Cytotoxicity and Utility of 1-Indanone in the Synthesis of Some New Heterocycles

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Benzo[*d*]imidazole 3 and 1,2,4-triazin-5(2*H*)-one 6 were prepared by the reaction of starting ethyl (3-hydroxy-1*H*-inden-2-yl)(oxo)-acetate 2 with *o*-phenylenediamine and thiosemicarbazide respectively. Reaction of 1,4-dihydro-1-phenylindeno[1,2-*c*]pyrazole-3-carbohydrazide 8 with phenylisothiocyanate gave thiosemicarbazide 9, and its reaction with chloroacetic acid or phenacylbromides led to the formation of thiazolidinone-4-one 10 or 1,3-thiazoles 12a, b. The reactivity of hydrazide 8 towards fluorinated aldehyde, phthalic anhydride, and hydrazonoyl chlorides 15a, b was studied to give fluorinated hydrazones, imide bis-hydrazones 13—16. The newly synthesized compounds were screened for their cytotoxic activities and compounds 6, 8, 9 and 10 were found the most potentially cytotoxic. The detailed synthesis, spectroscopic and biological data are reported.

Key words 1-indanone; pyrazole; hydrazide; 1,3-thiazole; hydrazonoyl chloride; cytotoxic and antitumor activity

Diketo-esters, the acylation products of active methylene components with dialkyl oxalate, are valuable multi-purpose intermediates in organic synthesis and their preparation is well documented. 2,4-Diketo-esters are used in the production of (*e.g.*) pyrazole-3(5)-ethyl esters and their derivatives which are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides,[1—3] plant growth regulators and protectants[4]; they are also used in the production of the 3(2*H*)-furanone ring system which is the key skeletal element of many natural product antitumor agents.[5] Recently, emphasis has been placed on synthesizing pyrazoles having novel functional groups attached either to C-3 or C-5 of the ring[6—10] due to their proven usefulness as intermediates in the preparation of new biological materials. For example, compounds including a pyrazole nucleus are potential human immunodeficiency virus-1 (HIV-1) inhibitors,[11] insecticides,[12] fungicides,[12] antiviral agents[13] and anticancer activity.[14] In relation with the above considerations and in continuation of our previous work in the synthesis of biologically active heterocycles,[15,16] we synthesized a series of new heterocycles using 1-indanone as synthon for evolution of their cytotoxic and antitumor activity.

Chemistry Chart 1 outlines the synthetic pathway leading to benzo[*d*]imidazole **3**. Ethyl 2-(2,3-dihydro-1-oxo-1*H*-inden-2-yl)-2-oxoacetate **2**, which is present in tautomeric form **2′**, was prepared by reacting the 1-indanone **1** with diethyl oxalate in the presence of sodium ethoxide according to reported methods.[17,18]

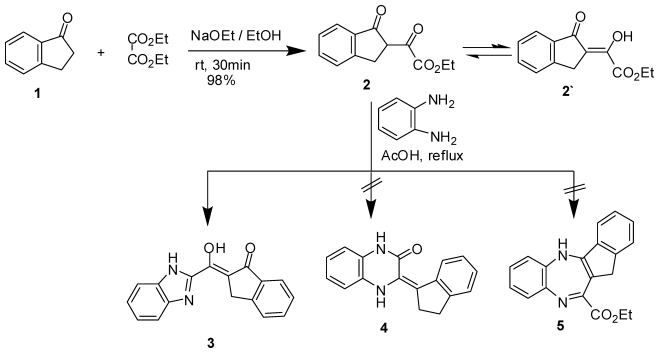

Chart 1. Reaction of Diketo-ester with *o*-Phenylenediamine

It has been reported that the condensation of *o*-phenylenediamine with aroylpyruvates led to the synthesis of benzimidazole nucleus[10,19] or quinoxalin-2-one,[20] while its condensation with ethyl 2-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-oxoacetate gave benzo-1,4-diazepine.[21,22] Based on the previous literature we report here the reaction of ethyl (3-hydroxy-1*H*-inden-2-yl)(oxo)-acetate **2** with *o*-phenylenediamine which furnished benzimidazole **3** (Chart 1).

The structure of the benzimidazole derivative **3** was based on spectral and analytical data. The mass spectrum of **3** displayed the molecular ion peak at *m*/*z* 278, which is assigned to $M^+ + 2$. ^{1}H-NMR also confirmed the assigned structure of **3** and excluded the structures **4** and **5**. The ^{1}H-NMR of **3** displayed two singlet protons at 11.87 and 13.45 ppm, assigned to NH and OH protons respectively.

