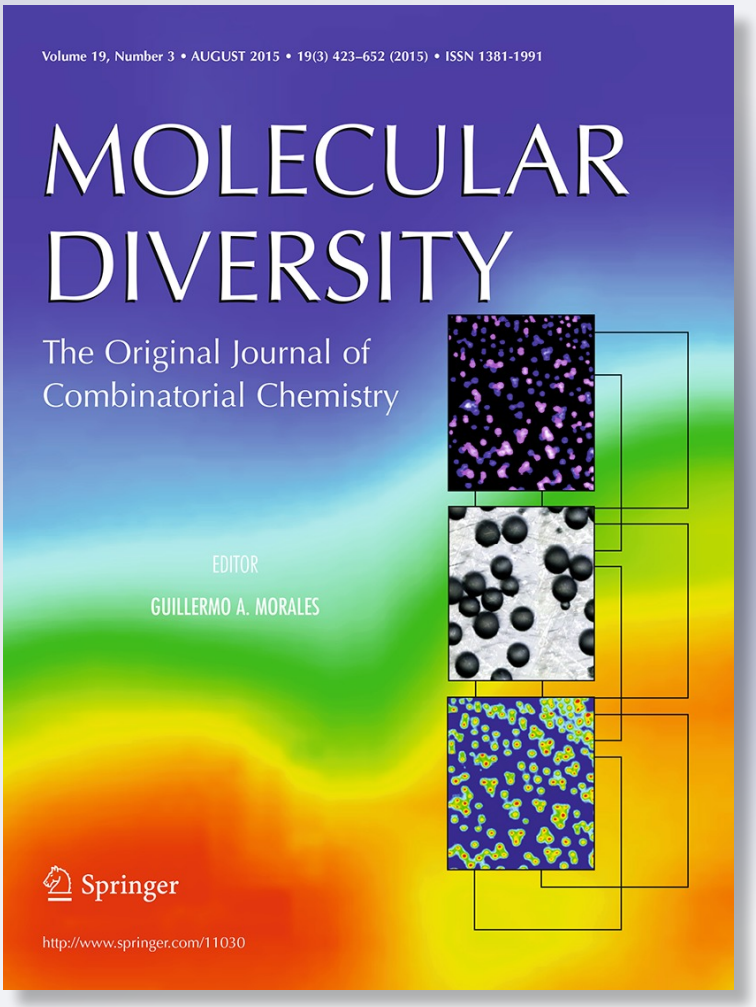
Efficient synthesis of highly substituted tetrahydroindazolone derivatives

Angela Scala, Anna Piperno, Francesco Risitano, Santa Cirmi, Michele Navarra & Giovanni Grassi

Molecular Diversity

ISSN 1381-1991
Volume 19
Number 3

Mol Divers (2015) 19:473-480
DOI 10.1007/s11030-015-9583-5



Springer

Mol Divers (2015) 19:473–480
DOI 10.1007/s11030-015-9583-5

FULL-LENGTH PAPER

Efficient synthesis of highly substituted tetrahydroindazolone derivatives

Angela Scala[1] · **Anna Piperno**[1] · **Francesco Risitano**[1] · **Santa Cirmi**[2] · **Michele Navarra**[2] · **Giovanni Grassi**[1]

Received: 22 October 2014 / Accepted: 12 March 2015 / Published online: 18 March 2015

Abstract A straightforward and efficient method for the synthesis of novel highly substituted and diversely functionalized indazolone derivatives has been developed. The transformation consists of a cyclocondensation of selected 1, 3, 3′-tricarbonyls with monosubstituted hydrazines. The starting β-triketones were prepared by an efficient chemo- and regioselective method under MW irradiation, exploiting the oxazolone chemistry. The reaction is easily accomplished under mild conditions and appears versatile, providing a synthetic diversification method with potential for drug-like compounds preparation.

Keywords Indazolone · Hydrazines · Oxazolone · β-Triketones

Introduction

Indazole- and indazolone-based compounds have recently received special attention in virtue of their useful properties [1] and biological activities, such as analgesic [2], anticancer [3,4], anti-inflammatory [5], antifertility [6], antimicrobial [7], antifungal [8], anti-angiogenic [9], antiproliferative [10] and cytotoxic [11].

Nonetheless, the synthesis of these privileged structures suffers from some limitations, such as the difficulties of regio- and stereochemical control. Accordingly, current efforts are directed towards the identification of new, efficient and selective synthetic strategies for the construction of highly substituted and diversely functionalized indazolone derivatives.

To address this issue, in the framework of our studies dealing with the design of poly functionalized heterocycles [12–18], we report herein the synthesis of a set of indazolone-based compounds, with the aim to maximize their molecular diversity by exploiting the oxazolone chemistry to functionalize the starting 1,3-dicarbonyls.

Indeed, it is well known the usefulness of oxazol-5-(4H)-ones as versatile intermediates for the preparation of highly substituted heterocycles and structurally complex amino acids [19]. Furthermore, our interest in the use of enolizable cyclic 1,3-dicarbonyls as building blocks for the synthesis of novel molecular architectures is well documented [17,18,20–22].

The proposed strategy appears versatile providing a synthetic diversification method with potential for drug-like compounds preparation. The biological relevance of selected novel compounds has been preliminarily assessed in vitro against HT-29 colorectal adenocarcinoma and HepG2 hepatocellular carcinoma cells, evaluating both the antiproliferative and the cytotoxic effects. Additionally, our indazolone scaffold includes necessary requirements for the optimization of pharmaceutical properties, such as the presence of an amino group in the side chain, which could be further exploited to improve the druggability by conjugation with aminoacids, peptides or biomaterials.

Electronic supplementary material The online version of this article (doi:10.1007/s11030-015-9583-5) contains supplementary material, which is available to authorized users.

