

UNIVERZITA PALACKÉHO V OLOMOUCI

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Katedra organické chemie



Syntéza 2-alkyl-2*H*-indazol-3-yl benzoátů a 2-alkyl-1,2-dihydro-3*H*-indazol-3-onů na pevné fázi prostřednictvím

Baeyer-Villigerovy oxidace s *N*-oxidem jako

intramolekulárním oxidantem

RIGORÓZNÍ PRÁCE

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Abstrakt:

Práce je zaměřena na syntézu 2-alkyl-2*H*-indazol-3-yl benzoátů a 2-alkyl-1,2-dihydro-3*H*-indazol-3-onů na pevné fázi. Pomocí bazicky katalyzované *C*-arylace 2-nitrobenzen-sulfonamidů, následované tvorbu vazby N-N došlo ke vzniku intermediátu, který dehydratoval na indazol-oxidy. Při použití trifluoroctové kyseliny o vysoké čistotě se podařilo dehydrataci předejít a katalyzovat intramolekulární Baeyer-Villigerovu oxidaci, kde *N*-oxid sloužil jako intramolekulární oxidační činidlo. Výsledkem pak byly indazol-estery, které hydrolyzovaly na příslušné indazolony. Zatímco při použití méně čisté trifluoroctové kyseliny vznikaly indazol-oxidy-ketony. Byl studován mechanismus formace výsledných esterů a podařilo se připravit malou knihovnu látek.

Klíčová slova:	pevná fáze, indazoly, indazol-oxidy, <i>C</i> -arylace, 2-nitrobenzensulfonamidy, intramolekulární oxidace
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Abstract:

This thesis studied the solid-phase synthesis of 2-alkyl-2*H*-indazol-3-yl benzoates and 2-alkyl-1,2-dihydro-3*H*-indazol-3-ones. Base-mediated *C*-arylation of 2-nitrobenzenesulfonamides, followed by N-N bond formation provided a reactive intermediate that spontaneously dehydrated to indazole oxides. Using redistilled trifluoroacetic acid prevented dehydration and catalyzed intramolecular Baeyer-Villiger oxidation with *N*-oxide as an intramolecular oxidant. The resulting indazole esters hydrolyzed to the corresponding indazolones. In contrast, reagent grade trifluoroacetic acid led to indazole oxides ketones. This thesis both prepared a small library of compounds and studied the reaction mechanism of ester formation.

Keywords: solid phase, indazoles, indazole oxides, *C*-arylation, 2-nitrobenzenesulfonamides, intramolecular oxidation
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1 Úvod

Tato rigorózní práce je tvořena třemi hlavními částmi – úvodem do problematiky 2-nitrobenzensulfonamidové chemie, která zahrnuje i komentář k předložené publikaci, dále je tvořena článkem publikovaným v mezinárodním impaktovaném časopise (Journal of Organic Chemistry) a doplňujícími informacemi k publikaci (Supporting Information).

Tématem rigorózní práce je syntéza farmakologicky relevantních dusíkatých heterocyklů na pevné fázi. Jedná se o příspěvek k širší oblasti chemie, která se na Katedře organické chemie v Olomouci studuje od roku 2008.

2 Seznámení s tematikou Nos chemie

2.1 Význam heterocyklů v medicíně

Heterocyklické sloučeniny jsou nedílnou součástí našich životů. Jako purinové a pyrimidinové báze tvoří stavební kameny nukleových kyselin podílejících se na předávání genetické informace. Mezi biogenními aminokyselinami, které kódují primární strukturu proteinů, rovněž nalezneme heterocyklické struktury, jedná se o histidin (imidazol), tryptofan (indol) a prolin (pyrrolidin). Heterocykly hrají klíčovou roli v řadě biologických pochodů, například ve fotosyntéze, kde zelené rostlinné barvivo chlorofyl, tetramer pyrrolu obklopující atom hořčíku, absorbuje sluneční záření a umožňuje tak tvorbu sacharidů z oxidu uhličitého a vody. U živočichů se analogický porfyrinový kruh s atomem železa uplatňuje jako krevní barvivo hemoglobin, tento metaloprotein zajišťuje transport kyslíku z plic do tkání a odstraňování oxidu uhličitého opačným směrem. Jako neurotransmitery serotonin (indol) a histamin (pyrazol) zprostředkovávají heterocykly přenos nervového signálu. Nesporný význam heterocyklů je dokreslován jejich zastoupením v řadě přírodních léčiv (papaverin, theobromin, chinin, atropin, prokain, morfin atd.), jsou součástí struktury syntetických léčiv napříč spektrem terapeutických účinků (diazepam, chlorpromazin, isoniazid, metronidazole, azidothymidin, barbituráty atd.). Více než 90 % nových léčiv obsahuje ve své struktuře heterocyklus.¹⁻³

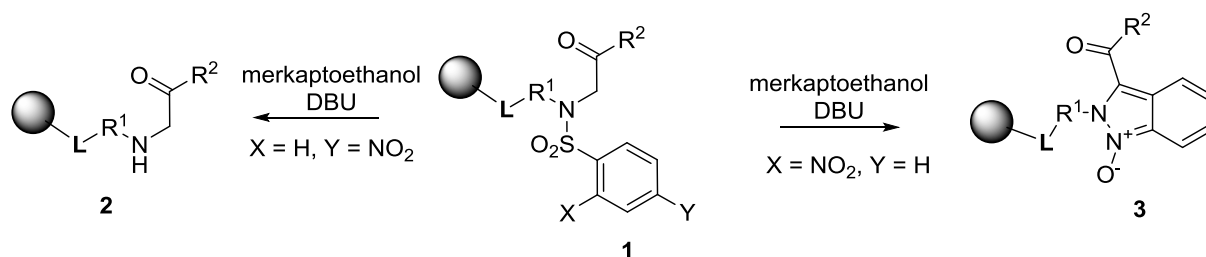
Vývoj nového léčiva vyžaduje otestování 10 000 nových sloučenin, než je nalezena látka s optimálními vlastnostmi. Přičemž existuje neprobádaný prostor biologicky zajímavých sloučenin. Při navrhování těchto sloučenin hrají stále důležitější roli látky odvozené od přírodních produktů. Dříve se testovaly rozsáhle knihovny strukturně podobných sloučenin, dnes se trend posouvá směrem k menším knihovám navrhovaných tak, aby splňovaly strukturní a funkční diverzitu (Diversity-Oriented Synthesis, DOS)⁴ a stále více se zohledňuje

podobnost s přírodními produkty (Biology-Oriented Synthesis, BIOS).⁵ Koncept „privilegovaných struktur“⁶ poukazuje na strukturní motivy, které se dokáží vázat k více receptorům, představují tak slibný farmakologický cíl. A právě heterocykly patří k privilegovaným strukturám.

Cílem této práce je vývoj nových syntetických postupů k dusíkatým heterocyklům na pevné fázi. Typické je spojení syntézy na pevné fázi s kombinatoriální chemií, která umožňuje rychlý přístup ke knihovně různě funkcionalizovaných sloučenin. K výhodám syntézy na pevné fázi patří jednoduchá izolace meziproductů bez nutnosti jejich plné charakterizace, dále možnost použití vysokovroucích rozpouštědel díky jejich jednoduchému odstranění pouhou filtrací, protože produkt je ukotven na polymerním nosiči.⁷ Předmětem této studie jsou deriváty indazolů. Sloučeniny s indazolovým skeletem a jejich *N*-oxidy jsou známy pro biologickou aktivitu, o čemž již bylo zpracováno review od Cerecetta a kol.⁸ Syntetické přístupy vedoucí k 1*H*- a 2*H*-indazolům byly shrnuty v review od Cankařové a kol.⁹ Podrobnější rešerše biologických vlastností indazolových derivátů je uvedena v publikaci, která tvoří stěžejní část této rigorózní práce.¹⁰

Tato práce navazuje na tematiku, kterou se naši katedře ve spolupráci s Univerzitou Notre Dame (Indiana, USA) pod vedením doktora Krchňáka podařilo otevřít v roce 2008. Klíčovým objevem zde bylo zjištění rozdílné reaktivity 4-nitrobenzensulfonamidů (Nos) a 2-Nos derivátů v bazickém prostředí. Záměrem byla *N*-alkylace s použitím Fukuyama¹¹ varianty Mistunobu reakce s následnou deprotekcí aktivující Nos skupiny. Zatímco 4-Nos skupina byla za tradičních podmínek ochráněna (2-merkptoethanol/DBU) odštěpena (**2**, Schéma 1), u 2-Nos derivátů došlo k tandemové reakci za formace vazby C-C následované vznikem N-N vazby, kdy byly izolovány indazol-oxidy (**3**).¹²

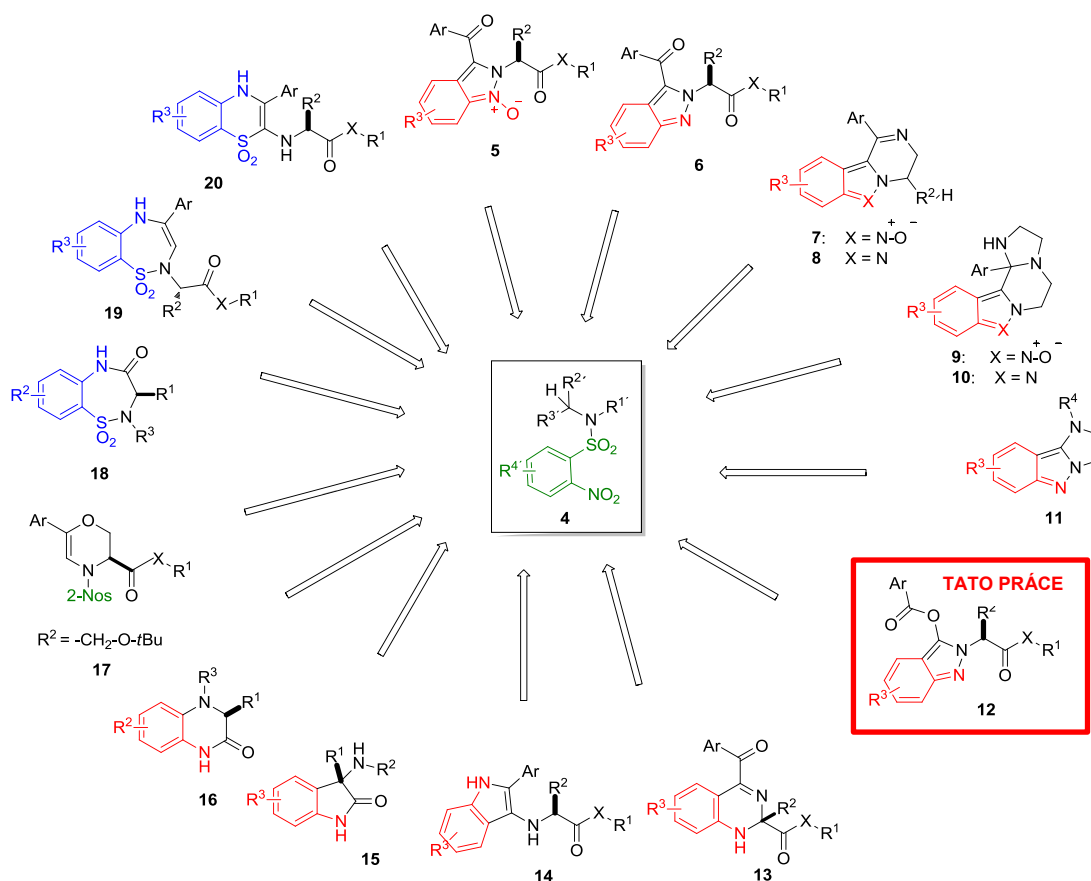
Schéma 1: Rozdílná reaktivita 4-Nos a 2-Nos derivátů za podmínek deprotekcce.



Vedle syntézy indazol-oxidů byla tato chemie až do současnosti rozšířena o celou řadu dalších heterocyklů obsahujících 5-, 6- a 7-členné jádro (Obrázek 1). 2-Nos deriváty tedy můžeme právem označit za „advanced interemediates“,¹³ tedy meziproducty v jistém smyslu „zvýhodněné“ ke tvorbě rozmanitých heterocyklů, přičemž může docházet k Smilesově^{14,15} typu přesmyku za odštěpení SO₂ (v Obr. 1 vzorec červeně) nebo může být Nos skupina

zachována a inkorporována včetně SO₂ skupiny (v Obr. 1 vzorec zeleně pokud Nos skupina zachována, modře pokud nitro zredukováno na amino). Konkrétní reakční podmínky a predispozice budou diskutovány v další části tohoto textu, který si bere za cíl seznámit čtenáře s touto problematikou.

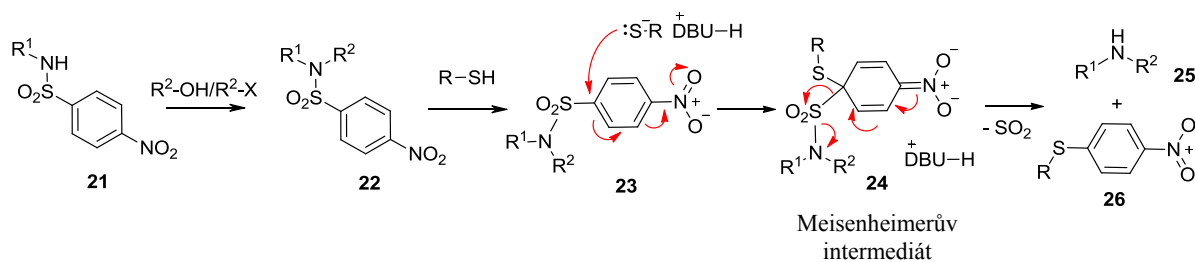
Obrázek 1: 2-Nos deriváty jako výchozí látky pro rozmanité druhy heterocyklů.



2.2 Role Nos derivátů v syntéze heterocyklů

2-Nos a 4-Nos skupiny představují efektivní protektivní a aktivační skupiny. Pro regioselektivní *N*-monoalkylaci primárních aminů na příslušné sekundární aminy včetně deprotektce za mírných podmínek byly poprvé představeny Fukuyamou a kol.¹¹ Jednalo se o velice efektivní provedení, do té doby používané metody měly zjevné nevýhody (vícenásobná alkylace, nutnost použití drsných reakčních podmínek apod.) Odstranění 2- nebo 4-Nos skupiny lze snadno docílit nukleofilní aromatickou substitucí za použití merkptoethanolu/DBU za tvorby Meisenheimerova komplexu (**24**, Schéma 2), který se rozpadá na požadovaný sekundární amin (**25**).

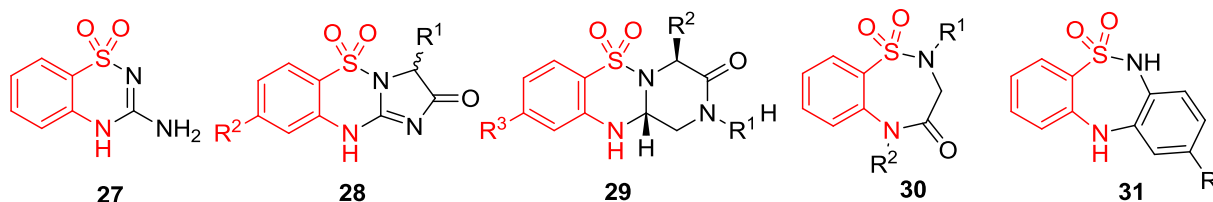
Schéma 2: Fukuyama alkylace za použití 2-, příp. 4-Nos aktivační skupiny.



Tato třístupňová metodologie, tedy substituce primárního aminu Nos skupinou, alkylace aktivovaného dusíku a deprotektce sulfonamidové skupiny, se brzo stala běžně používaná v syntéze na pevné fázi, zvláště v chemii peptidů.^{16,17} Brzy se stala oblíbenou metodou selektivní *N*-alkylace také u polyfunkčních nepeptidových molekul, např. v syntéze 4,7,8-trisubstituovaných 1,2,3,4-tetrahydrobenzo[*e*][1,4] diazepin-5-onů (2-Nos)¹⁸ a trisubstituovaných benzo[1,4]diazepin-5-onů (4-Nos)¹⁹ na pevné fázi.

2-Nos skupina může být vedle protektivní/aktivační funkce inkorporována do struktury heterocyklu jako “building blok”. 2-Nitrobenzensulfonyl chlorid může být totiž převeden na odpovídající sulfonamid, následuje redukce nitro skupiny na amino, která umožňuje finální cyklizaci. Takovéto začlenění do heterocyklu může poskytovat 6-členné kruhy (**27**,²⁰ **28**,²¹ **29**,²² Obrázek 2) a 7-členné kruhy benzothiadiazepin-1,1-dioxidů (**30**,²³ **31**²⁴). Struktury **28** a **29** byly připraveny na pevné fázi.

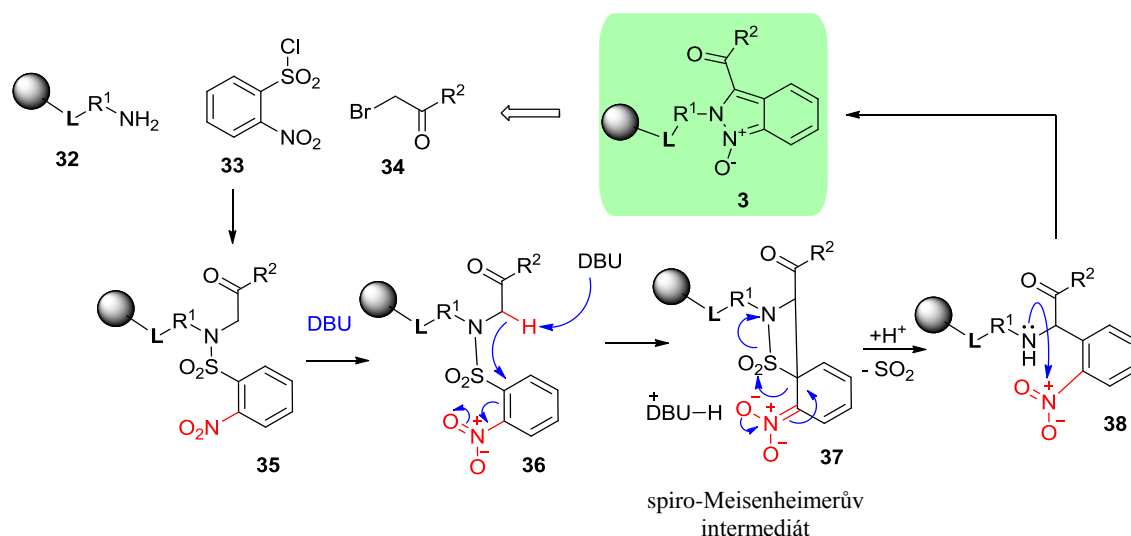
Obrázek 2: Příklady inkorporace 2-Nos skupiny do struktury heterocyklu.



2.3 C- a N-arylace 2-nitrobenzensulfonamidů

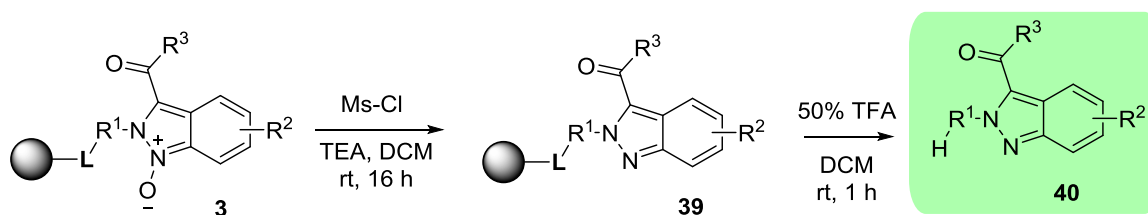
Během vývoje kombinatoriálních knihoven farmakologicky relevantních heterocyklických sloučenin naše skupina objevila zásadní rozdíl v reaktivitě 2- a 4-Nos derivátů. Přítomnost kyselého vodíku na alfa uhlíku (**35**, **36**, Schéma 3) a substituent se záporným mezomerním efektem v ortho poloze umožnily vznik spiro-Meisenheimerova intermediátu (**37**). Mechanismem nukleofilní aromatické substituce tedy došlo ke tvorbě nové vazby C-C. V tandemu následoval nukleofilní atak nitro skupiny amino skupinou za vzniku nové vazby N-N, výsledkem byl indazol-oxid (**3**).

Schéma 3: Mechanismus vzniku indazol-oxidu z 2-Nos derivátu, resp. C-arylace doprovázená vznikem nové vazby N-N.



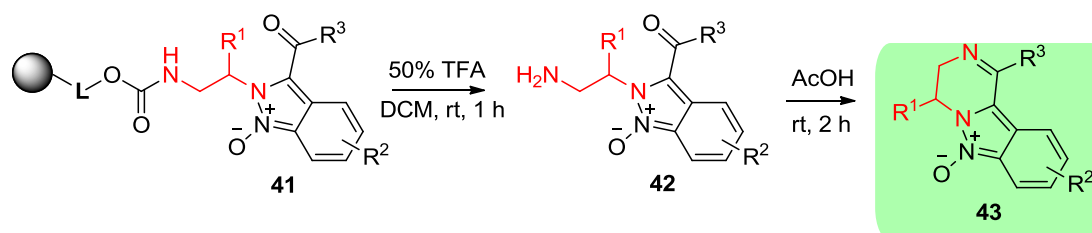
Tento tandem reakcí nabízí řadu možností pro syntézu dalších heterocyklických sloučenin. Indazol-oxidy (**3**, Schéma 4) byly za mírných podmínek (laboratorní teploty) deoxygenovány mesylchloridem v přítomnosti báze na příslušné indazoly (**40**).¹²

Schéma 4: Redukce indazol-oxidů na indazoly, vyobrazen jen závěr několikastupňové syntézy.



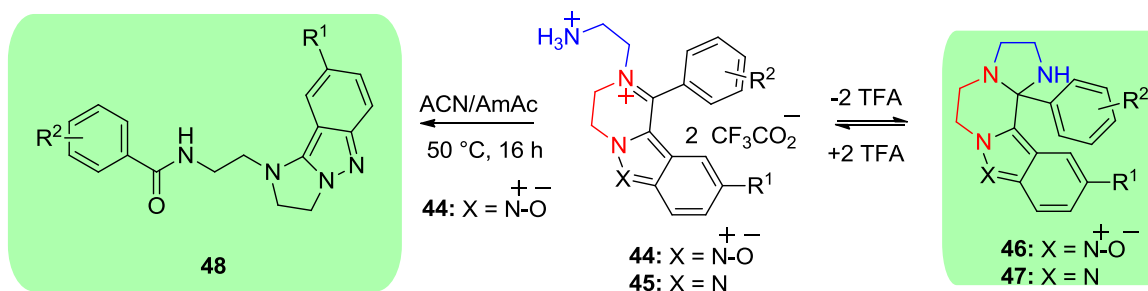
Komplexnějších sloučenin s dalším přikondenzovaným cyklem (**43**, Schéma 5) bylo dosaženo cyklizací ketonu s amino skupinou prvního "building bloku". I zde autoři rozšířili portfolium cílových látek také na indazoly pomocí redukce *N*-oxidů.²⁵

Schéma 5: Vybraná část několikastupňové syntézy 3,4-dihydropyrazino[1,2-*b*]indazol 6-oxidů.



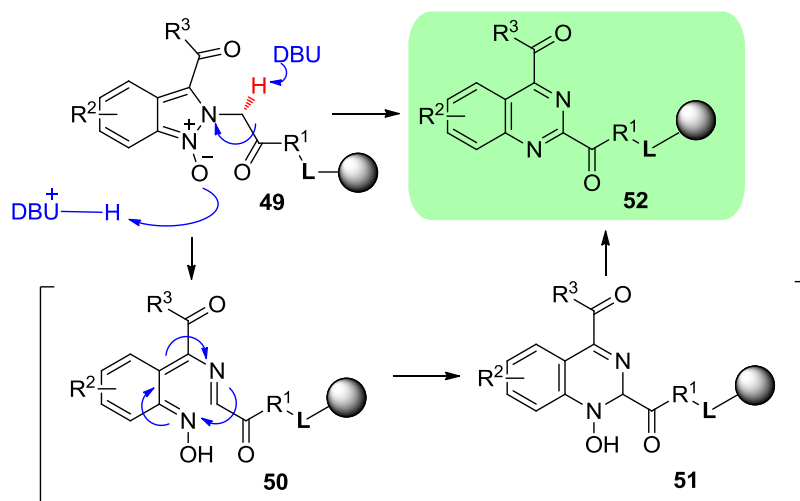
Prodloužením ukotvujícího diaminu o další ethylamino skupinu, tedy použitím diethylentriaminu jako building bloku, se podařilo připravit čtyřjaderné přikondenzované heterocyklické sloučeniny (**46**, **47**, Schéma 6).²⁶ Ukázalo se, že pH hraje u těchto derivátů velice důležitou roli. Při zahřevu indazol-oxidů (**44**) v neutrálním prostředí docházelo k překvapivému přesmyku (**48**).²⁷

Schéma 6: Rovnováha iminium-imidazolidin a přesmyk na 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoly.



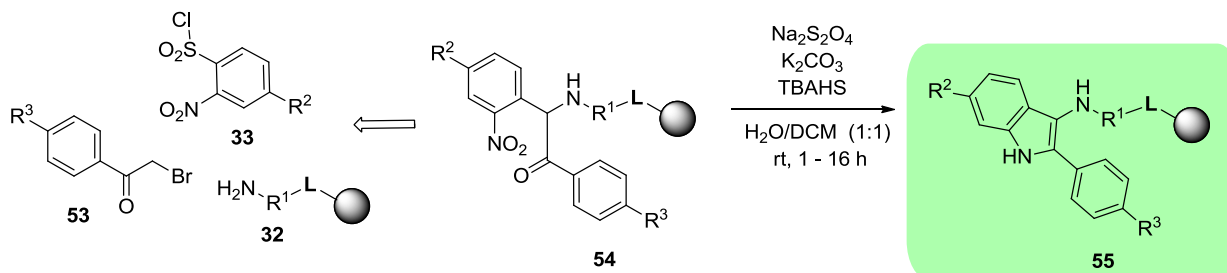
Pokud je v blízkosti indazol-oxidu kyselý alfa vodík (**49**, Schéma 7), dochází v bazickém prostředí k rozšíření cyklu na chinazoliny (**52**). Takovýto kyselý vodík je možný zavést do struktury lineárního intermediátu při použití amino kyseliny glycinu.²⁸ Jedná se o krásný příklad “scaffold hopping”,^{29,30} což je koncept ve vývoji nových léčiv, který je založený na modifikaci centrálního jádra molekuly, přičemž periferní substituenty zůstávají nezměněny.

Schéma 7: Rozšíření indazolového cyklu (**49**) na chinazoliny (**52**).



Dalším zajímavým příspěvkem do tématiky *C*-arylace je syntéza indolů (**55**, Schéma 8).³¹ V tandemu reakcí *C*-*C*, *N*-*N*, je třeba předejít finální cyklizaci na indazol-oxidy, tedy ihned po *C*-arylaci redukovat (**54**) nitro skupinu na amino a tím umožnit vznik indolů (**55**).

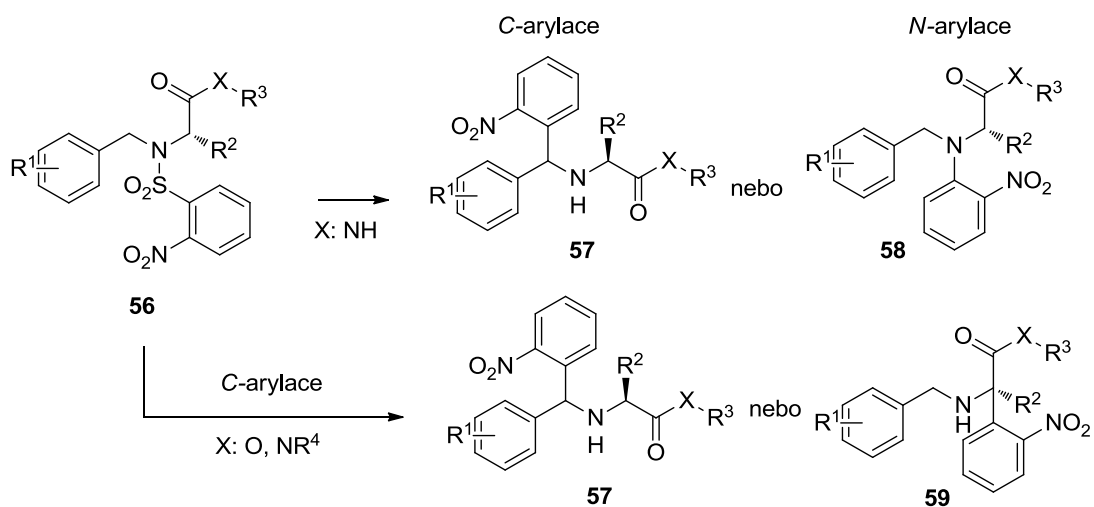
Schéma 8: Vybraná část vícestupňové syntézy indolů (**55**) na pevné fázi.



