JJC

Jordan Journal of Chemistry

Volume 14, Number 3, September 2019
Pages 121-130

ARTICLE

Synthesis and Properties of *N*1-(indan-4-yl)amidrazones Incorporating Piperazines and Related Congeners

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Received on: 24th Feb.2020; *Accepted on: 31th Mar. 2020*

Abstract: A selected set of new *N*1-(indan-4-yl)amidrazones **10a-p**, incorporating piperazines or related congeners, has been synthesized by reacting the hydrazonoyl chloride **9** (derived from 4-aminoindane) with the appropriate *sec*-cyclic amine in the presence of triethyl amine. Suggested chemical structures are supported by IR, ^{1}H-NMR, ^{13}C-NMR and high-resolution MS (ESI) spectral data, and further confirmed by single-crystal X-ray crystallography for 10n. The novel compounds were screened for their antitumor activity against human colon cancer cell lines. Amongst, amidrazones **10d** and **10f** were fairly active with LD_{50} values (μM) of 22.9 (HCT-116) and 55.8 (Caco) for **10d**, and 36.8 (HCT-116) and 67.2 (Caco) for **10f**.

Keywords: 4-aminoindane, hydrazonoyl chlorides, Japp-Klingemann reaction, amidrazones, antitumor activity.

Introduction

The indane ring system is an attractive scaffold for biologically active compounds. This motif is present in several marketed drugs exemplified by the antiinflammatory clidanac[1] and the diuretic indacrinone[2] (Figure. 1). Noteworthy is that the indane nucleus occurs in many natural products, found across a wide range of species, such as pterosin[3] and tripartin[4] (Figure. 1). The natural occurrence, synthesis, medicinal chemistry, and biological activities of various indanes have recently been reviewed[5].

On the other hand, we have recently reported on a variety of synthetic amidrazones, incorporating (substituted)piperazines and related congeners, some of which displayed high antitumor activity[6-10]. These compounds, represented by the general structures **1**[6], **2**[7], **3**[8], **4**[9] and **5**[10], were decorated with heteroaryl entities appended at the *N*1-position (Figure 2). The related *N*1-(aryl)amidrazones **6**[11] were previously reported to exhibit antitumor activity against a panel of cell lines, especially breast cancer, non-small-cell lung and CNS cancer ($IC_{50} \approx 4\ \mu M$)[11].

Quite recently, we have synthesized a new set of amidrazones **7**[12] incorporating an indan-5-yl entity at the *N*1-position (Figure 2). Amongst, the amidrozone with *N*4-(pyrimidin-2-yl)piperazine showed fair activity against breast cancer cells[12]. *In extensio* and for comparative study, we envisioned to follow-up further work in relation to the respective amidrazones bearing the isomeric *N*1-(indan-4-yl) motif. Accordingly, we report herein on the synthesis and antitumor activity of a selected set of the new *N*1-(indan-4-yl)amidrazones (**10 a-p**) shown in Scheme 1.

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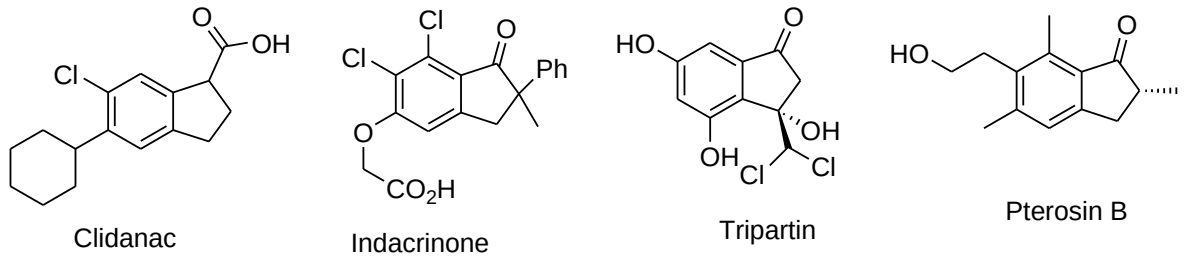
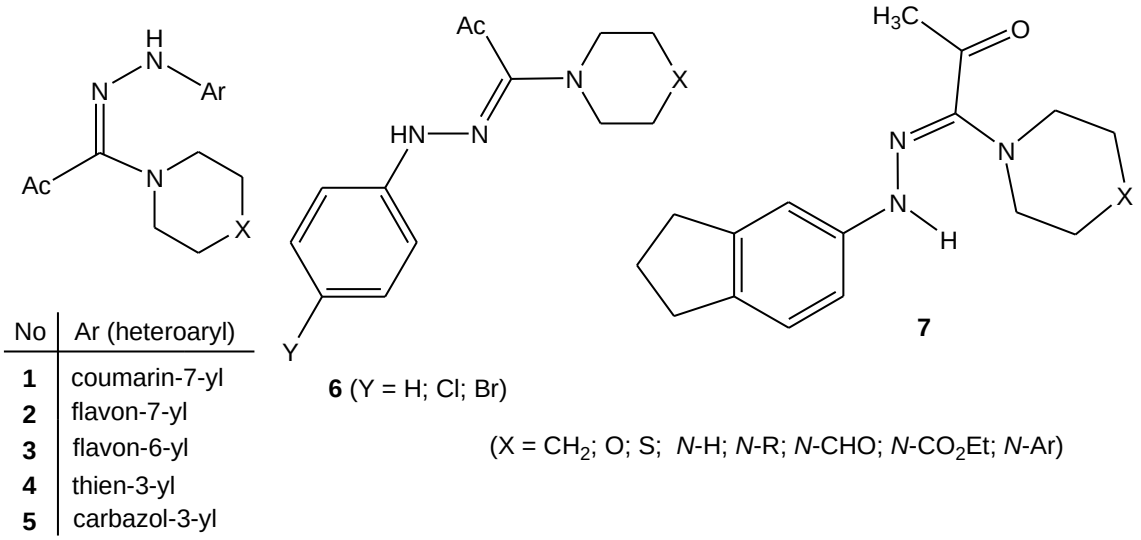


Figure 1: Examples of two indane-containing drugs (left), and of two naturally occurring indanes (right).



No	Ar (heteroaryl)
1	coumarin-7-yl
2	flavon-7-yl
3	flavon-6-yl
4	thien-3-yl
5	carbazol-3-yl

Figure 2: General chemical structures of the reported amidrazones.