✉ Giovanni Grassi
ggrassi@unime.it

[1] Dipartimento di Scienze Chimiche, Università di Messina, V.le F. Stagno D'Alcontres 31, 98166 Messina, Italy

[2] Dipartimento di Scienze del Farmaco e Prodotti per la Salute, Università V.le Annunziata, 98166 Messina, Italy

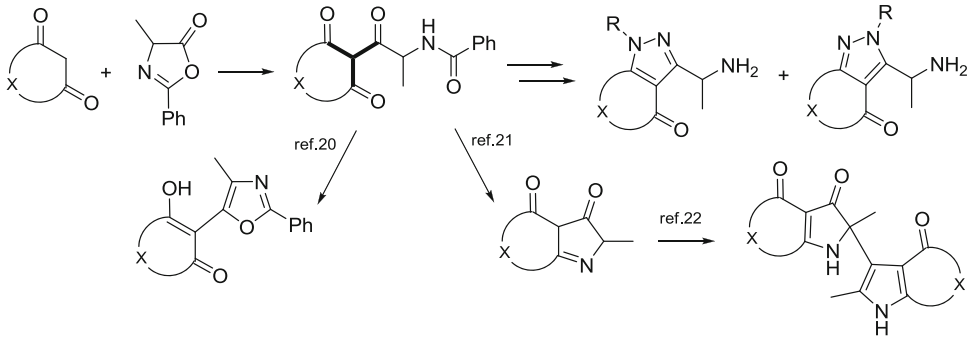
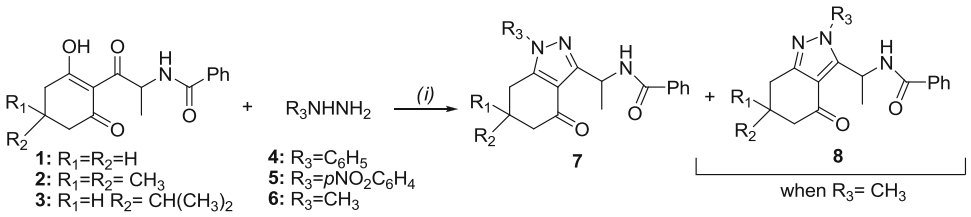


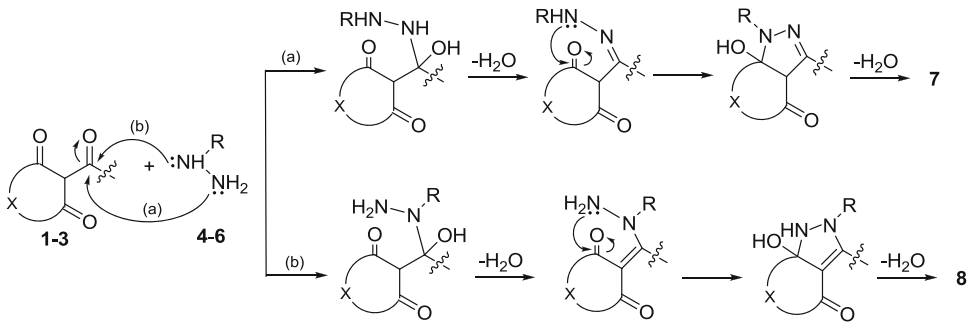
Fig. 1 Overview of our recent exploitation of oxazolone and β-triketones chemistry



Scheme 1 Synthetic route to tetrahydroindazolones **7** and **8**. (*i*) abs. EtOH, reflux, 5 h. Yields of compounds **7** and **8**

Entry	R_1	R_2	R_3	Product	Yield (%)[a]
a	H	H	C_6H_5	**7a**	73
b	H	H	$pNO_2C_6H_4$	**7b**	84
c	H	H	CH_3	**7c+8c**	58
d	CH_3	CH_3	C_6H_5	**7d**	81
e	CH_3	CH_3	$pNO_2C_6H_4$	**7e**	98
f	CH_3	CH_3	CH_3	**7f+8f**	66
g	H	$CH(CH_3)_2$	C_6H_5	**7g**	99
h	H	$CH(CH_3)_2$	$pNO_2C_6H_4$	**7h**	98
i	H	$CH(CH_3)_2$	CH_3	**7i+8i**	98

[a]Yield of pure isolated product



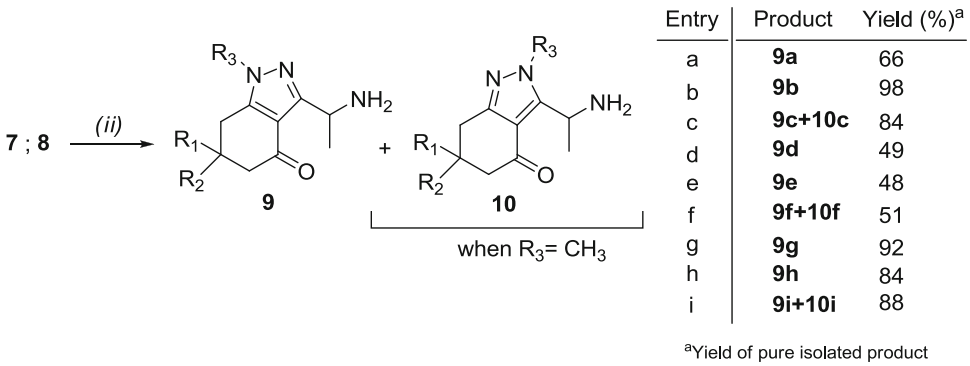
Scheme 2 Proposed mechanism for tetrahydroindazolones formation

Results and discussion

As reported in our previous study [20], starting from selected enolizable cyclic 1,3-dicarbonyls and 4-methyl-2-phenyl-1,3-oxazol-5(*4H*)-one, a series of powerful open-chain derivatives, bearing a Y-shaped 1, 3, 3′-tricarbonyl moiety, was prepared by an efficient chemo- and regioselective method under MW irradiation (Fig. 1). We have recently demonstrated that cyclic β-triketones and their enol derivatives represent useful building blocks for the construction of various heterocyclic systems [21–24], due to their high degree of functionalization and their well-known [25] high reactivity (Fig. 1).

To further expand our ongoing studies on their synthetic usefulness, we have herein investigated the cyclocondensation of selected 1, 3, 3′-tricarbonyls **1–3** with monosubstituted hydrazines **4–6** as ambident nucleophiles (Scheme 1).

The reaction proceeds efficiently in refluxing ethanol through nucleophilic attack at the exo-cyclic carbonyl of **1–3** with the formation of a non-isolated hydrazone intermediate, followed by intramolecular cyclocondensation (Scheme 2).



Entry	Product	Yield (%)[a]
a	**9a**	66
b	**9b**	98
c	**9c+10c**	84
d	**9d**	49
e	**9e**	48
f	**9f+10f**	51
g	**9g**	92
h	**9h**	84
i	**9i+10i**	88

[a]Yield of pure isolated product

Scheme 3 Synthetic route to indazolones **9** and **10**. (*ii*) 6N HCl, glacial CH3COOH, reflux, 24 h. Yields of compounds **9** and **10**

The reaction proceeds regioselectively yielding **7** as the sole product with arylhydrazines **4** and **5** because of the inherent differences between the nucleophilicities of the two nitrogens [26]. Indeed, the lower nucleophilicity of the internal nitrogen of arylhydrazines, due to the conjugation of the lone-pair in the aromatic ring, leads to the regioselective synthesis of 1,3-disubstituted tetrahydroindazolones **7**.