Za účelem hlubšího studia směru *C*-arylace byly navrženy “duální substráty” (**56**,

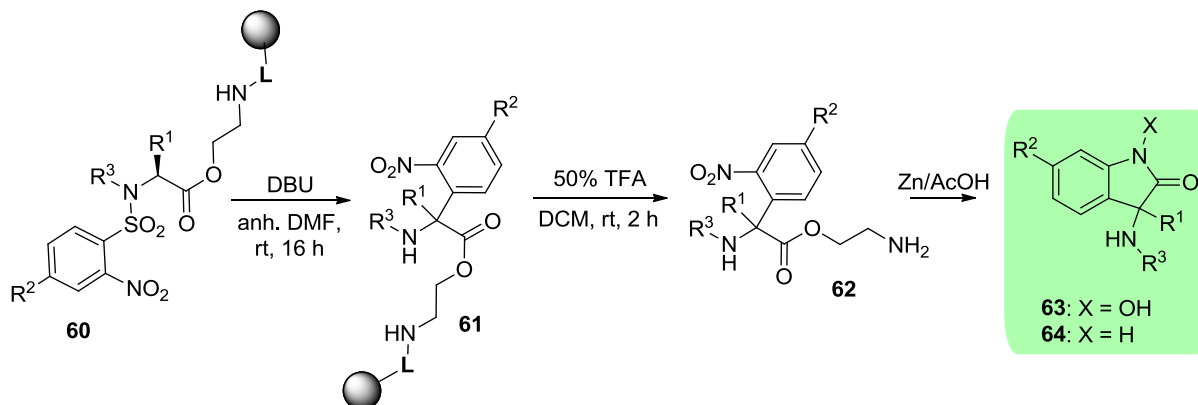
Schéma 9), kde byly možné dvě polohy C-arylace.¹³ Tyto substráty se lišily ukotvením ethanolaminu přes N nebo O konec, Dále byly substitovány amino kyselinou vázanou amidově nebo esterově. Terciární amid byl připraven z piperazinu. Pro přípravu těchto substrátů byl použit opět 2-Nos chlorid, ovšem místo bromoketonu různé benzyl alkoholy. Arylace tak mohla probíhat na benzylový sp³ uhlík (**57**) nebo na alfa uhlík (**59**) v závislosti na elektronových vlivech substituentů a na sterických parametrech. V případě sekundárních amidů dokonce docházelo k dalšímu typu Smilesova přesmyku vedoucímu k *N*-arylovaným derivátům (**58**).

Schéma 9: C-arylace (**57**, **59**) vs. *N*-arylace (**58**) u duálních substrátů.



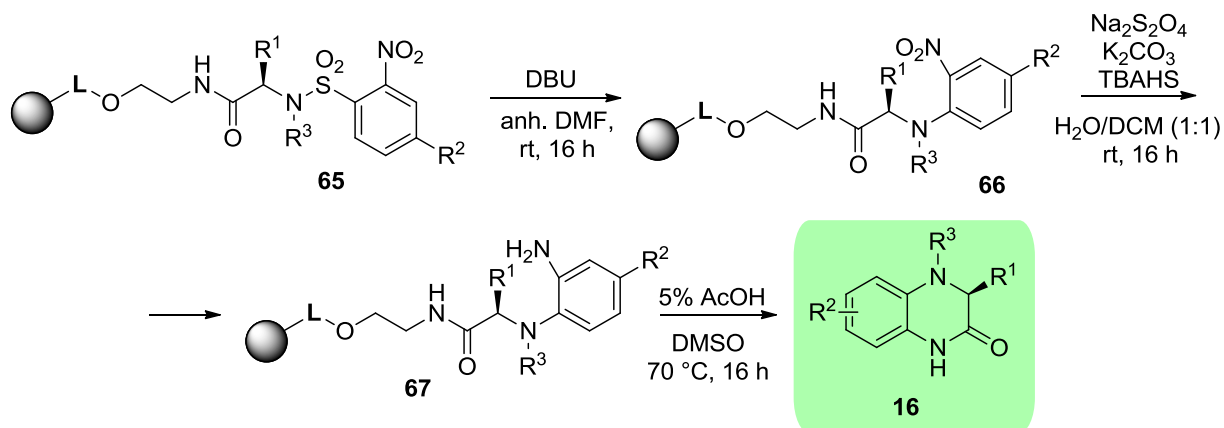
C-aryl deriváty do polohy benzylového uhlíku (**57**) představovaly intermediáty pro syntézu indazol-oxidů, případně chinazolinů,^{32,33} analogicky jako v případě Křupkové a kol.²⁸ Arylace do polohy alfa uhlíku (**59**, Schéma 9, resp. **61**, Schéma 10) byly získány velice zajímavé intermediáty pro syntézu 3-amino-2-oxindolů (**64**).³⁴

Schéma 10: Bazicky katalyzovaná C-arylace 2-Nos derivátů (**60**) na 3-amino-2-oxindoly (**64**), závěrečná část syntézy.



N-arylované deriváty (**58**, Schéma 9, resp. **66**, Schéma 11) byly vhodnými prekurzory pro syntézu dalšího typu heterocyklů, chinoxalinů (**16**). Na syntéze byla zajímavá finální cyklizace prostřednictvím „cyklického štěpení.“³⁵

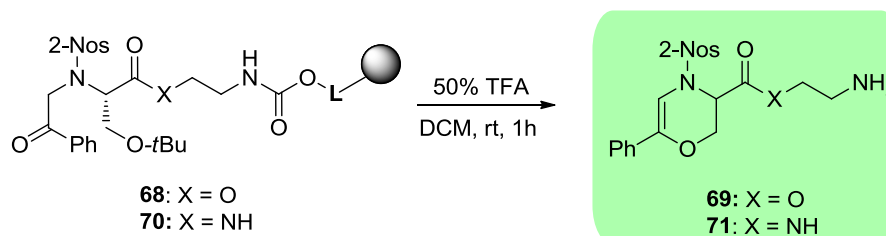
Schéma 11: Bazicky katalyzovaná *N*-arylace 2-Nos derivátů (**65**) na chinoxaliny (**16**), výsek syntézy.



2.4 Zachování 2-Nos skupiny jako substituentu

Při syntéze heterocyklů, například indolů³¹ a 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepin 1,1-dioxidů³⁶ byla popsána preference prekurzoru cyklizovat na morfoliny (**69**, **71**, Schéma 12), pokud byla jako “building blok” použita aminokyselina serin.

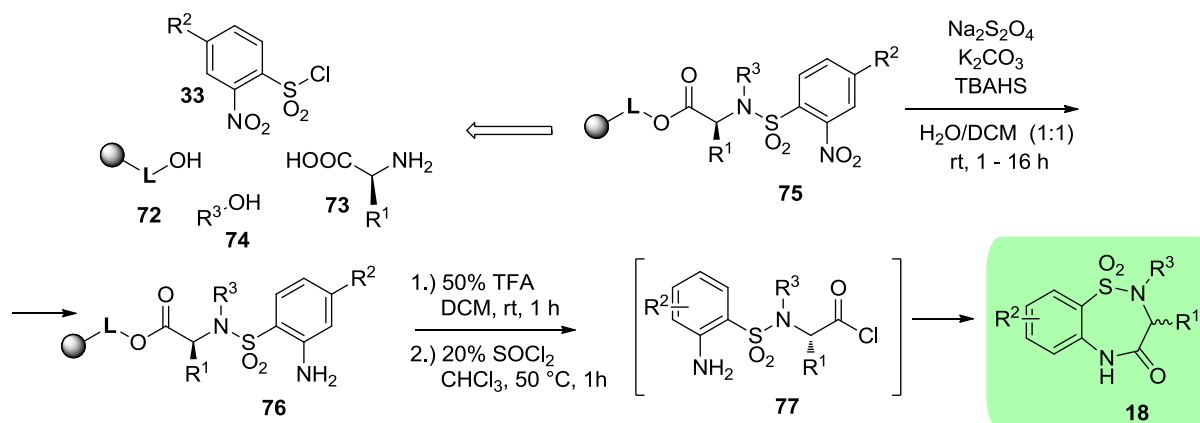
Schéma 12: Cyklizace 2-Nos derivátů serinu (**68**, **70**) na morfolin (**69**, **71**).



2.5 Inkorporace 2-Nos derivátů do struktury heterocyklu po redukci nitro skupiny

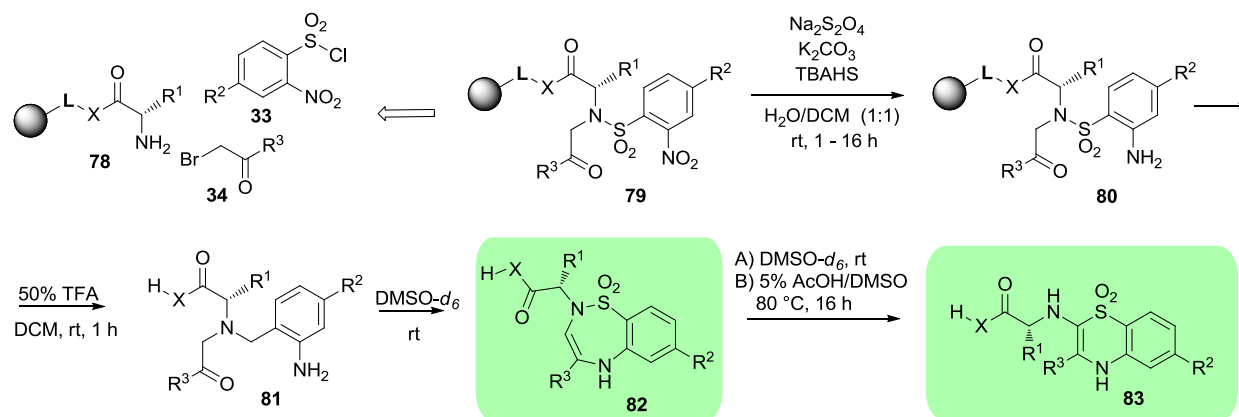
2,3-dihydrobenzo[*f*][1,2,5]thiadiazepin-4(5*H*)-on 1,1-dioxidy (**18**, Schéma 13)³⁷ byly připraveny z nosylované aminokyseliny, která byla takto aktivována pro Fukuyama alkylaci alkoholem a následovala redukce nitro skupiny. Po odštěpení z polymerního nosiče se 7-členný cyklus podařilo uzavřít aktivací karboxylové skupiny na acyl chlorid (**77**). U tohoto substrátu nebyla žádná migrace arylu pozorována.

Schéma 13: Výsek ze syntézy 2,3-dihydrobenzo[*f*][1,2,5]thiadiazepin-4(5*H*)-on 1,1-dioxidů.



Oproti tomu v syntéze dalších 7-členných heterocyklů (**82**, Schéma 14)³⁶ byly místo benzyl alkoholů pro derivatizaci amino skupiny použity bromoketony (**34**). Metylen vedle karbonylu byl aktivovaný pro případnou arylaci a příslušné indazoly a indoly byly v rámci této syntézy skutečně popsány jako vedlejší produkty. K finální cyklizaci (**82**) docházelo stáním v deuterovaném DMSO. Tyto látky (**82**) byly v DMSO stabilní pouze za nižších teplot. Už za pokojové teploty docházelo spontánně k zužování cyklu na 4*H*-benzo[*b*][1,4]thiazin 1,1-dioxidy (**83**) za tvorby nové vazby C-S.³⁸ Tento přesmyk bylo možno urychlit přidávkem 5% AcOH a záhřevem na vyšší teplotu. 6-členný heterocyklus (**83**) bylo možné získat i přímo z lineárního prekurzoru rovněž přidávkem kyseliny octové při zahřívání v DMSO.

Schéma 14: Výsek ze syntézy 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepin 1,1-dioxidů (**82**) a zužování cyklu na 4*H*-benzo[*b*][1,4]thiazin 1,1-dioxidy (**83**).



2.6 Komentář k předložené publikaci

Vzhledem k tomu, že syntéza indazol-oxidů poskytovala za mírných reakčních podmínek produkty o vysoké čistotě, byla tandemu tvorby nové vazby C-C následované N-N věnována další pozornost a podařilo se zjistit nové skutečnosti. Ukázalo se, že předstupeň vzniku indazol-oxidu (**89**) je 5-členný meziprodukt (**88**, Schéma 15), který na indazol-oxid spontánně dehydratuje.

Pomocí ^1H NMR byla sledována bazicky katalyzovaná přeměna signifikantních signálů C-arylu (**87**) na signály indazol-oxidu (**90**), přičemž byly zřetelné rostoucí intenzity signálů indazol-oxidu (**90**) na úkor signálů neznámého meziproduktu.

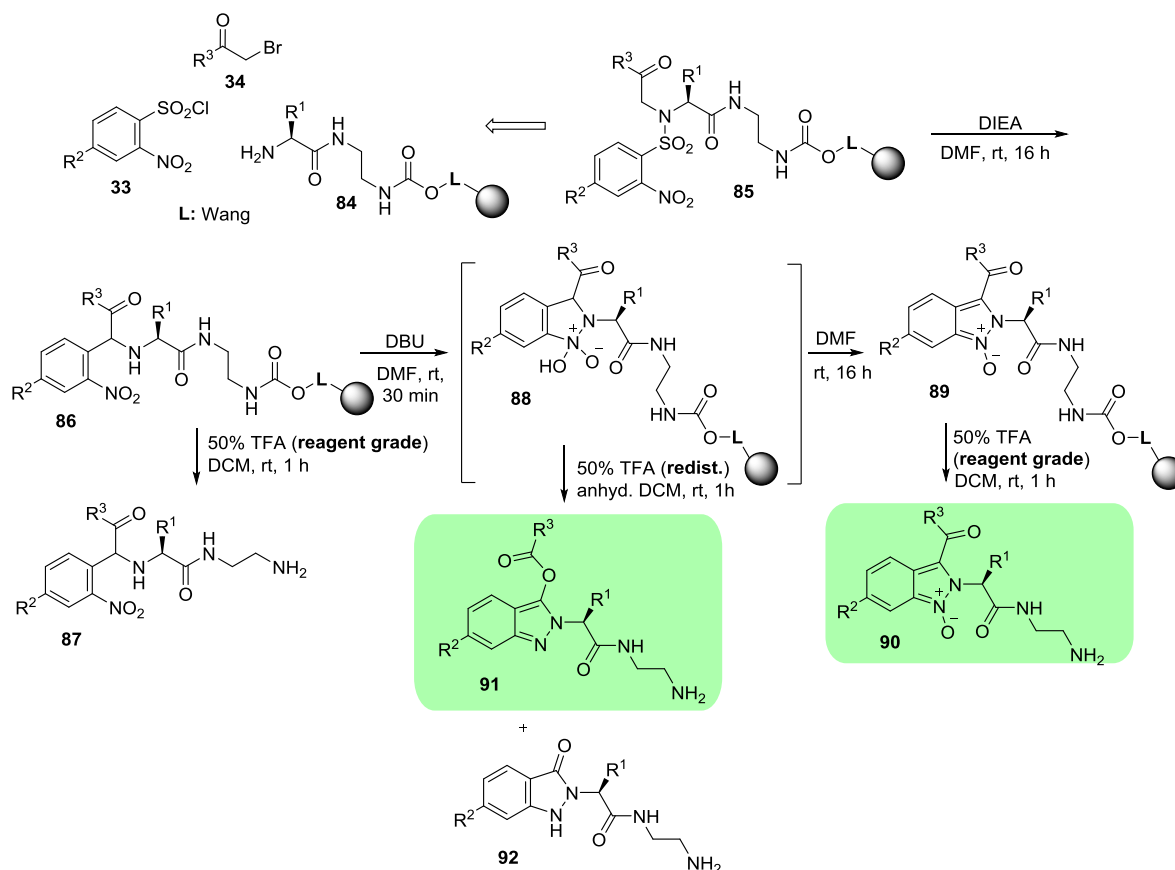
Intermediát se nepodařilo izolovat a plně charakterizovat, protože byl velice nestabilní. Byly však identifikovány reakční podmínky, za kterých tento prekuzor podléhá kysele katalyzované intramolekulární Baeyer-Villigerově oxidaci. Navíc se ukázalo, že právě tento meziprodukt v reakci funguje jako intramolekulární oxidační činidlo. Přičemž byl testován i externí oxidant, který se v Baeyer-Villigerově oxidaci běžně používá (mCPBA), ten však nevedl k tak působivým výsledkům. Intramolekulární Baeyer-Villigerovou oxidací s použitím *N*-oxidu jako oxidačního činidla totiž docházelo formálně k migraci kyslíku. Místo indazol-oxidu s keto skupinou (**90**), který vznikal dehydratací meziproduktu, byly získány indazoly s esterovou skupinou (**91**), přičemž obě finální látky (**90**, **91**) mají stejnou molekulovou hmotu.

Jestli výsledkem syntézy na pevné fázi bude indazol-oxid-keton (**90**), nebo indazol-ester (**91**), záleželo na čistotě použité TFA ve štěpícím koktejlu. Ketony a estery se podařilo od sebe rozlišit na základě UV a ^1H a ^{13}C NMR. Estery vždy částečně hydrolyzovaly na indazolony (**92**), vše je shrnuto v přehledném reakčním schématu (Schéma 15).

Je zde třeba zmínit, že samotná syntéza na pevné fázi hrála stěžejní roli v celé transformaci. S jejím použitím totiž bylo možné snadno odstranit rozpouštědlo, což umožnilo rychlý přístup k nestabilnímu intermediátu, který pak vstupoval do Baeyer-Villigerovy oxidace.

Na základě experimentů byl navržen mechanismus Baeyer-Villigerovy oxidace s *N*-oxidem jako intramolekulárním oxidantem.

Schéma 15: Estery z ketonů, alias syntéza 2-alkyl-2*H*-indazol-3-yl benzoatů a 2-alkyl-1,2-dihydro-3*H*-indazol-3-onů na pevné fázi.



2.7 Srhnutí

Deriváty 2-nitrobenzensulfonamidů (2-Nos) představují “zvýhodněné intermediáty” (advanced intermediates) v syntéze různých heterocyklů, považovaných za privilegované struktury. Na řadě příkladů bylo v tomto textu ilustrováno, jak je drobnou změnou v syntetickém přístupu možné získat rozdílné heterocykly. Klíčovou transformací je často migrace arylové skupiny, tzv. *C*- a *N*-arylace. 2-Nos deriváty vykazují zajímavou reaktivitu, zahrnující rovněž termicky a pH katalyzované přesmyky. Další výzkum této reaktivity je stále otevřenou kapitolou. Jedním z nejnovějších příspěvků je právě předložená rigorózní práce zabývající se Baeyer-Villigerovou oxidací ketonů na estery, kde *N*-oxid slouží jako intramolekulární oxidant.

2.8 Literatura

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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

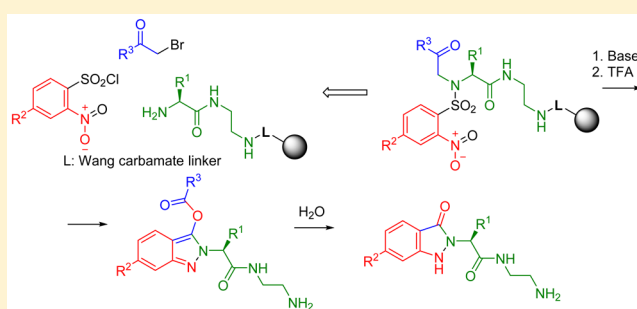
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S Supporting Information

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 thiazines⁷ (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

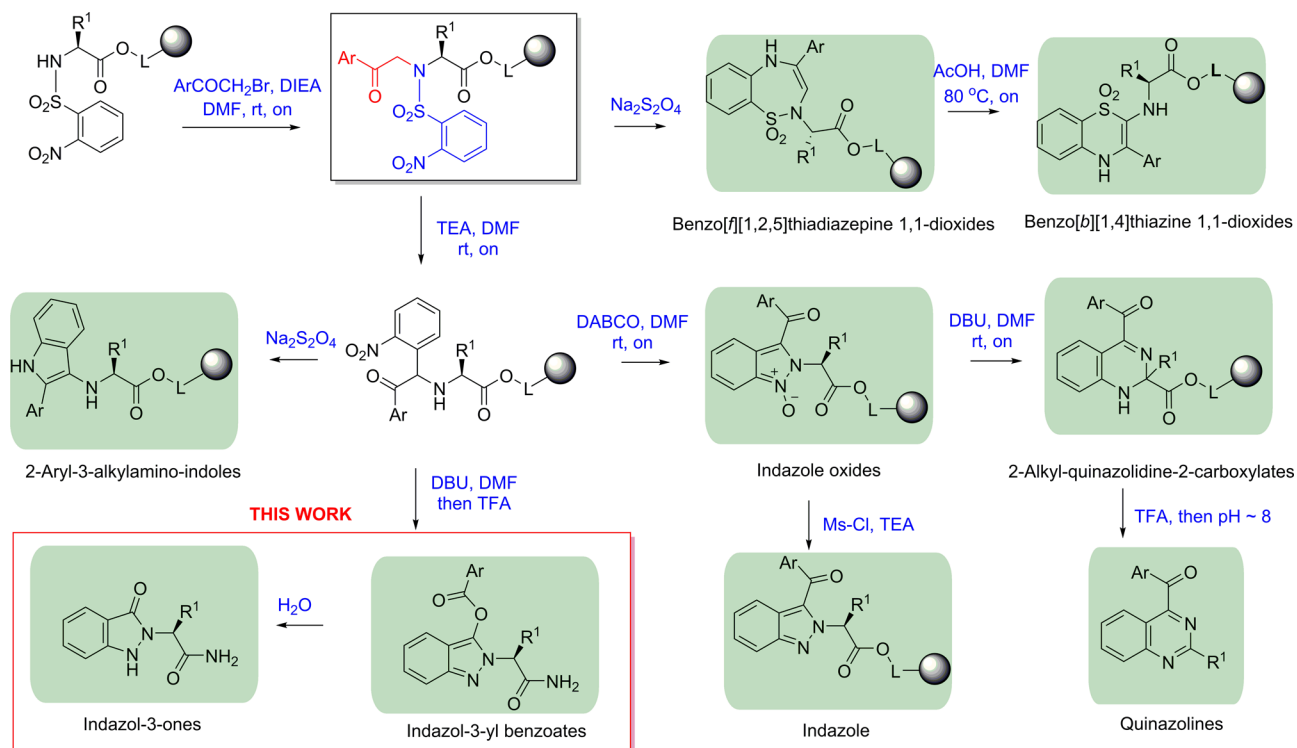
RESULTS AND DISCUSSION

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 procedure¹ using amino acids attached to a carbamate linker²⁶ on a Wang

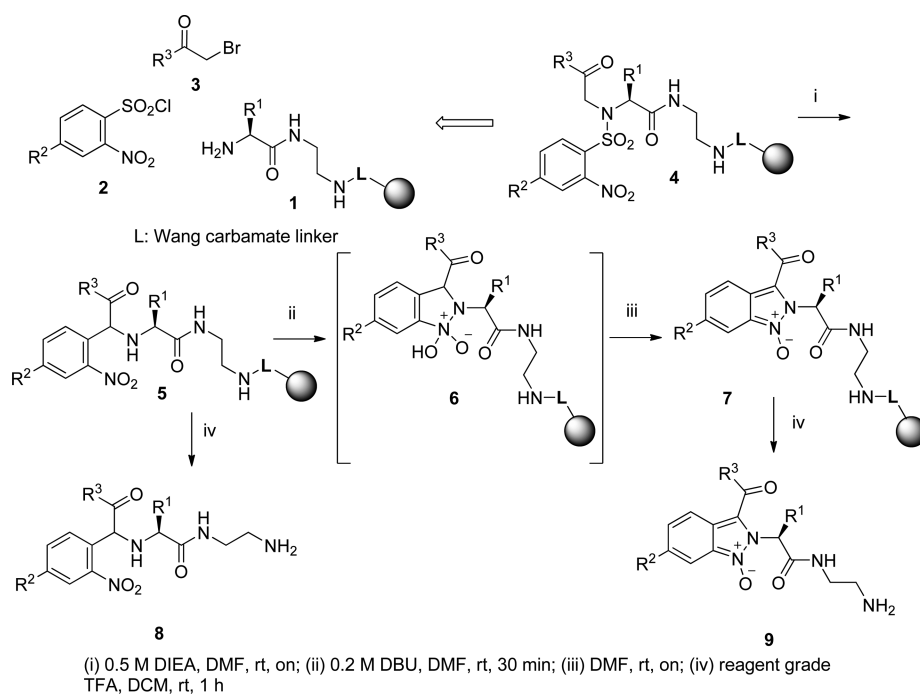
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Scheme 1. Diversity of Nitrogenous Heterocycles Prepared from N-Alkylated 2-Nos Intermediates



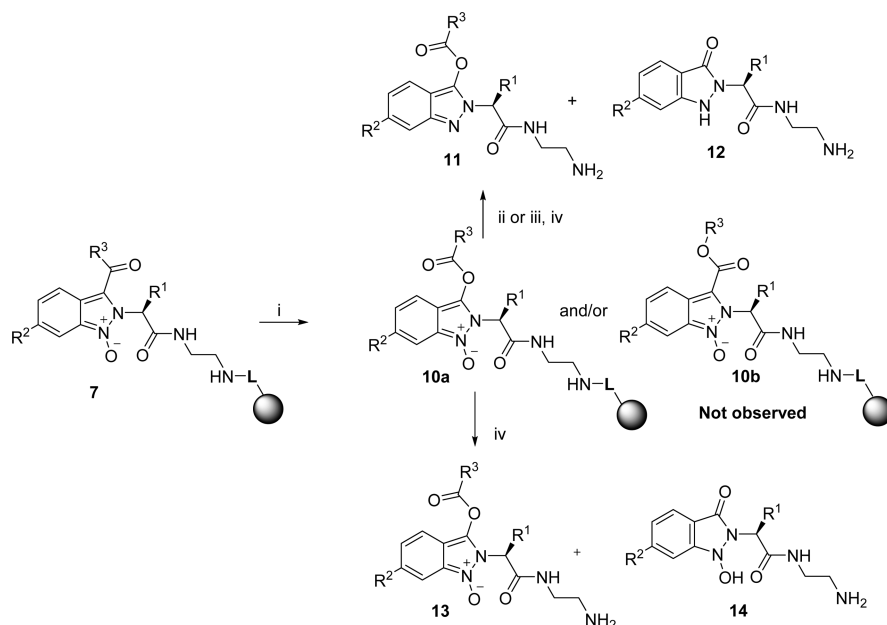
Scheme 2. Solid-Phase Synthesis of Indazole Oxides



resin²⁷ 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 ($R^1 = \text{CH}_3$), 2-Nos-Cl ($R^2 = \text{H}$), and α -bromoacetophenone ($R^3 = \text{H}$), with 3-chloroperbenzoic acid (mCPBA) in

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) Na₂S₂O₄, K₂CO₃, tetrabutylammonium hydrogen sulfate, H₂O/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 ¹H and ¹³C NMR spectra indicated the presence of **14**{1,1,1} along with benzoic acid.

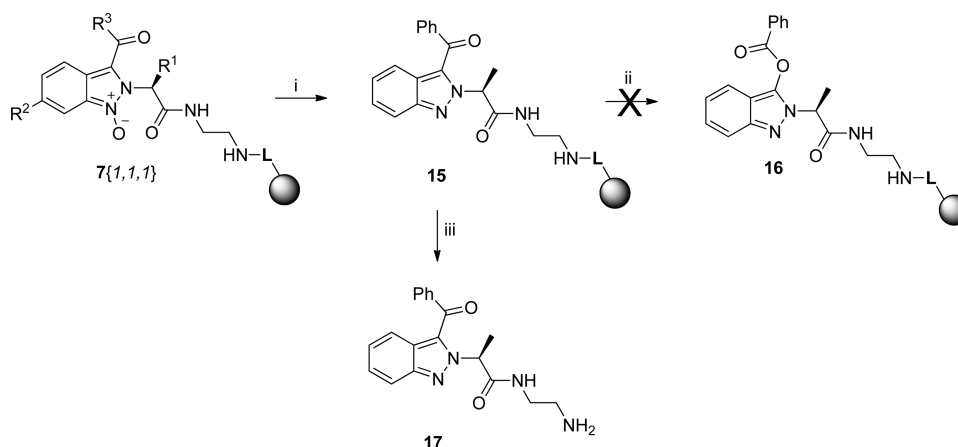
Because *N*-oxide ester **13**{1,1,1} was prone to hydrolysis, we reduced the *N*-oxide ester **10a**{1,1,1} on a solid support to

obtain ester **11**{1,1,1}. The reduction of *N*-oxide was performed using two methods: deoxygenation with mesyl chloride¹ and reduction with sodium dithionite.²⁸ Both reduction routes led to the formation of expected product **11**{1,1,1} and indazole **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 ¹H and ¹³C 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.

