Tetrahedron 69 (2013) 6474–6477

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of [1,2]oxazolo[5,4-*e*]indazoles as antitumour agents

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ARTICLE INFO

Article history:
Received 10 December 2012
Received in revised form 6 May 2013
Accepted 20 May 2013
Available online 29 May 2013

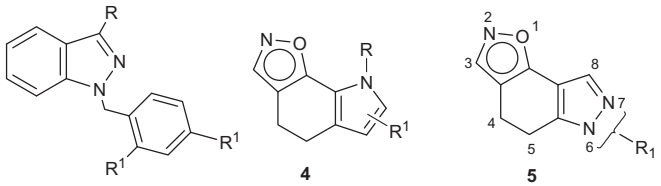
Keywords:
Lonidamine
[1,2]Oxazolo[5,4-*e*]indazoles
Enaminoketones
Hydroxylamine hydrochloride
Antiproliferative activity

ABSTRACT

A series of 40 derivatives of the [1,2]oxazolo[5,4-*e*]indazoles ring system have been prepared with good yields using a versatile and convenient route. Annelation of the [1,2]oxazole ring on the indazole-4-one system was achieved by reaction of the corresponding enaminoketones with hydroxylamine hydrochloride. Derivatives of the title ring system were tested by the National Cancer Institute of Bethesda and one of them (**13t**) showed growth-inhibitor activity against all the 54 human tumour cell lines generally at low micromolar concentrations.

1. Introduction

Although scarcely found in nature, pyrazoles are known for their wide range of pharmacological applications as herbicides, antipsychotic, antibacterial, antimycotic and antiinfiammatory agents.[1–3] Benzocondensation to the pyrazole nucleus, leads to indazole derivatives, which are reported to be endowed with remarkable antitumour activity by different mechanisms. Leading examples are Lonidamine **1** (LND) and analogues **2** and **3** (Chart 1). LND is a potent antitumour drug, used in the treatment of several neoplasia as breast, lung, kidney, bladder as well as sarcomas of soft tissue acting via inhibition of the energy metabolism, nowadays in phase III clinical trials.[4–6]



1 LND R = COOH R^1=Cl
2 YD-3 R = –C6H4–COOEt R^1=H
3 YC-1 R = –C4H2O–CH_2OH R^1=H

Chart 1. Structures of LND (**1**), YD-3 (**2**), YC-1 (**3**), [1,2]oxazolo[4,5-*g*]indole (**4**), [1,2]oxazolo[5,4-*e*]indazole (**5**).

Moreover LND acts as a photosensitizer thus potentiating the cytotoxic effect of UV light targeting mainly mitochondria and membrane structures.[7] The potent activity of LND, encouraged through the years the synthesis of several analogues,[8–11] and have attracted our attention also because of our recent interest on antitumour agents including those with photosensitizing properties,[12–22] encouraging us the development of new molecules containing the pyrazole core. We have recently turned our attention to the incorporation of the [1,2]oxazole moiety on tricyclic systems containing the pyrrole ring. In fact several examples of compounds incorporating an [1,2]oxazole are reported as potent antitumour agents.[23,24] Thus, we synthesized the ring system [1,2]oxazolo[4,5-*g*]indole **4**, which demonstrated very promising antitumour properties when tested at the NCI of Bethesda on a panel of 60 human tumour cell lines.[25]

In consideration of the potent antitumour activity of compounds bearing the pyrazole and [1,2]oxazole moieties we planned the synthesis of a series of [1,2]oxazolo[5,4-*e*]indazoles (**5**) with the intent of investigating the effect of the simultaneous presence in the tricyclic system of both the pyrazole and the [1,2]oxazole systems.