Conversely, the similar nucleophilicities of the two nitrogens of alkylhydrazines, such as **6**, induces a quite difficult regiochemical control [26], yielding inseparable regioisomeric mixtures of tetrahydroindazolones **7** and **8**. Therefore, the regioisomeric ratio was determined by ^{1}H-NMR spectroscopy on the crude reaction mixture, resulting in a 3. 5: 1 ratio.

The proposed synthetic methodology appears versatile, and it allows to maximize the molecular diversity of tetrahydroindazolone scaffold, using different enolizable cyclic 1,3-dicarbonyls and different aminoacids as starting materials for the oxazolone formation. Compounds **7** and **8**, not previously described in literature, have been obtained in good to excellent yields (58–99 %). Interestingly, to the best of our knowledge, the introduction of a functionalized chain at the pyrazole carbon is unprecedented, as only alkyl or aryl substituents (Me, Et, i-Pr, CF_3, cyclohexyl, Ph, thienyl, etc.) have been introduced so far [27–29].

Another advantage of our approach relies on the possibility to further modify the mentioned chain derived from the oxazolone ring opening. Indeed, the acid-promoted *N*-deprotection of the functionalized chain of **7** and **8** leads to the interesting amino derivatives **9** and **10** (Scheme 3), whose NH_2 group could be further derivatized to improve the pharmaceutical properties including pharmacokinetic and druggability, by conjugation with aminoacids, peptides or biomaterials.

The regioisomeric ratio for compounds **9** and **10** was determined by ^{1}H-NMR spectroscopy on the crude reaction mixture, resulting in a 3.5:1 ratio.

The structures of new products were determined on the basis of analytical and spectroscopic data (See "Experimental" section).

Structural assignment of regioisomers was based on gHMBCAD and confirmed by 2D-NOESY experiments carried out on compounds **7a** and on **7c+8c**.

The presence of a NOE correlation between the ortho protons of NC_6H_5 and the protons of the closer methylene group in **7a** suggested the exclusive formation of one regioisomer.

Conversely, in the mixture **7c+8c**, the two regioisomers can be conveniently distinguished on the basis of diagnostic correlations between the protons of NMe group on the pyrazole ring and the protons of the closer methylene group in **7c** and between the protons of NMe group on the pyrazole ring and the proton of the CH of the side chain in **8c**.

Several indazolone derivatives have been reported as anticancer agents [3,4,10,11]. Therefore, the antiproliferative effect of selected indazolones has been preliminarily screened in vitro against HT-29 colorectal adenocarcinoma and HepG2 hepatocellular carcinoma cells. To determine cell proliferation, both MTT and cell count assays were performed, while cytotoxicity was assessed by either lactate dehydrogenase (LDH) and trypan blue tests. (see Electronic Supplementary Material)

Conclusions

In summary, an efficient and straightforward route to novel highly substituted and diversely functionalized indazolone derivatives from enolizable cyclic 1, 3, 3′-tricarbonyls and monosubstituted hydrazines has been developed. The reaction is easily accomplished under mild conditions and appears versatile, making new compounds suitable for further studies. In addition, a preliminary screening has revealed that some of them display in vitro antiproliferative effect on HT-29 colorectal adenocarcinoma and HepG2 hepatocellular carcinoma cells, confirming the well-known biological relevance of this heterocyclic scaffold that may be exploited to design novel and more effective antiproliferative agents, by appropriate chemical modifications and decorations.

Experimental

General

Melting points were determined on a Kofler melting apparatus and are uncorrected. IR spectra were recorded in Nujol with a Nicolet Impact 410D spectrometer. ^{1}H and ^{13}C-NMR spectra were obtained on a Varian 500MHz spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz, respectively. Microanalyses and mass spectrometry analyses were carried out on a Carlo Erba EA 1102 and on a 3200 QTRAP (Applied Biosystem SCIEX), respectively. All solvents and reagents were obtained from commercial sources and purified before use if necessary. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100 mm) for column chromatography. Compounds **1**, **2** and **3** were prepared according to the literature [20,22].

Typical procedure for the preparation of compounds 7 and 8

To a stirred solution of **1, 2** or **3** (1 mmol) in abs EtOH (20 mL), hydrazine **4**, **5** or **6** (1.5 mmol) was added. The mixture was stirred and heated at reflux for approximately 5h. The progress of the reaction was monitored by TLC (CH_2Cl_2/AcOEt 9:1). After completion of reaction as checked by TLC, the reaction mixture was evaporated and purified by chromatographic column (CH_2Cl_2/AcOEt 9:1), affording compounds **7** and **8** as yellowish oil.

Analytical and spectral data of compounds 7 and 8

N-(1-(4-oxo-1-phenyl -4,5,6,7-tetrahydro-1H-indazol-3-yl) ethyl)benzamide **(7a)** (73 %); IR ($CHCl_3$): 3287, 1732, 1660, 1645; ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 1.55 (d, *J* = 7.0 Hz, 3H), 2.16–2.21 (m, 2H), 2.61–2.65 (m, 2H), 2.91–3.00 (m, 2H), 5.77 (dq, *J* = 7.0 Hz, 9.5 Hz, 1H), 7.41–7.48 (m, 3H Ar), 7.49–7.50 (m, 5H Ar), 7.91 (d, *J* = 7.0 Hz, 2H Ar), 8.94 (d, *J* = 9.5 Hz, 1H, NH);^{13}C NMR (125 MHz, $CDCl_3$) : δ = 22.2, 23.3, 23.3, 38.0, 44.0, 116.5, 123.6, 127.1, 127.1, 128.4, 129.3, 131.2, 134.5, 138.1, 151.4, 154.7, 165.8, 195.2; ESI-MS (m/z) = 360.14 $[M+1]^+$; Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.56; H, 5.92; N, 11.71.