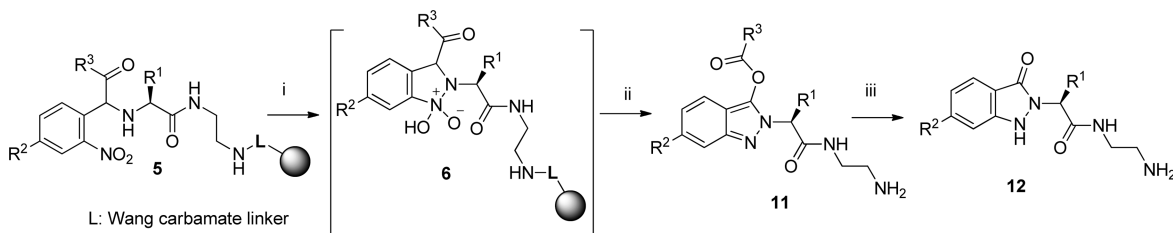
Because of the inherent instability of intermediate **6**, which is prone to spontaneous dehydration to indazole oxide **7**, the cleavage/rearrangement reaction conditions were critical for the successful preparation of indazole ester **11**. To develop a

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) H₂O, MeOH, rt, on

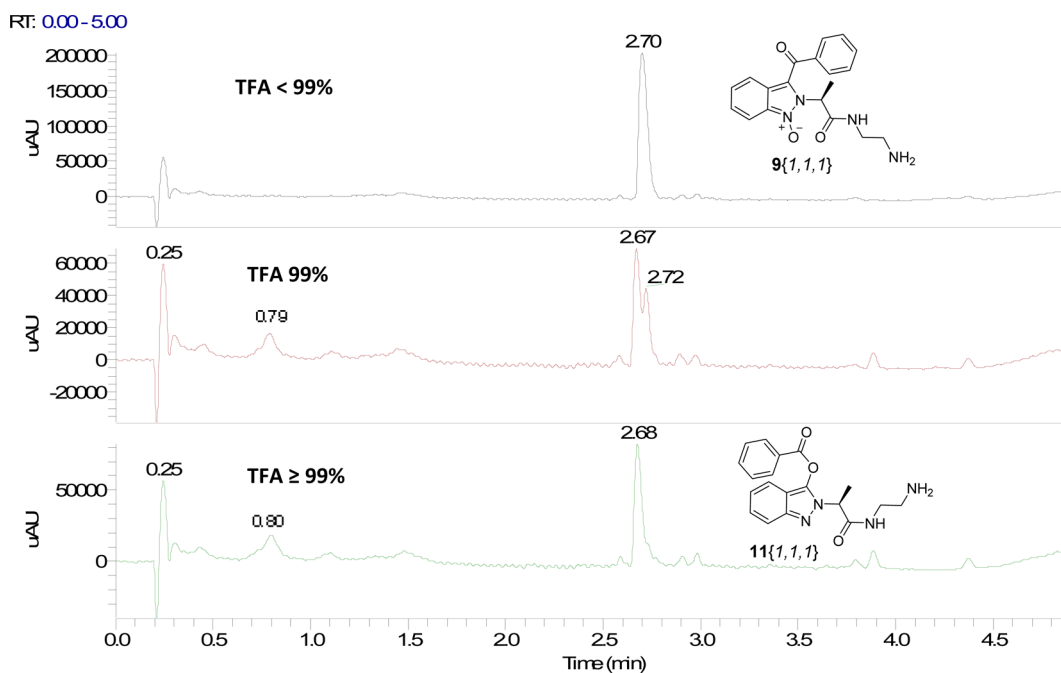


Figure 1. Crude LC traces of 9{1,1,1} and 11{1,1,1}.

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

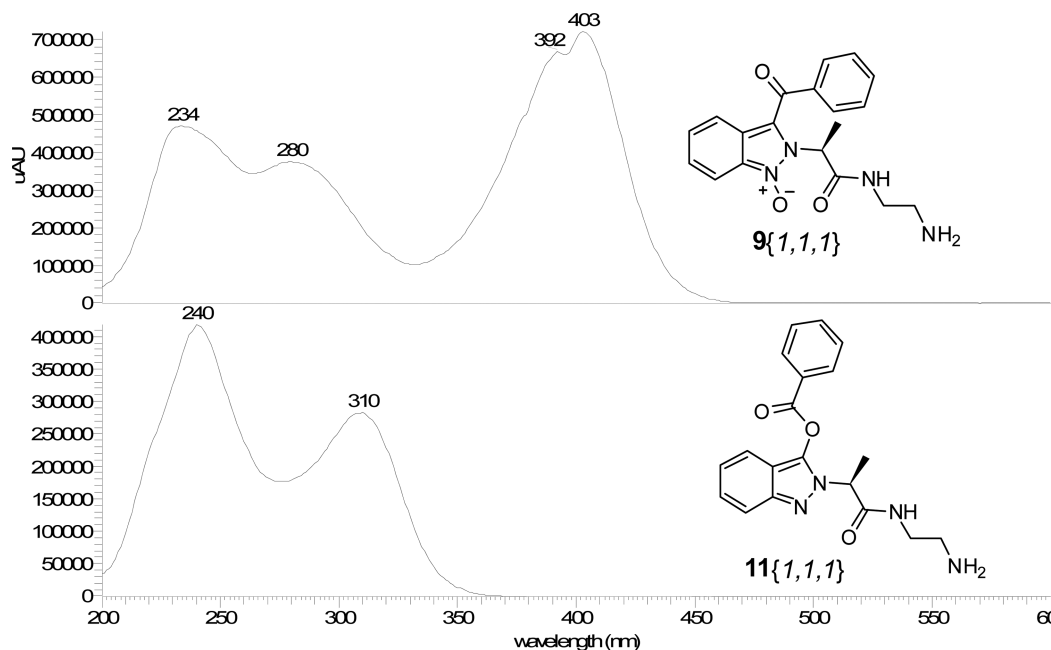


Figure 2. UV spectra of 9{1,1,1} and 11{1,1,1}.

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 \geq 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 \geq 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 ^1H 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 ^1H 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 ^1H 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

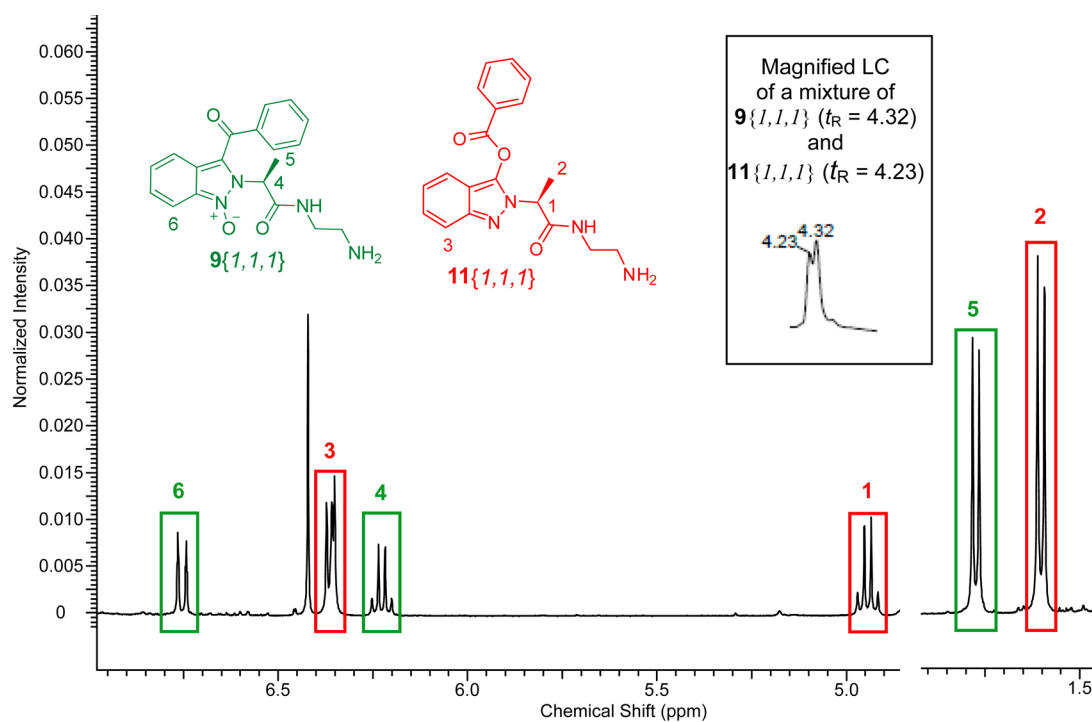
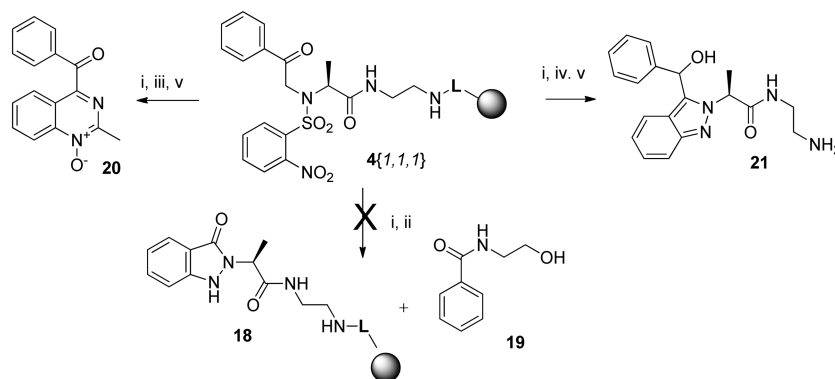


Figure 3. Zoomed ^1H NMR spectrum of a mixture of $9\{1,1,1\}$ and $11\{1,1,1\}$ diagnostic signals.

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) $\text{Na}_2\text{S}_2\text{O}_4$, K_2CO_3 , tetrabutylammonium hydrogen sulfate, $\text{H}_2\text{O}/\text{DCM}$ (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 quinazolinone **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 $\text{DMSO}-d_6$, and ^1H 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

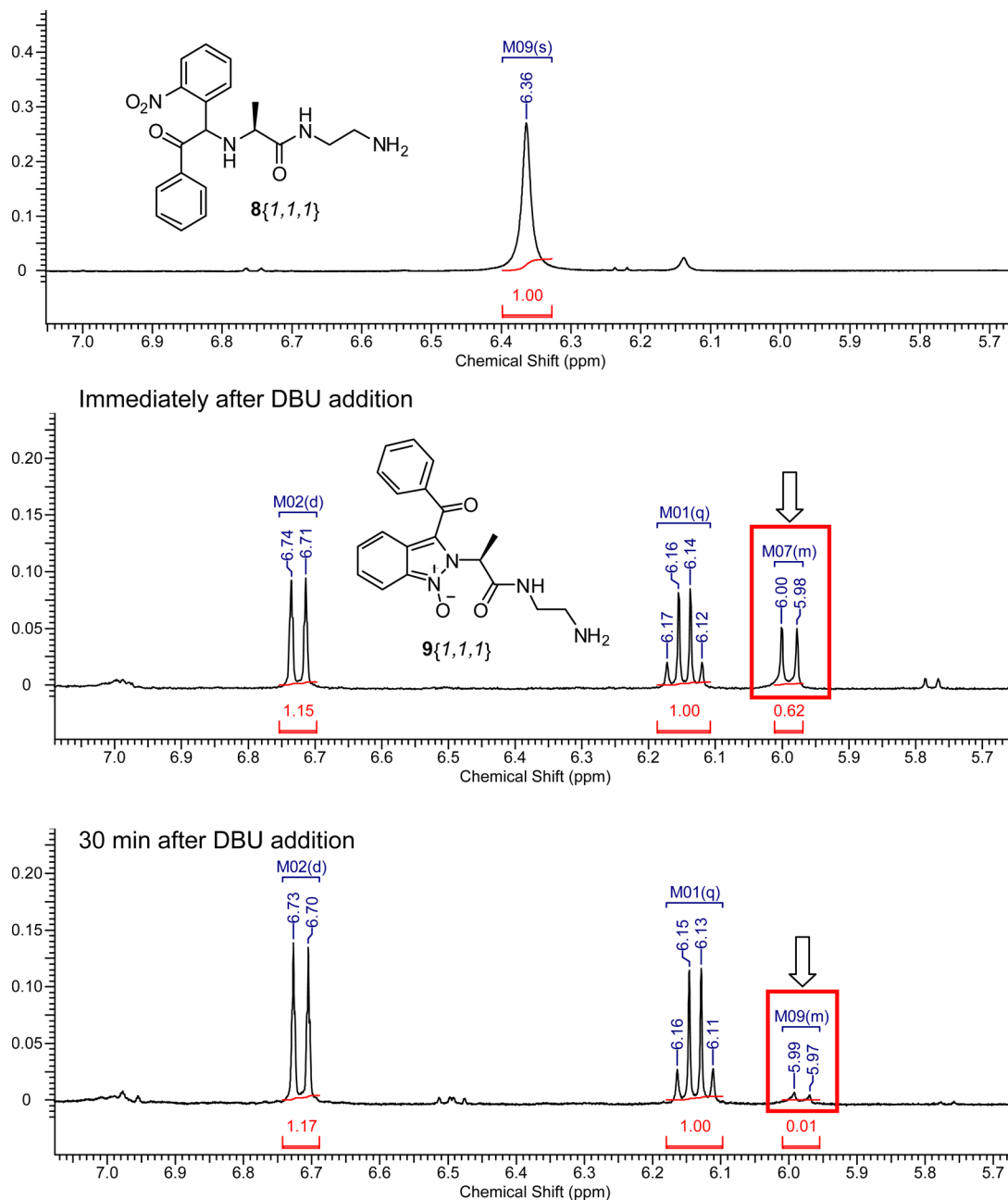
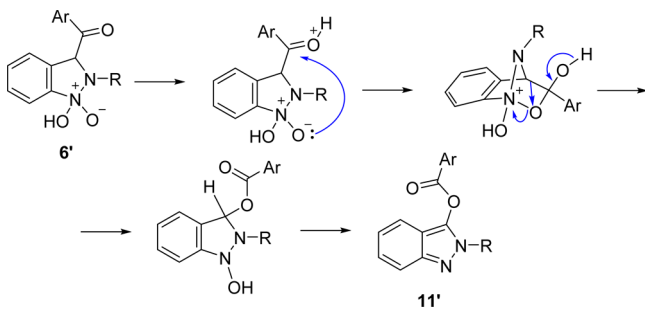


Figure 4. Zoomed ^1H NMR spectra of C-aryl **8**{1,1,1} and the eventual formation of ketone **9**{1,1,1} after the addition of DBU.

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 com-

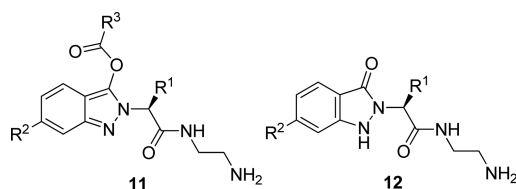
pounds. Table 1 lists the prepared compounds and demonstrates the versatility of this chemical transformation.

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

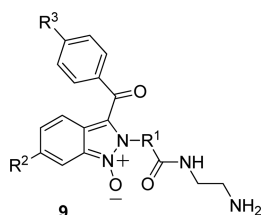
Table 1. Summary of the Synthesized Compounds: Esters (11) and Debenzoylated Products (12)



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) ₄ NH ₂	H	Ph	38/16	40/39
8	6{4,1,1}	CH ₂ O- <i>t</i> Bu	H	Ph	57/21	7/NI

^aThe purity is estimated from LC traces at 210–400 nm. The yields are calculated from ¹H 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

^aThe purity is estimated from LC traces at 210–400 nm. The yields are calculated from ¹H NMR spectra.

converted to 2-alkyl-2H-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-2H-indazol-3-yl benzoates **11** and their hydrolytic products, 2-alkyl-1,2-dihydro-3H-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

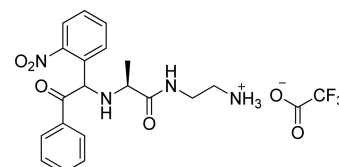
DCM and then three times with DMF. A solution of 0.5 M bromoacetophenone (5 mmol) and 0.5 M DIEA (5 mmol, 870 μ L) in 10 mL of DMF was added, and the syringe was shaken at ambient temperature overnight. The resin was washed five times with DMF and three times with DCM. If the conversion to resin **4** 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 μ L) 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 \geq 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 \geq 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 CH₃CN/H₂O–0.01% TFA (for compounds **8**, **9**, **11**, **12**, **14**) and CH₃CN/H₂O–NH₄CO (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.

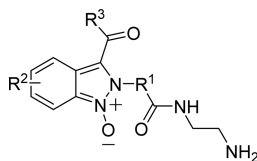
Analytical Data of Synthetic Compounds. 2-((2S)-2-((1-(2-Nitrophenyl)-2-oxo-2-phenylethyl)amino)propanamido)ethanaminium 2,2,2-trifluoroacetate **8**{1,1,1}.



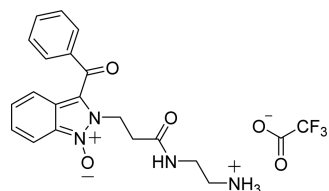
Yield 13.3 mg (34%) of amorphous solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (br s, 1H), 8.09 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.93 (m, 5H), 7.78–7.71 (m, 1H), 7.67–7.58 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.52–7.46 (m, 2H), 6.36 (s, 1H), 3.63 (q, *J* = 6.5 Hz, 1H), 3.31–3.15 (m, 2H), 2.88–2.75 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H). ¹³C 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,

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: 2H-Indazole 1-Oxides 9{ R^1, R^2, R^3 }.

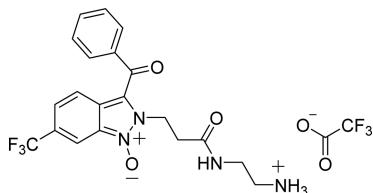


2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate 9{3,1,1}.



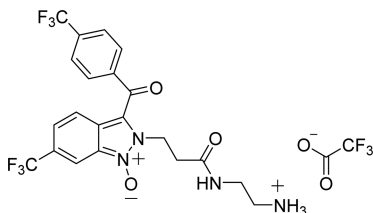
Yield 88.0 mg (95%) of amorphous solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.35 (t, $J = 5.7$ Hz, 1H), 8.02 (br s, 3H), 7.77–7.71 (m, 3H), 7.71–7.67 (m, 1H), 7.61–7.55 (m, 2H), 7.31 (ddd, $J = 8.7, 6.8, 0.8$ Hz, 1H), 7.18 (ddd, $J = 8.7, 6.8, 0.9$ Hz, 1H), 6.72 (d, $J = 8.7$ Hz, 1H), 5.03 (t, $J = 7.1$ Hz, 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. 1H 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.

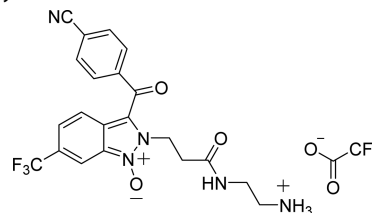
2-(3-((2-Ammonioethyl)amino)-3-oxopropyl)-6-(trifluoromethyl)-3-(4-(trifluoromethyl)benzoyl)-2H-indazole 1-Oxide 2,2,2-Trifluoroacetate 9{3,2,2}.



Yield 92.0 mg (71%) of amorphous solid. 1H 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,

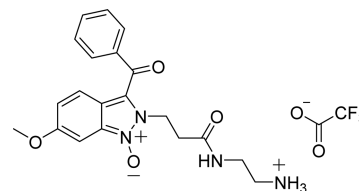
$J = 272.7$ Hz, 1C), 123.3 (q, $J = 2.5$ Hz, 1C), 122.1, 120.7, 117.2, 117.0 (q, $J = 297.8$ Hz, 1C), 112.2 (q, $J = 4.7$ Hz, 1C), 42.7, 38.7, 36.5, 32.8. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{18}F_6N_4O_3$ $[M + H]^+$ 489.1356, found 489.1354.

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



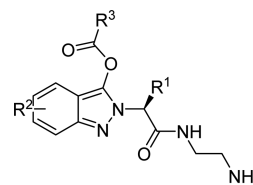
Yield 26.0 mg (26%) of amorphous solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (t, $J = 5.7$ Hz, 1H), 8.21–8.16 (m, 1H), 8.13–8.08 (m, 2H), 7.96–7.91 (m, 2H), 7.85 (br s, 3H), 7.50 (dd, $J = 9.2, 1.5$ Hz, 1H), 6.96 (dt, $J = 9.0, 0.7$ Hz, 1H), 5.04 (t, $J = 7.0$ Hz, 2H), 3.24 (q, $J = 6.1$ Hz, 2H), 2.88–2.77 (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}.

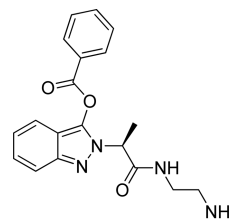


Yield 63.0 mg (37%) of amorphous solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (t, $J = 5.6$ Hz, 1H), 7.93 (br s, 3H), 7.77–7.69 (m, 3H), 7.58 (t, $J = 7.6$ Hz, 2H), 6.99 (d, $J = 2.2$ Hz, 1H), 6.88 (dd, $J = 9.3, 2.2$ Hz, 1H), 6.62 (d, $J = 9.3$ Hz, 1H), 5.01–4.93 (m, 2H), 3.84 (s, 3H), 3.31–3.21 (m, 2H), 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: 2H-Indazol-3-yl Benzoates 11{ R^1, R^2, R^3 }.



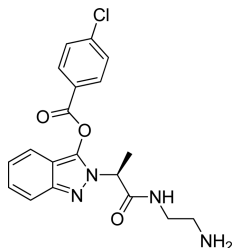
(S)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-2H-indazol-3-yl Benzoate 11{1,1,1}.



Yield 13.2 mg (33%) of amorphous solid. 1H 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),

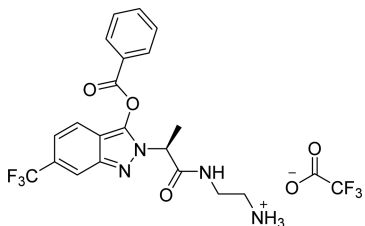
3.26–3.18 (m, 1H), 2.93–2.85 (m, 2H), 1.58 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 170.0, 167.1, 164.6, 143.0, 133.81, 133.78, 133.5, 129.4, 129.3, 124.9, 123.7, 118.5, 113.0, 56.7, 38.6, 36.8, 14.3. HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 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}.



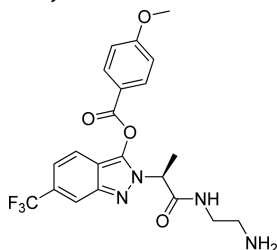
Yield 6.5 mg (17%) of amorphous solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (t, $J = 5.8$ Hz, 1H), 7.92–7.88 (m, 2H), 7.83 (dq, $J = 7.7, 0.7$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 4H), 7.54 (ddd, $J = 8.5, 7.2, 1.4$ Hz, 1H), 7.37 (ddd, $J = 7.9, 7.1, 0.8$ Hz, 1H), 6.50 (d, $J = 8.5$ Hz, 1H), 4.92 (q, $J = 7.3$ 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 $\text{C}_{19}\text{H}_{19}\text{ClN}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 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. ^1H 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 $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 421.1482, found 421.1480.

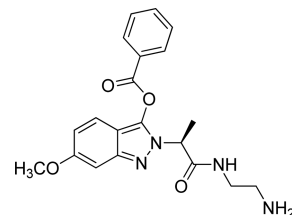
(*S*)-2-(1-((2-Aminoethyl)amino)-1-oxopropan-2-yl)-6-(trifluoromethyl)-2H-indazol-3-yl 4-Methoxybenzoate **11**{1,2,5}.



Yield 14.0 mg (16%) of amorphous solid. Slightly contaminated by 4-methoxybenzoic acid. ^1H 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,

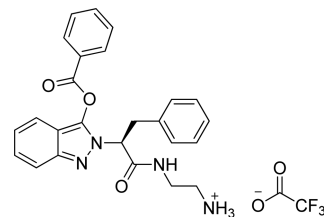
36.9, 14.6. HRMS (ESI-TOF) m/z calcd for $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 451.1588, found 451.1588.

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



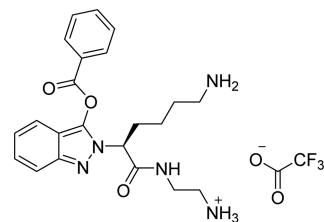
Yield 8.1 mg (21%) of amorphous solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.07 (t, $J = 5.8$ Hz, 1H), 7.87–7.81 (m, 2H), 7.81–7.76 (m, 3H), 7.73 (d, $J = 8.7$ Hz, 1H), 7.71–7.65 (m, 2H), 6.95 (dd, $J = 8.7, 2.1$ Hz, 1H), 5.74 (d, $J = 2.1$ Hz, 1H), 4.88 (q, $J = 7.2$ Hz, 1H), 3.51 (s, 3H), 3.50–3.43 (m, 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 $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 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}.



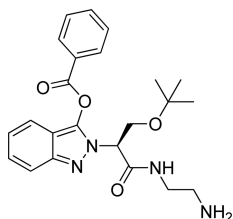
Yield 7.1 mg (16%) of amorphous solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.27 (t, $J = 5.9$ Hz, 1H), 7.84–7.74 (m, 4H), 7.60 (t, $J = 7.9$ Hz, 2H), 7.38 (ddd, $J = 8.6, 7.3, 1.4$ Hz, 1H), 7.34–7.27 (m, 3H), 7.19–7.14 (m, 1H), 7.13–7.07 (m, 3H), 6.01 (d, $J = 8.4$ Hz, 1H), 5.22 (dd, $J = 11.4, 4.3$ Hz, 1H), 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 $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 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}.



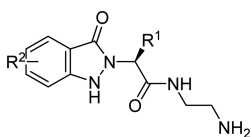
Yield 6.8 mg (16%) of amorphous solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.15 (t, $J = 5.8$ Hz, 1H), 7.87–7.72 (m, 8H), 7.72–7.66 (m, 2H), 7.49 (ddd, $J = 8.6, 7.3, 1.4$ Hz, 1H), 7.36 (ddd, $J = 7.9, 7.3, 0.7$ Hz, 1H), 6.27 (d, $J = 8.6$ Hz, 1H), 4.93 (dd, $J = 10.4, 4.9$ Hz, 1H), 3.49–3.43 (m, 1H, overlap 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 $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 410.2187, found 410.2186.

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

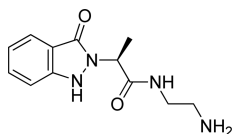


Yield 9.6 mg (21%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.20 (t, $J = 5.9$ Hz, 1H), 7.87–7.81 (m, 1H), 7.81–7.74 (m, 5H), 7.73–7.67 (m, 2H), 7.50 (ddd, $J = 8.5, 7.3, 1.4$ Hz, 1H), 7.38–7.33 (m, 1H), 6.30 (d, $J = 8.6$ Hz, 1H), 5.02 (dd, $J = 9.4, 5.3$ Hz, 1H), 3.94–4.02 (m, 1H), 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, $\text{DMSO-}d_6$) 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 $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 425.2183, found 425.2181.

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

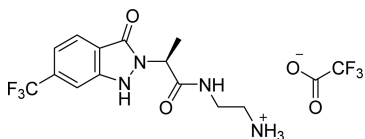


(*S*)-*N*-(2-Aminoethyl)-2-(3-oxo-1*H*-indazol-2(3*H*)-yl)propanamide **12**{1,1}.



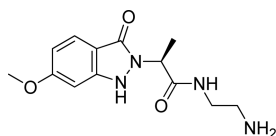
Yield 6.3 mg (22%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.04 (br s, 1H), 8.27 (t, $J = 5.6$ Hz, 1H), 7.83 (br s, 2H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.52 (ddd, $J = 8.3, 7.2, 1.2$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 5.03 (q, $J = 7.2$ Hz, 1H), 3.33 (quin, $J = 5.8$ Hz, 2H), 2.89 (q, $J = 5.9$ Hz, 2H), 1.47 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$ 249.1346, found 249.1348.

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



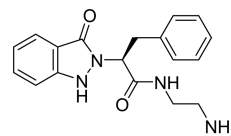
Yield 55.0 mg (72%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.74 (br s, 1H), 8.39 (t, $J = 5.6$ Hz, 1H), 7.96 (br s, 2H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.65 (s, 1H), 7.36 (dd, $J = 8.2, 0.8$ Hz, 1H), 5.11 (q, $J = 7.2$ Hz, 1H), 3.43–3.27 (m, 2H), 2.91 (t, $J = 6.3$ Hz, 2H), 1.51 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$ 317.1220, found 317.1228.

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



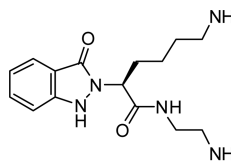
Yield 6.1 mg (22%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.89 (br s, 1H), 8.24 (t, $J = 5.7$ Hz, 1H), 7.81 (br s, 2H), 7.52 (d, $J = 9.1$ Hz, 1H), 6.73 (d, $J = 1.8$ Hz, 1H), 6.69 (dd, $J = 8.6, 2.1$ Hz, 1H), 4.95 (q, $J = 7.1$ Hz, 1H), 3.81 (s, 3H), 3.38–3.28 (m, 2H), 2.94–2.85 (m, 2H), 1.42 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$ $[\text{M} + \text{H}]^+$ 279.1452, found 279.1452.

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



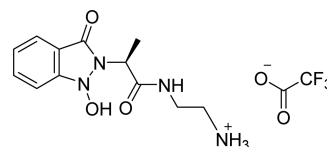
Yield 11.9 mg (36%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.11 (br s, 1H), 8.51 (t, $J = 5.6$ Hz, 1H), 7.94 (br s, 3H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.48 (ddd, $J = 8.3, 7.1, 1.2$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.15–7.08 (m, 4H), 7.04 (ddd, $J = 7.8, 7.1, 0.6$ Hz, 1H), 5.26 (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, $\text{DMSO-}d_6$) 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 $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$ 325.1659, found 325.1657.