2. Results and discussion

Our approach to the synthesis of the title ring system consisted on the preparation of a number of tetrahydroindazole-4-ones of

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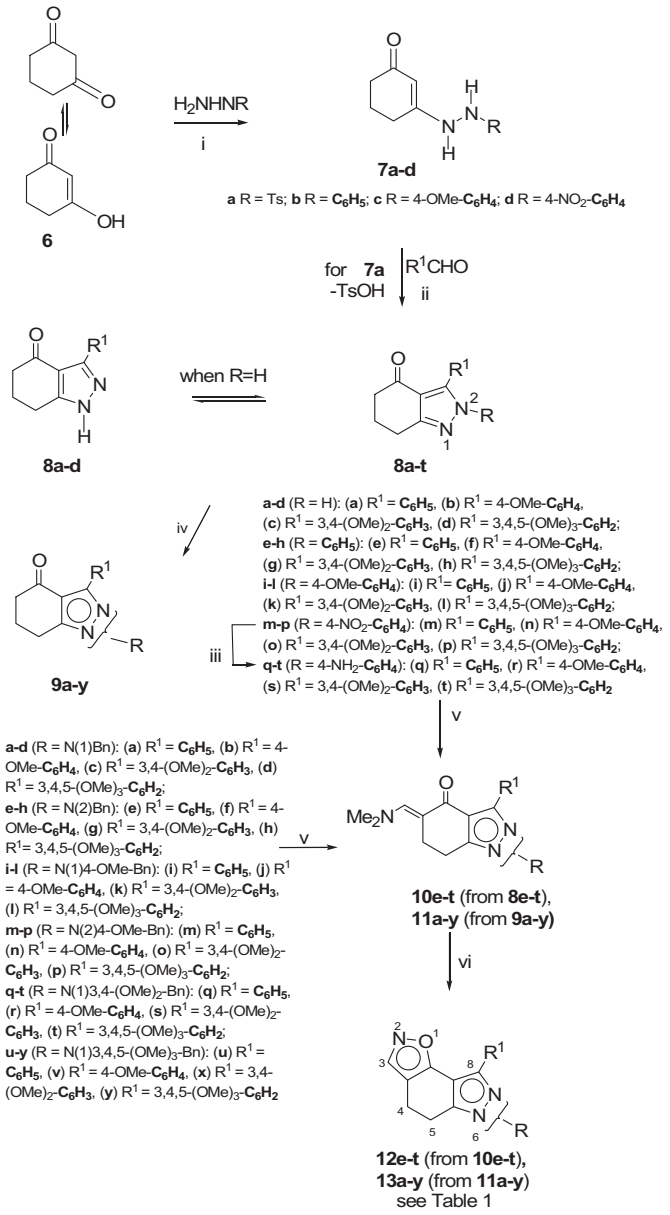
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.05.083

type **8** and **9**, which could be further functionalized in α position to the carbonyl group with an enamino functionality to give compounds **10** and **11**, key synthons for the annelation of the [1,2] oxazole moiety (Scheme 1). Tetrahydroindazol-4-ones **8a**–**t** were conveniently prepared by reaction of the commercially available cyclohexane-1,3-dione **6**, with substituted hydrazines to give achieve the corresponding hydrazones **7a**–**d** in very good yield (74–96%).



Scheme 1. Synthesis of [1,2]oxazolo[5,4-*e*]indazoles **12** and **13**. Reagents: (i) 80% AcOH/water (1:1) for **7a** or water for **7b**–**d**, 0 °C then rt 10 min–2 h, 74–96%; (ii) DMF, AcOH, piperidine, 80–100 °C, 50 min–3 h, 70–98%; (iii) EtOH, H_2, 10% Pd/C, 50–69%, rt, 24 h; (iv) benzylhalides, NaH, DMF, 0 °C then rt or reflux, 1–24 h, 10–83%; (v) DMFDMA, MW (PW 150, T 150 °C), 15 min–2 h, 45–98%; (vi) NH_2OH, MeOH/AcOH (2:1), reflux, 50 min, 50–92%.