Materials and Methods

4-Aminoindane, 3-chloropentane-2,4-dione, 4-(phenyl)peperidine, morpholine, thiomorpholine, piperazine and various *N*-substituted piperazine derivatives were purchased from Acros. Melting points (uncorrected) were measured by Fisher-Johns Melting Temperature Apparatus. IR spectra were measured as neat films on a Thermo Nicolet Nexus 670 ATR FT-IR instrument. ^{1}H, ^{13}C, DEPT 135, and 2D (COSY, HMQC, HMBC) NMR spectra were measured on a Bruker DPX-500 instrument (Bruker Avance-III) with TMS as internal standard. Chemical shifts are expressed in δ units; *J* values for ^{1}H-^{1}H, ^{1}H-F, and ^{13}C-F are given in Hertz. High-resolution mass spectra (HRMS) were measured by electrospray ionization (ESI) technique on a Brucker APEX-IV (7 Tesla) instrument.

Preparation of *N*-(2,3-dihydro-1*H*-inden-4-yl)-2-oxopropanehydrazonoyl chloride (9)

A solution of sodium nitrite (1.2 g, 0.17 mol) in water (2 mL) was added dropwise with efficient stirring at -5 to 0°C to a solution of (1.31 g, 0.01 mol) 4-aminoindane in 17% aqueous hydrochloric acid (27 mL); the solution was stirred for 30 min. This solution was then poured onto a cold (0 to -10 °C, ice-salt bath) solution of (13.5 g, 0.1 mol) 3-chloropentan-2,4-dione in 30 ml water containing 25 g sodium acetate trihydrate with vigorous stirring for 30 min. The reaction mixture was then diluted with 50 mL of cold water; the yellow precipitate was collected by suction filtration and purified on column chromatography (eluent: $CHCl_3$ /n-hexane – 4 : 1, v/v).

Light yellow solid; (yield 21%); M.p.: 62-66 °C. IR (ν_{max}, cm^{-1}): 3431, 3314, 3255, 2923, 2850, 1687, 1614, 1591, 1542, 1471, 1358, 1304, 1224, 1195, 1027. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.98 (m, 2H, H-2), 2.41 (s, 3H, $COCH_3$), 2.82 (t, J =7.3 Hz, 2H, H-1), 3.04 (t, J = 7.5 Hz, 2H, H-3), 6.92 (d, J = 7.3 Hz, 1H, H-7), 7.09 (pseudo t, 1H, H-6), 7.19 (d, J=8.0 Hz, 1H, H-5), 10.0 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.3 (C-2), 26.0 ($COCH_3$), 32.0 (C-3), 32.9 (C-1), 114.8 (C-5), 119.8 (C-7),

123.0 (-C=N), 127.6 (C-6), 131.0 (C-3a), 138.9 (C-4), 146.7 (C-7a), 188.2 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{12}H_{12}ClN_2O$ $[M+H]^+$ 235.06436, found 235.06562.

General Procedure for the Preparation of Compounds (10a-p)

All piperazine derivatives have been synthesized by adding triethylamine (2 mL) to a cold solution (0 to -10 °C) of compound (**9**) (0.25g, 1 mmol) and absolute ethanol (20 mL), stirring for 3 min, and then 2.11 mmol of the particular secondary amine was added. Stirring was continued at -5 to 0 °C for 2-4 h, and then at room temperature for 10-12 h. The reaction mixture was diluted with 200 ml cold water and stirred for 10 minutes. The resulting precipitate was collected by suction filtration, washed with ice-water, dried and purified on preparative silica gel TLC plates (eluent: $CHCl_3$/*n*-hexane - 8:2, v/v).

1-(Indan-4-yl-hydrazono)-1-morpholin-4-yl-propan-2-one (10a)

Orang solid; (yield 54%); M.p.: 116-118 °C. IR (ν_{max}, cm^{-1}): 3416, 3247, 2954, 2920, 2851, 1658, 1594, 1530, 1491, 1367, 1245, 1183, 1133, 1109, 1036. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.03 (m, 2H, H-2), 2.29 (s, 3H, $COCH_3$), 2.84 (t, J = 7.2 Hz, 2H, H-1), 2.89 (t, J = 7.2 Hz, 2H, H-3), 2.92 (br s, 4H, H-2', H-6'), 3.67 (br s, 4H, H-3', H-5'), 6.83 (d, J = 7.1 Hz, 1H, H-7), 7.10 (pseudo t, 1H, H-6), 7.18 (d, J = 7.9 Hz, 1H, H-5), 9.27 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 26.0 (CO*C*H$_3$), 29.8 (C-3), 33.0 (C-1), 48.1 (C-2', C-6'), 67.2 (C-3', C-5'), 111.9 (C-5), 118.2 (C-7), 127.9 (C-6), 129.2 (C-3a), 139.0 (C-4), 143.2 (-C=N), 145.9 (C-7a), 194.4 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{16}H_{22}N_3O_2$ $[M+H]^+$ 288.17065, found 288.17075.

1-(Indan-4-yl-hydrazono)-1-thiomorpholin-1-yl-propan-2-one (10b)

Yellow solid; (yield 72%); M.p.: 98-100 °C. IR (ν_{max}, cm^{-1}): 3415, 3259, 2907, 2850, 1662, 1594, 1526, 1492, 1367, 1248, 1181, 1124. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.03 (m, 2H, H-2), 2.28 (s, 3H, $COCH_3$), 2.70 (t, J = 4.5 Hz, 4H, H-2', H-6'), 2.84 (t, J = 7.5 Hz, 2H, H-1), 2.90 (t, J = 7.5 Hz, 2H, H-3), 3.10 (t, J = 4.5 Hz, 4H, H-3', H-5'), 6.83 (d, J = 7.3 Hz, 1H, H-7), 7.10 (pseudo t, 1H, H-6), 7.18 (d, J = 8.0 Hz, 1H, H-5), 9.13 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 25.9 (CO*C*H$_3$), 28.1 (C-2', C-6'), 30.0 (C-3), 33.0 (C-1), 50.4 (C-3', C-5'), 112.0 (C-5), 118.3 (C-7), 127.9 (C-6), 129.4 (C-3a), 139.0 (C-4), 144.3 (-C=N), 145.9 (C-7a), 194.4 (*C*OMe) ppm. HRMS (ESI) m/z: calcd for $C_{16}H_{22}N_3OS$ $[M+H]^+$ 304.14781, found 304.14770.

1-(Indan-4-yl-hydrazono)-1-piperazin-1-yl-propan-2-one (10c)

Light yellow solid; (yield 43%); M.p.: 186-190 °C. IR (ν_{max}, cm^{-1}): 3448, 3422, 3239, 2957, 2923, 2851, 1660, 1595, 1526, 1492, 1460, 1368, 1341, 1253, 1197, 1137, 1034. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (br s, 4H, H-2', H-6'), 2.23 (m, 2H, H-2), 2.48 (s, 3H, $COCH_3$), 2.98 (t, J = 7.4 Hz, 2H, H-3), 3.00 (t, J = 7.4 Hz, 2H, H-1), 3.20 (br s, 4H, H-3', H-5'), 5.32 (s, 1H, NH-piperazine), 6.94 (d, J = 7.3 Hz, 1H, H-7), 7.21 (pseudo t, 1H, H-6), 7.32 (d, J = 7.9 Hz, 1H, H-5), 9.27 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.1 (C-2), 25.7 (CO*C*H3), 29.5 (C-3), 29.7 (C-2', C-6'), 33.0 (C-1), 49.0 (C-3', C-5'), 111.0 (C-5), 118.2 (C-7), 127.7 (C-6), 128.7 (C-3a), 138.5 (C-4), 143.4 (-C=N), 146.1 (C-7a), 195.2 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{16}H_{23}N_4O$ $[M+H]^+$ 287.18664, found 287.18612.