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



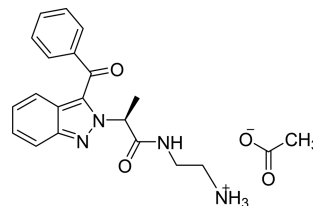
Yield 12.6 mg (39%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.02 (br s, 1H), 8.38 (t, $J = 5.5$ Hz, 1H), 7.89 (br s, 2H), 7.74 (br s, 2H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.52 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 8.2$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 4.98 (dd, $J = 9.7, 5.8$ Hz, 1H), 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, $\text{DMSO-}d_6$) 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 $\text{C}_{15}\text{H}_{23}\text{N}_5\text{O}_2$ $[\text{M} + \text{H}]^+$ 306.1925, found 306.1925.

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



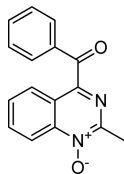
Yield 7.2 mg (24%) of amorphous solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.06 (t, $J = 5.7$ Hz, 1H), 7.88–7.81 (m, 2H), 7.83 (dd, $J = 7.5, 1.30$ Hz, 1H), 7.77 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.72 (td, $J = 7.5, 1.4$ Hz, 1H), 7.67 (td, $J = 7.4, 1.4$ Hz, 1H), 4.57 (q, $J = 6.9$ Hz, 1H), 3.45–3.34 (m, 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, $\text{DMSO-}d_6$) 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 $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_3$ $[\text{M} + \text{H}]^+$ 265.1295, found 265.1297.

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



Yield 19.5 mg (60%) of amorphous solid. ^1H 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 $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$ 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. ^1H 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 $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 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 ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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4 Doplňující informace k publikaci

Supporting Information

***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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Material and Methods

Solvents were used without further purification. The Rink amide resin (100-200 mesh, 1% DVB, 0.68 mmol/g) was used. Synthesis was carried out on Domino Blocks (www.torvig.com) in disposable polypropylene reaction vessels.

The volume of wash solvent was 10 mL per 1 g of resin (except Mitsunobu alkylation; the volume was 20mL per 1 g of resin). For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM, the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH.

The LC/MS analyses were carried out using two instruments. The first one comprised a 3 x 50 mm C18 reverse phase column, 5 μ m particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 °C. The second instrument comprised a 2.1 x 50 mm C18 reverse phase column, 2.6 μ m particles, at 30°C and flow rate of 800 μ L/min. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 10% to 80% of B in 2.5 minutes; kept for 1.5 minute, flow rate of 0.8 mL/min. The column was re-equilibrated with 10% solution B for 1 minute. The APCI source operated at discharge current of 5 μ A, vaporizer temperature of 400 °C and capillary temperature of 200 °C.

Purification was carried out on C18 reverse phase column 19 x 100 mm, 5 μ m particles, gradient was formed from 10 mM aqueous ammonium acetate and acetonitrile, flow rate 20 mL/min.

All ^1H and ^{13}C NMR experiments were performed at magnetic field strengths of 14.09 T corresponding to ^1H resonance frequencies of 599.89 MHz, and at ambient temperature ($\sim 21^\circ\text{C}$). ^1H spectra and ^{13}C spectra were referenced relative to the signal of DMSO (^1H $\delta = 2.49$ ppm, ^{13}C $\delta = 39.50$ ppm)

Figure S1. Atom numbering of compound 11{1,1,1}

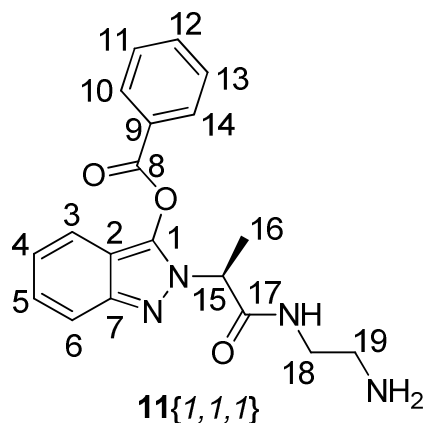
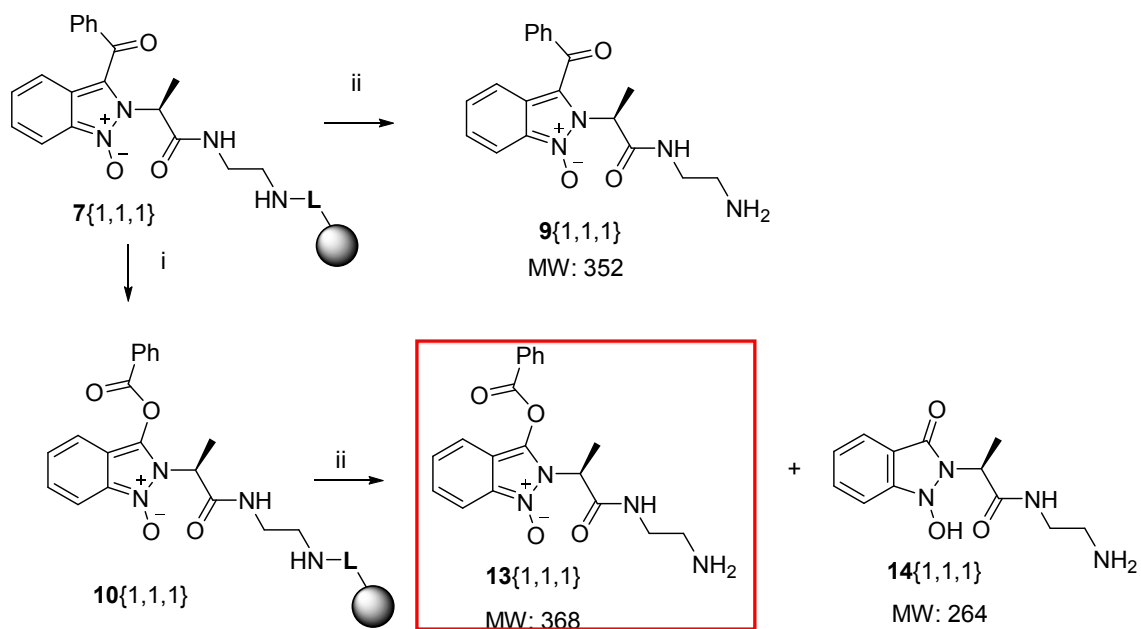


Table S1. NMR spectroscopic data (400 MHz, DMSO-*d*₆) for 11{1,1,1}

position	δ_C , type	δ_H (J in Hz)	HMBC
1	164.6, C		3, 15
2	118.6, C		4, 6
3	123.8, CH	7.81, m (overlap with 12)	5
4	125.0, CH	7.34, ddd (7.9, 7.2, 0.7)	6
5	133.6, CH	7.47, ddd (8.6, 7.3, 1.3)	3
6	113.1, CH	6.34, d (8.6)	4
7	143.0, C		3, 5
8	167.1, C=O		10, 14
9	133.78, C		10, 11, 13, 14
10	129.5, CH	7.85, m	12
11	129.4, CH	7.67, m	13
12	133.81, CH	7.52, t (7.50; overlap with 3)	10, 14
13	129.4, CH	7.67, m	11
14	129.5, CH	7.85, m	10, 12
15	56.8, CH	4.93, q (7.2)	16
16	14.4, CH ₃	1.58, d (7.2)	15
17	170.1, C=O		16, 18, 15, NH
18	36.9, CH ₂	3.22, m	19, NH
		3.47, dq (13.3, 6.5)	
19	38.6, CH ₂	2.89, m	18
NH		8.07, t (5.8)	
NH ₂		7.75, br. s.	

Scheme S1: Baeyer-Villiger oxidation on solid phase using *m*CPBA



(i) 0.5 M *m*CPBA, DCM, rt, 30 min - on; (ii) TFA/DCM (1:1), rt, 30 min.

The following LC traces are shown in Figure S2:

A) starting material, MW = 352, UV = 403 nm

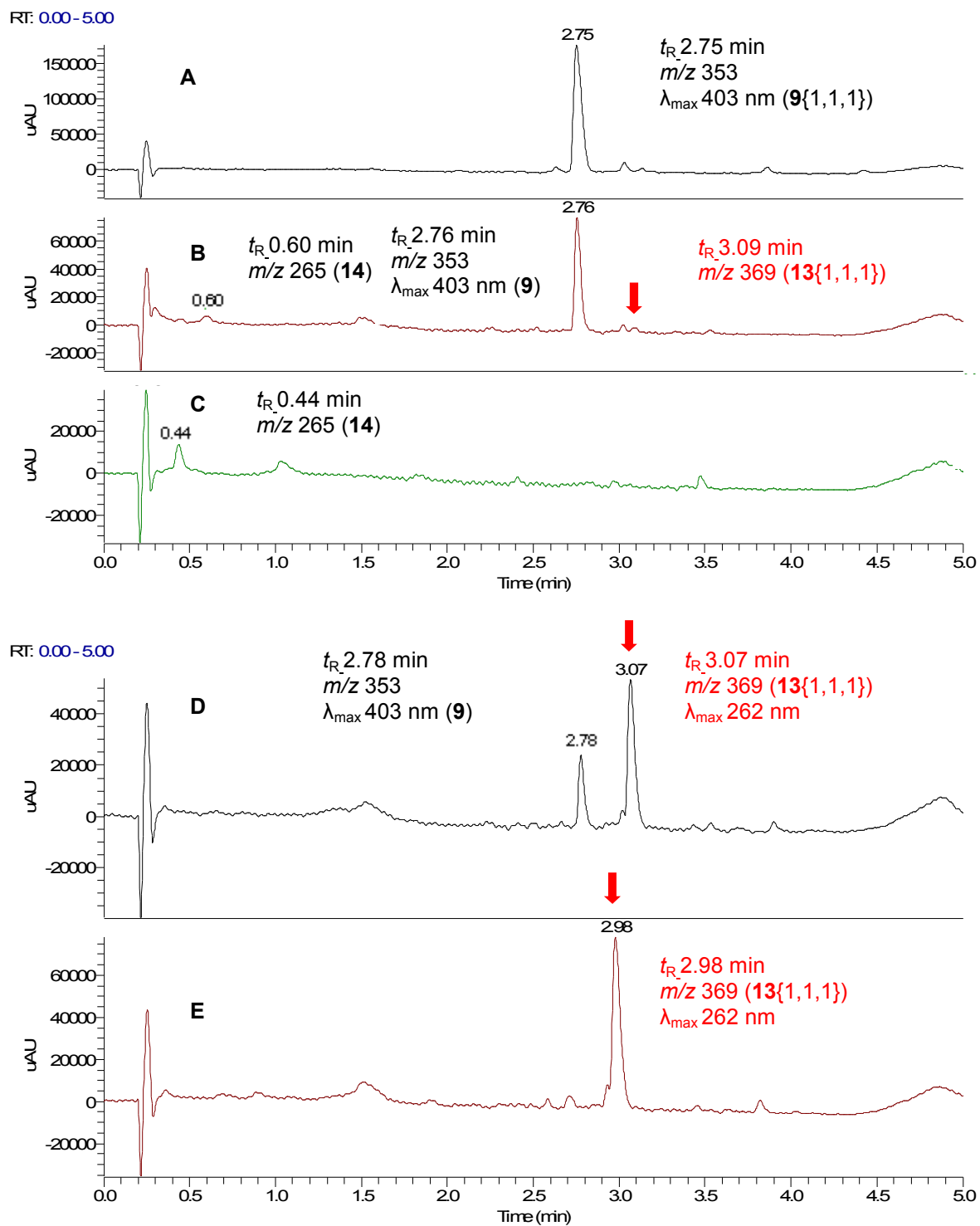
B) 0.5 M *m*CPBA/DCM (2 mL/60 mg of resin), rt, 30 min

C) 0.5 M *m*CPBA/DCM (2 mL/60 mg of resin), rt, overnight

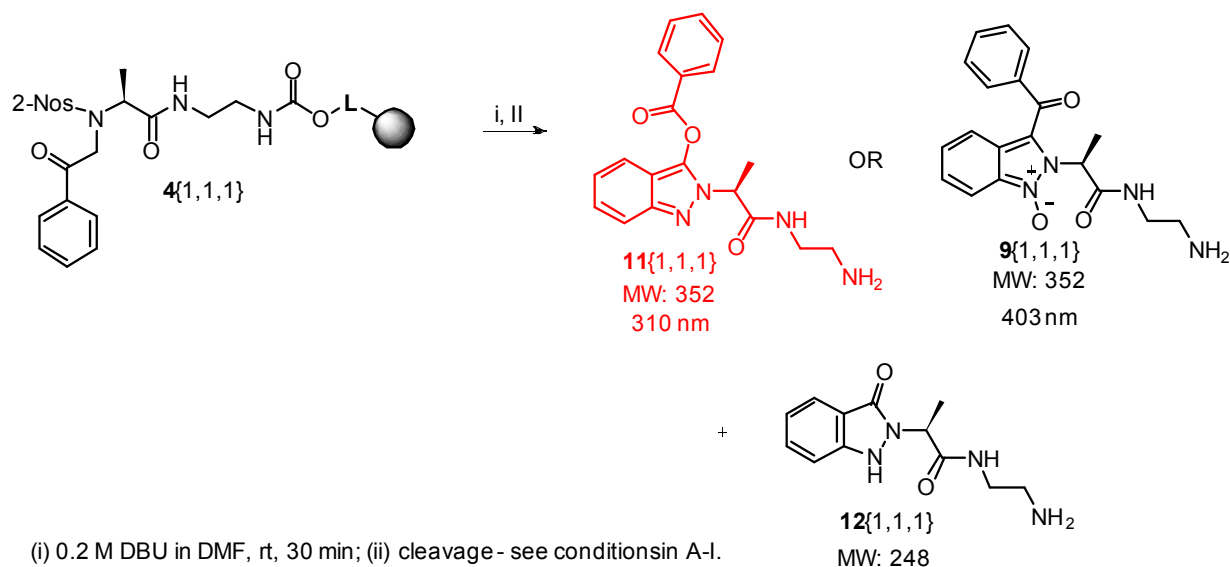
D) 0.5 M *m*CPBA/DCM (5 mL/20 mg of resin), rt, 30 min

E) 0.5 M *m*CPBA/DCM (5 mL/20 mg of resin), rt, 30 min + 30 min repeat

Figure S2. LC trace of crude material



Scheme S2: Baeyer-Villiger oxidation on solid phase using *N*-oxide as an internal oxidant



The following LC traces are shown in Figure S3:

Reaction conditions: Cleavage time 30 min; volume of cleavage cocktail for A-G 0.5 mL, for H and I 3 mL

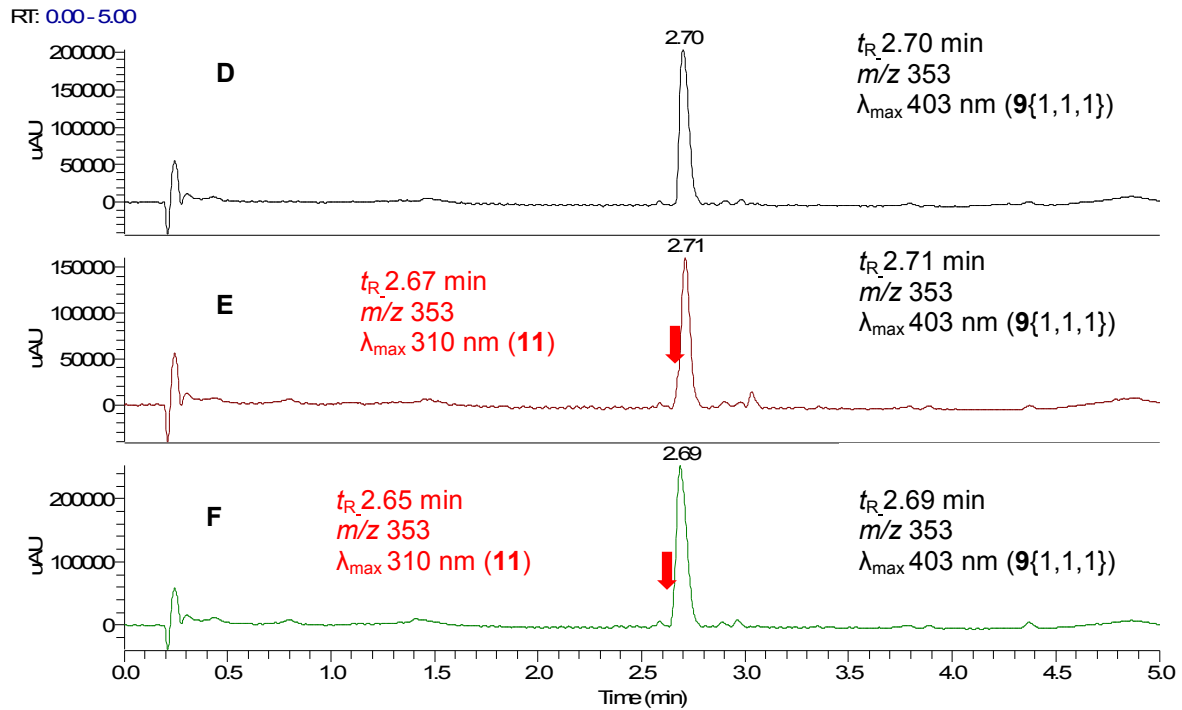
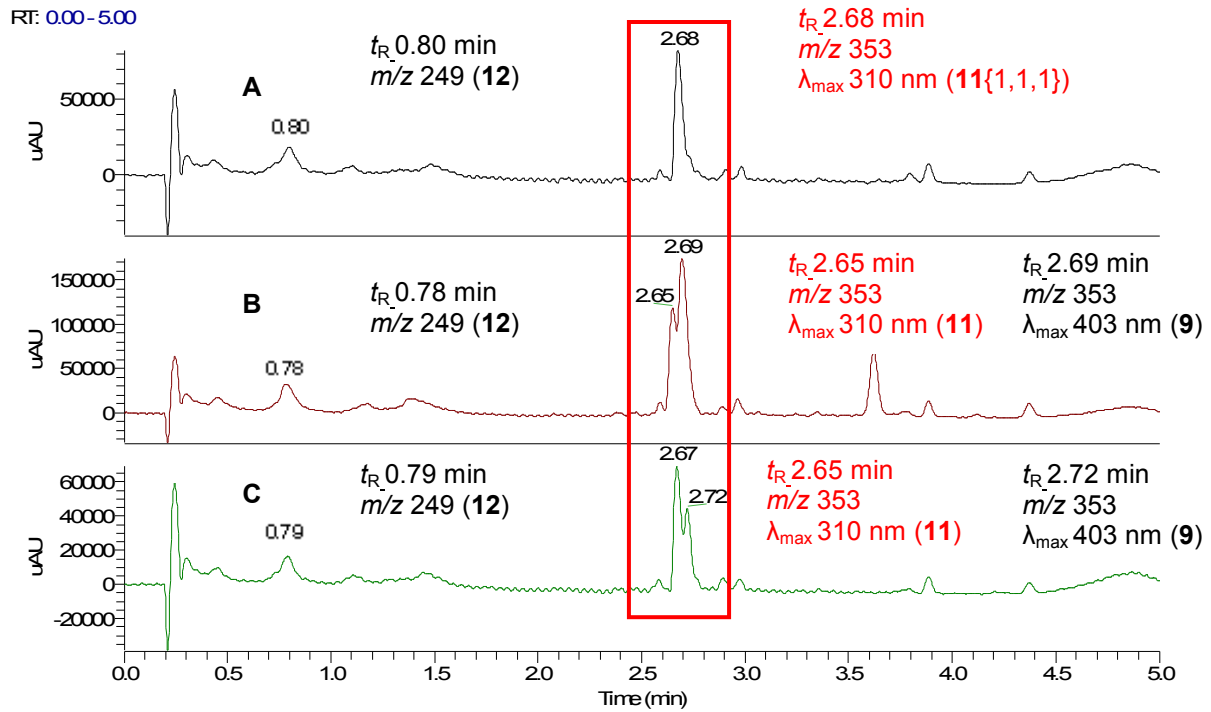
Analytical scale (~10 mg of resin):

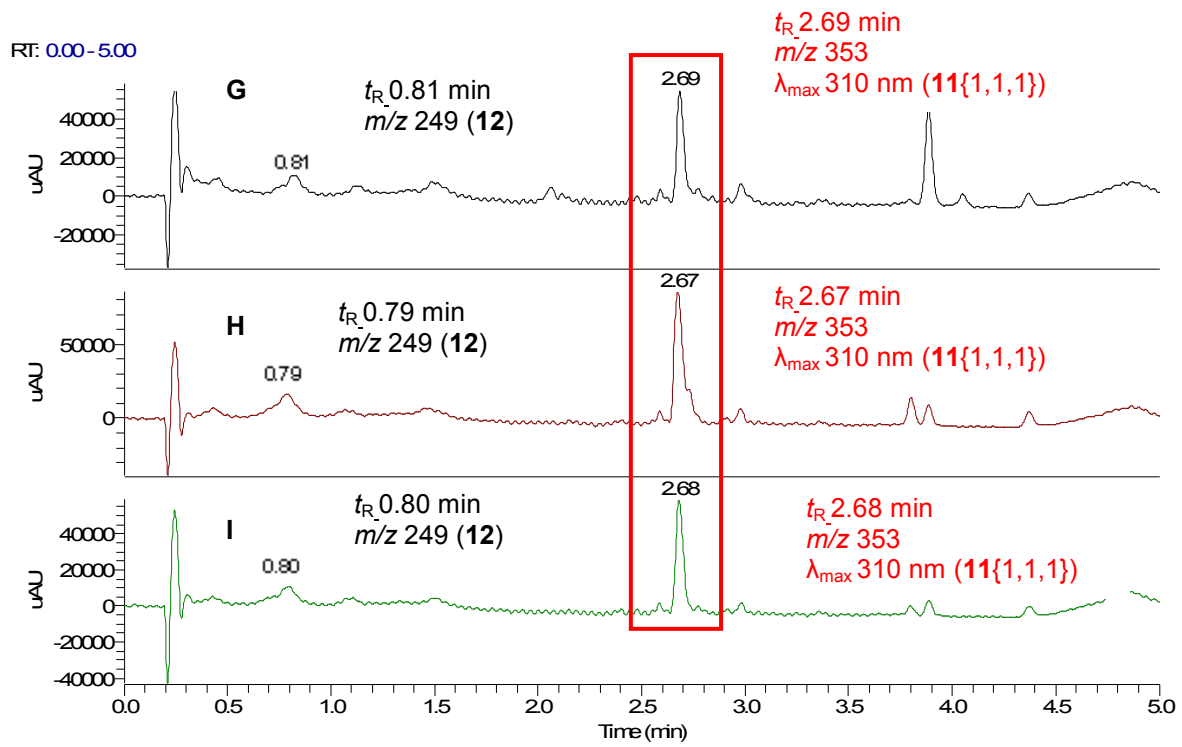
- A) 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM
- B) 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM/AIR (in syringe)
- C) 50% TFA(Sigma-Aldrich 99%)/DCM
- D) 50% TFA(Litolab < 99%)/DCM
- E) 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM – saturated by water
- F) 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM + 0.5% H₂O
- G) 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM + 1% TFA anhydride

Semi-prep scale (~60 mg of resin):

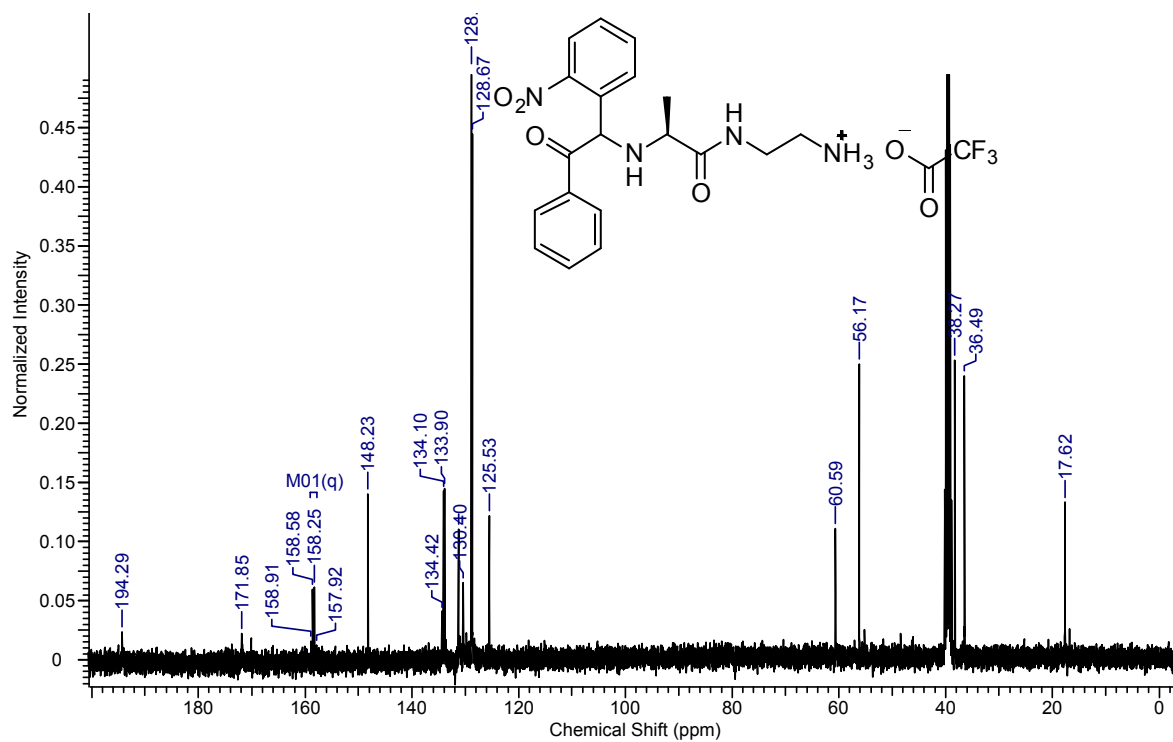
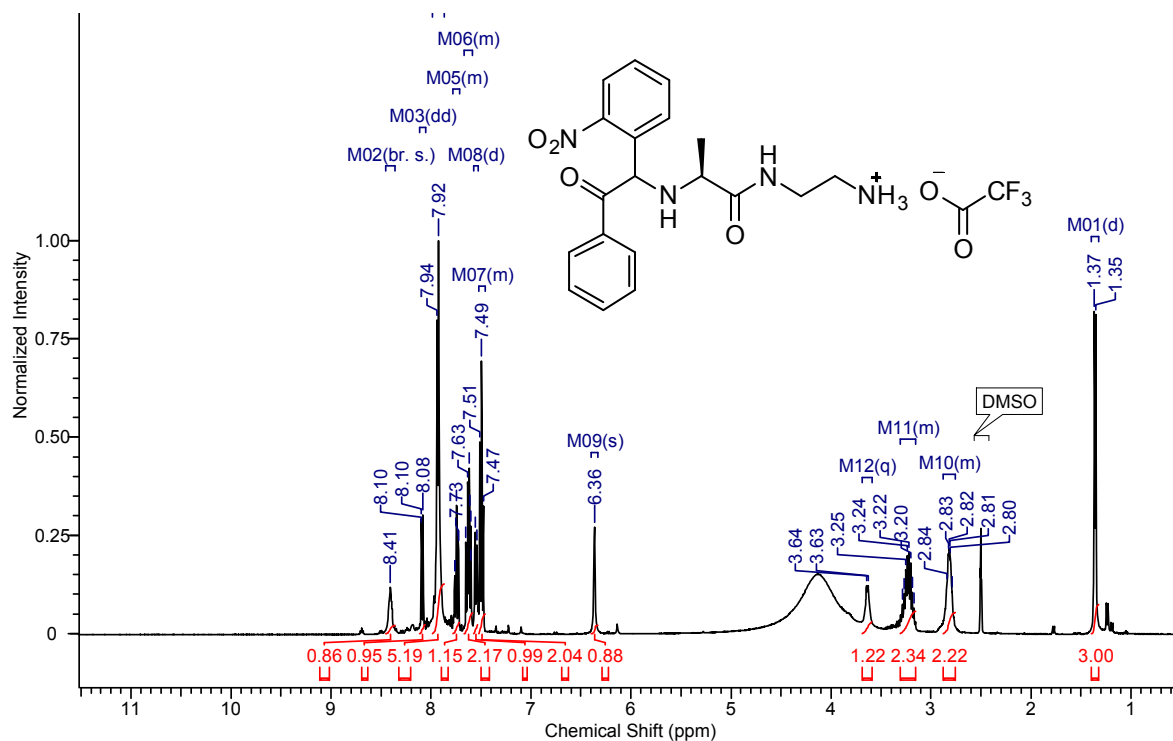
- H) preparative cleavage 50% TFA(Sigma-Aldrich 99%)/DCM
- I) preparative cleavage 50% TFA(Sigma-Aldrich, redistilled \geq 99%)/DCM