It is reported that aroylpyruvates were condensed with *S*-methylisothiosemicarbazide hydroiodide in pyridine to give 1,2,4-triazin-5(2*H*)-ones in moderate to good yields.[23] Thus, condensation of ethyl (3-hydroxy-1*H*-inden-2-yl)(oxo)-acetate **2** with thiosemicarbazide in refluxing ethanol containing a catalytic amount of hydrochloric acid afforded the corresponding 1,2,4-triazin-5(2*H*)-one **6** in 75% yield (Chart 2).

The chemical structure of **6** was well supported by spectral data such as IR, NMR, mass and elemental analysis. In the IR spectrum of **6**, a broad absorption bands in the 3303—3146 cm^{-1} indicates the presence of OH and 2NH groups in the compound, and its ^{1}H-NMR spectrum showed a singlet at δ 8.69, 9.59 and 12.89 ppm due to the 2NH and OH protons respectively. In addition, the mass spectrum of **6** showed a peak corresponding to $M^+ + 2$ at *m*/*z* 261.

Compound **2** was condensed with the phenylhydrazine hydrochloride to afford the known ethyl 1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carboxylate **7**.[24] Treatment of pyrazole-3-carboxylate **7** with excess hydrazine hydrate in refluxing ethanol gave the new hydrazide **8** in excellent yield (Chart 2).

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The chemical structure of hydrazide **8** was confirmed by spectral data and elemental analysis. In the IR spectrum of **8**, a broad absorption bands around 3312—3053 cm^{-1} indicates the presence of NH and NH_2 groups in the compound, and its ^{1}H-NMR spectrum showed a singlet at δ 4.50 and 9.50 ppm due to the NH_2 and NH protons, respectively. In addition, the mass spectrum of hydrazide **8** showed a peak corresponding to its molecular ion peak at *m*/*z* 290.

Acid hydrazides can be considered as useful intermediates leading to the formation of several heterocycles.[25—28] Acid hydrazides have long been known to react with isothiocyanates and α-haloketones to afford a variety of heterocyclic derivatives.[29—33] Thus, reaction of hydrazide **8** with phenyl isothiocyanate in absolute ethanol afforded thiosemicarbazides **9** in 89% yield. Condensation of the latter with chloroacetic acid in glacial acetic acid having an excess amount of fused sodium acetate afforded thiazolidin-4-one **10** in moderate yield. Refluxing of 4-thiazolidinone **10** with 4-flourobenzaldehyde in glacial acetic acid in the presence of an excess amount of fused sodium acetate yielded 5-(4-fluorobenzylidene)-4-oxo-3-phenylthiazolidines **11** in good yield. The one pot synthesis of 5-(4-fluorobenzylidene)-4-oxo-3-phenylthiazolidines **11** was also achieved by refluxing equimolar amounts of thiosemicarbazide **9**, chloroacetic acid and 4-flourobenzaldehyde in glacial acetic acid having an excess amount of fused sodium acetate. Treatment of thiosemicarbazide **9** with phenacylbromides, namely, phenacylbromide and 4-chlorophenacylbromide, in ethanol containing excess of anhydrous sodium acetate afforded 1,3-thiazole derivatives **12a,b** in 62 and 75% yields (Chart 3).

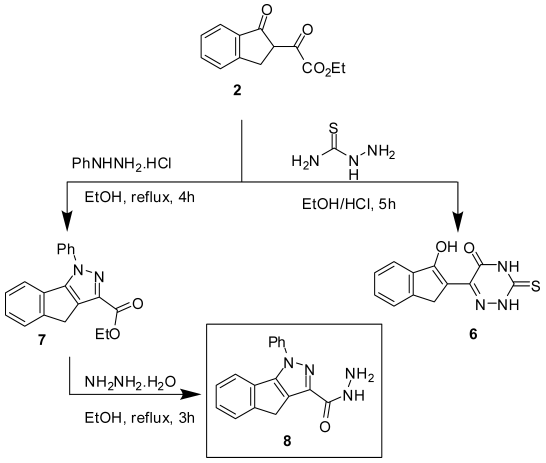

Chart 2

The IR spectrum of **10** showed an absorption band at 1715 cm^{-1} due to the carbonyl function of thiazolidinone moiety, the mass spectrum of **11** showed a peak corresponding to its molecular ion peak at *m*/*z* 571, while the ^{1}H-NMR of compound **12b** showed a singlet signal in the region 7.01 ppm corresponding to C-5 proton of the thiazole ring.

