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FACILE SYNTHESIS OF MODEL INDAZOLO[2,1-*c*][1,3,4]BENZO-TRIAZEPINE-5,13-DIONES

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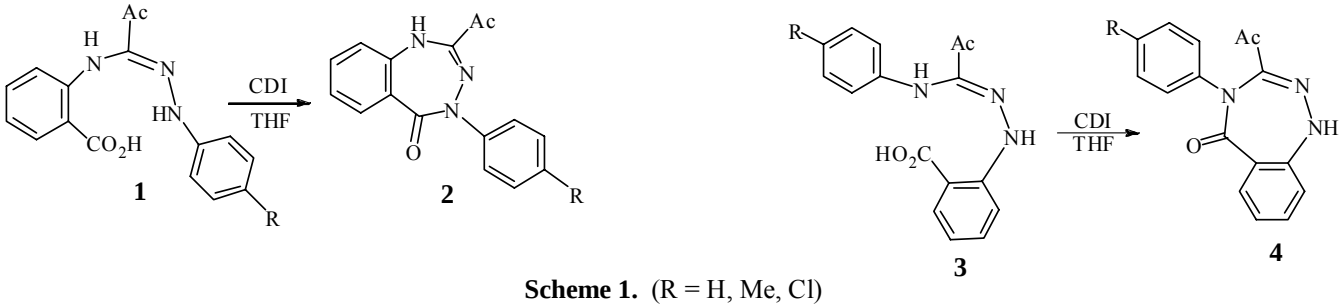
Abstract – In basic media, 2-aminobenzoic acids (**5**) react with 2-[*N*-(1-carboxyphenyl)]hydrazonoyl chlorides (**6**, **7**) (precursors of the reactive nitrile imine 1,3-dipolar species) to afford good yields of the corresponding 2-[*N'*-(1-carboxyphenyl-2-amino)hydrazino]benzoic acids (**8a-d**, **9a**). The latter acyclic adducts, in the presence of 1,1'-carbonyldiimidazole (CDI), undergo two consecutive lactamizations involving both activated carboxyl groups and the suitably located hydrazino-NH partners, to deliver the respective indazolo[2,1-*c*]-[1,3,4]benzotriazepin- 5,13-diones (**10a-d**, **11a**). Structural assignments for these novel tetracyclic products are based on analytical and spectral (IR, MS, NMR) data, and confirmed by single crystal X-ray structure determination for **10a**.

INTRODUCTION

Recently, we reported on a facile synthesis of model 1,4-dihydro-1,3,4-benzotriazepin-5-ones (**2**) *via* CDI-catalyzed cyclocondensation of *N*-arylamidrazones (**1**) incorporating a carboxyl group *ortho* to the amidrazone-NH group (Scheme 1).[1–3] Likewise, under similar conditions the isomeric amidrazones (**3**), having a carboxyl group *ortho* to the hydrazono-NH entity, underwent cyclocondensation with ultimate production of the respective 1,4-dihydro-1,2,4-benzotriazepin-5-ones (**4**)[4] (Scheme 1). These acyclic

adducts (**1**, **3**) are readily accessible by direct interaction of the particular areneamine component with the appropriate *N*-arylhydrazonoyl chloride in the presence of triethylamine.[1–4]

In light of these results we envisaged that amidrazone adducts, incorporating two carboxyl groups, each onto the *N*-phenylhydrazono moiety (ring A) and the *N*-phenylamidrazone (ring D) might experience double cyclocondensation to produce tetracyclic ring systems. Accordingly, the present work aims at investigations relating to the CDI-induced double ring-closures of selected 1,1'-dicarboxyl-amidrazone adducts **8a-d** / **9a** (Scheme 2).



Scheme 1. (R = H, Me, Cl)

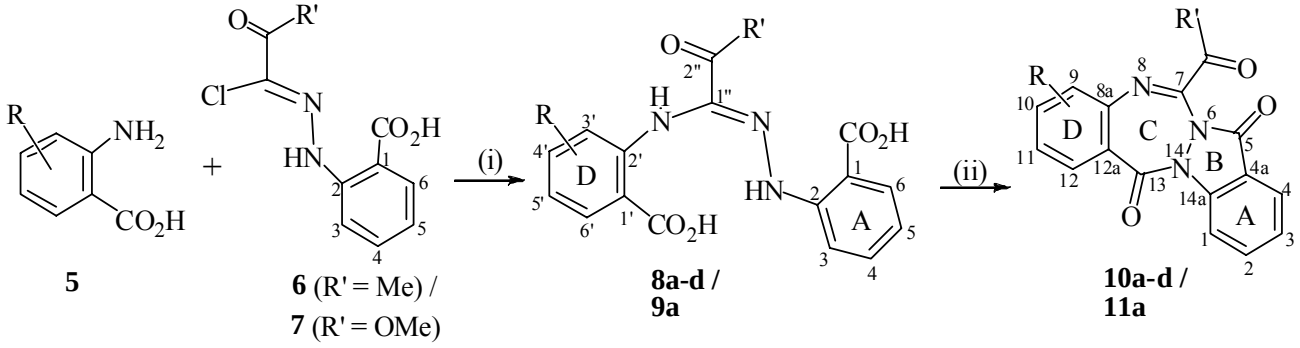
RESULTS AND DISCUSSION

As we observed in earlier work,[1-4] 2-aminobenzoic acids (**5a-d**), act as nitrogen nucleophiles in basic media and interact smoothly with the appropriate *N*-arylhydrazonoyl chlorides **6**, **7** (precursors of the respective 1,3-dipolar nitrile imines) to produce the corresponding 2-[*N*'-(1-carboxyphenyl-2-amino) hydrazino]benzoic acids **(8a-d**, **9a** / Scheme 2). The structures of the latter acyclic 1,1'-dicarboxyl-amidrazone adducts are in accordance with their elemental analyses, IR, MS and NMR spectral data that are given in the Experimental section.

Upon treatment with two equivalents of CDI, the acyclic adducts (**8a-d**, **9a**) are found to undergo two consecutive lactamization processes involving the two carboxyl groups, activated by CDI, and the appropriately located NH-moieties to deliver the respective indazolo[2,1-*c*][1,3,4]benzotriazepin-5,13-diones (**10a-d**, **11a**). The proposed structures of these novel tetracyclic end products are based on microanalytical and spectral (IR, MS and NMR) data, given in the Experimental section, and further confirmed by single crystal X-ray structure determination for **10a** (*vide infra*).