Figure S3. LC trace of crude material

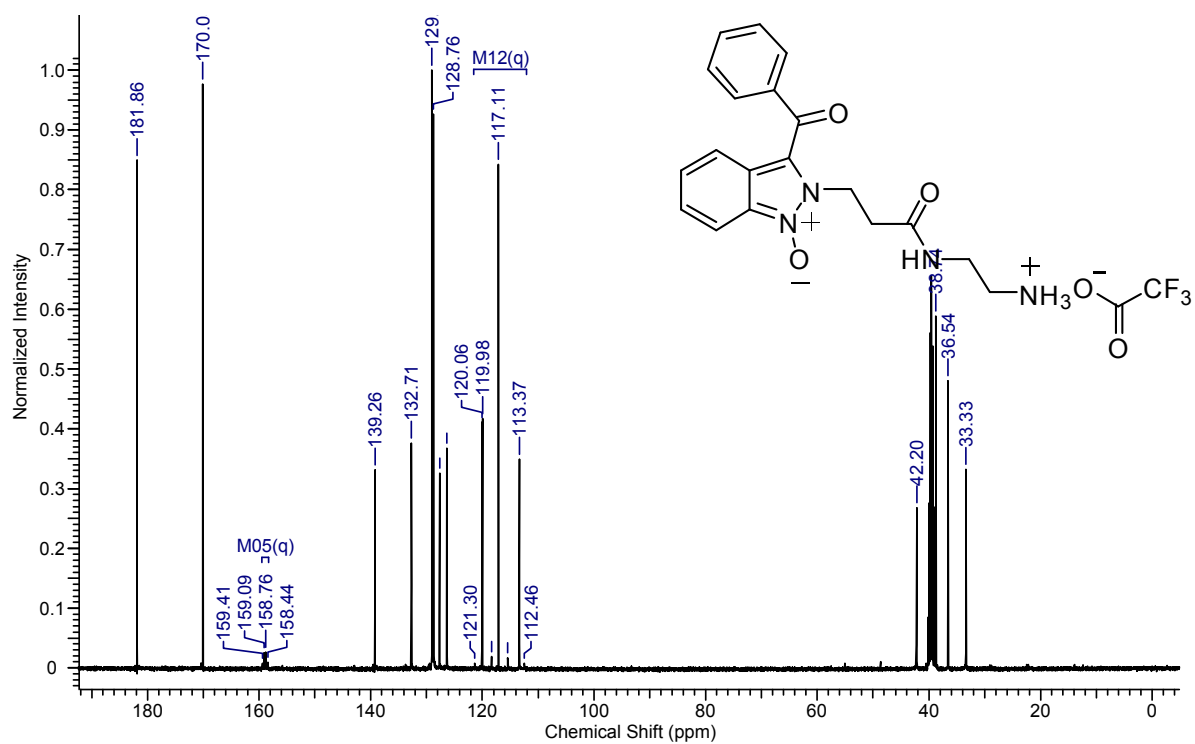
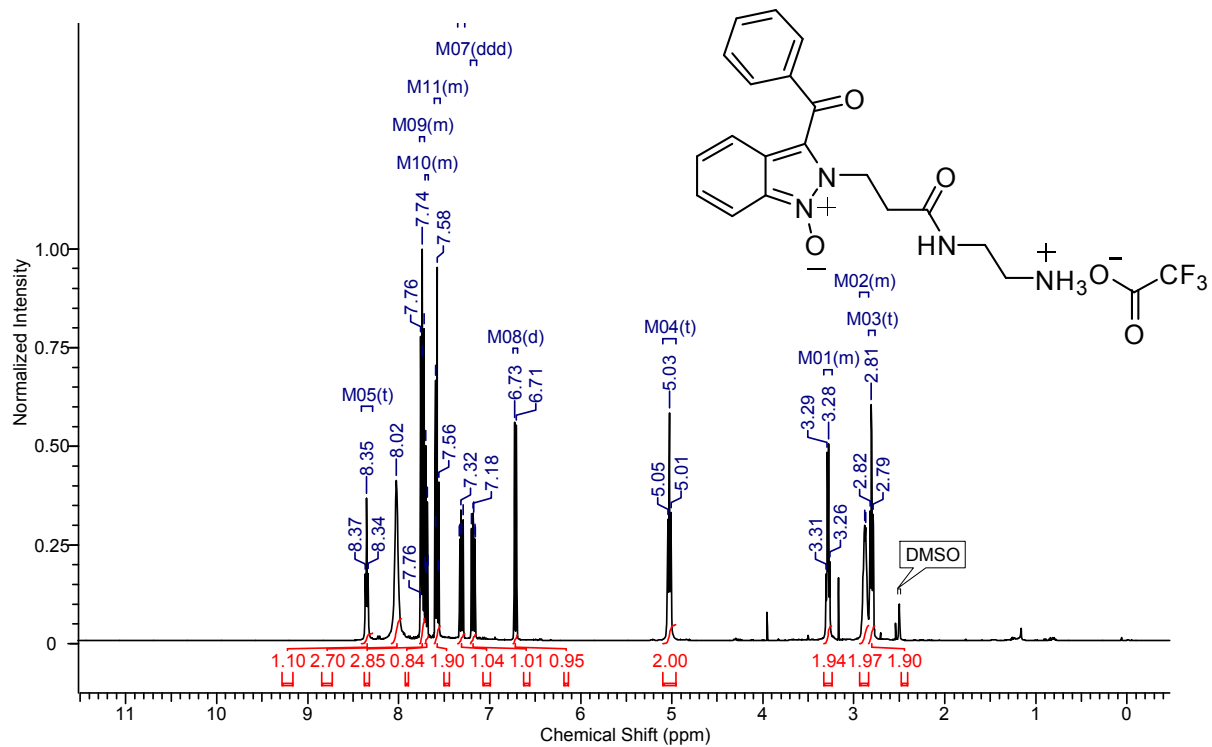




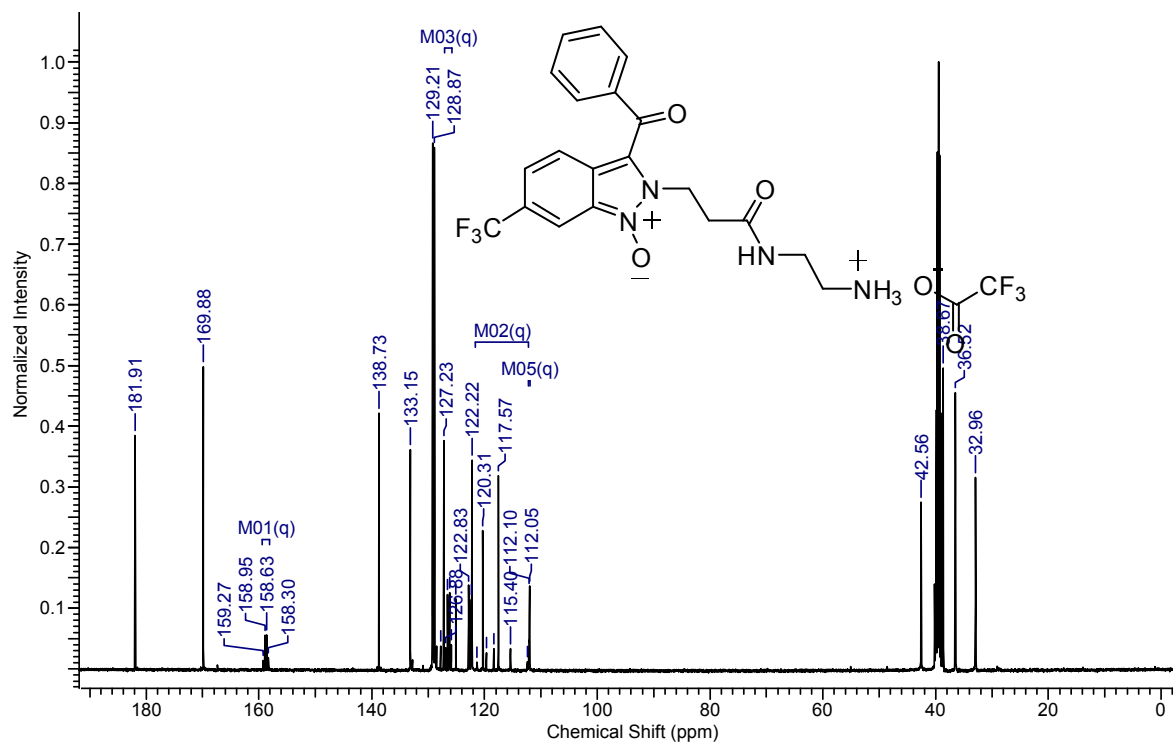
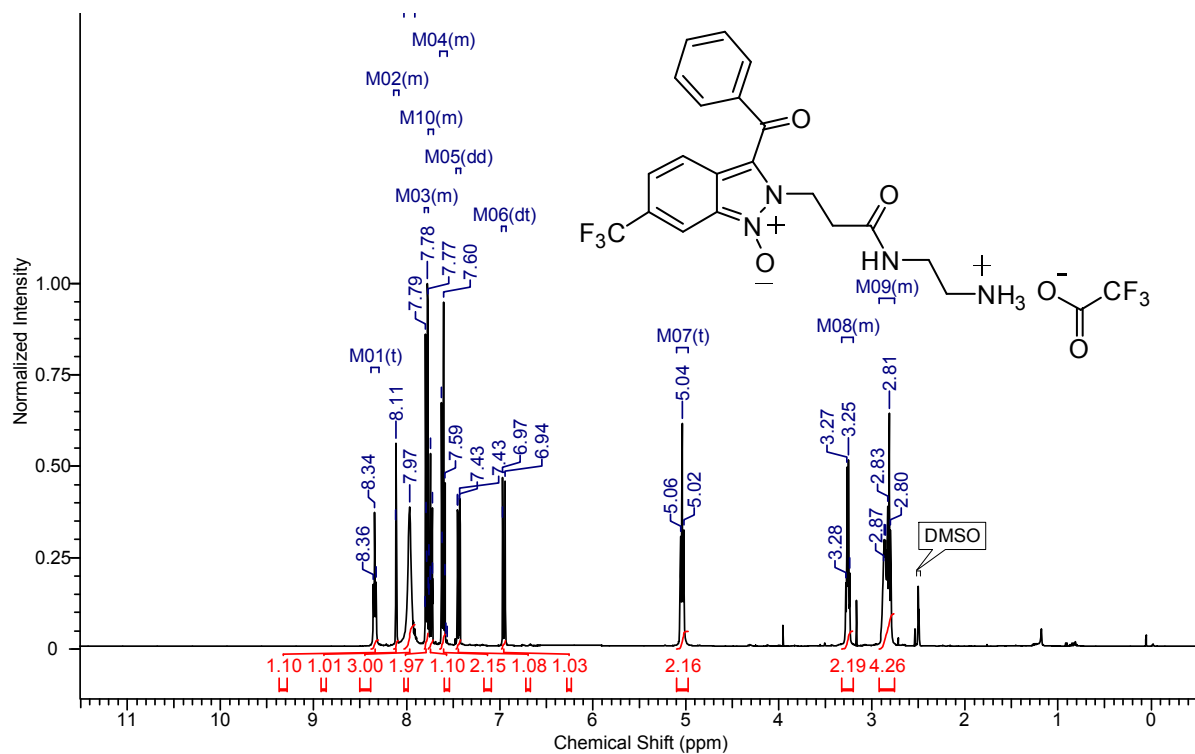
¹H and ¹³C NMR spectra (d₆-DMSO) of (2S)-N-(2-aminoethyl)-2-((1-(2-nitrophenyl)-2-oxo-2-phenylethyl)amino)propanamide 8{1,1,1}



¹H and ¹³C NMR spectra (d₆-DMSO) of 2-(3-((2-ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-2*H*-indazole 1-oxide 2,2,2-trifluoroacetate 9{3, 1, 1}

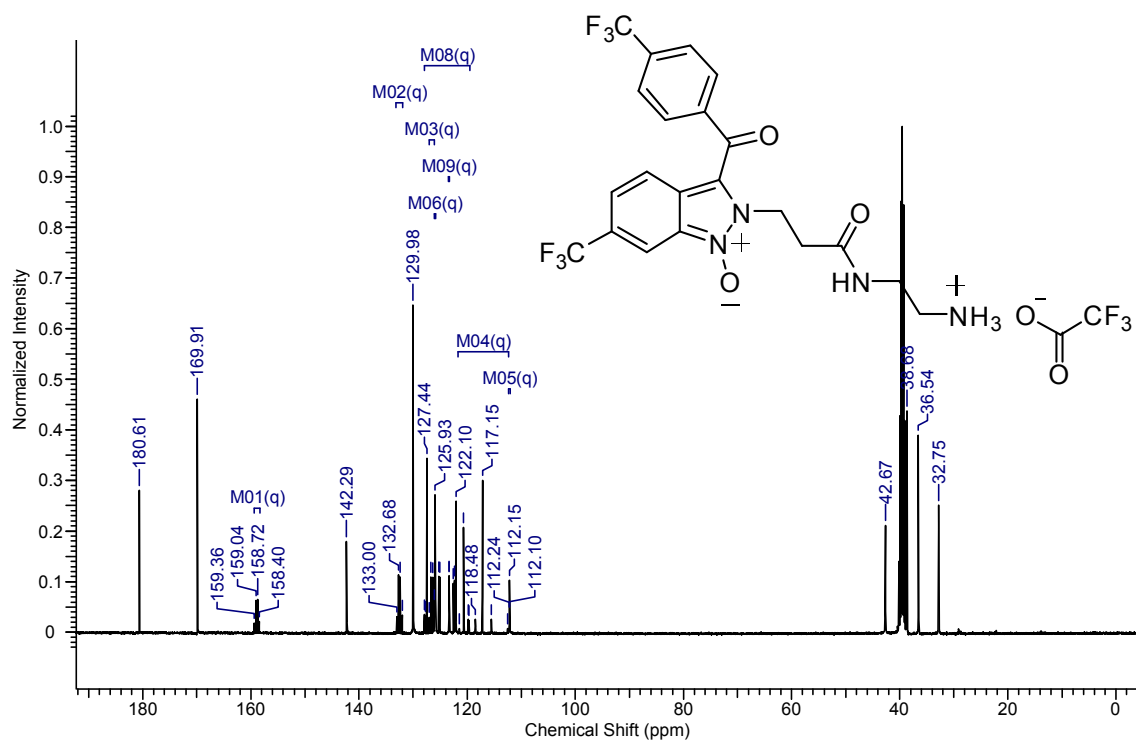
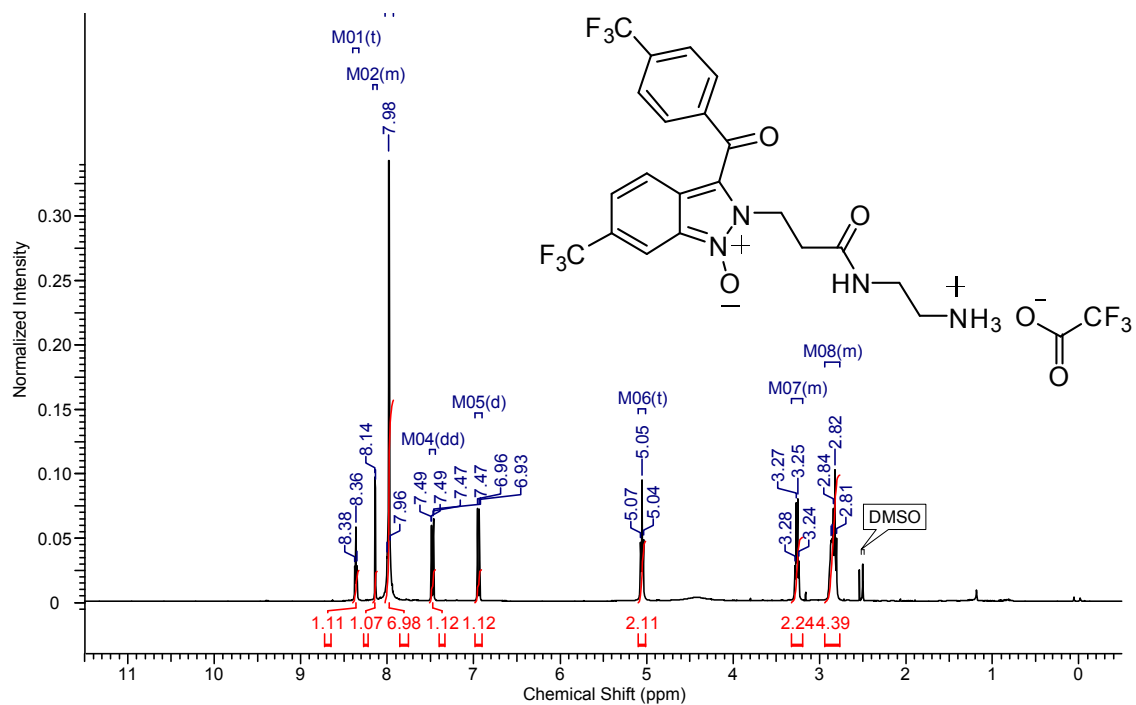


¹H and ¹³C NMR spectra (d₆-DMSO) of 2-(3-((2-ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-6-(trifluoromethyl)-2H-indazole 1-oxide 2,2,2-trifluoroacetate 9{3,2,1}

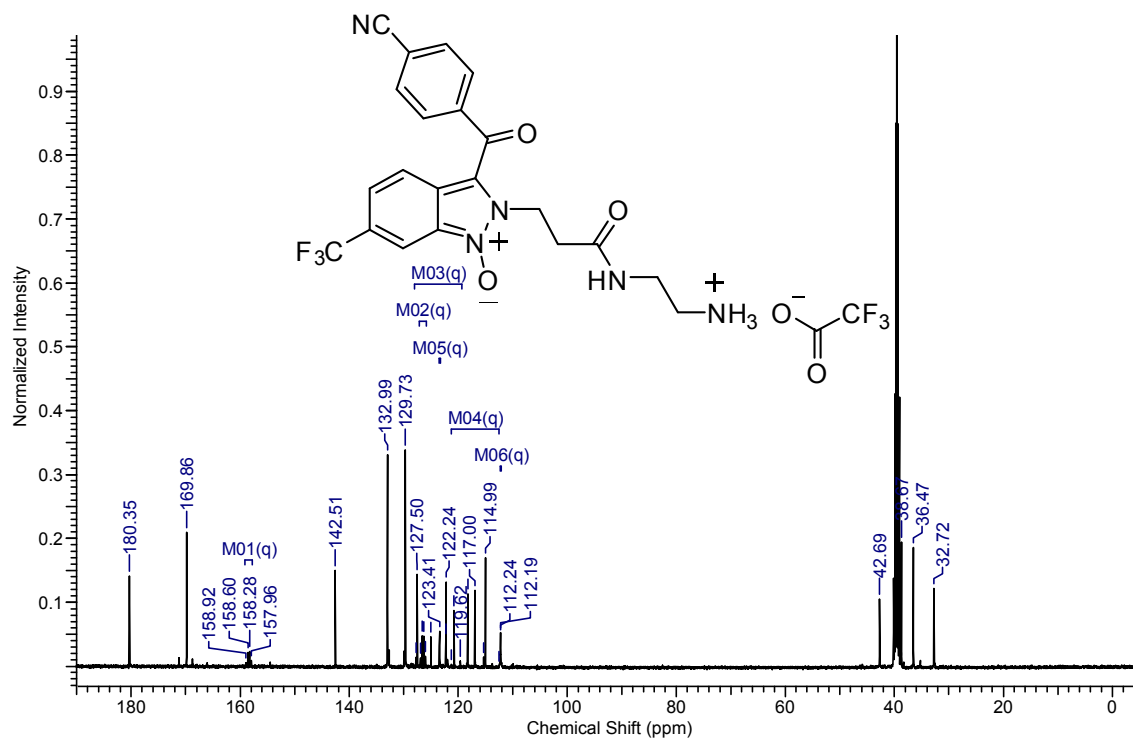
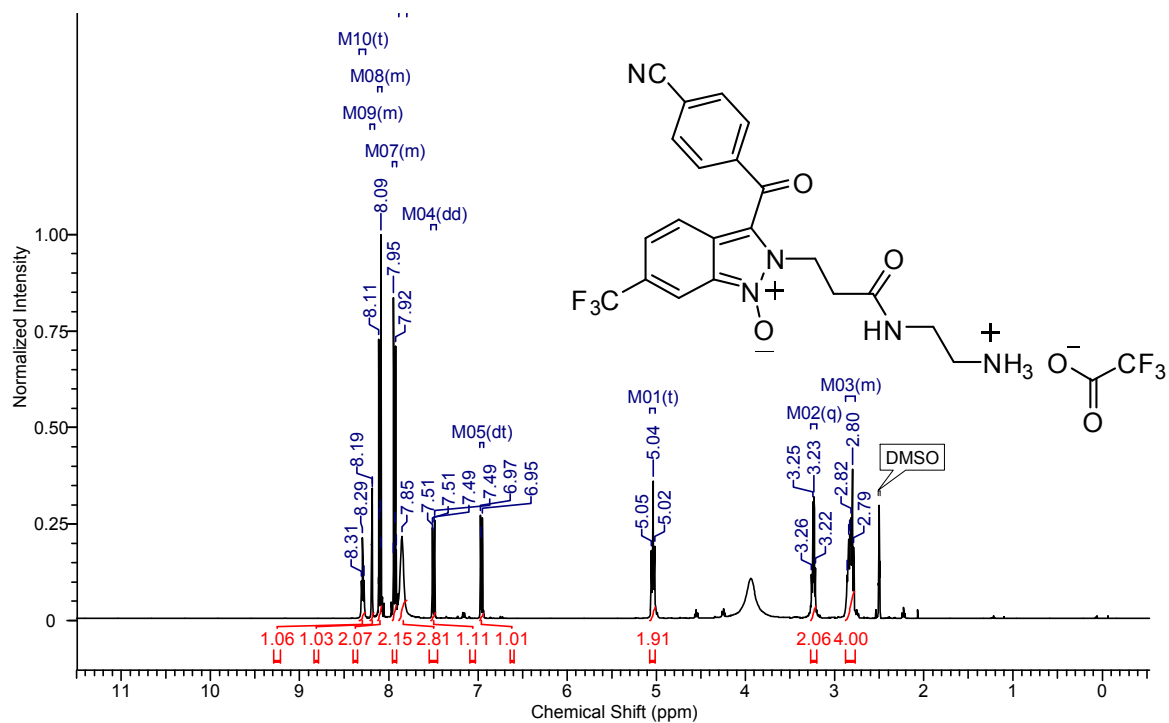


¹H and ¹³C NMR spectra (d₆-DMSO) of 2-(3-((2-ammonioethyl)amino)-3-oxopropyl)-6-(trifluoromethyl)-3-(4-(trifluoromethyl)benzoyl)-2H-indazole 1-oxide 2,2,2-trifluoroacetate

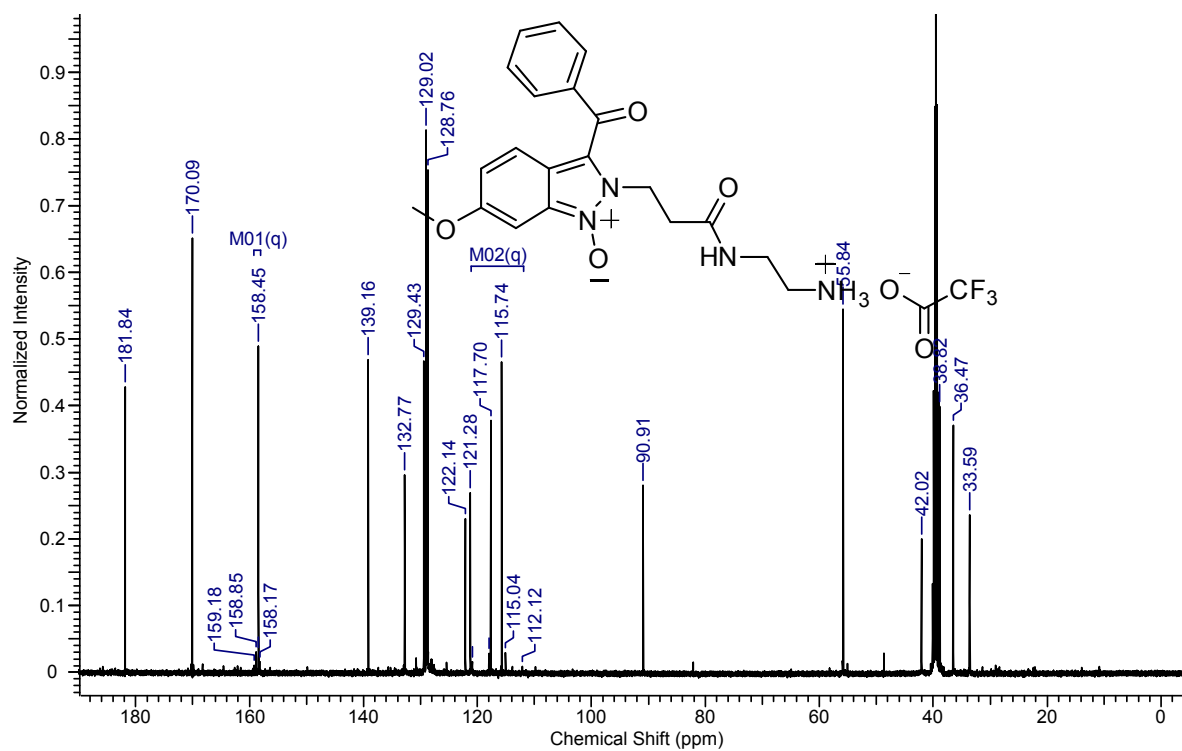
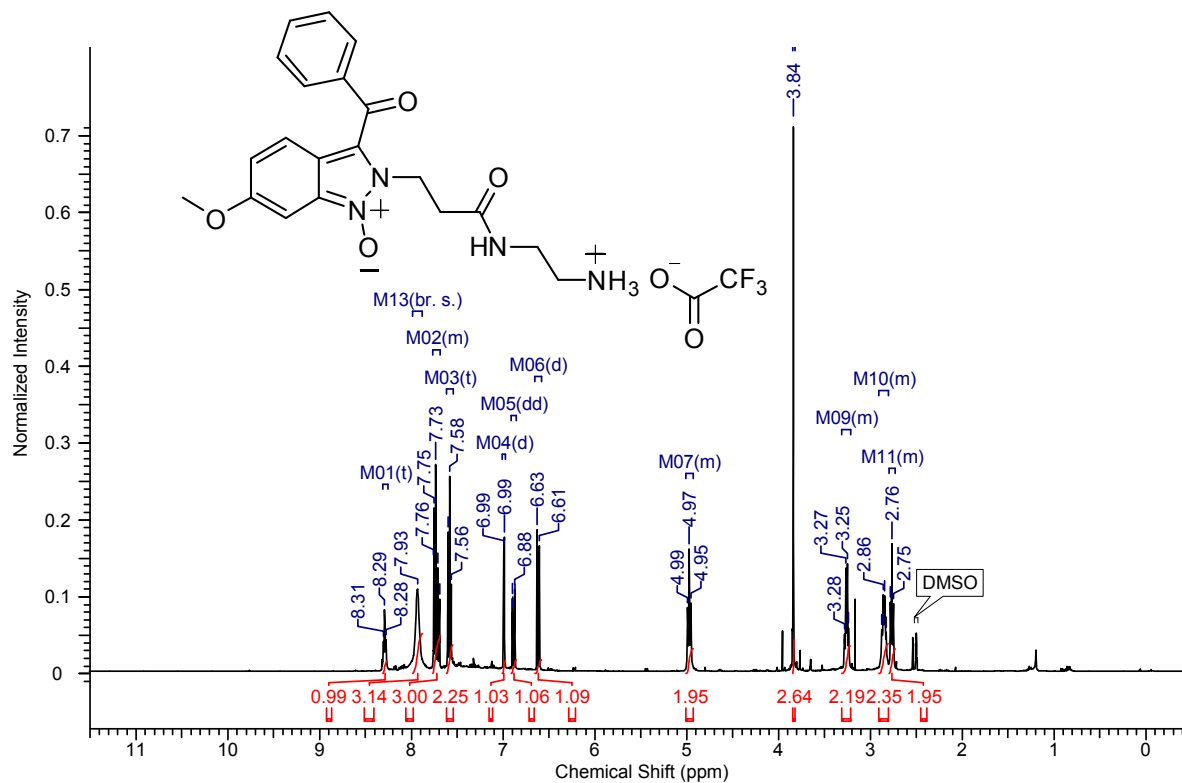
9{3,2,2}



