.1, 124.2, 111.1, 110.2, 94.8, 55.6, 52.3, 38.5, 36.7, 15.7. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}N_4O_3$ $[M + H]^+$ 279.1452, found 279.1452.

(S)-N-(2-Aminoethyl)-2-(3-oxo-1H-indazol-2(3H)-yl)-3-phenylpropanamide ***12****{2,1}.*



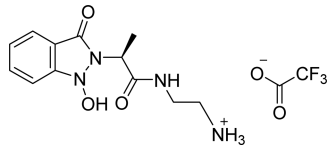
Yield 11.9 mg (36%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (br s, 1H), 8.51 (t, J = 5.6 Hz, 1H), 7.94 (br s, 3H), 7.52 (d, J = 7.8 Hz, 1H), 7.48 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.15−7.08 (m, 4H), 7.04 (ddd, J = 7.8, 7.1, 0.6 Hz, 1H), 5.26 (dd, J = 10.9, 4.7 Hz, 1H), 3.39−3.31 (m, 2H), 3.24 (dd, J = 14.1, 10.9 Hz, 1H), 2.88 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 161.1, 146.6, 137.2, 131.5, 128.8, 128.1, 126.4, 122.9, 120.8, 116.7, 112.6, 57.4, 38.3, 36.7, 35.7. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{20}N_4O_2$ $[M + H]^+$ 325.1659, found 325.1657.

(S)-6-Amino-N-(2-aminoethyl)-2-(3-oxo-1H-indazol-2(3H)-yl)-hexanamide ***12****{3,1}.*



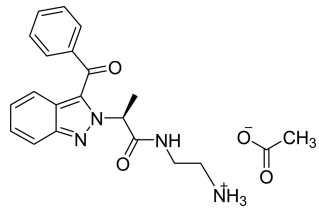
Yield 12.6 mg (39%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (br s, 1H), 8.38 (t, J = 5.5 Hz, 1H), 7.89 (br s, 2H), 7.74 (br s, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 4.98 (dd, J = 9.7, 5.8 Hz, 1H), 3.38−3.27 (m, 1H), 2.96−2.83 (m, 2H), 2.77−2.61 (m, 2H), 2.06−1.89 (m, 2H), 1.59−1.42 (m, 2H), 1.31−1.20 (m, 1H), 1.16−0.95 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.2, 161.5, 146.8, 131.7, 123.1, 120.9, 116.6, 112.8, 55.9, 38.6, 38.4, 36.7, 29.4, 26.4, 22.5. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{23}N_5O_2$ $[M + H]^+$ 306.1925, found 306.1925.

(S)-2-(2-(1-Hydroxy-3-oxo-1H-indazol-2(3H)-yl)propanamido)-ethanaminium 2,2,2-Trifluoroacetate ***14****.*



Yield 7.2 mg (24%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (t, J = 5.7 Hz, 1H), 7.88−7.81 (m, 2H), 7.83 (dd, J = 7.5, 1.30 Hz, 1H), 7.77 (dd, J = 7.8, 1.2 Hz, 1H), 7.72 (td, J = 7.5, 1.4 Hz, 1H), 7.67 (td, J = 7.4, 1.4 Hz, 1H), 4.57 (q, J = 6.9 Hz, 1H), 3.45−3.34 (m, 1H), 3.34−3.25 (m, 1H), 2.93−2.84 (m, 2H), 1.39 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.6, 166.3, 158.4 (q, J = 32.6 Hz, 1C), 147.1, 132.3, 130.9, 129.9, 127.1, 124.2, 116.7 (q, J = 298.1 Hz, 1C), 59.8, 38.5, 36.6, 14.4. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}N_4O_3$ $[M + H]^+$ 265.1295, found 265.1297.

(S)-2-(2-(3-Benzoyl-2H-indazol-2-yl)propanamido)ethanaminium Acetate ***17****.*



DOI: 10.1021/acs.joc.6b00251
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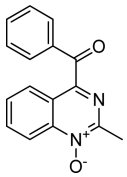
Yield 19.5 mg (60%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66−8.57 (m, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 7.0 Hz, 2H), 7.77−7.71 (m, 1H), 7.60 (t, J = 7.7 Hz, 2H), 7.37−7.30 (m, 1H), 7.16−7.08 (m, 1H), 6.83 (d, J = 8.6 Hz, 1H), 5.89 (q, J = 7.0 Hz, 1H), 3.24 (dt, J = 12.5, 6.2 Hz, 1H), 3.21−3.13 (m, 1H), 2.71 (t, J = 6.0 Hz, 2H), 1.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 185.9, 169.5, 146.6, 138.5, 133.3, 131.7, 129.4, 128.7, 126.0, 124.7, 122.9, 120.0, 118.5, 60.7, 40.0, 39.8, 17.7. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_4O_2$ $[M + H]^+$ 337.1659, found 337.1664.

4-Benzoyl-2-methylquinazoline 1-Oxide ***20***.



Yield 1.7 mg (5%) of amorphous solid, isolated from 1 g of resin, from which was earlier cleaved indazole oxide by cyclative cleavage. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, J = 8.5 Hz, 1H), 8.29−8.26 (m, 1H), 8.12 (ddd, J = 8.7, 7.1, 1.3 Hz, 1H), 8.01 (dd, J = 8.4, 1.3 Hz, 2H), 7.85 (ddd, J = 8.3, 7.1, 1.1 Hz, 1H), 7.76−7.72 (m, 1H), 7.58 (t, J = 7.8 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.1, 151.5, 146.7, 143.55, 135.7, 134.9, 134.2, 130.7, 129.9, 128.68, 126.6, 122.6, 118.2, 19.9. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{12}N_2O_2$ $[M + H]^+$ 265.0972, found 265.0944.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00251.

LC traces of crude products of oxidation and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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