Thus, the MS spectra of compounds **8-11** display the correct molecular ions as suggested by their molecular formulas, and for which the measured high resolution data are in good agreement with the calculated values. ^{1}H- and ^{13}C- signal assignments for adducts **8a-d**, **9a** followed from DEPT and 2D (COSY, HMQC, HMBC) experiments. Of the different benzenoid *CH*-nuclei, 6-H and 6'-H protons are the most deshielded, whilst the 3'-H proton and the *C*(H)-3 carbon are the most shielded nuclei. The ^{1}H

NMR spectra of **8a-d**, **9a** display three distinct singlets at *ca*. 10-10.8, 12-12.6 and 14-14.7 ppm assigned, respectively, to the exchangeable protons of the amidrazone-C(2')-NH, the hydrazone C(2)-NH and the two CO_2H protons. These signals are lacking in the ^1H NMR spectra of products **10a-d**, **11a** thus providing strong indication for the involvement of these functional groups in the two lactamization processes. In HMBC experiments for the acyclic adducts **8a-d** and **9a**, long-range correlations are observed between H-6 and C-2, H-3 and C-1, H-6' and C-2' as well as between H-3' and C-1'. For the tetracyclic derivatives **10a-d** and **11a**, strong three-bond correlations are also observed between H-1 and C-4a, H-9 and C-12a, H-4 and each of C-5 and C-14a as well as between H-12 and each of C-13 and C-8a.

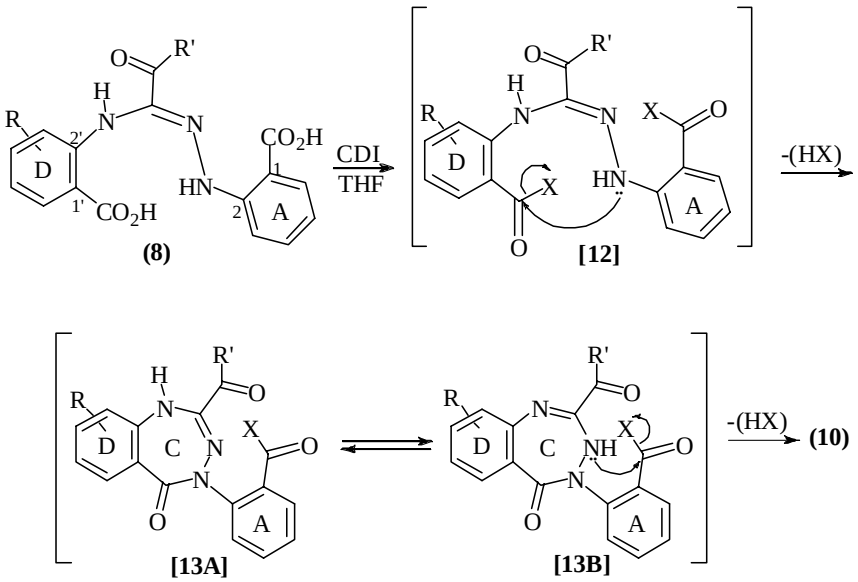


entry	compounds **8-11**			
	a	**b**	**c**	**d**
R	H	3'/ 9-Me	5'/11-Me	5'/ 11-Cl

compounds **8**, **10** (R' = Me) /
compounds **9**, **11** (R' = OMe)

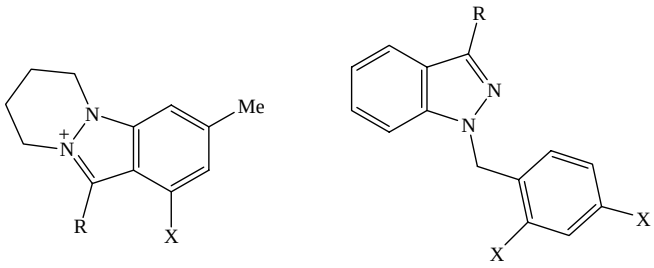
Scheme 2. (i) THF + MeOH, NEt_3 / 2 °C ⟶ rt, 6-8 h; (ii) THF + CDI / rt, 3-4 h.

The formation of the tetracyclic indazolotriazepines **10a-d**, **11a** from their precursors **8a-d**, **9a** is assumed to proceed through two consecutive cyclizations, each involving lactamization of one of the two carboxyl groups with a suitably located NH-group of the amidrazone moiety. Since the starting amidrazones exist exclusively in the tautomeric form represented by structures **8** / **9**, it follows that the sp^3-hybridized hydrazono-NH, attached to ring A, is the more nucleophilic and is expected to initiate the first lactamization process with the activated C(1')-carboxyl group (in ring D of [**12**]) to form the corresponding 1,4-dihydro-1,3,4-benzotriazepin-5-one intermediates [**13A**] as depicted in Scheme 3. The latter [**13A**] are probably in equilibrium with their 3,4-dihydro tautomers [**13B**] which eventually undergo a second cyclocondensation involving the other activated carboxyl group at C(1)-locus (ring A), and the nearby hydrazino-NH (ring C) to deliver the respective tetracyclic products (**10a-d**, **11a**).



Scheme 3. intermediates **12**, **13** (X = imidazol-1-yl)

In this context, it is worth mentioning that indazoles are of rare natural occurrence. Up to date nigellicine (**14a**),[5] nigellidine (**14b**),[6] and nigeglanine (**14c**)[7] (Chart 1) are the only known natural products having an indazole nucleus. Nonetheless, indazoles have recently received increased attention and numerous derivatives have been synthesized in pursuit of their interesting biological activities such as protein kinase inhibitors, in treatment of cancer cell proliferative disorders, Alzheimer disease, viral infections, auto-immune diseases and neuro-degenerative disorders.[8] Examples of medicinal applications include: the anticancer drugs lonidamine (**15a**),[9-11] Lonidamine (**15b**),[10] and the non-steroidal anti-inflammatory drugs Bendazac (**15c**)[12,13] and benzydamine (**15d**)[12,14] (Chart 1). Meanwhile, the chemistry of indazoles was comprehensively reviewed,[15,16] and their synthetic routes have recently been revived.[15-17]



14a (R = CO_2^- ; X = OH)
14b (R = 4-(OH)C_6H_4; X = O^-)
14c (R = H; X = O^-)

15a (X = Cl ; R = CO_2H)
15b (X = H ; R = CO_2H)
15c (X = H ; R = OCH_2CO_2H)
15d (X = H ; R = $O[CH_2]_3NMe_2$)

Chart 1

Compounds **10a-d**, **11a** are viewed as hybrids of indazole nucleus (rings A, B) condensed with 1,4-dihydro-1,3,4-benzotriazepine system (rings C, D). A number of synthetic derivatives of the former indazole nucleus are useful medicaments (*vide supra*), while the latter benzotriazepine system is

considered as an 3-aza-analog of 1,4-benzodiazepines, a unique class of central nervous system drugs that are widely used as tranquilizers[18] e.g. Valium (Librium). The newly constructed tetracyclic hybrids **10a-d**, **11a** are consequently envisaged to have promising potential biological activity.