N-(1-(1-(4-nitrophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7b)** (84 %); IR ($CHCl_3$): 3320, 1730, 1661, 1646, 1519, 1347; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 7.1 Hz, 3H), 2.21–2.24 (m, 2H), 2.63–2.67 (m, 2H), 3.03–3.08 (m, 2H), 5.74 (dq, *J*= 7.1 Hz, 9.8 Hz, 1H), 7.42–7.55 (m, 3H Ar), 7.73 (d, *J* = 8.8 Hz, 2H Ar), 7.86 (d, *J* = 8.0 Hz, 2H Ar), 8.34 (d, *J*= 8.8 Hz, 2H Ar), 8.76 (d, *J*= 9.8 Hz,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 23.3, 23.9, 37.9, 43.9, 117.8, 123.5, 124.9, 127.1, 128.5, 131.5, 134.1, 143.1, 146.5, 151.9, 155.8, 166.2, 195.0; ESI-MS (m/z) = 405.14 $[M+1]^+$; Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.36; H, 4.94; N, 13.88.

N-(1-(1-methyl-4-oxo-4,5,6,7-tetrahydro -1H -indazol-3-yl)ethyl)benzamide **(7c)** (45 %); IR ($CHCl_3$): 3270, 1730, 1656, 1638; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 7.1 Hz, 3H), 2.16–2.19 (m, 2H), 2.51–2.56 (m, 2H), 2.76–2.81 (m, 2H), 3.75 (s, 3H), 5.62 (dq, *J* = 7.1 Hz, 9.3 Hz, 1H), 7.40–7.45 (m, 3H Ar), 7.89 (d, *J* = 8.4 Hz, 2H Ar), 8.90 (d, *J* = 9.3 Hz,1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 22.8, 35.7, 37.7, 43.9, 115.1, 127.0, 128.3, 131.1, 134.4, 151.5, 153.6, 165.8, 194.6; ESI-MS (m/z) = 298.36 $[M+1]^+$; Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.70; H, 6.42; N, 14.16.

N-(1-(2-methyl-4-oxo-4,5,6,7-tetrahydro -2H-indazol-3-yl)ethyl)benzamide **(8c)** (13 %); IR ($CHCl_3$): 3270, 1730, 1656, 1638; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 7.1 Hz, 3H), 2.10–2.13 (m, 2H), 2.50–2.54 (m, 2H), 2.75–2.80 (m, 2H), 3.94 (s, 3H), 5.64 (dq, *J* = 7.1 Hz, 8.9 Hz, 1H), 7.40–7.45 (m, 3H Ar), 7.89 (d, *J* = 8.4 Hz, 2H Ar), 9.36 (d, *J* = 8.9 Hz,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 21.2, 35.7, 38.8, 41.0, 115.2, 127.1, 128.4, 131.5, 134.0, 146.8, 156.9, 166.1, 196.4; ESI-MS (m/z) = 298.36 $[M+1]^+$; Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.70; H, 6.42; N, 14.16.

N-(1-(6,6-dimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7d)** (81 %); IR ($CHCl_3$): 3294, 1730, 1670, 1630; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (s, 3H), 1.16 (s, 3H), 1.55 (d, *J* = 7.1 Hz, 3H), 2.47 (d, *J* = 16.4 Hz, 1H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.77 (d, *J* = 16.4 Hz, 1H), 2.87 (d, *J* = 16.4 Hz, 1H), 5.78 (dq, *J* = 7.1 Hz, 9.4 Hz, 1H), 7.41–7.48 (m, 3H Ar), 7.50–7.55 (m, 5H Ar), 7.92 (d, *J* = 10 Hz, 2H Ar), 8.96 (d, *J* = 9.4 Hz,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 27.8, 28.8, 35.8, 37.1, 44.0, 52.2, 115.7, 123.9, 127.2, 128.4, 128.4, 129.4, 131.2, 134.6, 138.1, 150.4, 154.8, 166.0, 194.4; ESI-MS (m/z) = 388.16 $[M+1]^+$; Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.41; H, 6.52; N, 10.86.

N-(1-(6,6-dimethyl-1-(4-nitrophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7e)** (98 %); IR ($CHCl_3$): 3448, 1732, 1673, 1630; 1521; 1345; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (s, 3H), 1.19 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H), 2.50 (d, *J* = 16.5 Hz, 1H), 2.58 (d, *J* = 16.5 Hz, 1H), 2.87 (d, *J* = 17.0 Hz, 1H), 2.96 (d, *J* = 17.0 Hz, 1H), 5.78 (dq, *J* = 7.0 Hz, 9.4 Hz, 1H), 7.41–7.49 (m, 3H Ar), 7.75 (d, *J* = 9.4 Hz, 2H), 7.90 (d, *J* = 10 Hz, 2H Ar), 8.40 (d, *J* = 9.4 Hz, 2H), 8.76 (d, *J* = 9.4 z,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 27.8, 28.4, 35.8, 37.5, 43.7, 51.8, 116.7, 123.5, 124.8, 126.9, 128.3, 131.2, 134.1, 142.9, 146.4, 150.9, 155.5, 166.0, 194.2; ESI-MS (m/z) = 388.16 $[M+1]^+$; Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.69; H, 5.61; N, 12.99.

N-(1-(1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7f)** (51 %); IR ($CHCl_3$): 3294, 1733, 1653, 1600; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 0.98 (s, 3H), 1.34 (d, J = 8.2 Hz, 3H), 2.20–2.32 (m, 2H), 2.44–2.58 (m, 2H), 3.58 (s, 3H), 5.48 (dq, J = 8.2 Hz, 9.0 Hz, 1H), 7.25–7.34 (m, 3H Ar), 7.75 (d, J = 7.3 Hz, 2H Ar), 8.89 (d, J = 9.0 Hz,1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 28.0, 35.0, 35.7, 43.9, 51.9, 114.0, 127.0, 128.3, 131.1, 134.4, 150.7, 153.4, 165.8, 193.9; ESI-MS (m/z) = 326.16 $[M+1]^+$; Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.17; H, 7.16; N, 12.93.

N-(1-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-2H-indazol-3-yl)ethyl)benzamide **(8f)** (14 %); IR ($CHCl_3$): 3294, 1733, 1653, 1600; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 0.95 (s, 3H), 1.35 (d, J = 8.2 Hz, 3H), 2.21–2.33 (m, 2H), 2.45–2.59 (m, 2H), 3.81 (s, 3H), 5.50 (dq, J = 8.2 Hz, 9.0 Hz, 1H), 7.25–7.34 (m, 3H Ar), 7.75 (d, J = 7.3 Hz, 2H Ar), 9.32 (d, J = 9.0 Hz,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 28.5, 35.2, 35.7, 41.1, 52.7, 114.2, 127.1, 128.4, 131.5, 133.9, 147.0, 156.2, 166.0, 195.9; ESI-MS (m/z) = 326.16 $[M+1]^+$; Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.17; H, 7.16; N, 12.93.