Treatment of acid hydrazide **8** with 4-fluorobenzaldehyde in refluxing ethanol having a catalytic amount of glacial acetic acid afforded the corresponding hydrazones **13** in 80% yield (Chart 4). The ^{1}H-NMR of **13** showed a singlet proton at 8.68 ppm attributed to –C<u>H</u>=N–. Treatment of carbohydrazide **8** with phthalic anhydride in refluxing glacial acetic acid furnished the corresponding imide **14** in 48% yield. The IR spectrum of **14** showed absorption bands at 1785, 1735, 1690 cm^{-1} characteristic of the three carbonyl groups, and its mass spectrum showed its molecular ion peak at *m*/*z* 420.

Reaction of hydrazide **8** with hydrazonoyl chlorides **15a**, **b** in refluxing neutral medium give the extra pure bis-hydrazono compounds **16a**, **b** in good yields. The formation of bis-hydrazono compounds **16a**, **b** was indicated by the absence of one carbonyl band in the IR spectra and appearance of two singlet NH protons around δ 10.21, and 10.52 in their ^{1}H-NMR spectra.

Cytotoxic Activity[34,35] The stock samples were diluted with Dulbecco's Modified Eagle's Medium (DMEM) to desired concentrations ranging from 1 to 100 μg/ml. The final concentration of dimethyl sulfoxide (DMSO) in each sample did not exceed 1% v/v. The cytotoxic activity of the com-