Benzaldehyde and its mono-, di- and tri-methoxy substituted derivatives were reacted with **7a**–**d** in a mixture of dimethylformamide and acetic acid in the presence of catalytic amount of piperidine to furnish the desired tetrahydroindazoles **8a**–**p** in 70–98% yields. The nitro derivatives **8m**–**p** were converted into the corresponding amino derivatives **8q**–**t** by reduction with H_2 and 10% Pd/C in reasonable yields (50–69%). From reaction of the tosylhydrazone **7a**, spontaneous elimination of toluenesulfonic acid occurred and the NH indazoles **8a**–**d** were obtained. Indazoles **8a**–**d** were then subjected to alkylation at the pyrrole nitrogen with benzylchlorides or bromides, in the presence of NaH yielding the N(1)-substituted derivatives **9a**–**y** (10–83%). Among these, the N(1)-benzyl and 4-methoxybenzyl derivatives **9a**–**d**, **i**–**l** were isolated as main components (65–83%) from mixtures with their corresponding N(2) regioisomers **9e**–**h**, **m**–**p** (10–15%), being the N(1) isomers the most favoured of the two. Spectroscopic data of **9e**–**h**, **m**–**p** are in agreement with the N(2) structure of **8e**–**t**.[26]

Recently we have reported that the enamino functionality can be introduced in α position to the annular carbonyl in tetrahydroindolone systems using *tert*-butoxybis(dimethylamino)methane (TBDMAM), in the case of poor reactive substrates,[17–22] or alternatively dimethylformamide dimethylacetal (DMFDMA), less reactive but indeed available at low cost. Thus, tetrahydroindazol-4-ones **8e**–**t** and **9a**–**y** were converted into the corresponding enaminoketones **10e**–**t** and **11a**–**y** in DMFDMA under microwave irradiation (PW 150, T 150 °C) in 45–95% and 68–98% yields, respectively.

Annelation of the [1,2]oxazole ring was accomplished by reaction of enaminoketones **10**, **11** with hydroxylamine hydrochloride as 1,3 dinucleophile, in refluxing ethanol and catalytic amount of acetic acid. By this route 40 derivatives (**12e**–**t**, **13a**–**y**) of the [1,2] oxazolo[5,4-*e*]indazoles were generally obtained in good yields (50–92%, Table 1).

Table 1
[1,2]Oxazolo[5,4-*e*]indazoles **12**, **13**

	R^1	R	Yields (%)
12e	C_6H_5	C_6H_5	56
12f	4-OMe–C_6H_4	C_6H_5	70
12g	3,4-$(OMe)_2$–C_6H_3	C_6H_5	78
12h	3,4,5-$(OMe)_3$–C_6H_2	C_6H_5	74
12i	C_6H_5	4-OMe–C_6H_4	86
12j	4-OMe–C_6H_4	4-OMe–C_6H_4	72
12k	3,4-$(OMe)_2$–C_6H_3	4-OMe–C_6H_4	90
12l	3,4,5-$(OMe)_3$–C_6H_2	4-OMe–C_6H_4	92
12m	C_6H_5	4-NO_2–C_6H_4	62
12n	4-OMe–C_6H_4	4-NO_2–C_6H_4	68
12o	3,4-$(OMe)_2$–C_6H_3	4-NO_2–C_6H_4	50
12p	3,4,5-$(OMe)_3$–C_6H_2	4-NO_2–C_6H_4	50
12q	C_6H_5	4-NH_2–C_6H_4	58
12r	4-OMe–C_6H_4	4-NH_2–C_6H_4	60
12s	3,4-$(OMe)_2$–C_6H_3	4-NH_2–C_6H_4	70
12t	3,4,5-$(OMe)_3$–C_6H_2	4-NH_2–C_6H_4	72
13a	C_6H_5	N(1)Bn	72
13b	4-OMe–C_6H_4	N(1)Bn	86
13c	3,4-$(OMe)_2$–C_6H_3	N(1)Bn	84
13d	3,4,5-$(OMe)_3$–C_6H_2	N(1)Bn	56
13e	C_6H_5	N(2)Bn	68
13f	4-OMe–C_6H_4	N(2)Bn	58
13g	3,4-$(OMe)_2$–C_6H_3	N(2)Bn	50
13h	3,4,5-$(OMe)_3$–C_6H_2	N(2)Bn	65
13i	C_6H_5	N(1)4-OMe–Bn	80
13j	4-OMe–C_6H_4	N(1)4-OMe–Bn	64
13k	3,4-$(OMe)_2$–C_6H_3	N(1)4-OMe–Bn	60
13l	3,4,5-$(OMe)_3$–C_6H_2	N(1)4-OMe–Bn	72
13m	C_6H_5	N(2)4-OMe–Bn	63
13n	4-OMe–C_6H_4	N(2)4-OMe–Bn	76
13o	3,4-$(OMe)_2$–C_6H_3	N(2)4-OMe–Bn	68
13p	3,4,5-$(OMe)_3$–C_6H_2	N(2)4-OMe–Bn	54
13q	C_6H_5	N(1)3,4-$(OMe)_2$–Bn	50
13r	4-OMe–C_6H_4	N(1)3,4-$(OMe)_2$–Bn	54
13s	3,4-$(OMe)_2$–C_6H_3	N(1)3,4-$(OMe)_2$–Bn	58
13t	3,4,5-$(OMe)_3$–C_6H_2	N(1)3,4-$(OMe)_2$–Bn	54
13u	C_6H_5	N(1)3,4,5-$(OMe)_3$–Bn	70
13v	4-OMe–C_6H_4	N(1)3,4,5-$(OMe)_3$–Bn	70
13x	3,4-$(OMe)_2$–C_6H_3	N(1)3,4,5-$(OMe)_3$–Bn	72
13y	3,4,5-$(OMe)_3$–C_6H_2	N(1)3,4,5-$(OMe)_3$–Bn	66