The present study also deals with structural determination of the indazolo[2,1-*c*]benzotriazepine ring system by X-ray crystal structure measurements for **10a**. A summary of data collection and refinement parameters is given in Table 1, and selected bond lengths and angles are provided in Table 2. The molecular structure of **10a**, based on crystallographic data, is displayed in Figures 1a, 1b and 2. The chiral compound **10a** crystallizes with two molecules, having the same chirality, in the asymmetric unit of the unit cell (Figures 1a and 1b). Both molecules are not related by symmetry, but each of them is linked *via* inversion centers (Wyckoff position 1e and 1b for molecule **I** and **II**, respectively) to its racemic counterpart *via* weak hydrogen bonds [C(36)-H(36B)···O(5)=C(33), d=2.34 Å, C(16)-H(16B)··· O(2)=C(13), d=2.34 Å], thus forming pairs which have their convex sides facing each other (Fig. 2). The geometries of the two independent molecules match extremely well, so that an overlay of both has a weighted mean deviation of only 0.030 Å with a maximum of 0.080 Å. This demonstrates that molecular scaffold is so rigid such that it does not cause a marked distortion by intermolecular interactions. The conformation of both molecules is similar as indicated by the torsion angles (N8-C7-N6-N14 63.0° and N12-C27-N26-N34 61.9°). The intramolecular, non-bonded O···O distances (O1···O3 and O4···O6) are in a range (2.926 and 2.907 Å, respectively) indicating insignificant repulsion; this explains why the above mentioned torsion is caused by the specific connectivity of the respective atoms. As a result of the torsion, the phenyl groups have interplanar angles of 58.0° and 58.7° for each molecule **I** and **II**, respectively.

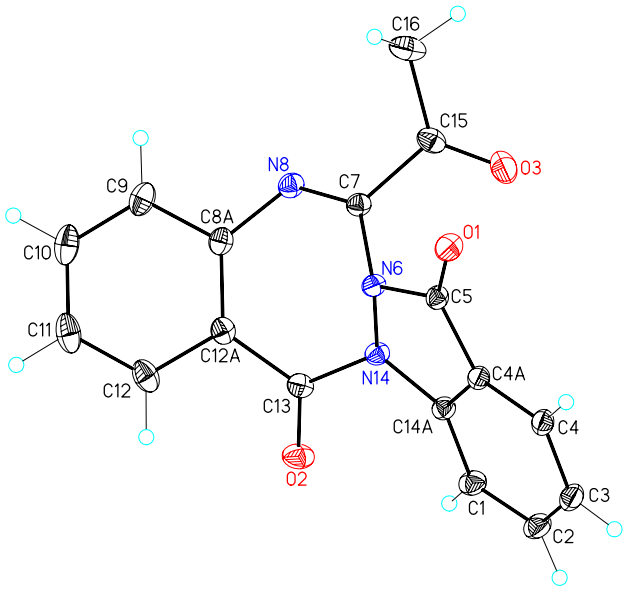


Figure 1a. Molecular structure of **10a**, molecule **I** with ADPs displayed at the 50 % level. The torsion angle N8-C7-N6-N14 is 63.0 ° and the intramolecular, non-bonding O1···O3 distance is 2.926 Å.

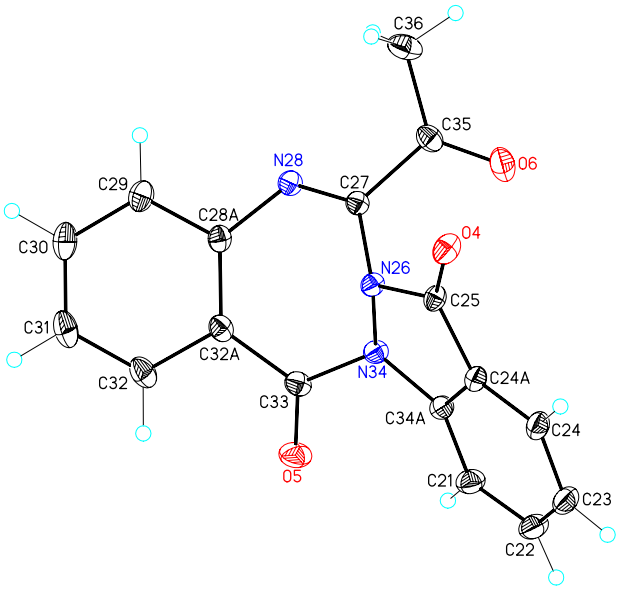


Figure 1b. Molecular structure of **10a**, molecule **II** with ADPs displayed at the 50 % level. The torsion angle N28-C27-N26-N34 is 61.9 ° and the intramolecular, non-bonding O4···O6 distance is 2.907 Å.