N-(1-(6-isopropyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7g)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (99 %); IR ($CHCl_3$): 3286, 1717, 1659, 1640; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 − −0.94 (m, 6H), 1.49 (d, J = 7.1 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H), 1.65–1.70 (m, 2H), 2.03–2.06 (m, 2H), 2.32–2.43 (m, 2H), 2.59–2.74 (m, 4H), 2.82–2.86 (m, 2H), 5.72 (dq, J = 7.1 Hz, 9.3 Hz, 2H), 7.31–7.48 (m, 16H Ar), 7.86 (d, J = 7.3 Hz, 2H Ar), 7.90 (d, J = 7.1 Hz, 2H Ar), 8.97 (d, J = 9.3 Hz, 1H, NH), 9.07 (d, J = 9.6 Hz,1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.5, 19.6, 19.6, 22.1, 22.2, 26.8, 26.9, 31.6, 31.8, 41.9, 42.0, 42.5, 42.7, 44.0, 116.5, 116.6, 123.8, 123.9, 127.1, 127.1, 127.2, 128.2, 128.4, 129.4, 129.9, 131.3, 132.9, 134.4, 138.0, 138.1, 151.5, 151.7, 154.5, 166.1, 195.1, 195.4; ESI-MS (m/z) = 402.54 $[M+1]^+$; Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.82; H, 6.81; N, 10.50.

N-(1-(6-isopropyl-1-(4-nitrophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7h)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (98 %); IR ($CHCl_3$): 3355, 1716, 1661, 1650; 1520; 1346; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 − −1.01 (m, 6H), 1.53 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 7.1 Hz, 3H), 1.76–1.79 (m, 2H), 2.13–2.14 (m, 2H), 2.40–2.50 (m, 2H), 2.68–2.86 (m, 4H), 2.90–3.05 (m, 2H), 5.70 (m, 2H), 7.41–7.56 (m, 6H Ar), 7.73 (d, J = 8.9 Hz, 2H Ar), 7.91 (d, J = 8.0 Hz, 2H Ar), 8.38 (d, J = 8.9 Hz, 2H Ar), 8.75 (d, J = 9.3 Hz, 1H, NH), 8.82 (d, J = 9.3 Hz,1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.3, 19.4, 19.5, 19.5, 21.7, 21.8, 27.3, 27.4, 31.6, 31.7, 41.7, 41.8, 42.5, 42.7, 43.9, 117.8, 117.8, 123.3, 123.5, 123.6, 124.9, 127.0, 127.0, 128.2, 128.4, 129.2, 131.4, 134.0, 142.9, 143.0, 146.5, 152.0, 152.1, 155.5, 166.2, 195.0, 195.1; ESI-MS (m/z) = 447.24 $[M+1]^+$; Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.30; H, 5.90; N, 12.50.

N-(1-(6-isopropyl-1-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-3-yl)ethyl)benzamide **(7i)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (76 %); IR ($CHCl_3$): 3274, 1714, 1655; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 − −1.00 (m, 6H), 1.47 (d, J = 5.4 Hz, 3H), 1.50 (d, J = 5.7 Hz, 3H), 1.72–1.76 (m, 2H), 2.11–2.12 (m, 2H), 2.25–2.36 (m, 2H), 2.42–2.56 (m, 2H), 2.57–2.79 (m, 2H), 2.81–2.84 (m, 2H), 3.75 (s, 3H), 5.59–5.61 (m, 2H), 7.38–7.46 (m, 6H Ar), 7.87 (d, J = 8.0 Hz, 2H Ar), 7.90 (d, J = 8.0 Hz, 2H Ar), 8.90 (d, J = 9.3 Hz, 1H, NH), 8.95 (d, J = 9.3 Hz,1H, NH);^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.6, 19.6, 19.6, 22.2, 24.9, 31.6, 31.8, 31.9, 35.8, 41.9, 41.9, 42.1, 42.3, 43.9, 115.2, 115.3, 127.1, 127.2, 127.2, 128.3, 128.5, 131.1, 131.5,134.6, 151.4, 151.6, 153.8, 153.8, 165.9, 194.4, 194.6; ESI-MS (m/z) = 340.14 $[M+1]^+$; Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.80; H, 7.44; N, 12.40.

N-(1-(6-isopropyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-2H-indazol-3-yl)ethyl)benzamide **(8i)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (22 %); IR ($CHCl_3$): 3274, 1714, 1655; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 − −0.97 (m, 6H), 1.47 (d, J = 5.4 Hz, 3H), 1.50 (d, J = 5.7 Hz, 3H), 1.69–1.73 (m, 2H), 1.99–2.10 (m, 2H), 2.25–2.36 (m, 2H), 2.42–2.56 (m, 2H), 2.57–2.79 (m, 2H), 2.85–2.90 (m, 2H), 3.94 (s, 3H), 5.62–5.64 (m, 2H), 7.38–7.46 (m, 6H Ar), 7.87 (d, J = 8.0 Hz, 2H Ar), 7.90 (d, J = 8.0 Hz, 2H Ar), 9.39 (d, J = 9.3 Hz, 1H, NH), 9.41 (d, J = 9.3 Hz,1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 21.0, 21.1, 21.1, 22.2, 26.5, 31.6, 31.8, 31.9, 36.9, 41.0, 42.7, 43.0, 43.0, 115.2, 115.3, 127.1, 127.2, 127.2, 128.3, 128.5, 131.1, 131.5,134.6, 151.4, 151.6, 153.8, 153.8, 165.9, 194.4, 194.6; ESI-MS (m/z) = 340.14 $[M+1]^+$; Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.80; H, 7.44; N, 12.40.

Typical procedure for the preparation of compounds 9 and 10

0.3 g of **7** and **8** were dispersed in 30 mL of a mixture of 6N HCl (15 mL) and glacial acetic acid (15 mL). The mixture was stirred and heated at reflux for approximately 24 h. After cooling, a 10 % solution of NaOH was added to reach pH 9–10. The aqueous solution was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered, evaporated under reduced pressure and purified by chromatographic column (CH_2Cl_2/AcOEt 9:1), affording compounds **9** and **10** as yellowish oil.