1-(Indan-4-yl-hydrazono)-1-(4-methylpiperazin-1-yl)-propan-2-one (10d)

Yellow solid; (yield 26%); M.p.: 68-70 °C. IR (ν_{max}, cm^{-1}): 3415, 3239, 2925, 2852, 2786, 1671, 1595, 1530, 1492, 1458, 1369, 1284, 1254, 1148, 1005. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.04 (m, 2H, H-2), 2.18 (s, 3H, NCH_3), 2.29 (s, 3H, $COCH_3$), 2.38 (br s, 4H, H-3', H-5'), 2.82 (t, J = 7.5 Hz, 2H, H-3), 2.84 (t, J = 7.5 Hz, 2H, H-1), 2.91 (br s, 4H, H-2', H-6'), 6.82 (d, J = 7.3 Hz, 1H, H-7), 7.09 (pseudo t, 1H, H-6), 7.17 (d, J = 7.9 Hz, 1H, H-5), 9.03 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 25.9 (CO*C*H$_3$), 29.5 (C-3), 32.9 (C-1), 46.5 (NCH_3), 47.6 (C-2', C-6'), 55.9 (C-3', C-5'), 111.3 (C-5), 118.1 (C-7), 128.0 (C-6), 128.8 (C-3a), 139.0 (C-4), 144.4 (-C=N), 145.8 (C-7a), 194.4 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{17}H_{25}N_4O$ $[M+H]^+$ 301.20229, found 301.20213.

1-(4-Ethylpiperazin-1-yl)-1-(indan-4-yl-hydrazono)-propan-2-one (10e)

Yellow solid; (yield 25%); M.p.: 84-86 °C. IR (ν_{max}, cm^{-1}): 3418, 3295, 2952, 2867, 2782,

2661, 1669, 1594, 1532, 1492, 1365, 1254, 1150, 1021. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.98 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 2.04 (m, 2H, H-2), 2.29 (s, 3H, $COCH_3$), 2.33 (q, J = 7.0 Hz, 2H, NCH_2CH_3), 2.43 (br s, 4H, H-3', H-5'), 2.82 (t, J = 7.3 Hz, 2H, H-3), 2.84 (t, J = 7.3 Hz, 2H, H-1), 2.92 (br s, 4H, H-2', H-6'), 6.82 (d, J = 7.1 Hz, 1H, H-7), 7.10 (pseudo t, 1H, H-6), 7.13 (d, J = 7.8 Hz, 1H, H-5), 9.06 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 12.5 (NCH_2CH_3), 25.0 (C-2), 25.9 ($COCH_3$), 29.5 (C-3), 32.9 (C-1), 47.7 (C-2', C-6'), 52.3 (NCH_2CH_3), 53.7 (C-3', C-5'), 111.3 (C-5), 118.1 (C-7), 128.0 (C-6), 128.8 (C-3a), 139.0 (C-4), 144.0 (-C=N), 145.8 (C-7a), 194.4 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{18}H_{27}N_4O$ $[M+H]^+$ 315.21794, found 315.21796.

1-[1-(Indan-4-yl-hydrazono)-2-oxopropyl]-piperazine-4-carbaldehyde (10f)

Yellow solid; (yield 83%); M.p.: 110-113 °C. IR (ν_{max}, cm^{-1}): 3417, 2958, 2914, 2855, 1681, 1654, 1594, 1527, 1492, 1440, 1367, 1256, 1195, 1137, 1008. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.03 (m, 2H, H-2), 2.29 (s, 3H, $COCH_3$), 2.84 (m, 2H, H-1), 2.92 (m, 2H, H-3), 2.84 and 2.92 (br s, 4H, H-2', H-6'), [3.47 (t, J = 4.9 Hz) and 3.50 (br s), 4H, H-3', H-5'], 6.84 (d, J = 7.3 Hz, 1H, H-7), 7.10 (pseudo t, 1H, H-6), 7.18 (d, J = 8.0 Hz, 1H, H-5), 8.02 (s, 1H, COH), 9.30 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C-2), 25.9 ($COCH_3$), 30.1 (C-3), 33.0 (C-1), 40.0 and 46.0 (C-3',C-5'), 47.6 and 48.7 (C-2', C-6'), 112.0 (C-5), 118.4 (C-7), 127.8 (C-6), 129.5 (C-3a), 139.0 (C-4), 143.1 (-C=N), 146.0 (C-7a), 161.6 (CHO), 194.5 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{17}H_{22}N_4NaO_2$ $[M+Na]^+$ 337.16350, found 337.16363.

Ethyl 4-[1-(indan-4-yl-hydrazono)-2-oxo-propyl]-piperazine-1-carboxylate (10g)

Light yellow solid; (yield 31%); M.p.: 62-64 °C. IR (ν_{max}, cm^{-1}): 3421, 3273, 2925, 2855, 1700, 1663, 1605, 1594, 1536, 1493, 1469, 1430, 1362, 1337, 1276, 1241, 1214, 1186, 1123, 1075, 1028. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.19 (m, 2H, H-2), 2.45 (s, 3H, $COCH_3$), 2.88 (t, J = 7.4 Hz, 2H, H-3), 2.98 (t, J = 7.5 Hz, 2H, H-1), 3.06 (br s, 4H, H-2', H-6'), 3.60 (br s, 4H, H-3', H-5'), 4.20 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 6.93 (d, J = 7.3 Hz, 1H, H-7), 7.20 (pseudo t, 1H, H-6), 7.30 (d, J = 8.1 Hz, 1H, H-5), 9.15 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7 ($CO_2CH_2CH_3$), 25.0 (C-2), 25.6 ($COCH_3$), 29.4 (C-3), 33.0 (C-1), 44.8 (C-3', C-5'), 47.7 (C-2', C-6'), 61.2 ($CO_2CH_2CH_3$), 110.9 (C-5), 118.2 (C-7), 127.9 (C-6), 128.3 (C-3a), 138.4 (C-4), 143.2 (-C=N), 145.9 (C-7a), 155.6 ($CO_2CH_2CH_3$), 194.8 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{19}H_{25}N_4O_3$ $[M+H]^+$ 357.19321, found 357.19277.