The structure of all synthesized compounds were confirmed by spectroscopic data (IR, ^{1}H and ^{13}C NMR) and elemental analysis (C, H, N) reported in the Supplementary data. [1,2]Oxazolo[5,4-*e*] indazoles **12** and **13** were submitted at the NCI of Bethesda for the in vitro antitumour screenings. Among these derivatives **12e**–**l**, **q**–**t** and **13a**–**y** were prescreened according to the NCI protocol at the 10^{-5} M dose on the full panel of 60 human cancer cell lines derived from nine human cancer cell types that have been grouped in disease sub-panels including leukaemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumour cell lines. Disappointingly, only 6-(3, 4-dimethoxylbenzyl)-8-(3,4,5-trimethoxyphenyl)-5,6-dihydro-4*H*-[1,2]oxazolo[5,4-*e*]indazole **13t**, was selected for further screenings at five concentrations at 10-fold dilution (10^{-4}–10^{-8} M) on the full panel reaching micromolar and submicromolar concentrations against all the 54 tested cell lines with a GI_{50} range of 0.11–58.1 μM and a pGI_{50} MG_MID value of 5.33 (see Table 2 in the supplementary data). In particular the best selectivity was observed against the HL-60(TB) cell line of the leukaemia sub-panel (0.11 μM) (Table 2). This latter subpanel together with the colon, the CNS and the breast cancer sub-panels are those towards which **13t** shows the best selectivity with GI_{50} ranges of 0.11–3.76 μM, 3.63–5.85 μM, 1.39–7.99 μM and 1.94–8.00 μM, respectively. Moreover with the exception of the NCI-H322M cell line (GI_{50} 58.1 μM) of the Non-Small Cell Lung cancer subpanel and the OVCAR-5 (GI_{50} 26.6 μM) and OVCAR-8 cell lines (GI_{50} 19.6 μM) of the ovarian cancer, compound **13t** shows activity in the low micromolar range (GI_{50} 3.17–6.85 μM and 3.02–7.28 μM) against the two sub-panels.

3. Conclusions

In conclusion, we have set up a simple and versatile pathway for the synthesis of new derivatives of the [1,2]oxazolo[5,4-*e*]indazole ring system.

Variously substituted indazol-4-ones were prepared and converted into the corresponding enaminoketones using DMFDMA for the direct introduction of the enamino functionality, thus giving us the chance to investigate the reactivity of pyrazole derivatives in comparison with our previous series containing the pyrrole moiety. Preliminary results of the in vitro studies at the NCI of Bethesda indicated the [1,2]oxazolo [5,4-*e*]indazole **13t** as a hit candidate of the series with inhibitory activity in the submicromolar and low micromolar range encouraging further optimization from a structural point of view.