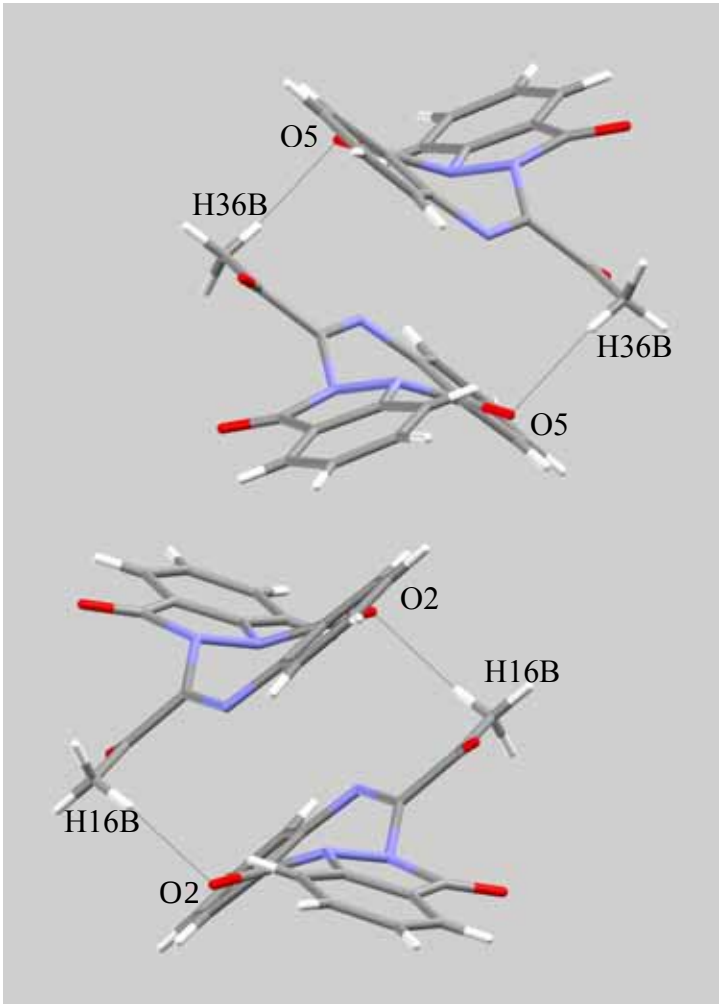


Figure 2. Crystal packing of **10a**, viewing down [011]. The racemic pairs of molecules **I** (upper pair) and of molecules **II** (bottom pair) are displayed with the intermolecular C-H···O hydrogen bonds at distances of 2.34 Å.

Table 1. Summary of the crystal data and structure refinement parameters for **10a**

Molecular formula	$C_{17}H_{11}N_3O_3$
Formula weight	305.29 Da
Temperature (K)	203(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	$P\ \bar{1}$
Unit cell dimensions	
a (Å)	10.7849(3)
b (Å)	11.5084(4)
c (Å)	11.9545(4)
α (°)	74.8367(16)
β (°)	77.7129(17)
γ (°)	76.8768(16)
Volume (Å^3)	1375.99(8)
Z	4
Calculated density (g / cm^3)	1.474
Absorption coefficient (mm^{-1})	0.104
F (000)	632
Crystal size (mm)	0.32 x 0.18 x 0.12
Theta range for data collection	1.79^o to 38.06^o
completeness to theta = 38.06^o	99.0%
Index range	$-18 \le h \le 18$; $-19 \le k \le 19$; $-20 \le I \le 20$
Reflections collected	115375
Independent reflections	14878 [R_{int} = 0.0441]
Reflections used	7392
Weight scheme	Calcd $w = 1 / [\sigma^2 (F_0)^2 + (0.0792P)^2 + 0.1127P]$ where $P = [(F_0)^2 + 2(F_c)^2] / 3$
Data / restraints / parameters	10532 / 0 / 415
Goodness-of-fit on F^2	1.036
Final *R* indices [$I < 2\sigma (I)$]	$R_1 = 0.0472$, $wR_2 = 0.1257$
R indices (all data)	$R_1 = 0.0721$, $wR_2 = 0.1442$
Largest difference peak (e. Å^{-3})	0.483
Largest difference hole (e. Å^{-3})	-0.234

Table 2. Selected bond lengths (Å) and angles (°) for **10a**

C(4A)-C(14A)	1.3898(11)	O(1)-C(5)-N(6)	122.87(7)
C(4A)-C(5)	1.4591(10)	N(6)-C(5)-C(4A)	105.38(6)
C(5)-N(6)	1.4212(9)	C(7)-N(6)-N(14)	113.96(6)
N(6)-C(7)	1.4148(10)	C(5)-N(6)-N(14)	109.65(6)
N(6)-N(14)	1.4275(9)	N(8)-C(7)-N(6)	123.83(7)
C(7)-N(8)	1.2725(10)	N(6)-C(7)-C(15)	117.55(7)
N(8)-C(8A)	1.4096(11)	C(7)-N(8)-C(8A)	122.31(7)
C(8A)-C(12A)	1.4052(12)	C(12A)-C(8A)-N(8)	27.08(7)
C(12A)-C(13)	1.4908(12)	C(8A)-C(12A)-C(13)	26.69(7)
C(13)-N(14)	1.3956(10)	O(2)-C(13)-N(14)	119.41(8)
N(14)-C(14A)	1.4131(10)	N(14)-C(13)-C(12A)	118.41(7)
O(1)-C(5)	1.2121(9)	C(13)-N(14)-N(6)	117.67(6)
O(2)-C(13)	1.2168(10)	C(14A)-N(14)-N(6)	106.77(6)
C(14A)-C(4A)-C(5)	108.55(6)	C(4A)-C(14A)-N(14)	109.53(6)
C(4)-C(4A)-C(5)	130.19(7)	C(1)-C(14A)-N(14)	128.53(8)

Antitumor Activity

Compound **10a** was tested using 10 μM concentration in aqueous DMSO against the panel of 60 human cancer cell lines used by the National Cancer Institute (NCI, USA). The most affected cell lines were NCI-H522 (from Non-Small Cell Lung Cancer), UO-31 (from Renal Cancer), SK-MEL-2 (from Melanoma), IGROV1 (from Ovarian Cancer), CCRF-CEM (from Leukemia), SNB-75 (from CNS Cancer) and Bt-549 (from Breast Cancer). The percentage growth inhibitions at 10 μM for these cell lines were 100 %, 79 %, 70 %, 66 %, 33 %, 30 % and 28 %, respectively.

p38 MAP Kinase Assay

Compounds **10a-d** and **11a** were assayed, as solution in aqueous DMSO, in concentrations ranging from 10^{-4} to 10^{-7} M according to protocols described previously.[19] However, these indazolo[2,1-*c*][1,3,4]-benzotriazepin-5,13-diones displayed insignificant inhibitory activity at concentrations of ≤ 10 μM.

In conclusion, an efficient and facile route is described for the synthesis of various substituted indazolo[2,1-*c*][1,3,4]benzotriazepin-5,13-diones (**10a-d**, **11a**) that are biologically active as antitumor agents. This versatile method utilizes readily available and inexpensive reactants, whereby the appropriate reactions are conducted at or below rt under mild conditions, and the target heterocycles are produced in fair overall yield.