1-[4-(2-Hydroxyethyl)-piperazin-1-yl]-1-(indan-4-yl-hydrazono)-propan-2-one (10h)

Yellow solid; (yield 83%); M.p.: 128-130 °C. IR (ν_{max}, cm^{-1}): 3485, 3416, 3271, 2952, 2904, 2807, 1662, 1594, 1535, 1493, 1459, 1365, 1335, 1309, 1255, 1194, 1146, 1058. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.04 (m, 2H, H-2), 2.29 (s, 3H, $COCH_3$), 2.40 (t, J = 6.1 Hz, 2H, CH_2CH_2OH), 2.49 (br s, 4H, H-3', H-5'), 2.82 (t, J = 7.1 Hz, 2H, H-3), 2.85 (t, J = 7.2 Hz, 2H, H-1), 2.92 (br s, 4H, H-2', H-6'), 3.48 (t, J = 6.1 Hz, 2H, CH_2CH_2OH), 6.82 (d, J = 7.2 Hz, 1H, H-7), 7.09 (pseudo t, 1H, H-6), 7.17 (d, J = 8.0 Hz, 1H, H-5), 9.06 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 26.0 ($COCH_3$), 29.5 (C-3), 32.9 (C-1), 47.7 (C-2', C-6'), 54.5 (C-3',C-5'), 59.1 (CH_2CH_2OH), 61.0 (CH_2CH_2OH), 111.3 (C-5), 118.1 (C-7), 128.0 (C-6), 128.8 (C-3a), 139.0 (C-4), 144.0 (-C=N), 145.8 (C-7a), 194.4 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{18}H_{26}N_4NaO_2$ $[M+Na]^+$ 353.19480, found 353.19563.

1-(Indan-4-yl-hydrazono)-1-(4-phenyl-piperazin-1-yl)-propan-2-one (10i)

Orange solid; (yield 98%); M.p.: 116-117 °C. IR (ν_{max}, cm^{-1}): 3415, 3273, 2945, 2862, 2816, 1663, 1593, 1539, 1494, 1361, 1331, 1247, 1185, 1128, 1024. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.01 (m, 2H, H-2), 2.32 (s, 3H, $COCH_3$), 2.83 (t, J = 7.5 Hz, 2H, H-3), 2.85 (t, J = 7.5 Hz, 2H, H-1), 3.08 (br s, 4H, H-2', H-6'), 3.23 (br s, 4H, H-3', H-5'), 6.77 (t, J = 7.2 Hz, 1H, H-4"), 6.84 (d, J = 7.3 Hz, 1H, H-7), 6.95 (d, J = 8.1 Hz, 2H, H-2", H-6"), 7.10 (pseudo t, 1H, H-6), 7.20 (pseudo t, 2H, H-3", H-5"), 7.21 (d, J = 7.7 Hz,1H, H-5), 9.21 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 26.0 ($COCH_3$), 29.7 (C-3), 32.9 (C-1), 47.8 (C-2', C-6'), 49.6 (C-3', C-5'), 111.7 (C-5), 116.2 (C-2", C-6"), 118.2 (C-7), 119.5 (C-4"), 128.0 (C-6), 129.2 (C-3a), 129.4 (C-3", C-5"), 139.0 (C-4), 143.7 (-C=N), 145.9 (C-7a), 151.6 (C-1"), 194.5 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{22}H_{27}N_4O$ $[M+H]^+$ 363.21794, found 363.21780.

1-[4-(4-Fluorophenyl)-piperazin-1-yl]-1-(indan-4-yl-hydrazono)-propan-2-one (10j)

Yellow solid; (yield 38%); M.p.: 110-112 °C. IR (ν_{max}, cm^{-1}): 3439, 3266, 2946, 2917, 2859, 2817, 1663, 1607, 1593, 1538, 1511, 1490, 1452, 1439, 1357, 1332, 1233, 1186, 1130, 1033. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.18 (m, 2H, H-2), 2.47 (s, 3H, $COCH_3$), 2.86 (t, J = 7.2 Hz, 2H, H-3), 2.98 (t, J = 7.3 Hz, 2H, H-1), 3.22 (br s, 4H, H-3', H-5'), 3.26 (br s, 4H, H-2', H-6'), 6.93 (d, J = 7.6 Hz, 1H, H-7), 6.96 (pseudo t, 2H, H-2", H-6"), 7.02 (pseudo t, 2H, H-3", H-5"), 7.21 (pseudo t, 1H, H-6), 7.32 (d, J = 7.9 Hz, 1H, H-5), 9.17 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0 (C-2), 25.6 ($COCH_3$), 29.4 (C-3), 33.0 (C-1), 48.0 (C-2', C-6'), 51.5 (C-3', C-5'), 110.9 (C-5), 115.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, C-3", C-5"), 118.0 (C-7), 118.1 (d, $^2J_{C\text{-}F}$ = 7.2 Hz, C-2", C-6"), 127.9 (C-6), 128.3 (C-3a), 138.5 (C-4), 143.4 (-C=N), 145.9 (C-7a), 148.0 (C-1"), 157.4 (d, $^1J_{C\text{-}F}$ = 239.1 Hz, C-4"), 195.0 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{22}H_{25}FN_4NaO$ $[M+Na]^+$ 403.19046, found 403.19242.

1-[4-(4-Chlorophenyl)-piperazin-1-yl]-1-(indan-4-yl-hydrazono)-propan-2-one (10k)

Light yellow solid; (yield 62%); M.p.: 154-156 °C. IR (ν_{max}, cm^{-1}): 3419, 3264, 2974, 2905, 2853, 1688, 1664, 1612, 1536, 1503, 1429, 1377, 1324, 1280, 1243, 1216, 1185, 1121, 1089, 1033. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.01 (m, 2H, H-2), 2.31 (s, 3H, $COCH_3$), 2.83 (t, J = 7.3 Hz, 2H, H-1), 2.86 (t, J = 7.3 Hz, 2H, H-3), 3.06 (br s, 4H, H-2', H-6'), 3.23 (br s, 4H, H-3', H-5'), 6.83 (d, J = 7.2 Hz, 1H, H-7), 6.95 (d, J = 8.5 Hz, 2H, H-2", H-6"), 7.10 (pseudo t, 1H, H-6), 7.20 (d, J = 8.8 Hz, 1H, H-5), 7.21 (d, J = 8.5 Hz, 2H, H-3", H-5"), 9.21 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (C-2), 26.0 ($COCH_3$), 29.8 (C-3), 32.9 (C-1), 47.7 (C-2', C-6'), 49.4 (C-3', C-5'), 111.6 (C-5), 117.6 (C-2", C-6"), 118.2 (C-7), 123.0 (C-4"), 127.9 (C-6), 129.1 (C-3", C-5"), 129.2 (C-3a), 139.0 (C-4), 143.5 (-C=N), 145.9 (C-7a), 150.4 (C-1"), 194.5 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{22}H_{26}{}^{35}ClN_4O$ $[M+H]^+$ 397.17897, found 397.17830; calcd. for $C_{22}H_{26}{}^{37}ClN_4O$ $[M+2+H]^+$ 399.17686, found 399.17555.