4. Experimental section

4.1. General

All melting points were taken on a Buchi–Tottoli capillary apparatus and were uncorrected; IR spectra were determined, in $CHBr_3$, with a Shimadzu FT/IR 8400S spectrophotometer; ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions (TMS as internal reference), at 200 and 50.3 MHz, respectively, using a Bruker Avance II series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel 230–400 Mesh ASTM or with a SEPACORE chromatography apparatus BÜCHI. Elemental analyses (C, H, N) were within ±0.4% of the theoretical values. Reaction under microwave irradiations was performed using a CEM Discover Labmate TM apparatus. Mass spectra were obtained using a Mariner™ mass spectrometer, Applied Biosystems (Foster City, CA). A Harvard model 11 syringe pump (Holliston, MA) was used to infuse the sample solutions. The ESI source was operated in positive ion mode with an electrospray voltage of 4.5 kV.

4.2. General procedure for the synthesis of compounds 7a–d (7a as an example)

To a solution of cyclohexane-1,3-dione **6** (2.8 g, 25 mmol) in 80% AcOH/water (1:1) (100 mL) for **7a** or water (100 mL) for **7b**–**d** (see supplementary data), a solution of suitable hydrazine (25 mmol) in water (70 mL) was added at 0 °C and the reaction mixture was stirred at rt. From the reaction mixture a solid was separated. Then it was filtered off and dried.

*4.2.1. 4-Methyl-N′-(3-oxocyclohex-1-en-1-yl)benzenesulfonohydrazide (**7a**).* This compound was obtained by reaction with tosylhydrazine after 10 min at rt according to a reported procedure.[26] White solid; R_f=0.15 (EtOAc); mp 205–206 °C; yield 82%; IR cm^{-1}: 3296 (NH), 3294 (NH), 1608 (CO). ^{1}H NMR (DMSO-d_6): δ 1.68–1.80 (2H, m, CH_2), 2.05 (2H, t, *J*=5.7 Hz, CH_2), 2.21 (2H, t, *J*=5.7 Hz, CH_2), 2.39 (3H, s, CH_3), 5.14 (1H, s, CH), 7.42 (2H, d, *J*=8.2 Hz, H-3′ and H-5′), 7.70 (2H, d, *J*=8.2 Hz, H-2′ and H-6′), 8.64 (1H, s, NH), 9.76 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 21.0 (q), 21.4 (t), 25.3 (t), 36.5 (t), 98.0 (d), 127.5 (d×2), 129.7 (d×2), 135.6 (s), 143.5 (s), 143.6 (s), 195.4 (CO). Anal. Calcd for $C_{13}H_{16}N_2O_3S$ (280.34): C, 55.70; H, 5.75; N, 9.99. Found: C, 55.91; H, 5.87; N, 9.75.

4.3. General procedure for the synthesis of compounds (8a–p)

To a solution of **7a**–**d** (7.14 mmol) in anhydrous DMF (8 mL), the suitable benzaldehyde (7.14 mmol), AcOH (0.35 mL) and piperidine (1.4 mL) were added. The reaction mixture was heated at 80–100 °C. Then, it was poured onto crushed ice and the solid collected and dried. For compounds **8b**–**p** see supplementary data.

*4.3.1. 3-Phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one (**8a**).* This compound was obtained from the reaction of **7a** with benzaldehyde after 1 h at 85 °C. White solid; R_f=0.20 (CH_2Cl_2/EtOAc 95:5); mp 187–188 °C; yield 92%; IR cm^{-1}: 3210 (NH), 1649 (CO). ^{1}H NMR (DMSO-d_6): δ 1.99–2.12 (2H, m, CH_2), 2.46 (2H, t, *J*=6.1 Hz, CH_2), 2.87 (2H, t, *J*=6.1 Hz, CH_2), 7.35–7.48 (3H, m, H-3″, H-4″ and H-5″), 8.04 (2H, d, *J*=7.5 Hz, H-2″ and H-6″), 13.38 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 21.6 (t), 23.0 (t), 39.2 (t), 113.9 (s), 114.0 (s), 127.9 (d×2), 128.2 (d×2), 128.5 (d), 131.5 (s) 153.8 (s), 192.7 (CO). Anal. Calcd for $C_{13}H_{12}N_2O$ (212.25): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.71; H, 5.53; N, 13.11. MS *m*/*z* 213 (MH^+). HRMS: $[MH]^+$, found 213.1058. $C_{13}H_{12}N_2O$ requires 213.1022.