EXPERIMENTAL

2-Aminobenzoic acid, 2-amino-3-methylbenzoic acid, 2-amino-5-methylbenzoic and 2-amino-5-chlorobenzoic acids were purchased from Merck, 3-chloro-2,4-pentanedione and 1,1'-carbonyl-diimidazole (CDI) from Acros. THF was dried over sodium wire for 24 h before use. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were determined, as KBr discs, on a Nicolet Impact-400 FT-IR instrument. NMR spectra were recorded on a Bruker-DPX 300 MHz-spectrometer. HRMS-ESI data for **8b-d**, **9a**, **10b-d** and **11a** were measured in positive ion mode by Electrospray (ESI) on APEX-Qe 94 instrument. The samples were dissolved in acetonitrile, diluted in spray solution (MeOH / water 1:1 v/v + 0.1 % formic acid) and infused using a syringe pump with a flow of 2 *u*L/min. External calibration was conducted using Arginine cluster in a mass range *m*/*z* 175-871. HRMS data for **8a** and **10a** were obtained with a MAT 95(S) mass spectrometer. Microanalyses were performed at the Microanalytical Laboratory-Inorganic Chemistry Department, Tübingen University, Germany.

2-[*N'*-(1-Chloro-2-oxopropylidene)hydrazino]benzoic acid (6)

This compound was prepared *via* the Japp-Klingemann reaction[20] that involves coupling of diazotized 2-aminobenzoic acid with 3-chloro-2,4-pentanedione according to a reported procedure.[4]

2-[*N'*-(1-Chloro-2-methoxy-2-oxoethylidene)hydrazino]benzoic acid (7)

This compound was prepared *via* the Japp-Klingemann reaction[20] that involves coupling of diazotized 2-aminobenzoic acid with methyl 2-chloro-3-oxobutanoate according to a standard procedure as reported for the homologous 2-[*N'*-(1-chloro-2-ethoxy-2-oxoethylidene)hydrazino]benzoic acid,[21] and for related *N*-arylhydrazonoyl chlorides.[22] Yield = 86 %, mp 215-216 °C. *Anal*. Calcd for $C_{10}H_9ClN_2O_4$: C, 46.80; H, 3.53; Cl, 13.81; N, 10.92. Found: C, 46.58; H, 3.42; Cl, 13.72; N, 10.76. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, CO_2Me), 7.05 (ddd, J = 7.6, 7.2, 0.8 Hz, 1H, H-5), 7.60 (m, 2H, H-3 + H-4), 7.92 (ddd, J = 7.6, 1.5, 0.7 Hz, 1H, H-6), 11.93 [s, 1H, N-*H*], 13.71 [br s, 1H, CO_2H]; ^{13}C NMR(75 MHz, DMSO-d_6): δ 54.0 (CO_2Me), 113.6 (C-1), 114.7 (C-3), 122.1 (C-5), 131.9 (C-6), 135.4 (C-4), 144.5 (C-2), 158.4 (Cl-*C*=N-), 159.8 (CO_2Me), 170.0 (CO_2H).

2-{*N'*-[1-(Carboxyphenyl-2-amino)-2-oxopropylidene]hydrazino}benzoic acid (8a)

Method (i) A homogeneous solution of 2-aminobenzoic acid (**5**: R=H)(1.65 g, 12 mmol) in aqueous MeOH and triethylamine (6 mL) was added dropwise to a stirred and cooled (0 ^{o}C) solution of **6** (2.41 g, 10 mmol) in THF (40 mL). Additional triethylamine (4 mL) was then introduced dropwise into the reaction mixture which was stirred at 0 ^{o}C for 2 h, then at rt for 4-5 days. The organic solvents were removed *in vacuo* from the reaction mixture, and then the aqueous solution was acidified with glacial

acetic acid. The resulting yellow precipitate was collected, washed with water, dried and recrystallized from MeOH. Yield = 1.57 g (46%), mp 212-214 °C. *Anal*. Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.71; H, 4.35; N, 12.18. IR (KBr): ν 3423, 3319, 3210, 2523, 1685, 1657, 1580, 1491, 1387, 1215 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.51 (s, 3H, COMe), 6.10 (dd, J = 8.0, 1.0 Hz, 1H, H-3'), 6.81 (dd, J = 7.9, 7.7 Hz, 1H, H-5'), 6.93 (dd, J = 7.4, 7.7 Hz, 1H, H-5), 7.32 (ddd, J = 8.0, 7.7, 1.5 Hz, 1H, H-4'), 7.57 (dd, J = 8.0, 7.6 Hz, 1H, H-4), 7.78 -7.84 (two suprerimposable sets, dd each, 2H, H-3 + H-6), 7.89 (dd, J = 7.9, 1.5 Hz, 1H, H-6'), 10.03 [s, 1H, C(2')-N*H*], 12.26 [s, 1H, C(2)-N*H*], 14.05 [br, 2H, 2CO_2H]; ^{13}C NMR(75 MHz, DMSO-d_6): δ 25.0 (CO*Me*), 112.9 (C-1), 114.2 (C-3), 114.8 (C-1'), 116.0 (C-3'), 119.4 (C-5'), 120.7 (C-5), 131.7 (C-6), 132.1 (C-6'), 134.3 (C-4'), 135.1 (C-4), 136.6 (NH-*C*=N-), 143.2 (C-2'), 145.6 (C-2), 169.9 [C(1) -*C*O_2H], 170.1 [C(1') -*C*O_2H], 193.8 (Me-*C*=O); EIMS *m/z* (%): 341 ($M^{+\cdot}$, 89), 323 (15), 264 (22), 190 (18), 146 (48), 134 (100), 119 (31), 105 (19), 91 (38), 65 (23); HRMS (EI): *m/z* calcd for $C_{17}H_{15}N_3O_5$ ($[M]^+$: 341.10114, found: 341.10255.

Method (ii) A solution of **5a** (1.65 g, 12 mmol) in MeOH (8 mL) was admixed with an 8 % aqueous $NaHCO_3$ solution (50 mL). The whole mixture was portionwise added to a cooled (~0 °C) and stirred solution of 6 (2.41 g, 10 mmol) in THF (40 mL). The reaction mixture was further stirred at ~0 °C for 1 h, then at rt for 5-6 h, and finally worked up as described in method (i) above. Yield of **8a** = 2.11 g (62 %); mp 201-202 °C (MeOH).