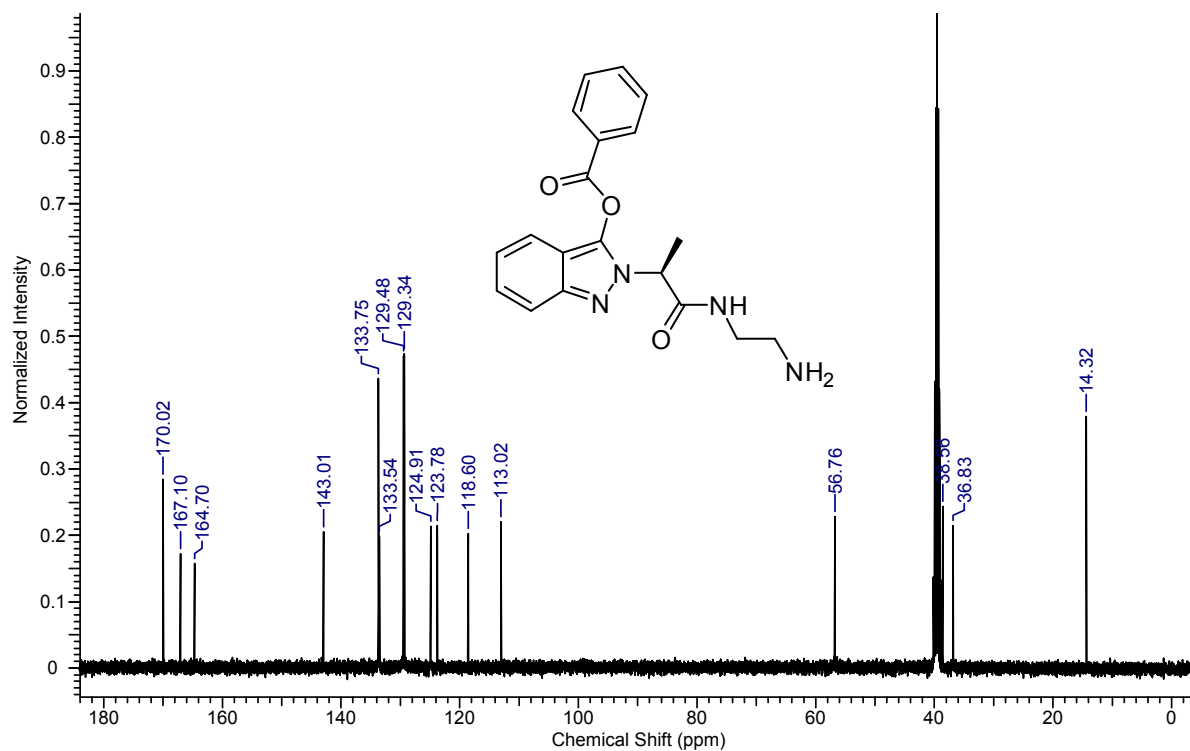
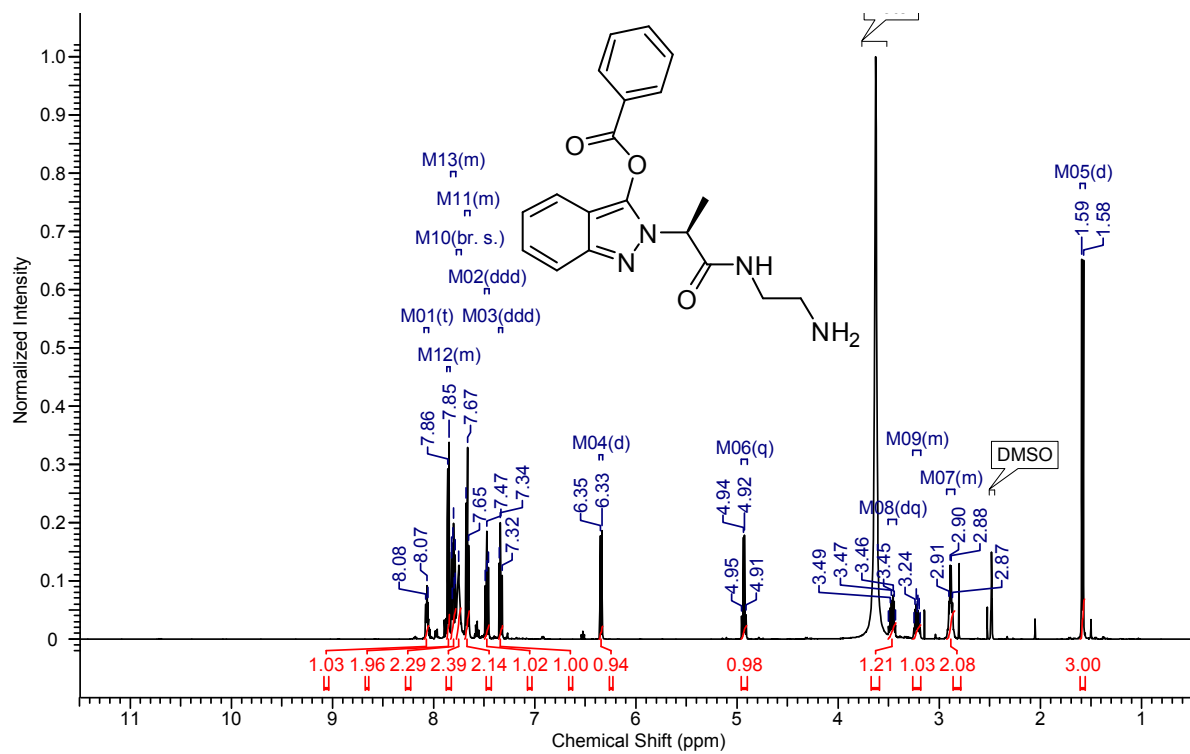
¹H and ¹³C NMR spectra (d₆-DMSO) of 2-(3-((2-ammonioethyl)amino)-3-oxopropyl)-3-(4-cyanobenzoyl)-6-(trifluoromethyl)-2H-indazole 1-oxide 2,2,2-trifluoroacetate 9{3,2,3}



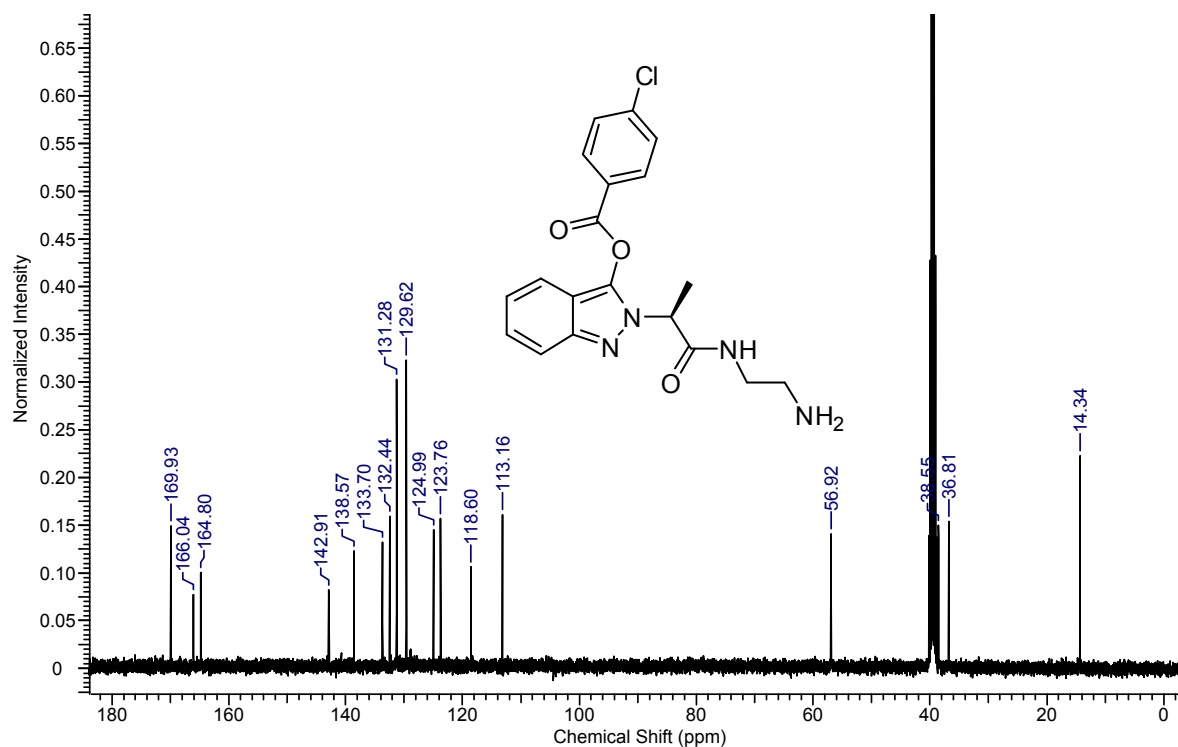
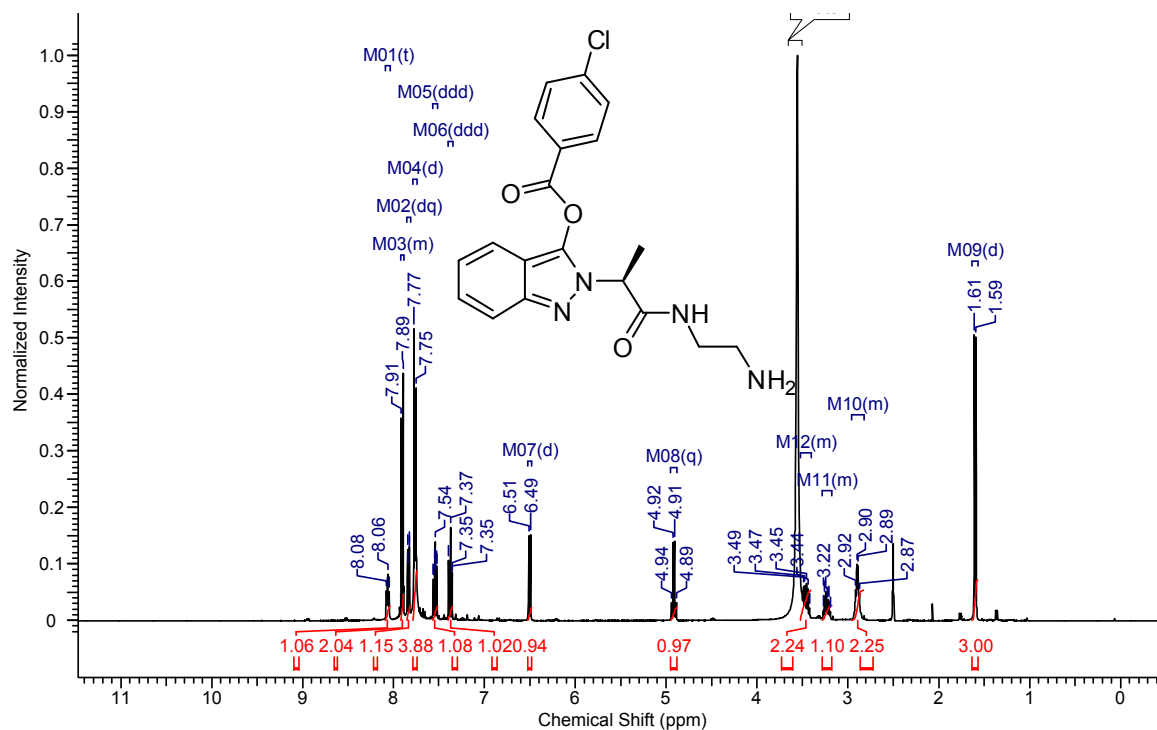
¹H and ¹³C NMR spectra (d₆-DMSO) of 2-(3-((2-ammonioethyl)amino)-3-oxopropyl)-3-benzoyl-6-methoxy-2H-indazole 1-oxide 2,2,2-trifluoroacetate **9**{3,3,1}



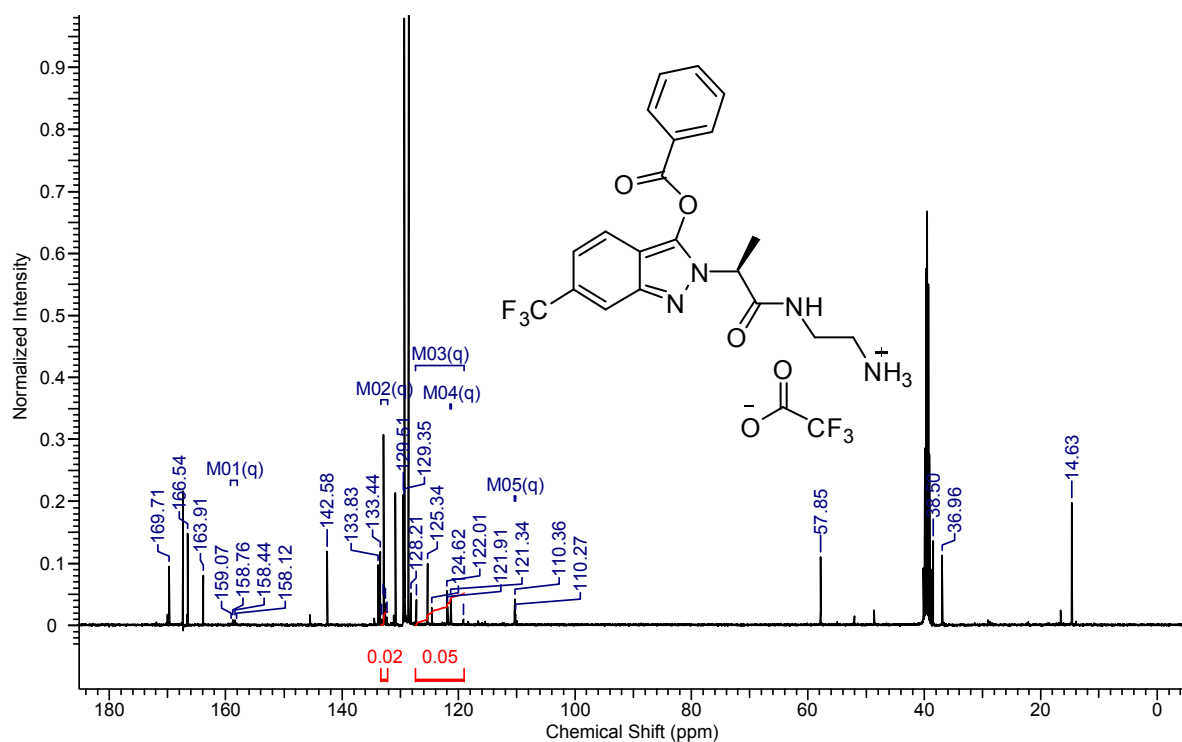
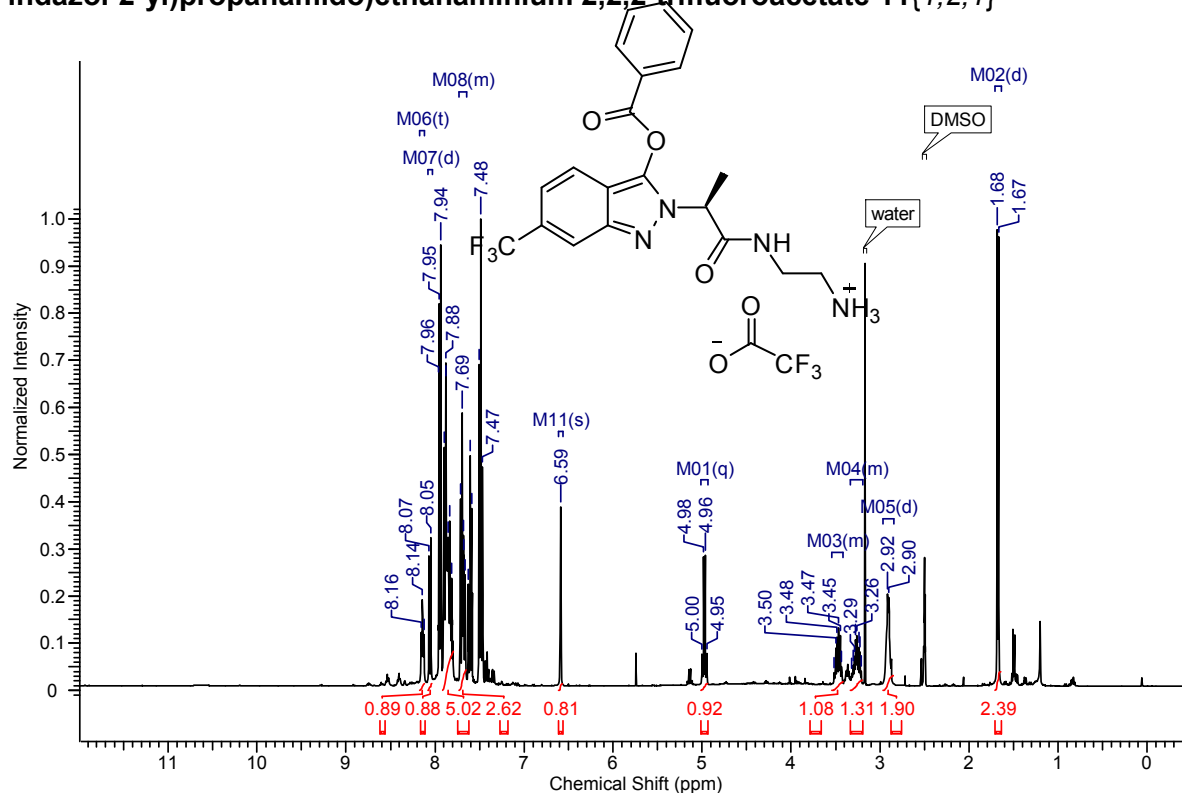
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(1-((2-aminoethyl)amino)-1-oxopropan-2-yl)-2H-indazol-3-yl benzoate 11{1,1,1}



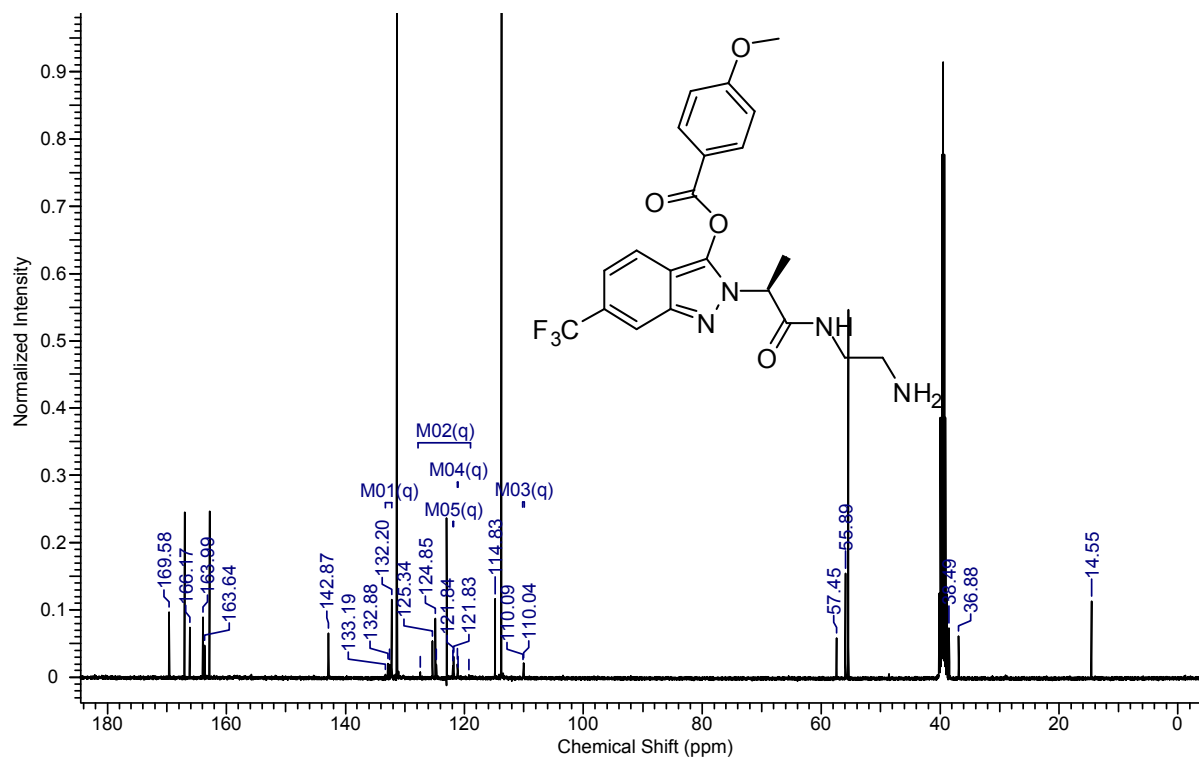
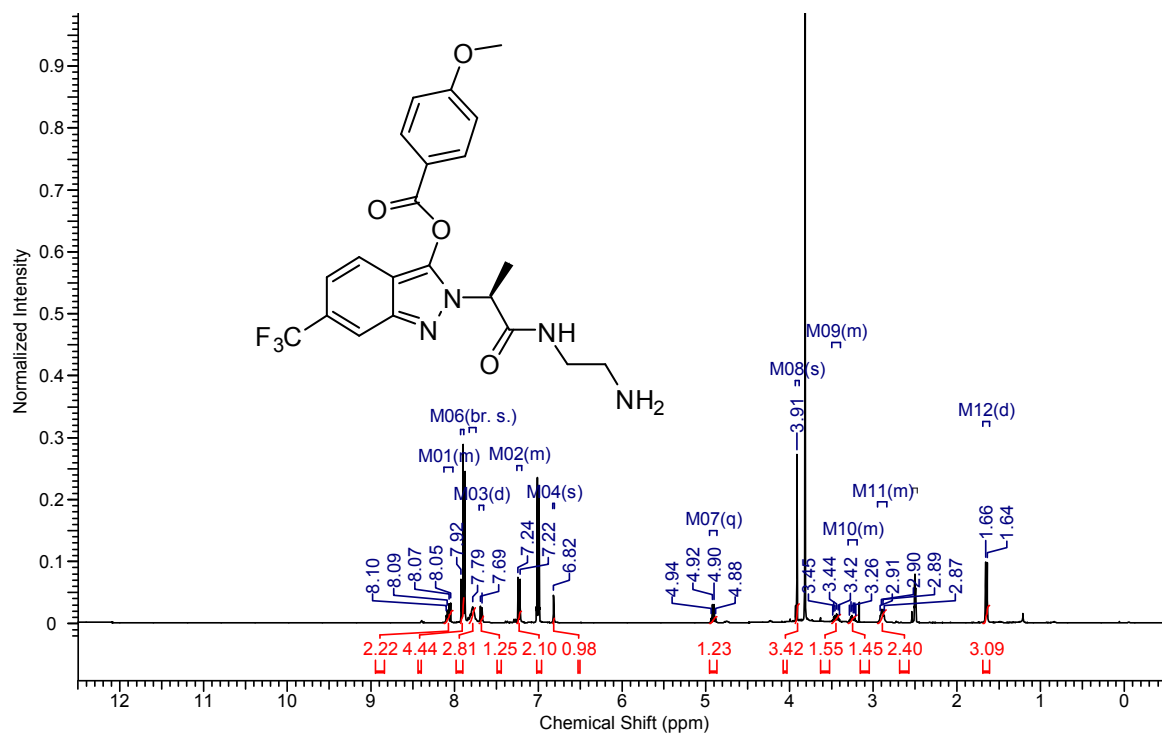
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(1-((2-aminoethyl)amino)-1-oxopropan-2-yl)-2H-indazol-3-yl 4-chlorobenzoate 11{1,1,4}



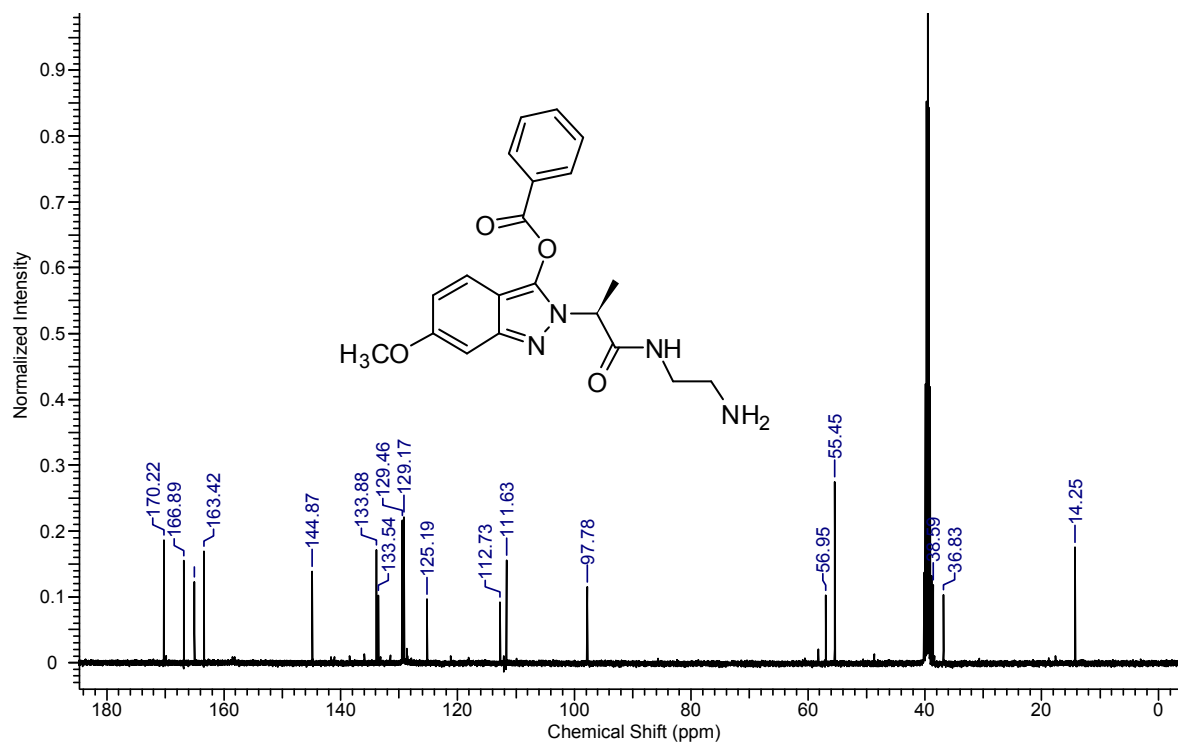
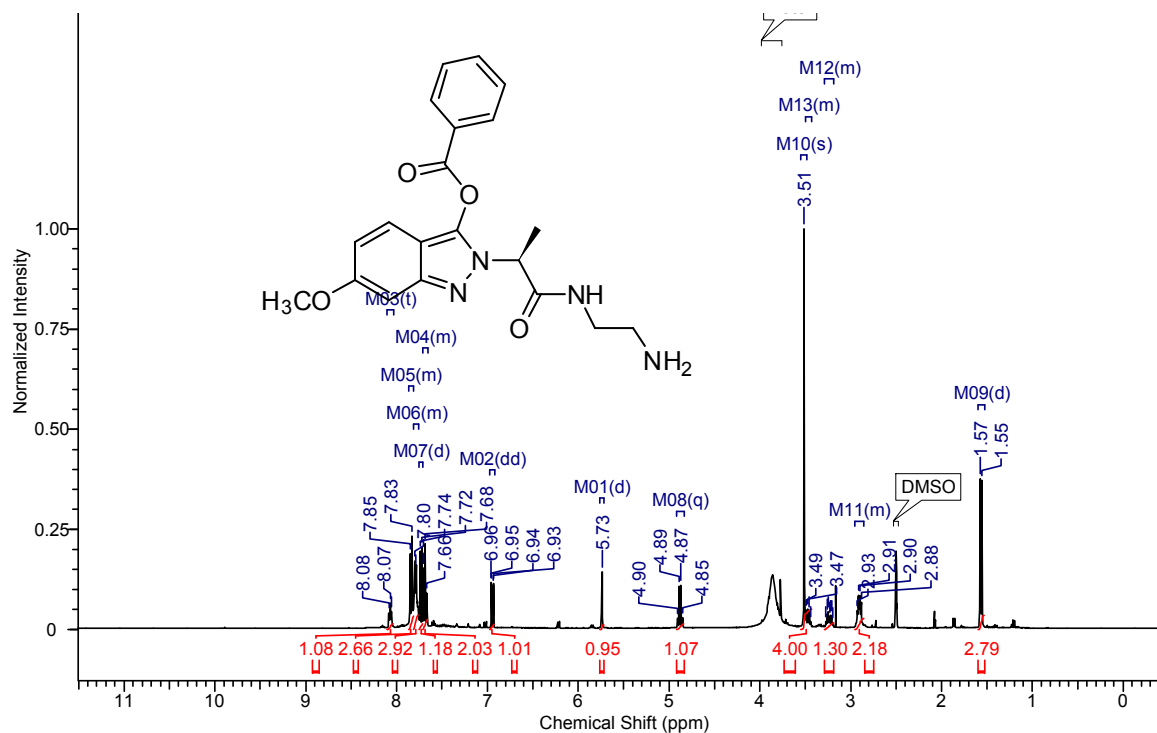
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(2-(3-(benzoyloxy)-6-(trifluoromethyl)-2H-indazol-2-yl)propanamido)ethanaminium 2,2,2-trifluoroacetate 11{1,2,1}