Analytical and spectral data of compounds 9 and 10

3-(1-Aminoethyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one **(9a)** (66 %); IR ($CHCl_3$): 3353, 1668, 1652; ^{1}H NMR

(500 MHz, $CDCl_3$): 1.50 (d, J = 6.9 Hz, 3H), 2.19–2.22 (m, 2H), 2.57–2.60 (m, 2H), 3.02–3.05 (m, 2H), 4.34 (q, J = 6.9 Hz, 1H), 7.38–7.48 (m, 5H Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 23.4, 23.5, 38.3, 45.9, 116.6, 123.8, 128.1, 129.3, 138.5, 150.8, 158.8, 193.8; ESI-MS (m/z) = 256.35 $[M + 1]^+$; Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.59; H, 6.74; N, 16.50.

3-(1-Aminoethyl)-1-(4-nitrophenyl)-6,7-dihydro-1H-indazol-4(5H)-one **(9b)** (98 %); IR ($CHCl_3$): 3367, 1668, 1598, 1520, 1346; ^{1}H NMR (500 MHz, $CDCl_3$): 1.50 (d, J = 7.1 Hz, 3H), 2.11–2.14 (m, 2H), 2.52–2.55 (m, 2H), 2.90–2.92 (m, 2H), 4.37 (q, J = 7.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 2H Ar), 8.36 (d, J = 8.9 Hz, 2H Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 23.5, 24.0, 38.1, 45.7, 113.3, 123.3, 124.9, 143.5, 146.4, 151.2, 158.7, 193.6; ESI-MS (m/z) = 301.15 $[M+1]^+$; Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 60.01; H, 5.41; N, 18.70.

3-(1-Aminoethyl)-1-methyl-6,7-dihydro-1H-indazol-4(5H)-one **(9c)** (65 %); IR ($CHCl_3$): 3394, 1655, 1640; ^{1}H NMR (500 MHz, $CDCl_3$): 1.30 (d, J = 6.5 Hz, 3H), 2.02–2.10 (m, 2H), 2.30–2.42 (m, 2H), 2.65–2.70 (m, 2H), 3.70 (s, 3H), 4.10 (q, J = 6.5 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 22.0, 22.9, 35.6, 38.0, 45.6, 115.1, 150.9, 157.6, 193.4; ESI-MS (m/z) = 194.20 $[M + 1]^+$; Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.10; H, 7.79; N, 21.70.

3-(1-Aminoethyl)-2-methyl-6,7-dihydro-2H-indazol-4(5H)-one **(10c)** (19 %); IR ($CHCl_3$): 3394, 1655, 1640; ^{1}H NMR (500 MHz, $CDCl_3$): 1.32 (d, J = 6.5 Hz, 3H), 2.02–2.10 (m, 2H), 2.30–2.42 (m, 2H), 2.65–2.70 (m, 2H), 3.73 (s, 3H), 4.10 (q, J = 6.5 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 22.0, 22.30, 36.7, 37.0, 45.9, 115.1, 150.9, 157.6, 193.4; ESI-MS (m/z) = 194.20 $[M + 1]^+$; Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.10; H, 7.79; N, 21.70.

3-(1-Aminoethyl)-6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one **(9d)** (49 %); IR ($CHCl_3$): 3351, 1670, 1598; ^{1}H NMR (500 MHz, $CDCl_3$): 1.05 (s, 3H), 1.06 (s, 3H), 1.45 (d, J = 6.7 Hz, 3H), 2.37 (s, 2H), 2.73 (s, 2H), 4.30 (q, J = 6.7 Hz, 1H), 7.36–7.47 (m, 5H Ar);^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 28.2, 28.3, 35.6, 37.1, 45.8, 52.4, 115.6, 123.8, 128.1, 129.3, 138.4, 150.0, 158.5, 193.2; ESI-MS (m/z) = 256.35 $[M + 1]^+$; Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.09; H, 7.44; N, 14.88.

3-(1-Aminoethyl)-6,6-dimethyl-1-(4-nitrophenyl)-6,7-dihydro-1H-indazol-4(5H)-one **(9e)** (48 %); IR ($CHCl_3$): 3360, 1658, 1620; 1523; 1344; ^{1}H NMR (500 MHz, $CDCl_3$): 1.08 (s, 6H), 1.45 (d, J = 6.6 Hz, 3H), 2.41 (s, 2H), 2.86 (s, 2H), 4.31 (q, J = 6.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H Ar), 8.30 (d, J = 8.4 Hz, 2H Ar);^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 28.2, 28.2, 35.8, 37.6, 45.6, 52.1, 116.9, 123.4, 124.9, 143.4, 146.3, 150.5, 159.2, 193.2; ESI-MS (m/z) = 328.17 $[M + 1]^+$; Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.20; H, 6.10; N, 17.09.

3-(1-Aminoethyl)-1,6,6-trimethyl-6,7-dihydro-1H-indazol-4(5H)-one **(9f)** (40 %); IR ($CHCl_3$): 3354, 1657, 1610; ^{1}H NMR (500 MHz, $CDCl_3$): 1.07 (s, 3H), 1.08 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H), 2.29 (s, 2H), 2.57 (s, 2H), 3.68 (s, 3H), 4.17 (q, J = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 28.5, 35.3, 35.4, 45.5, 52.2, 114.1, 150.2, 157.5, 192.7; ESI-MS (m/z) = 222.20 $[M + 1]^+$; Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.15; H, 8.70; N, 18.95.

3-(1-Aminoethyl)-2,6,6-trimethyl-6,7-dihydro-2H-indazol-4(5H)-one **(10f)** (11 %); IR ($CHCl_3$): 3354, 1657, 1610; ^{1}H NMR (500 MHz, $CDCl_3$): 1.02 (s, 6H), 1.38 (d, J = 6.4 Hz, 3H), 2.29 (s, 2H), 2.57 (s, 2H), 3.79 (s, 3H), 4.17 (q, J = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 28.4, 35.3, 35.4, 45.7, 52.2, 114.1, 150.2, 157.5, 192.7; ESI-MS (m/z) = 222.20 $[M + 1]^+$; Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.15; H, 8.70; N, 18.95.

3-(1-Aminoethyl)-6-isopropyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one **(9g)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (92 %); IR ($CHCl_3$): 3363, 1664, 1598; ^{1}H NMR (500 MHz, $CDCl_3$): 0.95 (d, J = 7.1 Hz, 6H), 0.96 (d, J = 7.1 Hz, 6H), 1.51 (d, J = 6.7 Hz, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.70–1.75 (m, 2H), 2.00–2.10 (m, 2H), 2.30–2.40 (m, 2H), 2.65–2.72 (m, 2H), 2.75–2.80 (m, 2H), 2.90–2.95 (m, 2H), 4.30 (q, J = 6.7 Hz, 2H), 7.40–7.52 (m, 10H Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.6, 22.0, 22.1, 26.9, 31.8, 42.0, 42.7, 45.9, 116.6, 123.8, 128.1, 129.4, 138.5, 151.5, 151.0, 158.3, 193.9; ESI-MS (m/z) = 298.20 $[M + 1]^+$; Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.72; H, 7.81; N, 14.11.