4.4. General procedure for the synthesis of compounds (8q–t)

To a solution of **8m**–**p** (1.5 mmol) in ethanol, palladium 10% on carbon was added and the reaction mixture was stirred under hydrogen atmosphere for 24 h. Then it was filtered and the filtrate was dried under reduced pressure. The crude was purified by chromatography column, using dichloromethane: ethyl acetate (9:1) as eluent. For compounds **8r**–**t** see supplementary data.

*4.4.1. 2-(4-Aminophenyl)-3-phenyl-2,5,6,7-tetrahydro-4H-indazol-4-one (**8q**).* This compound was obtained from **8m**. Yellow solid; R_f=0.14 (CH_2Cl_2/EtOAc 95:5); mp 207–208 °C; yield 69%; IR cm^{-1}: 3430–3346 (NH_2), 1664 (CO). ^{1}H NMR (DMSO-d_6): δ 2.01–2.14 (2H, m, CH_2), 2.43 (2H, t, *J*=6.1 Hz, CH_2), 2.84 (2H, t, *J*=6.1 Hz, CH_2), 5.37 (2H, s, NH_2), 6.44 (2H, d, *J*=8.7 Hz, H-2′ and H-6′), 6.83 (2H, d, *J*=8.7 Hz, H-3′ and H-5′), 7.23–7.35 (5H, m, Ar). ^{13}C NMR (DMSO-d_6): δ 22.7 (t), 23.0 (t), 39.3 (t), 113.2 (d×2), 115.7 (s), 126.6 (d×2), 127.2 (s), 127.7 (d×2), 128.7 (d), 128.8 (s), 130.2 (d×2), 142.2 (s), 148.7 (s), 155.9 (s), 193.0 (CO). Anal. Calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.08; H, 5.92; N, 13.77. MS *m*/*z*

304 (MH^+). HRMS: $[MH]^+$, found 304.1409. $C_{19}H_{17}N_3O$ requires 304.1444.

4.5. General procedure for the synthesis of compounds (9a–y)

To a solution of **8a–d** (5.7 mmol) in anhydrous DMF (14 mL), NaH (5.7 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h at rt. The suitable benzyl halide (8.55 mmol) was added at 0 °C and the reaction mixture was stirred at rt or at reflux. Then, it was poured onto crushed ice and the solid collected and dried. Purification by chromatography column, using dichloromethane as eluent, gave the expected product. For compounds **9b–y** see supplementary data.

*4.5.1. 1-Benzyl-3-phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one (**9a**).* This compound was obtained from the reaction of **8a** with benzyl bromide after 24 h at rt. White solid; R_f=0.61 (CH_2Cl_2/EtOAc 95:5); mp 91–92 °C; yield 69%; IR cm^{-1}: 1667 (CO). ^1H NMR (DMSO-d_6): δ 2.00–2.12 (2H, m, CH_2), 2.44 (2H, t, J=6.2 Hz, CH_2), 2.91 (2H, t, J=6.2 Hz, CH_2), 5.41 (2H, s, CH_2), 7.25–7.45 (8H, m, Ar), 8.03 (2H, d, J=7.5 Hz, H-2″ and H-6″). ^{13}C NMR (DMSO-d_6): δ 21.2 (t), 22.5 (t), 38.6 (t), 52.3 (t), 115.0 (s), 127.4 (d×2), 127.7 (d), 127.8 (d×2), 128.3 (d×2), 128.4 (d), 128.7 (d×2), 132.2 (s), 136.3 (s) 149.3 (s), 151.8 (s), 192.2 (CO). Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37): C, 79.44; H, 6.00; N, 9.26. Found: C, 79.32; H, 6.19; N, 9.08. MS m/z 303 (MH^+). HRMS: $[MH]^+$, found 303.1521. $C_{20}H_{18}N_2O$ requires 303.1491.