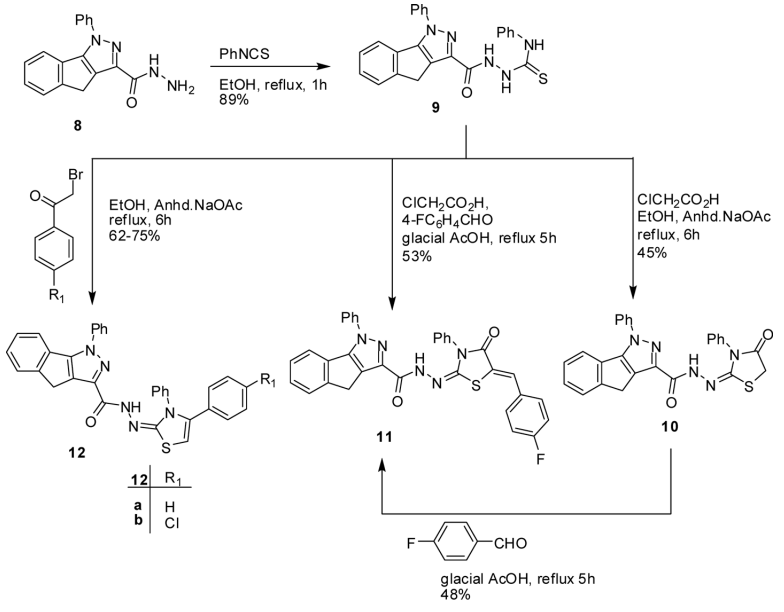

Chart 3. Synthesis of 1,3-Thiazoles

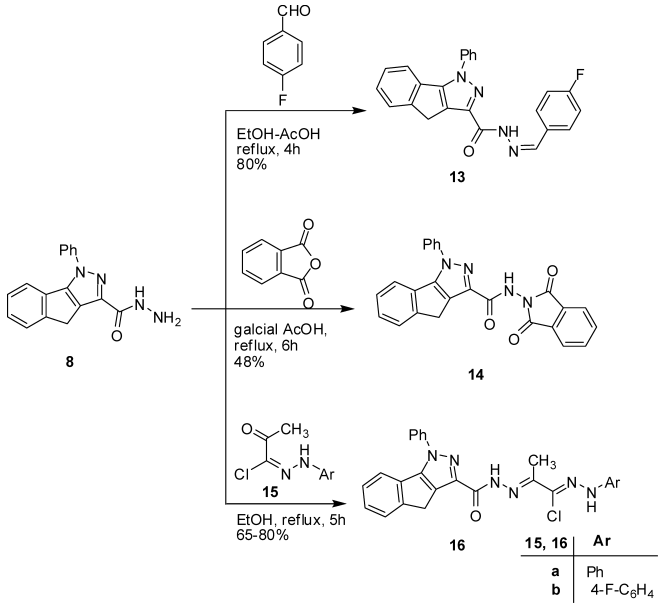

Chart 4. Different Reactions with Hydrazide

Table 1. Characteristics of the Synthesized Compounds

Compd. No.	Formula (MW)	Calculated (Found) C	H	N	mp, °C	Yield, %
3	$C_{17}H_{12}N_2O_2$ (276.09)	73.90 (74.19)	4.38 (4.42)	10.14 (10.29)	>300	83
6	$C_{12}H_9N_3O_2S$ (259.04)	55.59 (55.69)	3.50 (3.46)	16.21 (16.18)	275—276	62
8	$C_{17}H_{14}N_4O$ (290.12)	70.33 (70.52)	4.86 (4.64)	19.30 (19.58)	165—167	86
9	$C_{24}H_{19}N_5OS$ (425.13)	67.74 (67.44)	4.50 (4.65)	16.46 (16.17)	210—212	89
10	$C_{26}H_{19}N_5O_2S$ (465.13)	67.08 (67.18)	4.11 (4.39)	15.04 (15.25)	235—237	45
11	$C_{33}H_{22}FN_5O_2S$ (571.15)	69.34 (69.23)	3.88 (3.67)	12.25 (12.37)	212—214	53 (a) 48 (b)
12a	$C_{32}H_{23}N_5OS$ (525.16)	73.12 (73.21)	4.41 (4.55)	13.32 (13.47)	260—261	62
12b	$C_{32}H_{22}ClN_5OS$ (559.12)	68.62 (68.69)	3.96 (3.83)	12.50 (12.66)	271—272	75
13	$C_{24}H_{17}FN_4O$ (396.14)	72.72 (72.79)	4.32 (4.38)	14.13 (14.33)	185—186	80
14	$C_{25}H_{16}N_4O_3$ (420.12)	71.42 (71.61)	3.84 (3.91)	13.33 (13.38)	255—257	48
16a	$C_{26}H_{21}ClN_6O$ (468.15)	66.59 (66.63)	4.51 (4.61)	17.92 (17.99)	271—272	68
16b	$C_{26}H_{20}ClFN_6O$ (486.14)	64.13 (64.26)	4.14 (4.29)	17.26 (17.31)	260—262	79

pounds was tested against malignant human hepatoma (HepG2) cell line, human lung fibroblast cell line (WI38), human Caucasian breast adenocarcinoma (MCF-7) and normal African green monkey kidney (Vero) cell line. The % viability of cells was examined visually. 5-Fluoruracil was used as a standard anticancer drug for comparison.

Briefly, cells were batch cultured for 10 d, then seeded in 96 well-plates of 10×10^3 cells/well in fresh complete growth medium in 96-well microtiter plastic plates at 37 °C for 24 h under 5% CO_2 using a water jacketed carbon dioxide incubator (Sheldon, TC2323, Cornelius, OR, U.S.A.). The medium was aspirated, fresh medium (without serum) was added and cells were incubated either alone (negative control) or with different concentrations of sample to give a final concentration of (100—50—20—10—5—2 and 1 μg/ml). Cells were suspended in DMEM medium, 1% antibiotic-antimycotic mixture (10000 U/ml potassium penicillin, 10000 μg/ml streptomycin sulfate and 25 μg/ml Amphotericin B) and 1% L-glutamine in 96-well flat bottom microplates at 37 °C under 5% CO_2. After 96 h of incubation, the medium was again aspirated, trays were inverted onto a pad of paper towels, the remaining cells rinsed carefully with medium, and fixed with 3.7% (v/v) formaldehyde in saline for at least 20 min. The fixed cells were rinsed with water, and examined. The cytotoxic activity was identified as confluent, relatively unaltered monolayers of stained cells treated with compounds. Cytotoxicity was estimated as the concentration that caused approximately 50% loss of the monolayer. The assay was used to examine the newly synthesized compounds. 5-Fluoruracil was used as a positive control.