2-{*N'*-[1-(Carboxyphenyl-2-amino-3-methyl)-2-oxopropylidene]hydrazino}benzoic acid (8b)

This compound was prepared from 2-amino-3-methylbenzoic acid (**5**: R = 3-Me)(2.06 g , 12 mmol) and **6** (2.41 g, 10 mmol) by following the same procedure and experimental conditions described in method (ii) above for obtaining **8a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 1.95 g (55 %), mp 210-211 °C. *Anal*. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.57; H, 4.68; N, 11.72. ^1H NMR (300 MHz, DMSO-d_6): δ 2.33 [br s, 3H, C(3')-Me], 2.47 (s, 3H, COMe), 6.74 (dd, J = 7.6, 7.8 Hz, 1H, H-5'), 6.81 (dd, J = 7.6, 7.5 Hz, 1H, H-5), 6.95 (d, J = 7.8 Hz, 1H, H-4'), 7.33 (dd, J = 7.7, 7.5 Hz, 1H, H-4), 7.60 (d, J = 7.7 Hz, 1H, H-3), 7.71 (d, J = 7.6 Hz, 1H, H-6'), 7.85 (d, J = 7.6 Hz, 1H, H-6), 10.50 [br s, 1H, C(2')-N*H*], 12.44 [s, 1H, C(2)-N*H*], 14.24 [br, 2H, 2CO_2H]; ^{13}C NMR(75 MHz, DMSO-d_6): δ 18.6 [C(3')-*Me*], 24.7 (CO*Me*), 112.0 (C-1), 113.1 (C-3), 118.8 (C-1'), 119.1 (C-5), 119.9 (C-5'), 127.4 (C-3'), 132.0 (C-4'), 132.3 (C-4), 133.4 (C-6'), 133.8 (C-6), 138.2 (NH-*C*=N-), 145.3 (C-2'), 145.8 (C-2), 172.5 [C(1) -*C*O_2H], 173.2 [C(1') -*C*O_2H], 192.3 (Me-*C*=O); HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N_3O_5$[M + H^+]: 356.12465, found: 356.1241; *m/z* calcd for $C_{18}H_{17}N_3O_5Na$ [M + Na^+]: 378.10659, found: 378.10606.

2-{*N'*-[1-(Carboxyphenyl-2-amino-5-methyl)-2-oxopropylidene]hydrazino}benzoic acid (8c)

This compound was prepared from 2-amino-5-methylbenzoic acid (**5**: R = 5-Me)(1.81 g, 12 mmol) and **6** (2.41 g, 10 mmol) by following the same procedure and experimental conditions described in method (ii) above for obtaining **8a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 2.06 g (58 %), mp > 300 (darkens at 220 °C). *Anal*. Calcd for C_{18} $H_{17}N_3$ O_5: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.62; H, 4.71; N, 11.75. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.09 [br s, 3H, C(5')-Me], 2.46 (s, 3H, COMe), 6.09 (d, J = 7.8 Hz, 1H, H-3'), 6.79 (dd, J = 7.5, 7.7 Hz, 1H, H-5), 6.86 (d, J = 7.8 Hz, 1H, H-4'), 7.35 (dd, J = 7.8, 7.5 Hz, 1H, H-4), 7.58 (d, J = 7.8 Hz, 1H, H-3), 7.64 (d, J = 1.0 Hz, 1H, H-6'), 7.91 (d, J = 7.7 Hz, 1H, H-6), 10.54 [br s, 1H, C(2')-N*H*], 12.56 [s, 1H, C(2)-N*H*], 14.38 [br, 2H, 2CO_2H]; ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6 [C(5')-*Me*], 25.9 (CO*Me*), 113.3 (C-3), 116.1 (C-3'), 118.8 (C-1), 119.6 (C-5), 126.8 (C-1'), 118.4 (C-5'), 131.7 (C-4'), 132.1 (C-4), 132.2 (C-6'), 132.5 (C-6), 137.4 (NH-*C*=N-), 141.4 (C-2'), 145.2 (C-2), 172.0 [C(1) -*C*O_2H], 173.5 [C(1') -*C*O_2H], 192.9 (Me-*C*=O); EIMS *m / z* (%): 341 ($M^{+\cdot}$, 89), 323 (15), 264 (22), 190 (18), 146 (48), 134 (100), 119 (31), 105 (19), 91 (38), 65 (23). HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N_3O_5$ [M+H^+]: 356.12465, found 356.12414; *m/z* calcd for $C_{18}H_{17}N_3O_5Na$ [M+Na^+]: 378.10659, found: 378.10607.

2-{*N'*-[1-(Carboxyphenyl-2-amino-5-chloro)-2-oxopropylidene]hydrazino}benzoic acid (8d)

This compound was prepared from 2-amino-5-chlorobenzoic acid (**5**: R = 5-Cl)(1.81 g, 12 mmol) and **6** (2.41 g, 10 mmol) by following the same procedure and experimental conditions described in method (ii) above for obtaining **8a**. The pale-green product was recrystallized from $CHCl_3$/pet. ether. Yield = 2.37 g (63 %), mp > 300 °C. *Anal*. Calcd for C_{17} H_{14} Cl N_3 O_5: C, 54.34; H, 3.76; Cl, 9.43; N, 11.18. Found: C, 54.08; H, 3.72; Cl, 9.18; N, 11.20. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.56 (s, 3H, COMe), 6.14 (d, J = 7.9 Hz, 1H, H-3'), 6.83 (dd, J = 7.2, 7.4 Hz, 1H, H-5), 7.08 (dd, J = 7.9, 1.0 Hz, 1H, H-4'), 7.36 (dd, J = 8.0, 7.2 Hz, 1H, H-4), 7.62 (dd, J = 8.0, 1.1Hz, 1H, H-3), 7.84 (d, J = 1.0 Hz, 1H, H-6'), 7.88 (dd, J = 7.7, 1.4 Hz, 1H, H-6), 10.75 [s, 1H, C(2')-N*H*], 12.59 [s, 1H, C(2)-N*H*], 14.65 [br, 2H, 2CO_2H]; ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.7 (CO*Me*), 113.4 (C-3), 117.4 (C-3'), 119.9 (C-5), 121.5 (C-1), 123.2 (C-1'), 130.4 (C-6'), 130.5 (C-4'), 131.2 (C-5'), 132.0 (C-4), 132.3 (C-6), 136.7 (NH-*C*=N-), 142.9 (C-2'), 145.0 (C-2), 170.9 [C(1)-*C*O_2H], 171.2 [C(1')-*C*O_2H], 192.8 (Me-*C*=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_5$ [M + H^+]: 376.07002, found: 376.06946; *m/z* calcd for $C_{17}H_{14}ClN_3O_5Na$ [M + Na^+]: 398.05197, found: 398.05143.