4.6. General procedure for the synthesis of compounds (10e–t, 11a–y)

To a solution of the suitable ketone **8e–t**, **9a–y** (0.66 mmol) in anhydrous DMF (2 mL), DMFDMA (0.88 mL, 6.6 mmol) was added and the mixture was stirred under microwave irradiation (PW 150, T 150 °C). The reaction mixture was poured onto crushed ice and solid was filtered off and dried. For compounds **10f–t**, **11a–y** see supplementary data.

*4.6.1. 5-[(Dimethylamino)methylidene]-2,3-diphenyl-2,5,6,7-tetrahydro-4H-indazol-4-one (**10e**).* This compound was obtained from **8e** after 30 min. Brown solid; R_f=0.68 (CH_2Cl_2/EtOAc 95:5); mp 147–148 °C; yield 83%; IR cm^{-1}: 1643 (CO). ^1H NMR (DMSO-d_6): δ 2.79 (2H, t, J=6.2 Hz, CH_2), 2.99 (2H, t, J=6.2 Hz, CH_2), 3.07 (6H, s, 2× CH_3), 7.17–7.34 (11H, m, Ar and CH). ^{13}C NMR (DMSO-d_6): δ 22.7 (t), 23.4 (t), 43.2 (q×2), 102.6 (s), 117.5 (s), 125.4 (d×2), 127.5 (d×2), 127.6 (d), 128.5 (d), 128.8 (d×2), 129.1 (s), 130.5 (d×2), 139.2 (s), 142.1 (s), 148.4 (d), 154.7 (s), 181.5 (CO). Anal. Calcd for $C_{22}H_{21}N_3O$ (343.42): C, 76.94; H, 6.16; N, 12.24. Found: C, 77.11; H, 5.93; N, 12.01.

4.7. General procedure for the synthesis of compounds (12e–t, 13a–y)

To a solution of the suitable enaminones **10e–t**, **11a–y** (1.0 mmol) in methanol:acetic acid (2:1), hydroxylamine hydrochloride (1.1 mmol) was added and the reaction mixture was heated at reflux for 50 min. The solvent was evaporated, the residue poured onto crushed ice and the precipitated was filtered, dried and purified by flash chromatography using dichloromethane as eluent. For compounds **12f–t**, **13a–y** see supplementary data.

*4.7.1. 7,8-Diphenyl-5,7-dihydro-4H-[1,2]oxazolo[5,4-e]indazole (**12e**).* This compound was obtained from the reaction of **10e**. Light green solid; R_f=0.38 (CH_2Cl_2/EtOAc 95:5); mp 157–158 °C; yield 56%. ^1H NMR ($CDCl_3$): δ 2.92 (2H, t, J=7.2 Hz, CH_2), 3.08 (2H, t, J=7.2 Hz, CH_2), 7.23–7.46 (10H, m, Ar), 8.15 (1H, s, H-3). ^{13}C NMR ($CDCl_3$): δ 19.0 (t), 22.0 (t), 109.0 (s), 110.2 (s), 125.1 (d×2), 127.6 (d), 128.5 (d×2), 128.6 (s), 129.0 (d×2), 129.1 (d), 129.7 (d×2), 137.6 (s), 139.5 (s), 148.7 (d), 152.0 (s), 161.7 (s). Anal. Calcd for $C_{20}H_{15}N_3O$ (313.35): C, 76.66; H, 4.82; N, 13.41. Found: C, 76.47; H, 4.98; N, 13.59. MS m/z 314 (MH^+). HRMS: $[MH]^+$, found 314.1314. $C_{20}H_{15}N_3O$ requires 314.1288.

Acknowledgements

This work was financially supported by Ministero dell'Istruzione dell'Università e della Ricerca. We thank the National Cancer Institute (Bethesda, MD) for the antitumour tests reported in this paper.

Supplementary data

Table 2 describing the GI_{50} values of compound **13t**, the spectroscopic data (IR, ^1H and ^{13}C NMR) and elemental analysis (C, H, N) of compounds **7b–d**, **8b–p**, **9b–y**, **10f–t**, **11a–y** are reported in the supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.083.

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