Table 2. Perecentage Viability of Tested Compounds on Different Cell Lines

Compound	Concentration (10—100 μg/ml)	% viability HEPG2	WI 38	VERO	MCF 7
3	100	81	79	77	89
6	100	19	12	65	21
8	100	22	12	18	20
9	100	24	14	27	38
10	100	22	16	30	28
11	100	79	74	80	84
12a	100	81	79	77	89
12b	100	78	92	95	92
13	100	92	89	78	95
16a	100	84	88	93	90
16b	100	78	79	83	82
5-FU	20	Zero	5	8	Zero

Cytotoxicity results are summarized in Table 2. The samples were classified into 2 categories based on their cytotoxicity. Compounds **6**, **8**, **9** and **10** were potentially cytotoxic (% viability in HEPG2, WI38 and MCF7 cell lines 40 μg/ml) while other compounds were moderately cytotoxic (40 μg/ml<% viability<100 μg/ml). Viro cell compounds **8**, **9** and **10** had potential cytotoxicity. The compound samples in the first category were used for a further bioassay guided experiment.

Conclusion

New benzimidazole, 1,2,4-triazin-5(2*H*)-one, 4-thiazolidinone, 1,3-thiazole, hydrazone, imide and bis-hydrazone derivatives were prepared using 1-indanone as starting material. The cytotoxicity of newly synthesized compounds was identified; compounds **6**, **8**, **9** and **10** are the most potentially cytotoxic.

Experimental

Chemistry All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the calculated values) were obtained from the microanalytical unit, Cairo University, Giza, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H-NMR spectra were recorded at

270 MHz on a Varian EM-360 spectrometer using tetramethyl silane (TMS) as an internal standard. Chemical shift (δ) values are given in parts per million. The mass spectra were determined using a Varian MAT CH-5 spectrometer (70 eV). Ethyl (3-hydroxy-1*H*-inden-2-yl)(oxo)-acetate **2**[17,18]; ethyl 1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carboxylate **7**,[24] hydrazonoyl chlorides[36] were prepared according to the procedures reported in the literature.

2-[(1*H*-Benzimidazol-2-yl)(hydroxy)methylene]-2,3-dihydro-1*H*-inden-1-one 3 A solution of ethyl 2-(2,3-dihydro-1-oxo-1*H*-inden-2-yl)-2-oxoacetate **2** (4.64 g, 20 mmol) and *o*-phenylenediamine (2.48 g, 23 mmol) in glacial acetic acid (30 ml) was refluxed for 4 h. The formed reddish orange precipitate was isolated by filtration, washed with ethanol, dried and recrystallized from AcOH–H_2O (2 : 1, v/v). IR (KBr) ν_{max}/cm^{-1} 3161 (NH), 1687 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 4.09 (s, 2H, indane-3-CH_2), 7.05—7.67 (m, 8H, ArH), 11.87 (s, 1H, NH, D_2O exchangeable), 13.45 (s, 1H, OH, D_2O exchangeable); MS *m*/*z* (%) 278 (M^++2, 22), 277 (M^++1, 16), 64 (100).

6-(3-Hydroxy-1*H*-inden-2-yl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one 6 To a solution of ethyl 2-(2,3-dihydro-1-oxo-1*H*-inden-2-yl)-2-oxoacetate **2** (2.32 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) in absolute ethanol (20 ml), three drops of conc. HCl were added and the reaction mixture was refluxed for 5 h. The formed yellow precipitate was isolated by filtration, washed with ethanol, dried and recrystallized from DMF–H_2O (5 : 1, v/v) to give **6**. IR (KBr) ν_{max}/cm^{-1} 3303 (OH), 3224, 3146 (2NH), 1640 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.92 (s, 2H, indane-3-CH_2), 7.39—7.74 (m, 4H, ArH), 8.69 (s, 1H, NH, D_2O-exchangeable), 9.59 (s, 1H, NH), 12.89 (s, 1H, OH); MS *m*/*z* (%) 261 (M^++2, 46), 277 (M^++1, 16), 55 (100).

1,4-Dihydro-1-phenylindeno[1,2-c]pyrazole-3-carbohydrazide 8 Hydrazine hydrate (1.0 g, 20 mmol) was added to ethyl 1,4-dihydro-1-phenylindeno[1,2-*c*]pyrazole-3-carboxylate **7** (3.04 g, 10 mmol) in absolute ethanol (40 ml). The reaction mixture was heated under reflux for 4 h and was then left to cool to room temperature. The precipitate that formed was filtered off, dried and recrystallized from ethanol. IR (KBr) ν_{max}/cm^{-1} 3312—3153 (NH_2, NH), 1669 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.81 (s, 2H, indane-3-CH_2), 4.50 (s, 2H, NH_2, D_2O-exchangeable), 7.33—7.81 (m, 9H, ArH), 9.50 (s, 1H, NH, D_2O-exchangable); MS *m*/*z* (%) 290 (M^+, 35), 259 (100).