2-{*N'*-(1-[Carboxyphenyl-2-amino)-2-methoxy-2-oxoethylidene]hydrazino}benzoic acid (9a)

This compound was prepared from 2-aminobenzoic acid (**5a**) (1.65 g, 12 mmol) and **7** (2.57 g, 10 mmol) by following the same procedure and experimental conditions described above in method (ii) for obtaining **8a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 2.14 g (60 %), mp 211-212 °C. *Anal*. Calcd for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76.Found: C, 57.21; H, 4.18; N, 11.64.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H, CO_2Me), 6.15 (dd, J = 8.0, 1.1 Hz, 1H, H-3'), 6.82 (ddd, J = 8.1, 7.9, 1.1 Hz, 1H, H-5'), 6.91 (ddd, J = 8.0, 7.8, 1.1 Hz, 1H, H-5), 7.34 (ddd, J = 8.1, 8.0, 1.4 Hz, 1H, H-4'), 7.55 (ddd, J = 7.8, 7.7, 1.4 Hz, 1H, H-4), 7.68 (dd, J = 7.7, 1.1 Hz, 1H, H-3), 7.79 (dd, J = 8.0, 1.4 Hz, 1H, H-6), 7.89 (dd, J = 7.9, 1.4 Hz, 1H, H-6'), 9.54 [s, 1H, C(2')-N*H*], 11.32 [s, 1H, C(2)-N*H*], 12.91 [br s, 2H, CO_2H]; ^{13}C NMR(75 MHz, DMSO-d_6): δ 53.0 (CO_2Me), 112.7 (C-1), 114.1 (C-3), 114.4 (C-1'), 115.3 (C-3'), 119.4 (C-5'), 120.4 (C-5), 129.1 (NH-*C*=N-), 131.6 (C-4'), 132.1 (C-4), 134.6 (C-6), 135.1 (C-6'), 143.9 (C-2'), 145.8 (C-2), 163.2 (CO_2Me), 169.9 [C(1) -CO_2H], 170.2 [C(1') -CO_2H]; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N_3O_6$ [M+H$^+$]: 358.10391, found 358.10342; *m/z* calcd for $C_{17}H_{15}N_3O_6Na$ [M+Na$^+$]: 380.08585, found 380.08534.

7-Acetyl-5*H*,13*H*-indazolo[2,1-*c*][1,3,4]benzotriazepine-5,13-dione (10a)

1,1'-Carbonyldiimidazole (CDI) (0.82 g, 5 mmol) was added to a cooled (0 °C) and stirred solution of **8a** (0.68 g, 2 mmol) in dry THF (40 mL), and the resulting mixture was further stirred at rt for 2-3 h. The reaction mixture was then immediately treated with cold water (40 mL), most of the solvent THF was allowed to evaporate in the fume hood, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residual off –white product was recrystallized from $CHCl_3$/pet. ether. Yield = 0.34 g (56 %), mp 173-174 ^{o}C. *Anal*. Calcd for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.76. Found: C, 67.02; H, 3.55; N, 13.72. ν_{max} (KBr)/cm^{-1} 1737; 1710; 1682; 1587; 1462; 1370; 1300; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 3H, COMe), 7.46 (ddd, J = 7.8, 7.4, 1.4 Hz, 1H, H-3), 7.49 (ddd, J = 7.9, 7.3, 1.3 Hz, 1H, H-11), 7.54 (dd, J = 8.0, 1.3 Hz, 1H, H-9), 7.70 (ddd, J = 8.0, 7.3, 1.4 Hz, 1H, H-10), 7.80 (ddd, J = 8.2, 7.4, 1.3 Hz, 1H, H-2), 7.94 (ddd, J = 7.8, 1.3, 0.7 Hz, 1H, H-4), 8.10 (ddd, J = 7.9, 1.4, 0.4 Hz, 1H, H-12), 8.28 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H, H-1); ^{13}C NMR(75 MHz, $CDCl_3$): δ 26.6 (CO*Me*), 116.8 (C-1), 118.2 (C-4a), 124.8 (C-4), 125.9 (C-12a), 126.5 (C-3), 129.1 (C-11), 129.5 (C-9), 132.0 (C-12), 134.1 (C-10), 135.8 (C-2), 142.7 (C-8a), 144.9 (C-14a), 150.2 (C-7), 164.6 (C-13), 166.1 (C-5), 191.9 (Me*C*=O); EIMS *m/z* (%): 305 (M$^{+\cdot}$, 45), 263 (35), 235 (15), 130 (100), 102 (24), 89 (16).HRMS (EI): *m/z* calcd for $C_{17}H_{11}N_3O_3$ [M$^+$]: 305.08270, found: 305.08206.

7-Acetyl-9-methyl-5*H*,13*H*-indazolo[2,1-*c*][1,3,4]benzotriazepine-5,13-dione (10b)

This compound was prepared from **8b** (0.71 g, 2 mmol) and CDI (0.82 g, 5 mmol) by following the same procedure and experimental conditions described above for obtaining **10a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 0.33 g (52 %), mp 161-162 °C. *Anal*. Calcd for $C_{18}H_{11}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.55; H, 4.13; N, 13.02. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H, COMe), 2.56 [br s, 3H, C(9)-Me], 7.37 (dd, J = 7.6, 7.8 Hz, 1H, H-11), 7.46 (dd, J = 7.6, 7.3 Hz, 1H, H-3), 7.56 (dq, J = 7.7, 0.8 Hz, 1H, H-10), 7.80 (ddd, J = 8.4, 7.3, 1.2 Hz, 1H, H-2), 7.93 (dd, J = 7.6, 1.0

Hz, 1H, H-12), 7.96 (ddd, *J* = 7.6 Hz, 1.2, 0.8 Hz, 1H, H-4), 8.29 (ddd, *J* = 8.4, 1.2, 0.8 Hz, 1H, H-1); ^{13}C NMR(75 MHz, $CDCl_3$): δ 18.6 [C(9)-Me], 26.5 (CO*Me*), 116.5 (C-1), 118.2 (C-4a), 124.8 (C-4), 126.1 (C-12a), 126.3 (C-3), 128.9 (C-11), 129.9 (C-12), 135.6 (C-10), 135.8 (C-2), 137.4 (C-9), 140.9 (C-8a), 144.8 (C-14a), 149.0 (C-7), 164.6 (C-13), 166.3 (C-5), 191.5 (Me-*C*=O); HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3O_3$ [M + H^+]: 320.10352, found: 320.10293; *m/z* calcd for $C_{18}H_{13}N_3O_3Na$ [M + Na^+]: 342.08546, found: 342.08488.