4-{4-[1-(Indan-4-yl-hydrazono)-2-oxopropyl]-piperazin-1-yl}-benzonitrile (10l)

Light yellow solid; (yield 61%); M.p.: 189-192 °C (dec.). IR (ν_{max}, cm^{-1}): 3423, 3276, 2948, 2912, 2848, 2209, 1664, 1606, 1592, 1544, 1520, 1490, 1398, 1358, 1332, 1249, 1182, 1128, 1097, 1027. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.18 (m, 2H, H-2), 2.47 (s, 3H, $COCH_3$), 2.87 (t, J = 7.4 Hz, 2H, H-3), 2.98 (t, J = 7.5 Hz, 2H, H-1), 3.26 (br s, 4H, H-2', H-6'), 3.44 (br s, 4H, H-3', H-5'), 6.93 (d, J = 8.9 Hz, 2H, H-2", H-6"), 6.95 (d, J = 7.3 Hz, 1H, H-7), 7.22 (pseudo t, 1H, H-6), 7.32 (d, J = 8.0 Hz, 1H, H-5), 7.56 (d, J = 8.9 Hz, 2H, H-3", H-5"), 9.17 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0 (C-2), 25.6 ($COCH_3$), 29.5 (C-3), 33.0 (C-1), 47.6 (C-2', C-6'), 48.5 (C-3', C-5'), 101.0 (C-4"), 111.0 (C-5), 114.6 (C-2", C-6"), 118.3 (C-7), 120.0 (C≡N), 127.9 (C-6), 128.4 (C-3a), 133.5 (C-3", C-5"), 138.4 (C-4), 142.9 (-C=N), 146.0 (C-7a), 153.5 (C-1"), 194.9 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{23}H_{26}N_5O$ $[M+H]^+$ 388.21319, found 388.21405.

1-(Indan-4-yl-hydrazono)-1-[4-(4-methoxy-phenyl)-piperazin-1-yl]-propan-2-one (10m)

Dark yellow solid; (yield 50%); M.p.: 118-121 °C. IR (ν_{max}, cm^{-1}): 3417, 3286, 2923, 2851, 1729, 1660, 1586, 1539, 1498, 1442, 1388, 1356, 1331, 1253, 1183, 1127, 1029. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.13 (m, 2H, H-2), 2.43 (s, 3H, $COCH_3$), 2.81 (t, J = 7.4 Hz, 2H, H-3), 2.93 (t, J = 7.4 Hz, 2H, H-1), 3.16 (br s, 4H, H-2', H-6'), 3.22 (br s, 4H, H-3', H-5'), 3.77 (s, 3H, -OCH_3), 6.86 (d, J = 9.0 Hz, 2H, H-3", H-5"), 6.88 (d, J = 7.3 Hz, 1H, H-7), 6.94 (d, J = 9.0 Hz, 2H, H-2", H-6"), 7.16 (pseudo t, 1H, H-6), 7.27 (d, J = 8.0 Hz, 1H, H-5), 9.12 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0 (C-2), 25.6 ($COCH_3$), 29.4 (C-3), 33.0 (C-1), 48.0 (C-3', C-5'), 52.0 (C-2', C-6'), 55.6 (-OCH_3), 110.9 (C-5), 114.5 (C-3", C-5"), 118.0 (C-7), 118.4 (C-2", C-6"), 127.8 (C-6), 128.3 (C-3a), 138.6 (C-4), 143.6 (-C=N), 145.7 (C-1"), 145.9 (C-7a), 154.1 (C-4"), 195.0 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{23}H_{29}N_4O_2$ $[M+H]^+$ 393.22850, found 393.22767.

1-(Indan-4-yl-hydrazono)-1-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-one (10n)

Light brown solid; (yield 33%); M.p.: 122-124 °C. IR (ν_{max}, cm^{-1}): 3419, 3273, 2942, 2842, 1662, 1592, 1538, 1488, 1437, 1362, 1334, 1311, 1245, 1184, 1129, 1029. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.17 (m, 2H, H-2), 2.47 (s, 3H, $COCH_3$), 2.87 (t, J = 7.4 Hz, 2H, H-3), 2.98 (t, J = 7.4 Hz, 2H, H-1), 3.23 (br s, 4H, H-2', H-6'), 3.67 (br s, 4H, H-3', H-5'), 6.71 (pseudo t, 1H, H-5"), 6.74 (d, J = 8.6 Hz, 1H, H-3"), 6.93 (d, J =

7.3 Hz, 1H, H-7), 7.21 (pseudo t, 1H, H-6), 7.33 (d, J = 8.0 Hz, 1H, H-5), 7.54 (pseudo t, 1H, H-4"), 8.25 (d, J = 4.4 Hz, 1H, H-6"), 9.21 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.9 (C-2), 25.6 ($COCH_3$), 29.4 (C-3), 33.0 (C-1), 46.5 (C-3', C-5'), 47.8 (C-2', C-6'), 107.4 (C-3"), 110.9 (C-5), 113.8 (C-5"), 118.1 (C-7), 127.9 (C-6), 128.4 (C-3a), 137.5 (C-4"), 138.6 (C-4), 143.5 (-C=N), 145.9 (C-7a), 148.0 (C-6"), 159.5 (C-2"), 194.9 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{21}H_{26}N_5O$ $[M+H]^+$ 364.21319, found 364.21309.

1-(Indan-4-yl-hydrazono)-1-(4-pyrimidin-2-yl-piperazin-1-yl)-propan-2-one (10o)

Light yellow solid; (yield 47%); M.p.: 123-126 °C. IR (ν_{max}, cm^{-1}): 3448, 3236, 3028, 2934, 2837, 1736, 1659, 1587, 1547, 1499, 1439, 1355, 1309, 1258, 1182, 1135, 1033. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.14 (m, 2H, H-2), 2.41 (s, 3H, $COCH_3$), 2.85 (t, J = 7.4 Hz, 2H, H-3), 2.94 (t, J = 7.3 Hz, 2H, H-1), 3.12 (br s, 4H, H-2', H-6'), 3.90 (br s, 4H, H-3', H-5'), 6.52 (t, J = 4.8 Hz, 1H, H-5"), 6.89 (d, J = 7.3 Hz, 1H, H-7), 7.16 (pseudo t, 1H, H-6), 7.28 (d, J = 8.0 Hz, 1H, H-5), 8.32 (d, J = 4.8 Hz, 2H, H-4", H-6"), 9.20 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0 (C-2), 25.6 ($COCH_3$), 29.7 (C-3), 33.0 (C-1), 44.9 (C-3', C-5'), 47.8 (C-2', C-6'), 110.3 (C-5"), 110.9 (C-5), 118.1 (C-7), 127.9 (C-6), 128.4 (C-3a), 138.5 (C-4), 143.5 (-C=N), 145.9 (C-7a), 157.7 (C-4", C-6"), 161.1 (C-2"), 194.9 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{20}H_{23}N_6O$ $[M+H]^+$ 363.19388, found 363.19352.