3-(1-Aminoethyl)-6-isopropyl-1-(4-nitrophenyl)-6,7-dihydro-1H-indazol-4(5H)-one **(9h)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (84 %); IR ($CHCl_3$): 3343, 1668, 1598; ^{1}H NMR (500 MHz, $CDCl_3$): 0.97 (d, J = 6.6 Hz, 6H), 1.00 (d, J = 6.6 Hz, 6H), 1.49 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.72–1.76 (m, 2H), 2.09–2.11 (m, 2H), 2.35–2.44 (m, 2H), 2.60–2.64 (m, 2H), 2.78–2.81 (m, 2H), 2.93–2.97 (m, 2H), 4.35 (q, J = 6.6 Hz, 2H), 7.72 (d, J = 8.5 Hz, 4H Ar), 8.37 (d, J = 8.5 Hz, 4H Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.6, 22.0, 27.5, 31.7, 42.0, 42.7, 45.8, 117.9, 123.4, 125.0, 143.5, 146.3, 151.5, 158.8, 193.7; ESI-MS (m/z) = 343.20 $[M+1]^+$; Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.18; H, 6.50; N, 16.32.

3-(1-Aminoethyl)-6-isopropyl-1-methyl-6,7-dihydro-1H-indazol-4(5H)-one **(9i)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (68 %); IR ($CHCl_3$): 3476, 1660, 1600; ^{1}H NMR (500 MHz, $CDCl_3$): 0.89-0.93 (m, 12H), 1.33 (d, J = 6.6 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 1.60–1.68 (m, 2H), 1.98–2.05 (m, 2H), 2.17–2.21 (m, 2H), 2.37–2.47 (m, 4H), 2.73–2.77 (m, 2H), 3.67 (s, 3H), 4.13 (q, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.6, 22.1, 24.8, 31.7, 35.6, 42.1, 42.1, 42.2, 45.6, 45.6, 115.1, 151.1, 151.1, 157.4, 193.2, 193.3; ESI-MS (m/z) = 236.30 $[M+1]^+$; Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.38; H, 8.94; N, 17.90.

3-(1-Aminoethyl)-6-isopropyl-2-methyl-6,7-dihydro-2H-indazol-4(5H)-one **(10i)** (two diastereomers, in a 1:1 molar ratio racemic mixture) (20%); IR ($CHCl_3$): 3476, 1660, 1600; ^{1}H NMR (500 MHz, $CDCl_3$): 0.88-0.92 (m, 12H), 1.33 (d, $J = 6.6$ Hz, 3H), 1.34 (d, $J = 6.6$ Hz, 3H), 1.42–1.43 (m, 2H), 1.85–1.90 (m, 2H), 2.17–2.21 (m, 2H), 2.37–2.47 (m, 4H), 2.73–2.77 (m, 2H), 3.76 (s, 3H), 4.13 (q, $J = 6.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7, 19.7, 22.0, 26.5, 31.7, 36.3, 42.6, 42.8, 43.6, 115.1, 151.1, 151.1, 157.4, 193.2, 193.3; ESI-MS (m/z) = 236.30 $[M+1]^+$; Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.38; H, 8.94; N, 17.90.

Acknowledgments This work was partially supported by MIUR (Project PRIN 20109Z2XRJ_010).