7-Acetyl-11-methyl-5*H*,13*H*-indazolo[2,1-*c*][1,3,4]benzotriazepine-5,13-dione (10c)

This compound was prepared from **8c** (0.71 g, 2 mmol) and CDI (0.82 g, 5 mmol) by following the same procedure and experimental conditions described above for obtaining **10a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 0.39 g (61 %), mp 151-152 °C (softens at 138 °C). *Anal*. Calcd for $C_{18}H_{11}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.46; H, 4.08; N, 13.10. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 [br s, 3H, C(11)-Me], 2.69 (s, 3H, COMe), 7.45 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H, H-3), 7.46 (dd, *J* = 8.0, 0.5 Hz, 1H, H-9), 7.50 (ddq, *J* = 8.0, 1.3, 0.6 Hz, 1H, H-10), 7.79 (ddd, *J* = 8.5, 7.4, 1.3 Hz, 1H, H-2), 7.91 (dq, *J* = 1.3, 0.6 Hz, 1H, H-12), 7.95 (ddd, *J* = 7.9 Hz, 1.3, 0.7 Hz, 1H, H-4), 8.28 (ddd, *J* = 8.5, 1.4, 0.7 Hz, 1H, H-1); ^{13}C NMR(75 MHz, $CDCl_3$): δ 21.2 [C(11)-Me], 26.5 (CO*Me*), 116.7 (C-1), 118.3 (C-4a), 124.7 (C-4), 125.6 (C-12a), 126.4 (C-3), 129.6 (C-9), 132.3 (C-12), 134.9 (C-10), 135.7 (C-2), 139.8 (C-11), 140.4 (C-8a), 144.8 (C-14a), 149.5 (C-7), 164.8 (C-13), 166.1 (C-5), 191.8 (Me-*C*=O); HRMS (ESI): *m / z* calcd for $C_{18}H_{14}N_3O_3$ [M + H^+]: 320.10352, found: 320.10293; *m/z* calcd for $C_{18}H_{13}N_3O_3Na$ [M + Na^+]: 342.08546, found: 342.08490.

7-Acetyl-11-chloro-5*H*,13*H*-indazolo[2,1-*c*][1,3,4]benzotriazepine-5,13-dione (10d)

This compound was prepared from **8d** (0.75 g, 2 mmol) and CDI (0.82 g, 5 mmol) by following the same procedure and experimental conditions described above for obtaining **10a**. The solid product was recrystallized from $CHCl_3$/pet. ether. Yield = 0.39 g (58 %), mp 141-142 °C. *Anal*. Calcd for $C_{17}H_{10}ClN_3O_3$: C, 60.10; H, 2.97; Cl, 10.44; N, 12.37. Found C, 59.86; H, 3.02; Cl, 10.36; N, 12.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, COMe), 7.48 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H, H-3), 7.49 (dd, *J* = 8.0, 7.6, 0.4 Hz, 1H, H-9), 7.64 (dd, *J* = 8.0, 2.4 Hz, 1H, H-10), 7.80 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H, H-2), 7.95 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1H, H-4), 8.07 (dd, *J* = 2.4, 0.4 Hz, 1H, H-12), 8.25 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H, H-1); ^{13}C NMR(75 MHz, $CDCl_3$): δ 26.6 (CO*Me*), 116.8 (C-1), 118.2 (C-4a), 124.9 (C-4), 126.7 (C-3), 127.2 (C-12a), 131.0 (C-9), 131.8 (C-12), 134.1 (C-10), 135.3 (C-11), 136.0 (C-2), 141.1 (C-8a), 144.8 (C-14a), 150.4 (C-7), 163.3 (C-13), 166.0 (C-5), 191.7 (Me-*C*=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{11}ClN_3O_3$ [M+H^+]: 340.04889, found: 340.04838; *m/z* calcd for $C_{17}H_{10}ClN_3O_3Na$ [M + Na^+]: 362.03084, found: 362.03039.

Methyl 5,13-dioxo-5*H*,13*H*-indazolo[2,1-*c*][1,3,4]benzotriazepine-7-carboxylate (11a)

This compound was prepared from **9a** (0.72 g, 2 mmol) and CDI (0.82 g, 5 mmol) by following the same procedure and experimental conditions described above for obtaining **10a**. Yield = 0.37 g (58 %), mp 221-223 °C. *Anal*. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.42; H, 3.44; N, 12.96. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, CO_2Me), 7.45 (ddd, J = 7.8, 7.5, 1.4 Hz, 1H, H-3), 7.50 (ddd, J = 8.0, 7.3, 1.3 Hz, 1H, H-11), 7.58 (ddd, J = 8.0, 1.3, 0.5 Hz, 1H, H-9), 7.70 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H, H-10), 7.82 (ddd, J = 8.3, 7.5, 1.3 Hz, 1H, H-2), 7.96 (ddd, J = 7.8, 1.3, 0.7 Hz, 1H, H-4), 8.11 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H, H-12), 8.33 (ddd, J = 8.3, 1.4, 0.7 Hz, 1H, H-1); ^{13}C NMR(75 MHz, $CDCl_3$): δ 54.1 (CO_2*Me*), 116.9 (C-1), 117.6 (C-4a), 124.8 (C-4), 125.4 (C-12a), 126.5 (C-3), 129.1 (C-11), 129.6 (C-9), 132.0 (C-12), 134.3 (C-10), 136.1 (C-2), 142.5 (C-8a), 145.3 (C-14a), 149.3 (C-7), 160.2 (*C*O_2Me), 164.6 (C-13), 165.6 (C-5); HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_3O_4$ [M+H$^+$]: 322.08278, found: 322.08223; *m/z* calcd for $C_{17}H_{11}N_3O_4Na$ [M+Na$^+$]: 344.06472, found: 344.06418.

COLLECTION OF X-RAY DIFFRACTION DATA AND STRUCTURE ANALYSIS OF 10a

Pale yellow block crystals were grown by allowing a clear solution of **10a** in hot MeOH to evaporate slowly at rt such that its volume was reduced by about 40 % over 4-5 days. The crystal data collection was made with a Siemens SMART CCD diffractometer [Mo-Kα-radiation, graphite monochromator] operating in the omega scan mode (0.3 °). The data were reduced with the Siemens-Bruker program suite XSCANS,[23] and the structure was solved by the direct method using SHELXTL PLUS programs.[24] All non-hydrogen atoms were refined anisotropically by full-matrix, least-squares procedure based on F^2 using all unique data. The hydrogen atoms were placed in calculated positions and treated as riding groups, with the 1.2 fold (1.5 fold for methyl groups) isotropic displacement parameters of the equivalent Uij of the corresponding carbon atom.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis of **10a** have been deposited with the Cambridge Crystallographic Data Center under the depository No. CCDC-677254. Copies of information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: (deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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