1-(Indan-4-yl-hydrazono)-1-(4-phenylpiperidin-1-yl)-propan-2-one (10p)

Light yellow solid; (yield 50%); M.p.: 98-101 °C. IR (ν_{max}, cm^{-1}): 3415, 3270, 3033, 2930, 2845, 1660, 1617, 1596, 1527, 1493, 1380, 1262, 1233, 1133, 1012. ^{1}H NMR (500 MHz, DMSO-d_6) δ: [1.75 (br s) and 1.79 (m), 4H, H-3', H-5'], 2.05 (m, 2H, H-2), 2.31 (s, 3H, $COCH_3$), 2.48 (m, 1H, H-4'), 2.85 (t, J = 7.7 Hz, 2H, H-1), [2.87 (m) and 3.20 (m), 4H, H-2', H-6'], 2.90 (t, J = 7.7 Hz, 2H, H-3), 6.83 (d, J = 7.3 Hz, 1H, H-7), 7.11 (pseudo t, 1H, H-6), 7.17 (m, 1H, H-4"), 7.20 (d, J = 8.0 Hz, 1H, H-5), 7.29 (m, 4H, H-2", H-3", H-5", H-6"), 9.09 (s, 1H, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C-2), 26.0 ($COCH_3$), 29.7 (C-3), 33.0 (C-1), 34.1 (C-3', C-5'), 42.0 (C-4'), 48.8 (C-2', C-6'), 111.7 (C-5), 118.1 (C-7), 127.2 (C-2", C-6"), 127.9 (C-6), 126.6 (C-4"), 128.8 (C-3", C-5"), 129.1 (C-3a), 139.2 (C-4), 144.6 (-C=N), 145.9 (C-7a), 146.7 (C-1"), 194.6 (*C*OMe) ppm. HRMS (ESI) m/z: calcd. for $C_{23}H_{28}N_3O$ $[M+H]^+$ 362.22269, found 362.22233.

Collection of X-ray diffraction data and structure analysis of compound 10n

A suitable single crystal of **10n**, with approximate dimensions of 0.4 × 0.3 × 0.2 mm^3, was epoxy-mounted on a glass fiber. Data for **10n** were then collected at room temperature (*T*= 293 K) using an Xcalibur, Eos Diffractometer. Data were acquired and processed to give Shelx-format *hkl* files using CrysAlisPro software[23]. Cell parameters were determined and refined using CrysAlisPro[23]. A multiscan absorption collection was applied with maximum and minimum transmission factors of 1.000 and 0.705, respectively. The structure was solved using Olex2[24] with the ShelXS[25] structure solution program using Direct Methods and refined with the ShelXL[26] refinement package using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in calculated positions and refined using a riding model.

CCDC 1983215 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

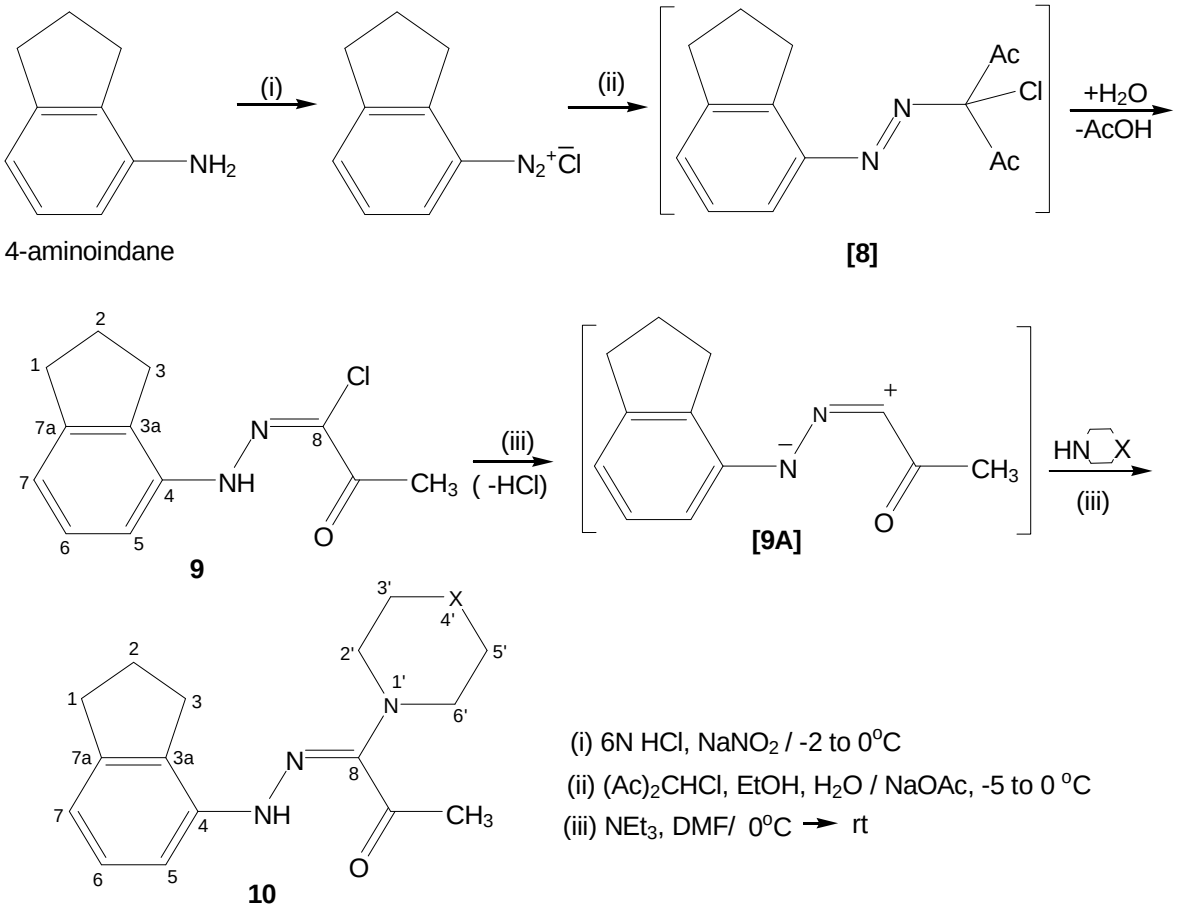
Cell lines and cell culture

The HCT-116 and Cao-2 colon cancer cell lines were obtained from American Type Culture Collections (ATCC) and cultured in DMEM/F12. All media were supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco Invitrogen), 1% of 2 mM L-glutamine (Lonza), 50 IU/mL penicillin (Lonza), and 50 µg/ mL streptomycin (Lonza) and cells were maintained at 37°C, 5% CO_2 humidified incubator.