References

1. Jia J, Xu QC, Li RC, Tang X, He YF, Zhang MY, Zhang Y, Xing GW (2012) Tetrahydroindazolone substituted 2-aminobenzamides as fluorescent probes: switching metal ion selectivity from zinc to cadmium by interchanging the amino and carbamoyl groups on the fluorophore. Org Biomol Chem 10:6279–6286. doi:10.1039/C2OB25852H
2. Fletcher SR, Mclver E, Lewis S, Burkamp F, Leech C, Mason G, Boyce S, Morrison D, Richards G, Sutton K, Jones AB (2006) The search for novel TRPV1-antagonists: from carboxamides to benzimidazoles and indazolones. Bioorg Med Chem Lett 16:2872–2876. doi:10.1016/j.bmcl.2006.03.004
3. Wang H, Han H, Von Hoff DD (2006) Identification of an agent selectively targeting DPC4 (deleted in pancreatic cancer locus 4)-deficient pancreatic cancer cells. Cancer Res 66:9722–9730. doi:10.1158/0008-5472.CAN-05-4602
4. Kawanishi N, Sugimoto T, Shibata J, Nakamura K, Masutani K, Ikuta M, Hirai H (2006) Structure-based drug design of a highly potent CDK 1,2,4,6 inhibitor with novel macrocyclic quinoxalin-2-one structure. Bioorg Med Chem Lett 16:5122–5126. doi:10.1016/j.bmcl.2006.07.026
5. Abouzid KAM, El-Abhar HS (2003) Synthesis and antiinflammatory activity of novel indazolones. Arch Pharmacal Res 26:1–8. doi:10.1007/BF03179922
6. Cerecetto H, Gerpe A, Gonzalez M, Aran VJ, De Ocariz CO (2005) Pharmacological properties of indazole derivatives: recent developments. Mini Rev Med Chem 5:869–878. doi:10.2174/138955705774329564
7. Yakaiah T, Lingaiah BPV, Narsaiah B, Kumar KP, Murthy USN (2008) GdCl(3) catalysed Grieco condensation: a facile approach for the synthesis of novel pyrimidine and annulated pyrimidine fused indazole derivatives in single pot under mild conditions and their anti-microbial activity. Eur J Med Chem 43:341–347. doi:10.1016/j.ejmech.2007.03.031
8. Park JS, Yu KA, Kang TH, Kim SH, Suh YG (2007) Discovery of novel indazole-linked triazoles as antifungal agents. Bioorg Med Chem Lett 17:3486–3490. doi:10.1016/j.bmcl.2007.03.074
9. Huang LJ, Shih ML, Chen HS, Pan SL, Teng CM, Lee FY, Kuo SC (2006) Synthesis of N^2-(substituted benzyl)-3-(4-methylphenyl)indazoles as novel anti-angiogenic agents. Bioorg Med Chem 14:528–536. doi:10.1016/j.bmc.2005.08.032
10. Rakib E, Oulemda B, Abouricha S, Bouissane L, Mouse HA, Zyad A (2007) In vitro cytotoxicity evaluation of some substituted indazole derivatives. Lett Drug Des Discov 4:467–470. doi:10.2174/157018007781788589
11. Huang KH, Veal JM, Fadden RP, Rice JW, Eaves J, Strachan J, Barabasz AF, Foley BE, Barta TE, Ma W, Silinski MA, Hu M, Partridge JM, Scott A, DuBois LG, Freed T, Steed PM, Ommen AJ, Smith ED, Hughes PF, Woodward AR, Hanson GJ, McCall WS, Markworth CJ, Hinkley L, Jenks M, Geng L, Lewis M, Otto J, Pronk B, Verleysen K, Hall SE (2009) Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective and orally active antitumor agents. J Med Chem 52:4288–4305. doi:10.1021/jm900230j
12. Cordaro M, Grassi G, Risitano F, Scala A (2010) N-substituted and N-unsubstituted 1,3-oxazolium-5-olates cycloaddition reactions with 3-substituted coumarins. Tetrahedron 66:2713–2717. doi:10.1016/j.tet.2010.02.009
13. Altieri E, Cordaro M, Grassi G, Risitano F, Scala A (2010) Regio and diastereoselective synthesis of functionalized 2,3-dihydrofuro[3,2-c]-coumarins via a one-pot three-component reaction. Tetrahedron 66:9493–9496. doi:10.1016/j.tet.2010.10.023
14. Altieri E, Cordaro M, Grassi G, Risitano F, Scala A (2010) An improved diastereoselective synthesis of spiroazoles using multicomponent domino transformations. Synlett 14:2106–2108. doi:10.1055/s-0030-1258516
15. Cordaro M, Grassi G, Rescifina A, Chiacchio U, Risitano F, Scala A (2011) Stereodefined ring contraction-rearrangement of thiocoumarins to new fused benzo[b]thiophene derivatives. Tetrahedron 67:608–611. doi:10.1016/j.tet.2010.11.061
16. Romeo R, Giofrè SV, Iaria D, Sciortino MT, Ronsisvalle S, Chiacchio MA, Scala A (2011) Synthesis of 5-alkynyl isoxazolidinyl nucleosides. Eur J Org Chem 28:5690–5695. doi:10.1002/ejoc.201100767
17. Scala A, Cordaro M, Risitano F, Colao I, Venuti A, Sciortino MT, Primerano P, Grassi G (2012) Diastereoselective multicomponent synthesis and anti-HSV-1 evaluation of dihydrofuran-fused derivatives. Mol Divers 16:325–333. doi:10.1007/s11030-012-9367-0
18. Cordaro M, Risitano F, Scala A, Rescifina A, Chiacchio U, Grassi G (2013) Self-catalyzed Mannich-type reaction of enolizable cyclic 1,3-dicarbonyls to acyclic nitrones: an entry to functionalized beta-enamino diones. J Org Chem 78:3972–3979. doi:10.1021/jo400331b
19. Piperno A, Scala A, Risitano F, Grassi G (2014) Oxazol-5-(4H)-ones. Part 1. Synthesis and reactivity as 1,3-dipoles. Curr Org Chem. doi:10.2174/1385272819666140915213429
20. Cordaro M, Grassi G, Risitano F, Scala A (2009) A new construction of diversely functionalized oxazoles from enolizable cyclic 1,3-dicarbonyls and 5(4H)-oxazolones. Synlett 1:103–105. doi:10.1055/s-0028-1087483
21. Scala A, Cordaro M, Mazzaglia A, Risitano F, Venuti A, Sciortino MT, Grassi G (2011) Synthesis and anti HSV-1 evaluation of novel indole-3,4-diones. Med Chem Commun 2:172–175. doi:10.1039/COMD00190B
22. Scala A, Cordaro M, Mazzaglia A, Risitano F, Venuti A, Sciortino MT, Grassi G (2013) Aldol-type compounds from water-soluble indole-3,4-diones: synthesis, kinetics, and antiviral properties. Mol Divers 17:479–488. doi:10.1007/s11030-013-9448-8
23. Scala A, Ficarra S, Russo A, Barreca D, Giunta E, Galtieri A, Grassi G, Tellone E (2015) A new erythrocyte-based biochemical approach to predict the antiproliferative effects of heterocyclic scaffolds: The case of indolone. Biochim Biophys Acta (BBA) 1850:73–79. doi:10.1016/j.bbagen.2014.09.022
24. Rescifina A, Scala A, Sciortino MT, Colao I, Siracusano G, Mazzaglia A, Chiacchio U, Grassi G (2015) Decorated 6,60,7,70-tetrahydro-1H,10H–2,30-biindole scaffold as promising candidate for recognition of the CDK2 allosteric site. Med Chem Commun 6:311–318. doi:10.1039/c4md00364k
25. Rubinov DB, Rubinova IL, Akhrem AA (1999) Chemistry of 2-acylcycloalkane-1,3-diones. Chem Rev 99:1047–1065. doi:10.1021/cr9600621

26. Kim J, Song H, Bum Park S (2010) Orthogonal regioselective synthesis of N-alkyl-3-substituted tetrahydroindazolones. Eur J Org Chem 20:3815–3822. doi:10.1002/ejoc.201000516
27. Chans GM, Moyano EL, Yranzo GI (2011) Novel synthesis of 2-thienylcarbonyl-cyclohexane-1,3-dione as building block for indazolones and isoxazolones. Aust J Chem 64:638–646. doi:10.1071/CH11015
28. Huang KH, Veal JM, Fadden RP, Rice JW, Eaves J, Strachan JP, Barabasz AF, Foley BE, Barta TE, Ma W, Silinski MA, Hu M, Partridge JM, Scott A, DuBois LG, Freed T, Steed PM, Ommen AJ, Smith ED, Hughes PF, Woodward AR, Hanson GJ, McCall WS, Markworth CJ, Hinkley L, Jenks M, Geng L, Lewis M, Otto J, Pronk B, Verleysen K, Hall SE (2009) Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective and orally active antitumor agents. J Med Chem 52:4288–4305. doi:10.1021/jm900230j
29. Song H, Lee H, Kim J, Park SB (2012) Regioselective construction and screening of 1,3-disubstituted tetrahydroindazolones in enantiomerically pure pairs. ACS Comb Sci 14:66–74. doi:10.1021/co200150d