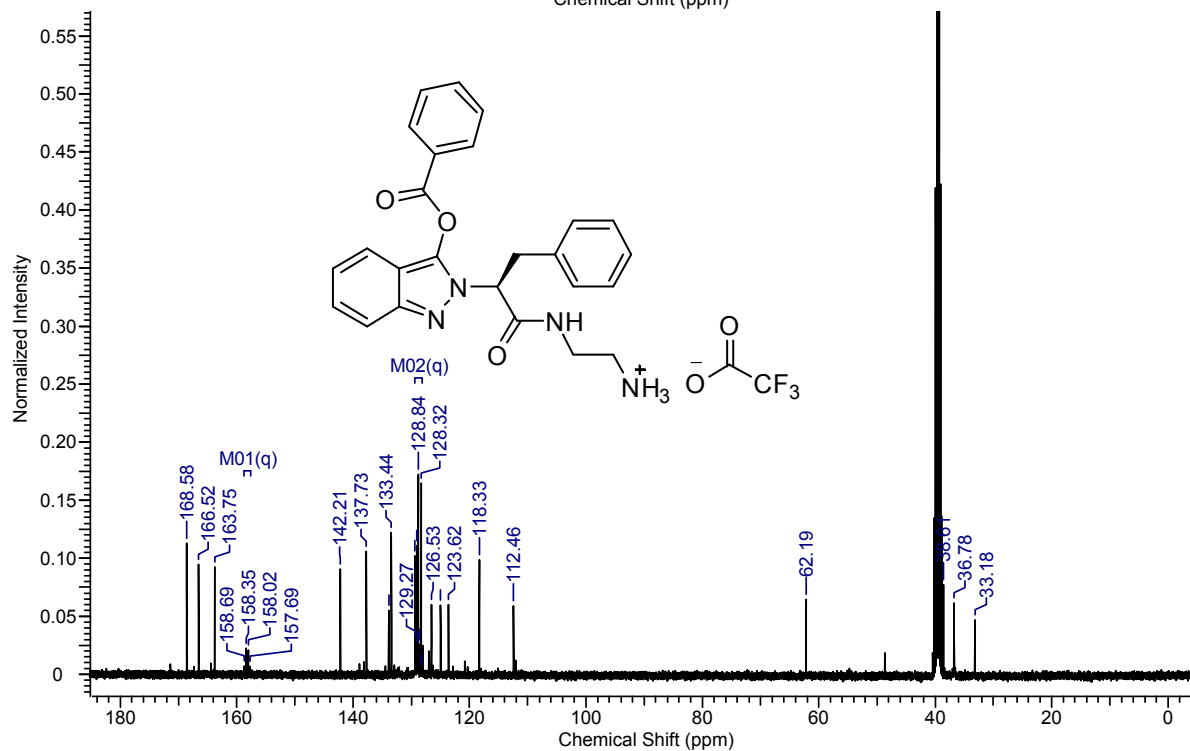
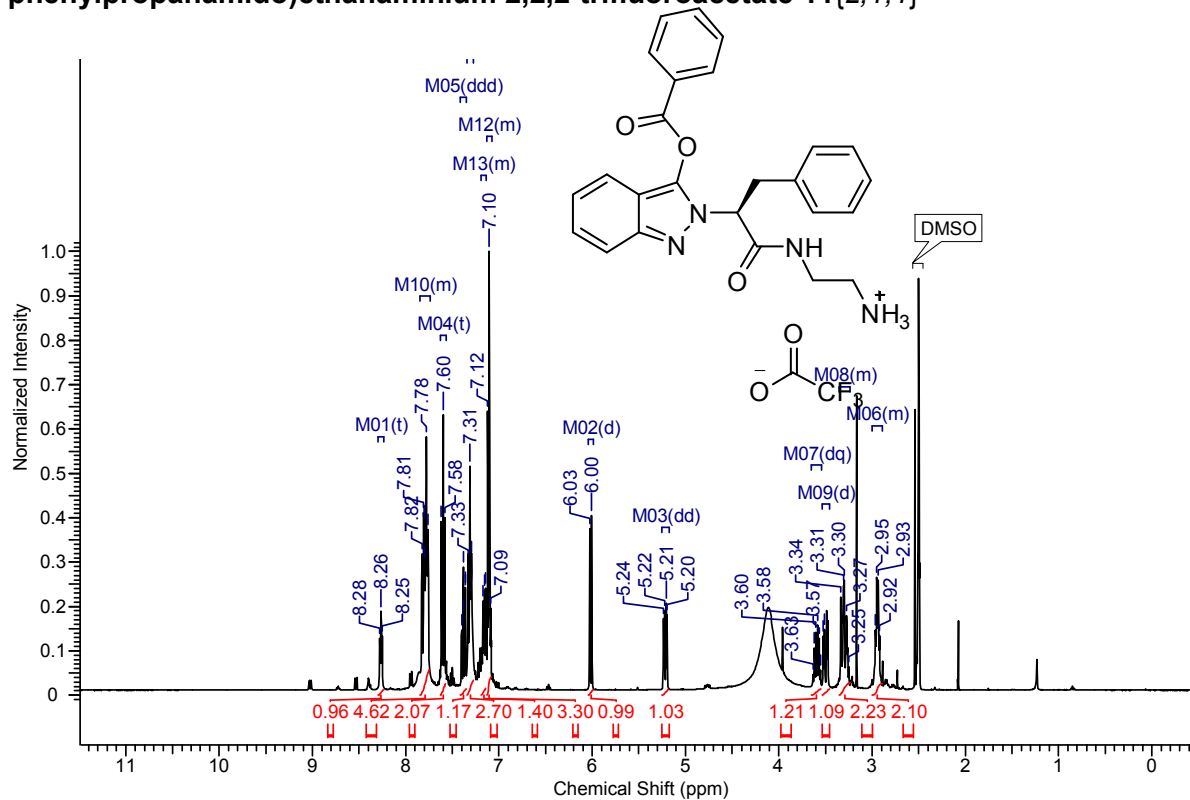
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(1-((2-aminoethyl)amino)-1-oxopropan-2-yl)-6-(trifluoromethyl)-2H-indazol-3-yl 4-methoxybenzoate 11{1,2,5}



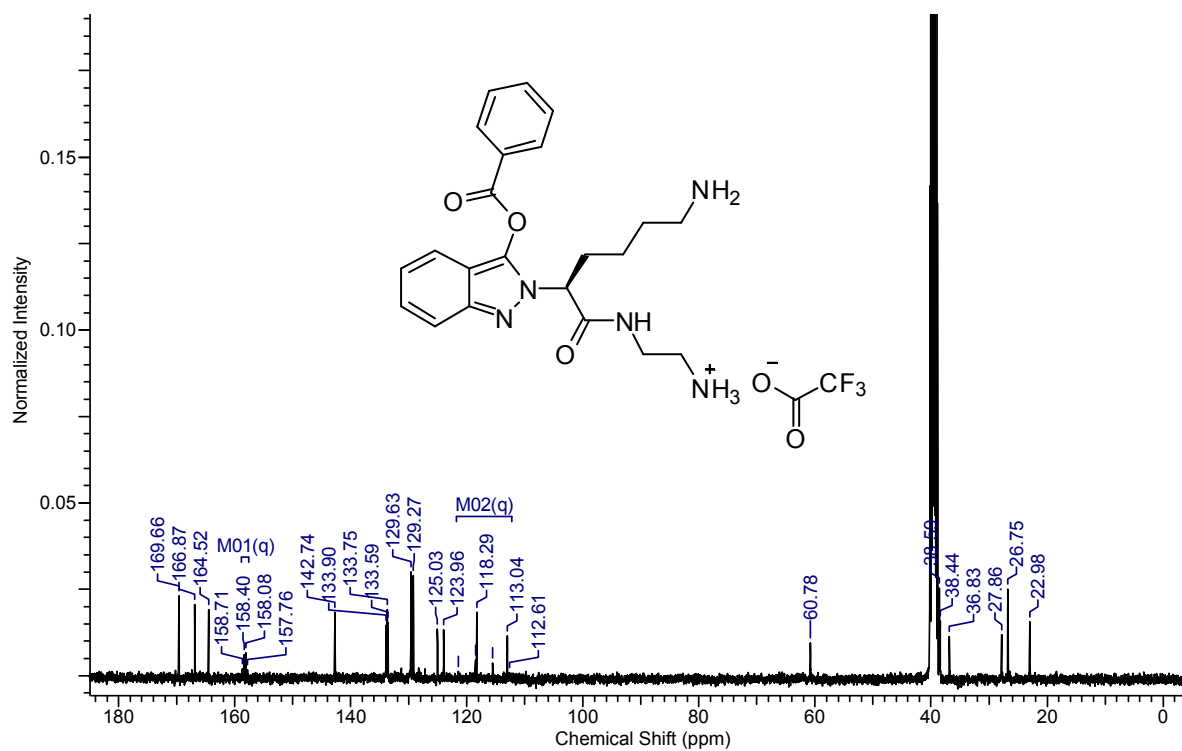
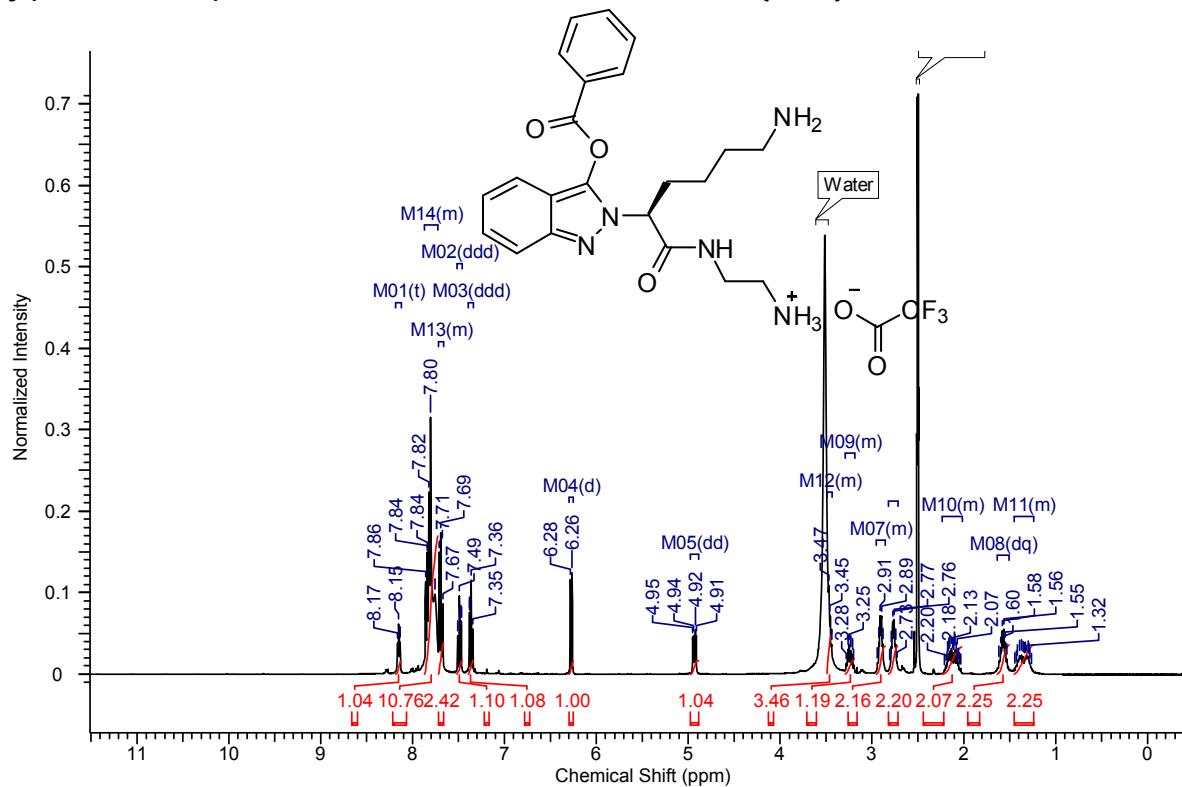
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(1-((2-aminoethyl)amino)-1-oxopropan-2-yl)-6-methoxy-2H-indazol-3-yl benzoate 11{1,3,1}



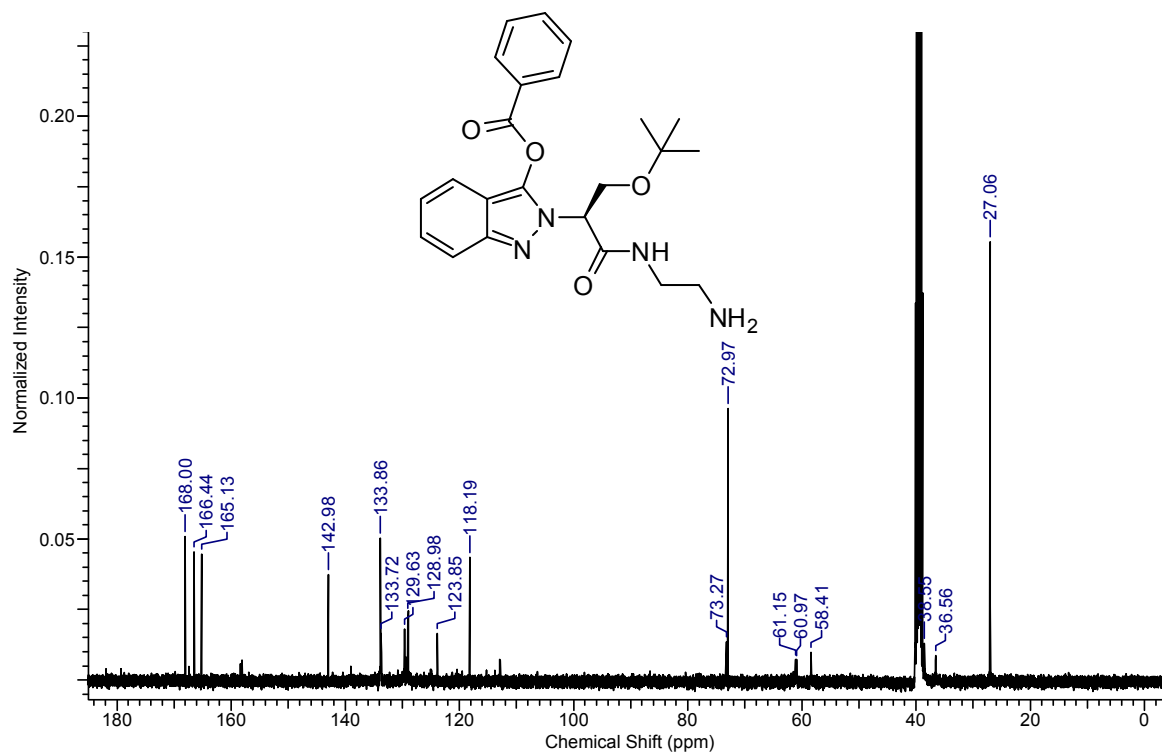
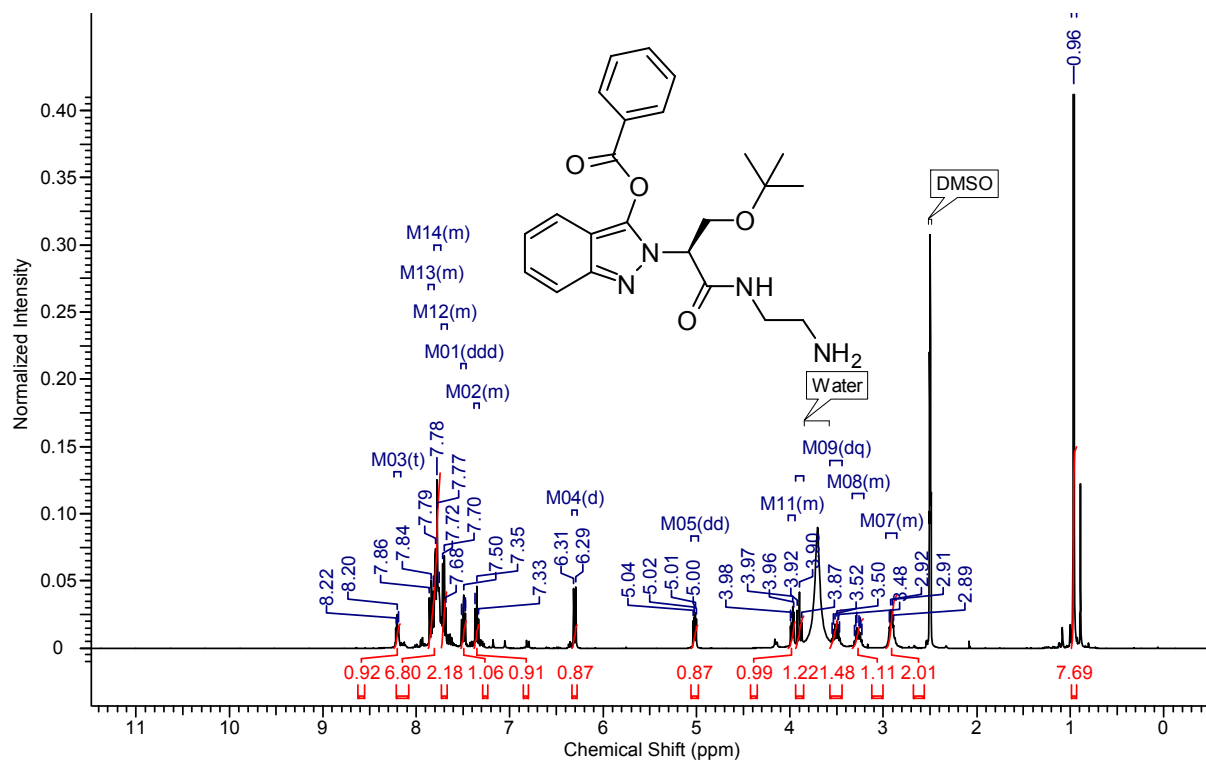
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(2-(3-(benzyloxy)-2H-indazol-2-yl)-3-phenylpropanamido)ethanaminium 2,2,2-trifluoroacetate 11{2,1,1}



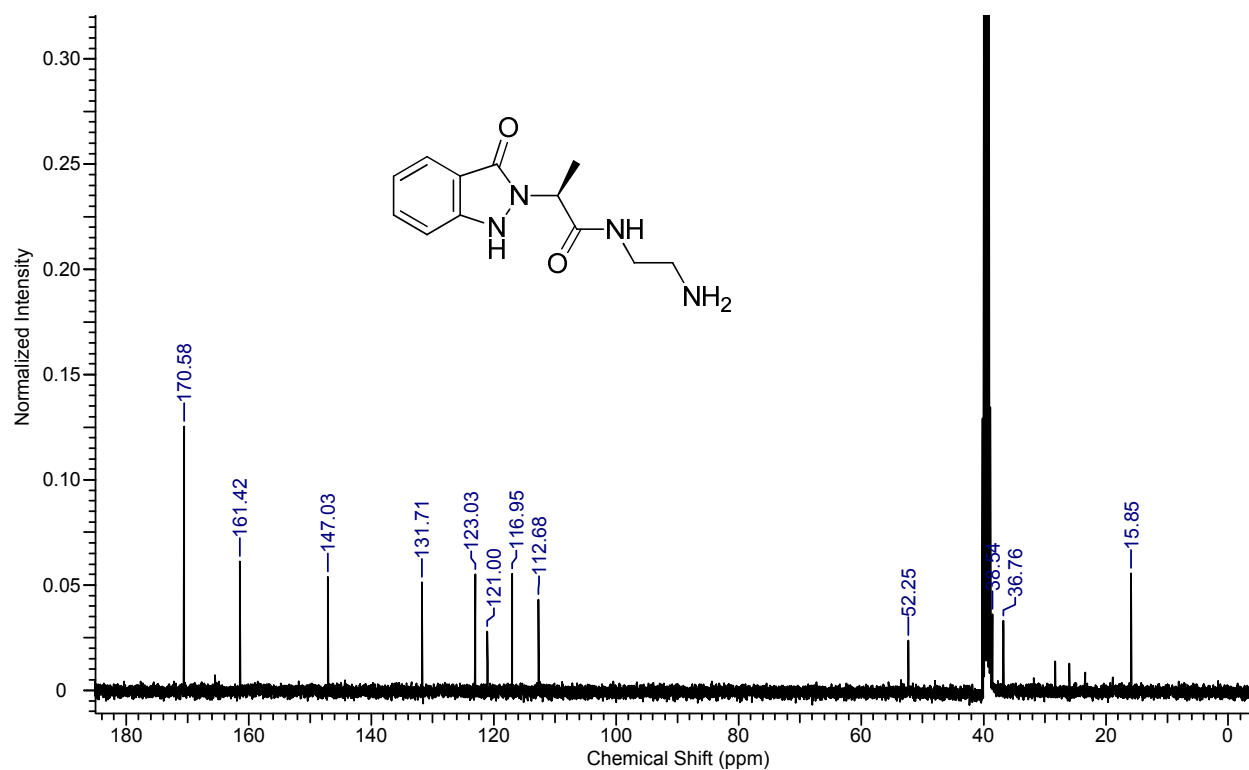
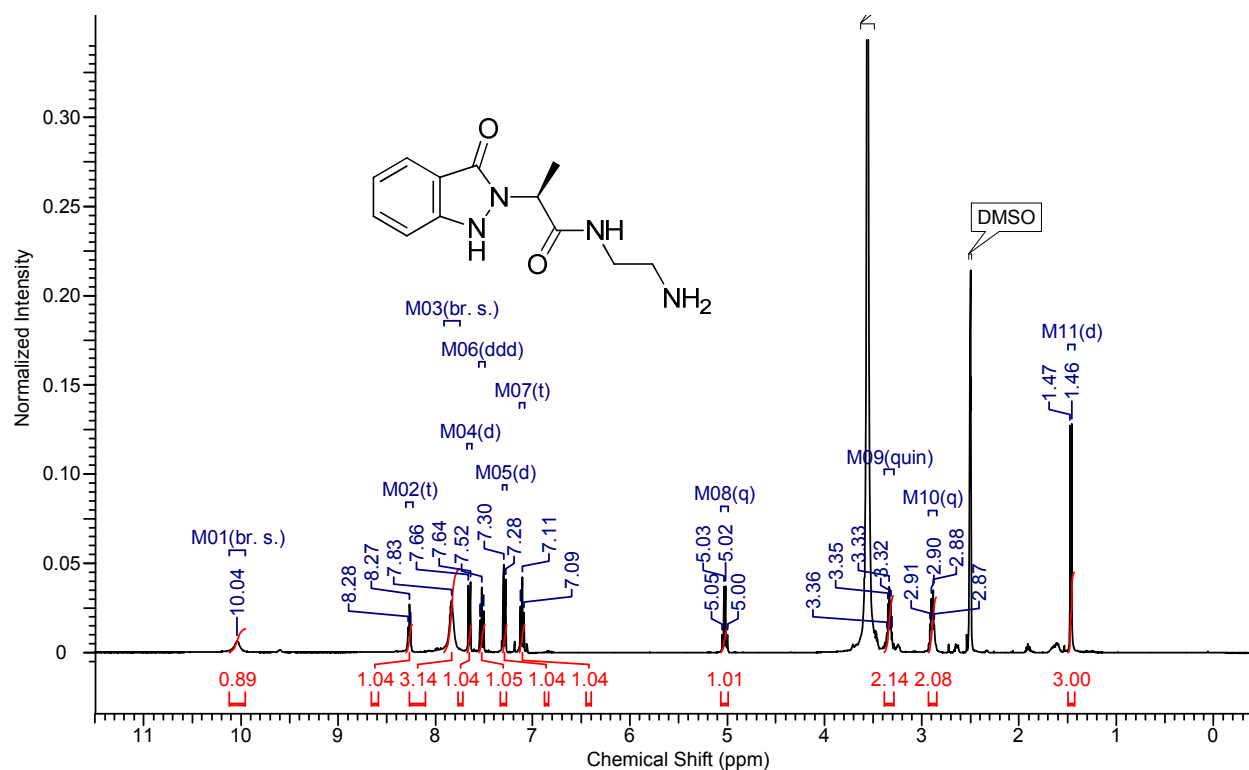
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(6-amino-2-(3-(benzoyloxy)-2H-indazol-2-yl)hexanamido)ethanaminium 2,2,2-trifluoroacetate 11{3,1,1}



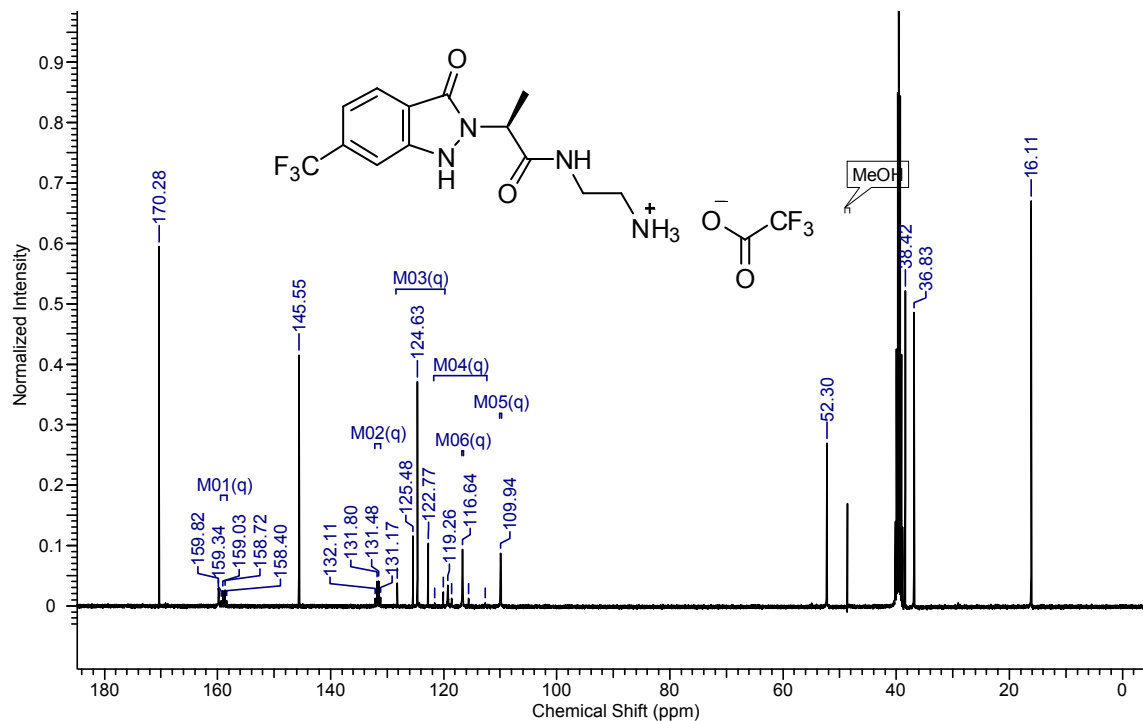
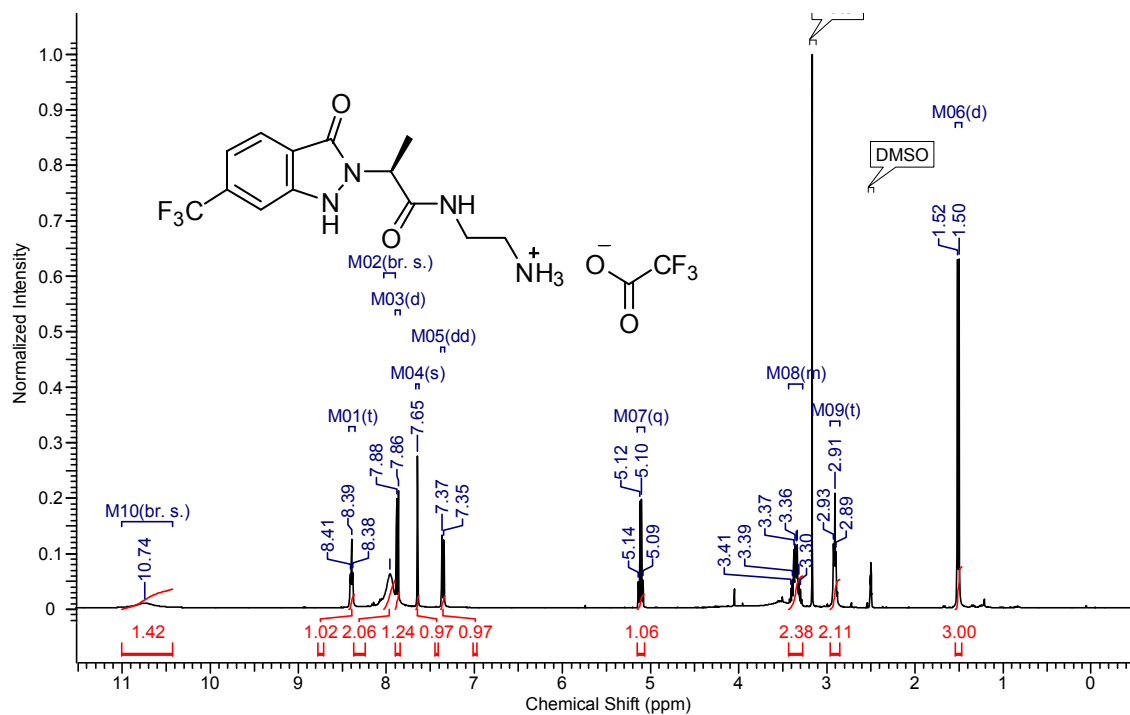
¹H and ¹³C NMR spectra (*d*₆-DMSO) of (S)-2-(1-((2-aminoethyl)amino)-3-(tert-butoxy)-1-oxopropan-2-yl)-2*H*-indazol-3-yl benzoate 11{4, 1, 1}