Cell proliferation assay

HCT-116 and Cao-2 cells were seeded at a density of 1×10^4 and 4×10^4 cells per well in 96-well plates in appropriate medium. In all assays, the drugs were dissolved in DMSO immediately before the addition to cell cultures and equal amounts of the solvent were added to control cells. Cell viability was assessed, after 3 days of treatment, with tetrazolium dye 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), obtained from Sigma (Dorset, UK). The IC_{50} concentrations (µM) were obtained from the

Scheme 1: Synthesis of compounds 10a-p.



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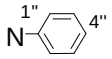
X	O	S	NH	NMe	NEt	N−CHO	N-CO_2Et	NCH_2CH_2OH	

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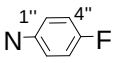
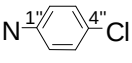
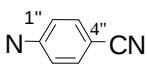
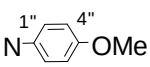
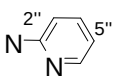
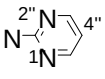
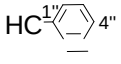
X							

.Scheme 1: Synthesis of compounds 10a-p

dose-response curves using Graph Pad Prism Software 5 (San Diego, California, USA, www.graphpad.com).

Results and Discussion

The synthesis of the target *N*1-(indan-4-yl)amidrazones **10a-p** commenced with the preparation of the appropriate *N*1-(indan-4-yl)hydrazonyl chloride **9** (Scheme 1). The latter precursor **9** is readily accessible *via* direct coupling of 4-indanediazonium chloride (freshly prepared by diazotization of 4-aminoindane) with 3-chloropentane-2,4-dione in aqueous ethanol buffered with sodium acetate; the resulting intermediate azo compound **8** underwent conversion to the corresponding hydrazone structure **9** via loss of an acetyl group (Japp-Klingemann reaction)[13–15].

Piperazines and the related *sec*-cyclic amine congeners acting as nitrogen nucleophiles, are expected to add readily onto *N*1-(indan-4-yl)nitrilimine [**9A**] (the reactive 1,3-dipole generated *in situ* from its hydrazonoyl chloride **9** in the presence of triethylamine) to produce the respective amidrazone adducts **10a-p** (Scheme

1). This mode of nucleophile addition of various nucleophiles onto 1,3-dipolar species is well documented in the literature[16-21], and several related amidrazone adducts were obtained from the reaction of amines with hydrazonoyl chlorides[7, 8, 22].

The new compounds **9** and **10a-p** were characterized by IR, MS, and NMR spectral data. These data, detailed in the experimental section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H- and ^{13}C- signal assignments to the different carbons and their attached and/or neighboring hydrogens.

X-Ray Structure

An X-ray crystal structure determination was performed to confirm the structure of **10n** as a representative of the set. A summary of data collection and refinement parameters is given in Table 1, while selected sets of bond lengths and bond angles for **10n** are provided in Table 2. The molecular structure of **10n**, based on crystallographic data, is displayed in Figure. 3.

Table 1: Summary of the crystal data and structure refinement parameters for 10n.

Empirical formula	$C_{21}H_{25}N_5O$
Formula weight	363.46
Temperature/K	293
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	8.0818(8)
b (Å)	8.5650(8)
c (Å)	14.3652(14)
β/°	97.530(10)
Volume/Å^3	985.79(17)
Z	2
Calculated density (g / cm^3)	1.224
Absorption coefficient (mm^{-1})	0.079
F(000)	388.0
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	6.964 to 58.294
Index ranges	$-10 \le h \le 6$, $-11 \le k \le 10$, $-16 \le l \le 19$
Reflections collected	5328
Independent reflections	3843 [R_{int} = 0.0156, R_{sigma} = 0.0384]
Data/restraints/parameters	3843/1/246
Final R indexes [I>=2σ (I)]	R_1[a] = 0.0439, wR_2[b] = 0.0990
Final R indexes [all data]	R_1[a] = 0.0549, wR_2[b] = 0.1082
Goodness-of-fit[c] on F^2	1.046
Largest difference peak (e. Å^{-3})	0.16
Largest difference hole (e. Å^{-3})	-0.13

[a] $R1 = \Sigma \,||F_o| - |F_c|| / \Sigma |F_o|$;
[b] $wR^2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$;
[c] GoF = $S = [\Sigma w(F_o^2 - F_c^2)^2 / (n_{obs} - n_{param})]^{1/2}$.

Table 2: Selected bond lengths (Å) and angles (deg) for 10n.

Bond Lengths		Bond angles	
N2– N1	1.335(2)	C8– N2– N1	117.1(2)
N2– C8	1.297(3)	N2– N1– C4	119.82(19)
N1– C4	1.401(3)	C8– N3– C11	115.7(2)
N3– C8	1.428(3)	C8– N3– C14	113.4(2)
N3– C11	1.474(3)	C14– N3– C11	110.67(19)
N3– C14	1.471(3)	C15– N4– C12	122.0(2)
N4– C15	1.371(3)	C15– N4– C13	123.2(2)
N4– C12	1.459(3)	C12– N4– C13	112.6(2)
N4– C13	1.461(3)	C19– N5– C15	117.2(2)
N5– C15	1.353(4)	N4– C15– C16	122.6(2)
N5– C19	1.344(4)	N5– C15– N4	116.6(2)
O1– C9	1.223(3)	N5– C15– C16	120.7(2)
C8– C9	1.485(3)	N2– C8– N3	121.0(2)
C9– C10	1.494(4)	O1– C9– C10	121.2(3)

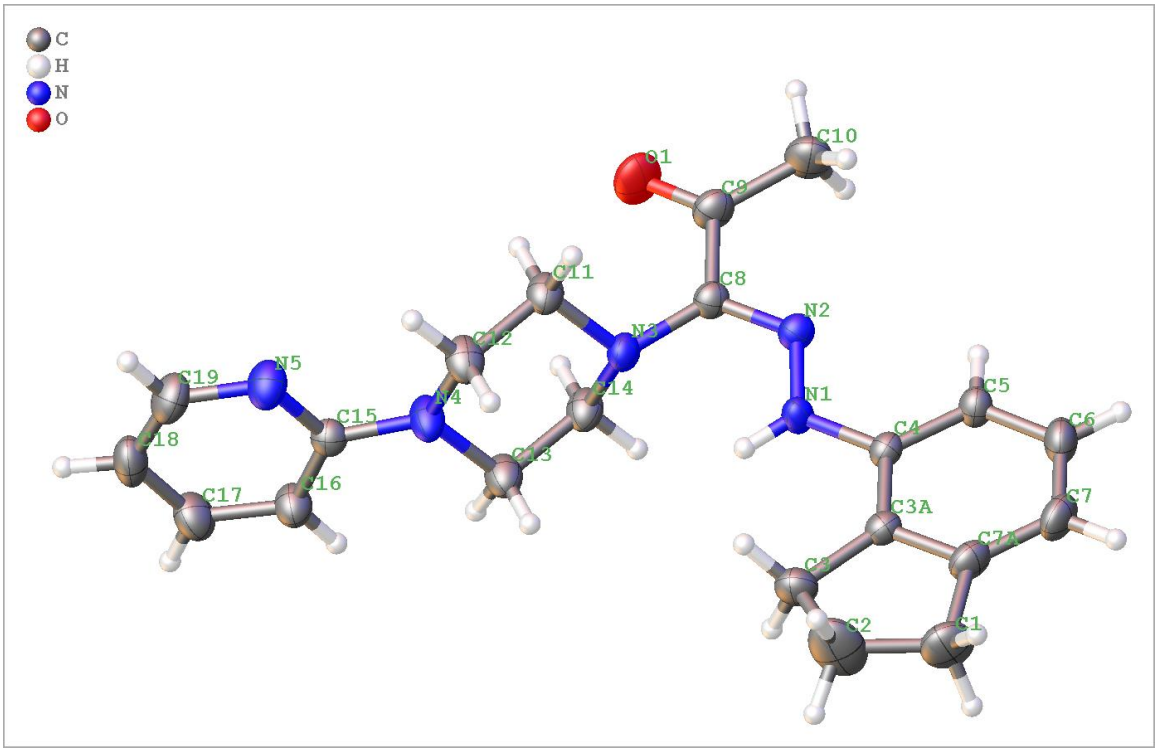


Figure 3. The molecular structure and atom numbering scheme of 10n. Thermal ellipsoids are drawn at 30% probability level.

Antitumor Activity

The antitumor activity of compounds **10a-p** against colon cancer HCT-116 and Cao-2 was evaluated by cell viability assay using the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). Doxorubicin was used as positive control. However, only compounds **10d** and **10f** showed fair activity against HCT-116 cells with IC_{50} values of 22.9 µM and 36.8 µM, respectively, as well as against Cao-2 with IC_{50} values of 55.9 µM and 67.2 µM, respectively. The rest compounds were inactive at ≤ 100 µM. Compound **10d** and **10f** can be considered as lead structures for further manipulations.

Acknowledgement

The authors wish to thank the Deanship of Scientific Research at The University of Jordan, Amman-Jordan, for financial support.

References

[1] Juby, P. F.; Partyka, R. A.; Hudyma, T. W., *US Patent* **1971**, *US* 3,565,943.

[2] Woltersdorf, O. W.; deSolms, S. J.; Stokker, G. E.; Cragoe, E. J., *J. Med. Chem.* **1984**, *27*, 840.

[3] Bardouille, M.; Mootoo, B. S.; Hirotsu, K.; Clardy, J., *Phytochemistry* **1978**, *17*, 275.

[4] Kim, S. H.; Kwon, S. H.; Park, S. H.; Lee, J. K.; Bang, H. S.; Nam, S. J.; Kwon, H. C.; Shin, J.; Oh, D. C., *Org. Lett.* **2013**, *15*, 1834.

[5] Vilums, M.; Heuberger, J.; Heitman, L. H.; IJzerman, A. P., *Med. Res. Rev.* **2015**, *35*, 1097.

[6] Mustafa, M. S.; El-Abadelah, M. M.; Zihlif, M. A.; Naffa, R.; Mubarak, M. S., *Molecules* **2011**, *16*, 4305.

[7] Abu-Aisheh, M. N.; Mustafa, M. S.; El-Abadelah, M. M.; Naffa, R. G.; Ismail, S. I.; Zihlif, M. A.; Mubarak, M. S., *Eur. J. Med. Chem.* **2012**, *54*, 65.

[8] Habashneh, A. Y.; El-Abadelah, M. M.; Zihlif, M. A., *Arch. Pharm.* **2014**, *347*, 415.

[9] Abadleh, M. M.; El-Abadelah, M. M.; Sabri, S. S.; Mohammed, H. H.; Zihlif, M. A.; Voelter, W., *Z. Naturforsch.* **2014**, *69b*, 811.

[10] Abdullah, A. H.; Zahra, J. A.; El-Abadelah, M. M.; Sabri, S. S.; Khanfar, M. A.; Matar, S. A.; Voelter, W., *Z. Naturforsch.* **2016**, *71b*, 857.

[11] Abdel-Jalil, R. J.; El-Momani, E. Q.; Hamad, M.; Voelter, W.; Mubarak, M. S.; Smith, B. H.; Peters, D. G., *Monatsh. Chem.* **2010**, *141*, 251.

[12] Daldoom, E. S.; Sabri, S. S.; El-Abadelah, M. M.; Khanfar, M. A.; Bardaweel, S.; Zahra, J. A., Lett.Org. Chem. accepted.

[13] Phillips, R. R., *Org. React.* **1959**, *10*, 143.

[14] Yao, H.-C.; Resnick, P., *J. Am. Chem. Soc.* **1962**, *84*, 3514.

[15] Neplyuev, V. M.; Bazavova, I. M.; Lozinskii, M. O., *Zh. Org. Khim.* **1989**, *25*, 2225.

[16] Butler, R. N.; Scott, F. L., *Chem. Ind.* (London) **1970**, 1216.

[17] Hegarty, A. F.; Aylward, J. B.; Scott, F. L., *J. Chem. Soc. C* **1967**, 2587.

[18] Galishe, V. A.; Chisokletov, V. N.; Petrov, A. A., *Zh. Obshch. Khim.* **1975**, *45*, 1695.

[19] Shawali, A. S.; Parkanyi, C., *J. Heterocycl. Chem.* **1980**, *17*, 833.

[20] Hassaneen, H. M.; Mousa, H. A. H.; Abed, N. M., *Heterocycles* **1988**, *27*, 695.

[21] Benincori, T.; Sanniclolo, F., *J. Org. Chem.* **1988**, *53*, 1309.

[22] Awad, E. D.; El-Abadelah, M. M.; Matar, S.; Zhilif, M. A.; Naffa, R. G.; El-Momani, E. Q.; Mubarak, M. S., *Molecules* **2012**, *17*, 227.

[23] CrysAlisPro (version 1.171.35.11), Agilent Technologies Ltd., Yarnton (UK) 2011.

[24] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., *J. Appl. Cryst.* **2009**, *42*, 339.

[25] Sheldrick, G. M., *Acta Cryst.* **2008**, *A64*, 112.

[26] Sheldrick, G. M., *Acta Cryst.* **2015**, *C71*, 3.