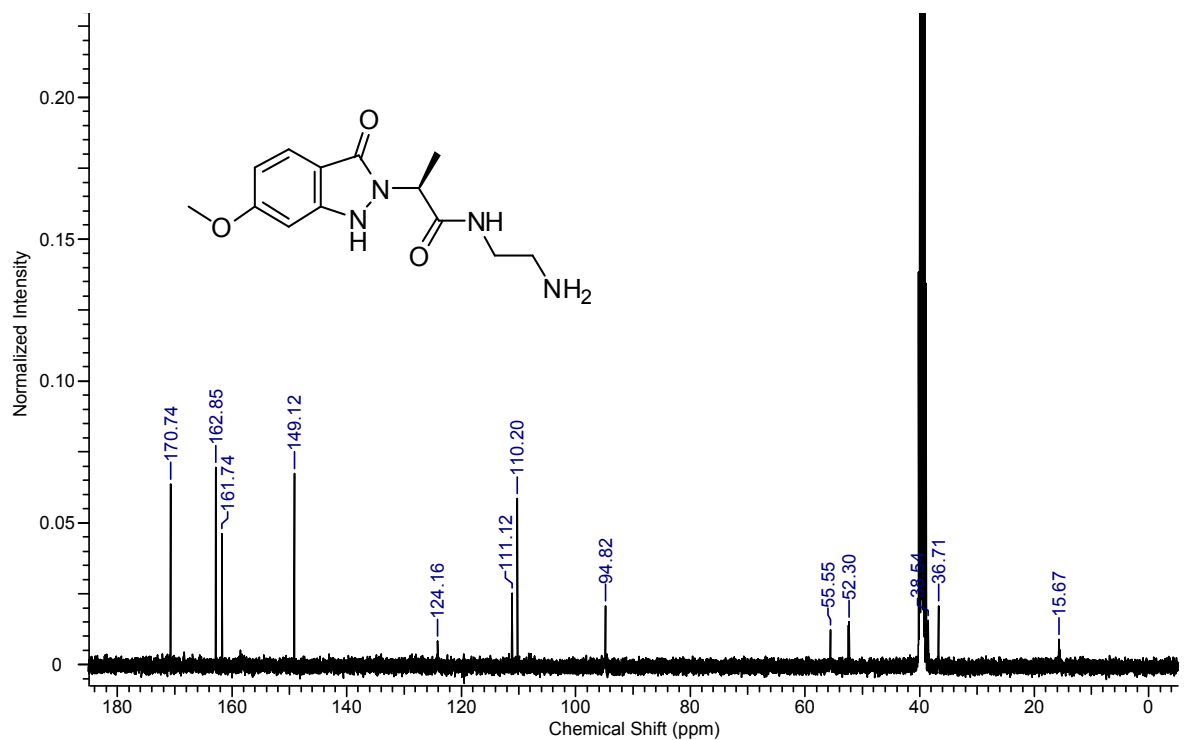
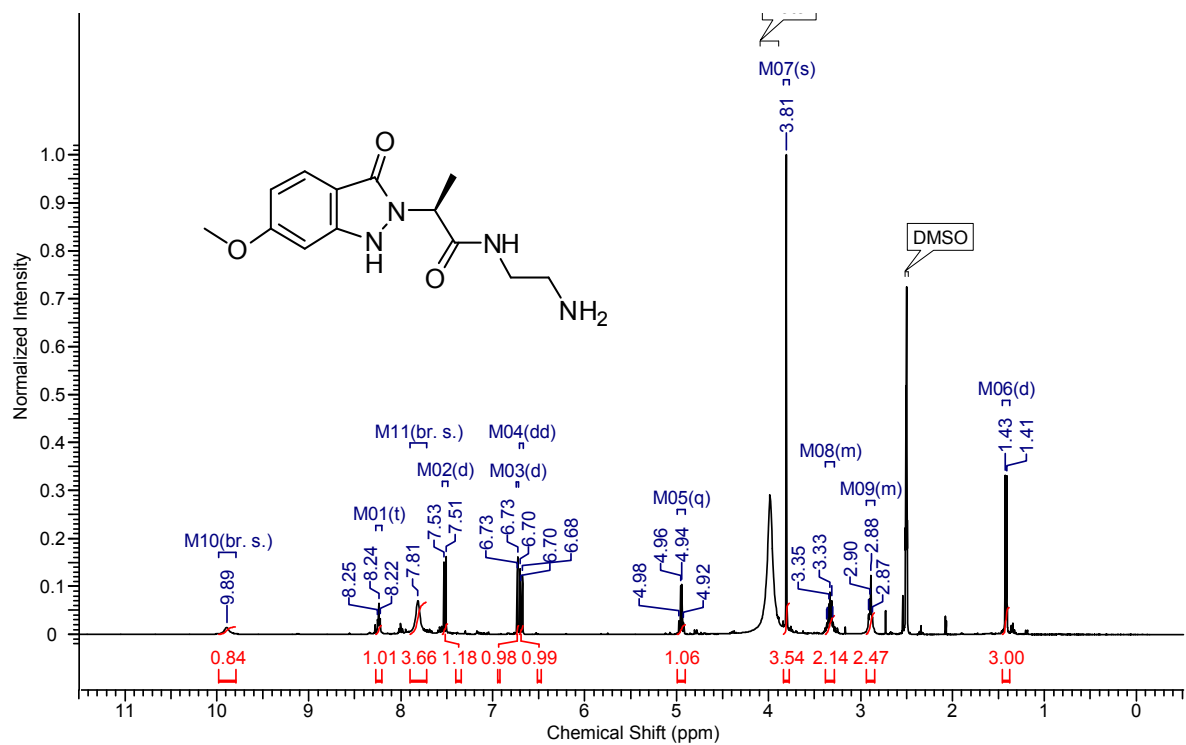
¹H and ¹³C NMR spectra (*d*₆-DMSO) of (*S*)-*N*-(2-aminoethyl)-2-(3-oxo-1*H*-indazol-2(3*H*)-yl)propanamide 12{1,1}



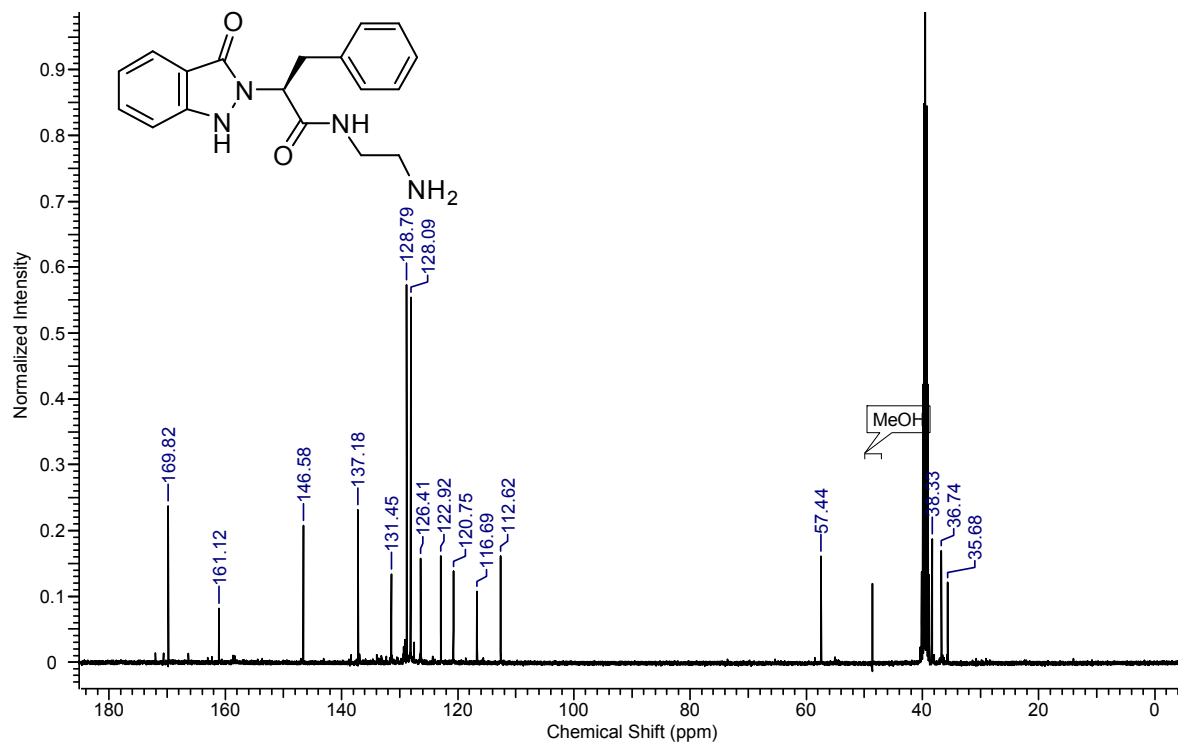
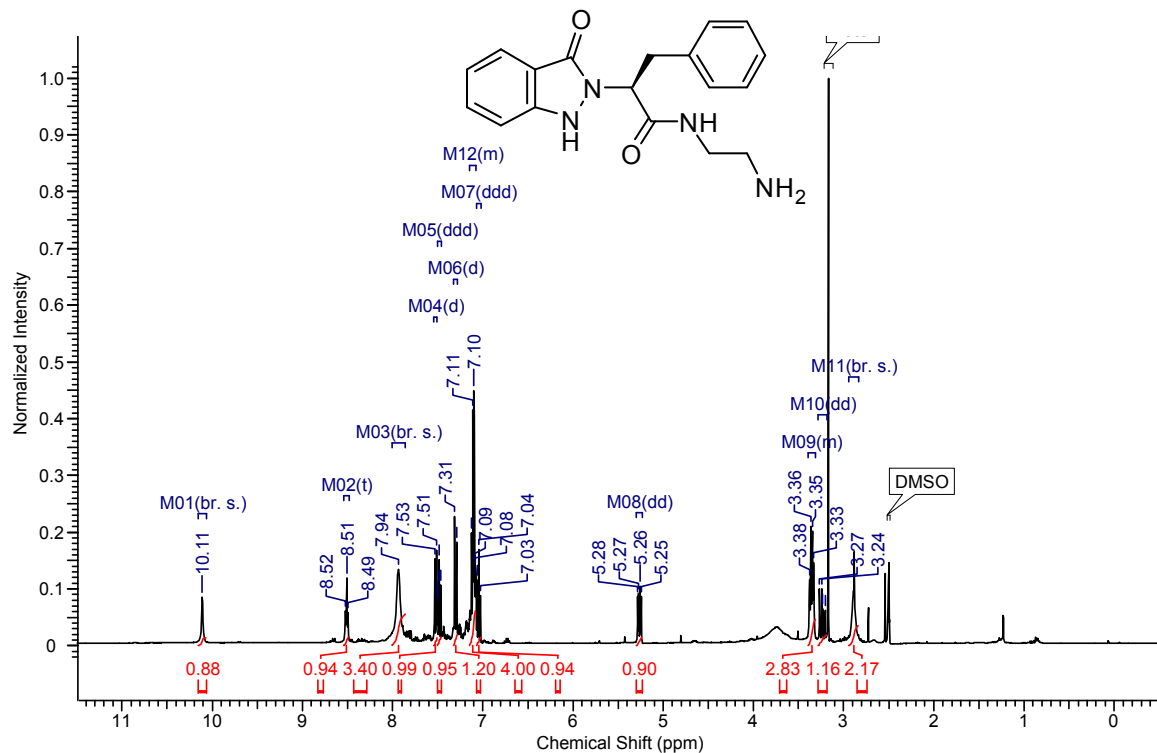
¹H and ¹³C NMR spectra (*d*₆-DMSO) of (S)-2-(2-(3-oxo-6-(trifluoromethyl)-1*H*-indazol-2(3*H*)-yl)propanamido)ethanaminium 2,2,2-trifluoroacetate 12{1,2}



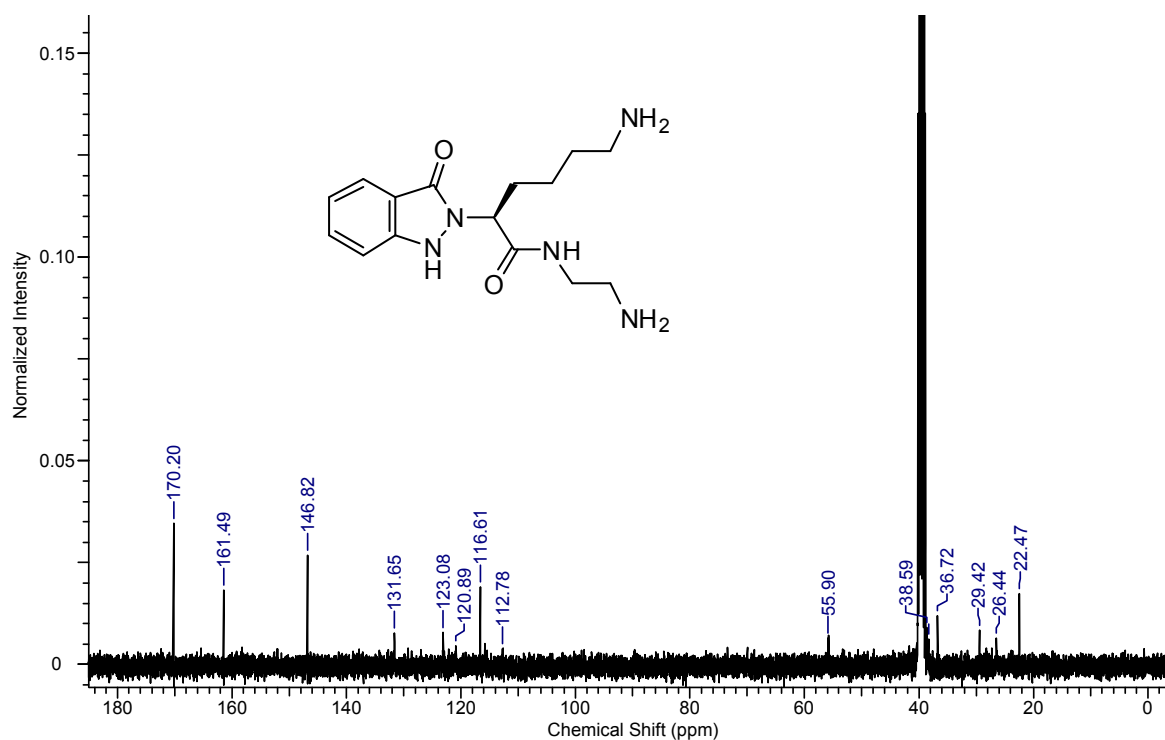
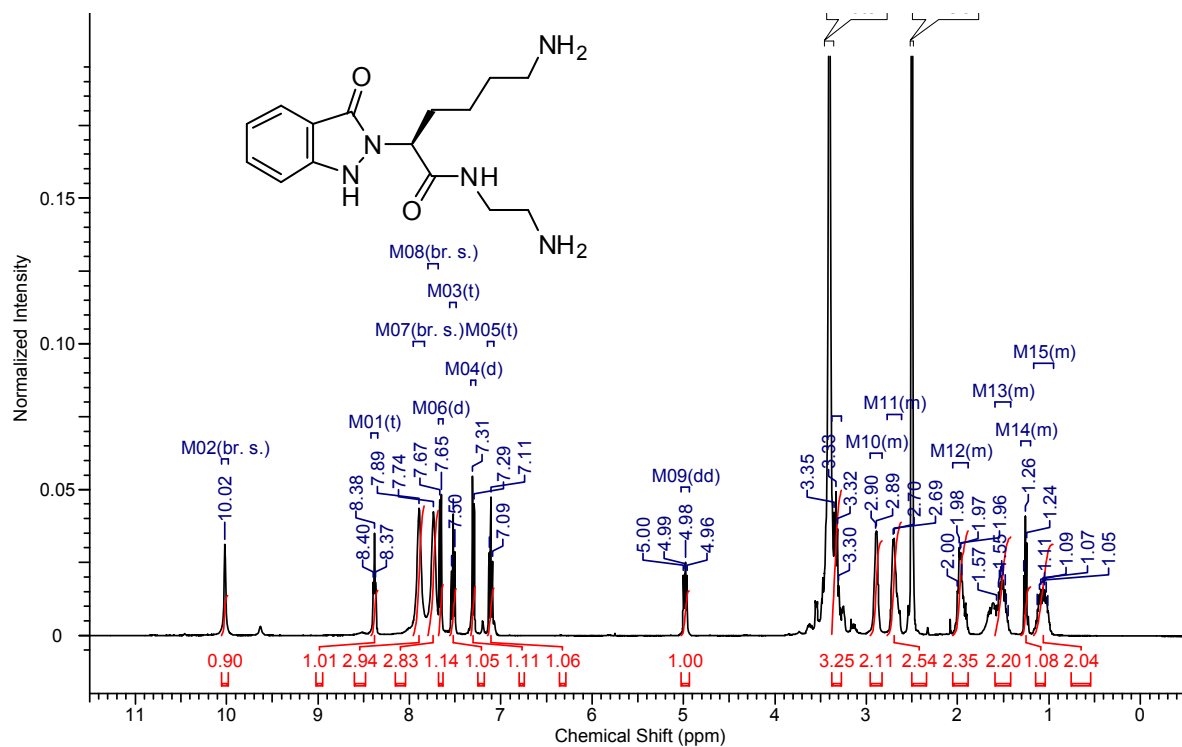
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-N-(2-aminoethyl)-2-(6-methoxy-3-oxo-1H-indazol-2(3H)-yl)propanamide 12{1,3}



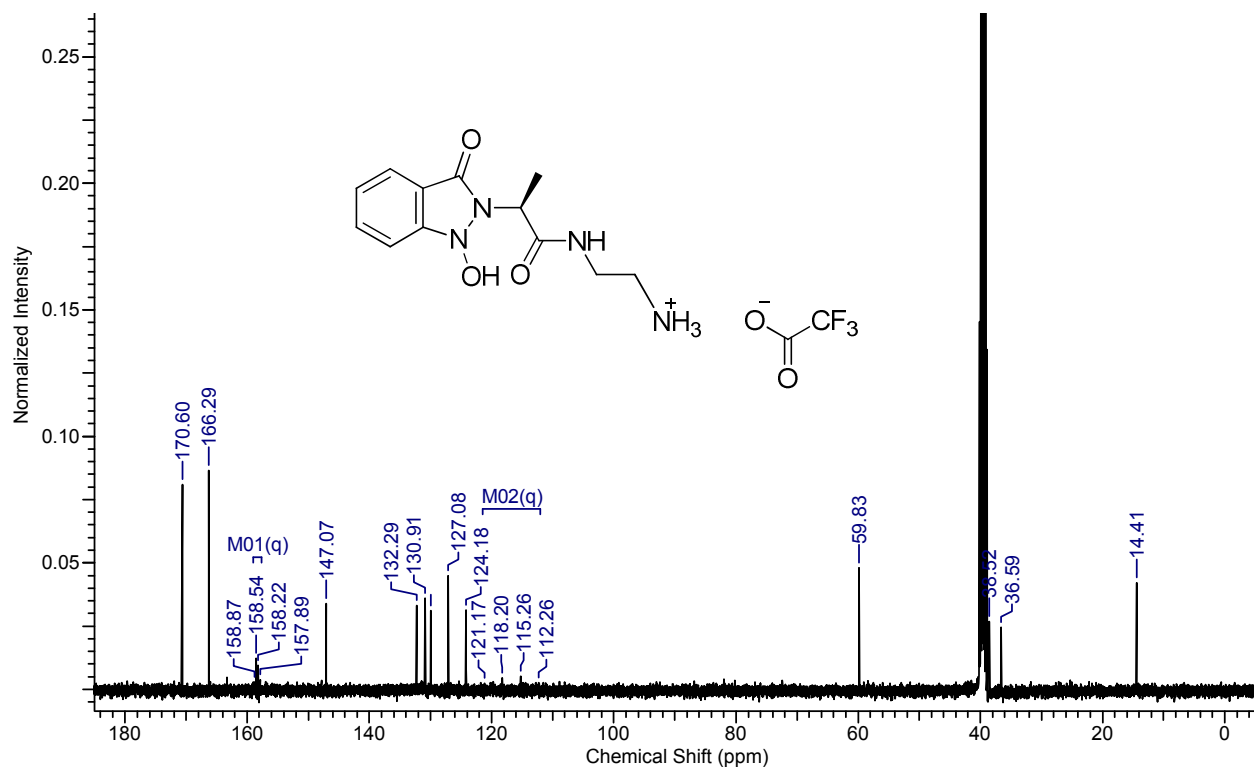
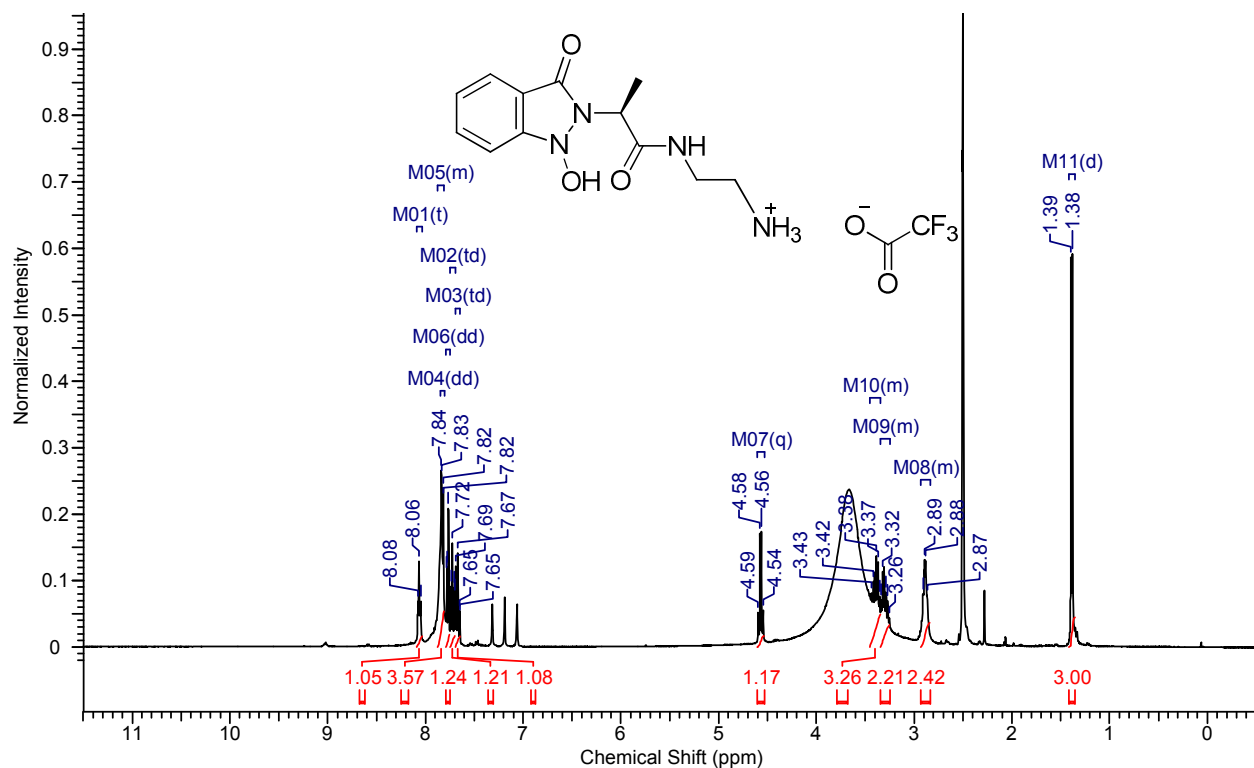
¹H and ¹³C NMR spectra (*d*₆-DMSO) of (*S*)-*N*-(2-aminoethyl)-2-(3-oxo-1*H*-indazol-2(3*H*)-yl)-3-phenylpropanamide **12**{2,1}



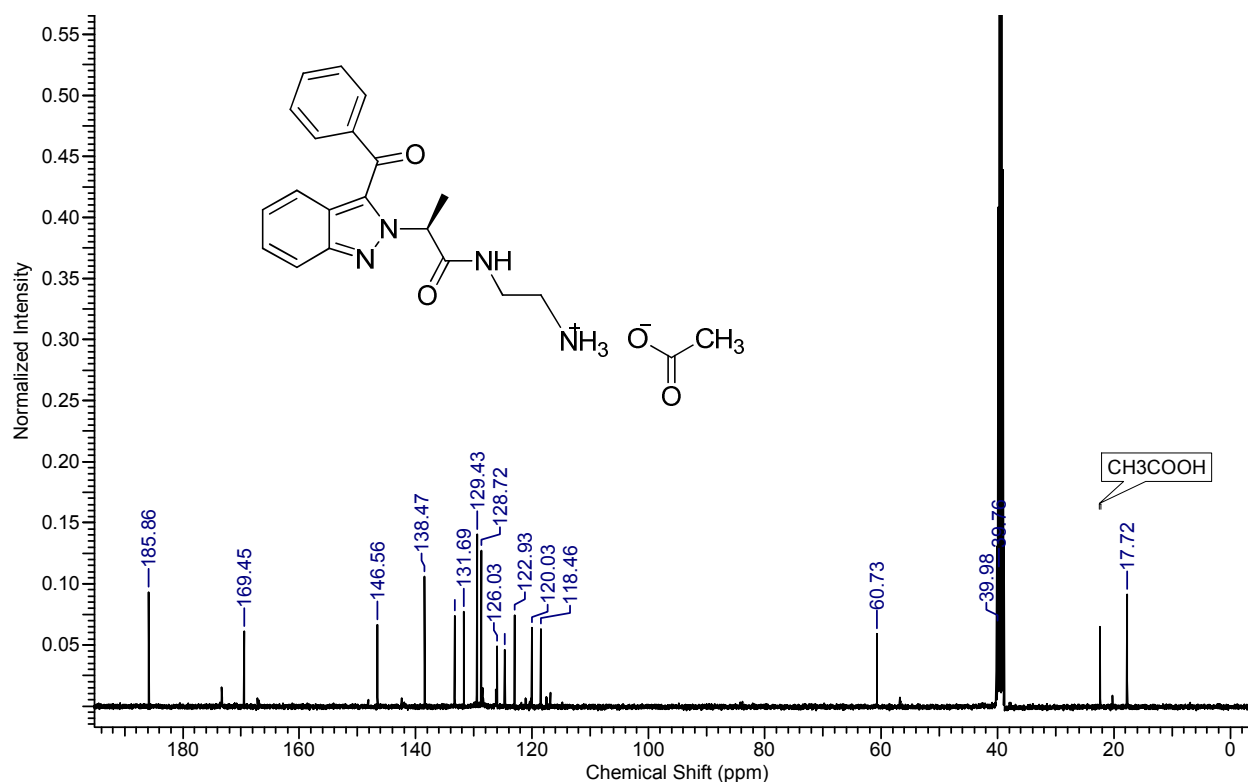
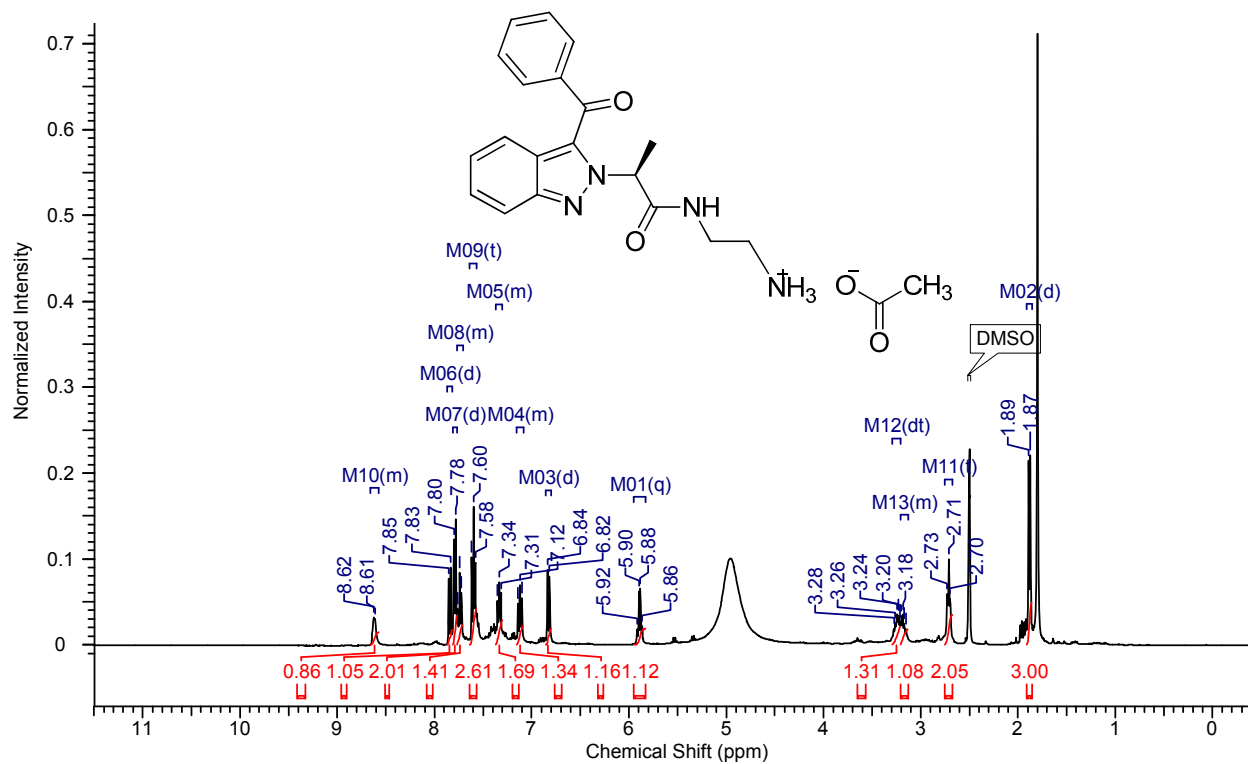
¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-6-amino-N-(2-aminoethyl)-2-(3-oxo-1H-indazol-2(3H)-yl)hexanamide 12{3,1}



¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(2-(1-hydroxy-3-oxo-1H-indazol-2(3H)-yl)propanamido)ethanaminium 2,2,2-trifluoroacetate 14



¹H and ¹³C NMR spectra (d₆-DMSO) of (S)-2-(2-(3-benzoyl-2H-indazol-2-yl)propanamido)ethanaminium acetate 17



¹H and ¹³C NMR spectra (d₆-DMSO) of 4-benzoyl-2-methylquinazoline 1-oxide 20