***N*-Phenyl-2-(1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonyl)hydrazine-carbothioamide 9** A mixture of **8** (1.45 g, 5 mmol) and phenylisothiocyanate (0.67 g, 5 mmol) in absolute ethanol (30 ml) was heated under reflux for 1 h. The formed solid was filtered off, washed with ethanol, dried and recrystallized from EtOH/*N*,*N*-dimethylformamide (DMF) (3 : 1, v/v). IR (KBr) ν_{max}/cm^{-1} 3209—3107 (3NH), 1642 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.36 (s, 2H, indane-3-CH_2), 7.11—7.51 (m, 14H, ArH), 9.45 (s, 1H, NH, D_2O-exchangeable), 9.87 (s, 1H, NH, D_2O-exchangeable), 10.20 (s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%) 427 (M^++2, 8), 426 (M^++1, 12), 426 (M^+, 23), 259 (100).

1,4-Dihydro-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene)-1-phenylindeno[1,2-*c*]pyrazole-3-carbohydrazide 10 A mixture of **9** (0.425 g, 1 mmol) and chloroacetic acid (0.1 g, 1 mmol) in glacial acetic acid (30 ml) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 6 h. The reaction mixture was cooled and the resulting precipitate was filtered off and recrystallized from ethanol to give **10**. IR (KBr) ν_{max}/cm^{-1} 3227 (NH), 1651, 1715 (2C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.92 (s, 2H, indane-3-CH_2), 6.92 (s, 2H, thiazolidine-H), 7.29—7.83 (m, 14H, ArH), 9.87 (s, 1H, NH, D_2O-exchangeable).

***N*′-[5-(4-Fluorobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]-1,4-dihydro-1-phenylindeno[1,2-*c*]pyrazole-3-carbohydrazide 11** Method A: To a solution of 4-thiazolidinone **10** (0.465 g, 1 mmol) and 4-flurobenzaldehyde (0.12 g, 1 mmol) in glacial acetic acid (20 ml), anhydrous sodium acetate (0.33 g, 4 mmol) was added and the reaction mixture was refluxed for 5 h then left to cool at room temperature. The formed solid was filtered off, dried and recrystallized from EtOH.

Method B: A mixture of **9** (0.425 g, 1 mmol), chloroacetic acid (0.1 g, 1 mmol) and 4-flurobenzaldehyde (0.12 g, 1 mmol) in glacial acetic acid (20 ml) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 5 h. The reaction mixture was left to cool and the formed solid was filtered off, washed with water, dried and recrystallized from EtOH. IR (KBr) ν_{max}/cm^{-1} 3230 (NH), 1656, 1692 (2C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 2H, indane-3-CH_2), 7.28—7.86 (m, 18H, ArH), 11.85 (s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%) 571 (M^+, 28), 259 (100).

Synthesis of Compounds 12a, b A mixture of **9** (0.425 g, 1 mmol) and appropriate phenacyl bromide (1 mmol) in absolute ethanol (30 ml) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 6 h. The formed solid was filtered off, washed with water, dried and recrystallized from EtOH/DMF to give the corresponding carbohydrazides **12a**, **b**.

N′-(3,4-Diphenylthiazol-2(3*H*)-ylidene)-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbohydrazide **12a**: IR (KBr) ν_{max}/cm^{-1} 3248 (NH), 1642 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.90 (s, 2H, indane-3-CH_2), 7.03 (s, 1H, thiazole-H), 7.13—7.95 (m, 19H, ArH), 11.15 (s, 1H, NH, D_2O-exchangeable).

N′-(4-(4-Chlorophenyl)-3-phenylthiazol-2(3*H*)-ylidene)-1-phenyl-1,4-dihydroindeno-[1,2-*c*]pyrazole-3-carbohydrazide **12b**: IR (KBr) ν_{max}/cm^{-1} 1648 (C=O), 3245 (NH); ^{1}H-NMR (DMSO-d_6) δ: 3.92 (s, 2H, indane-3-CH_2), 7.01 (s, 1H, thiazole-H), 7.18—7.91 (m, 18H, Ar-H), 11.10 (s, 1H, NH, D_2O exchangeable).

***N*′-(4-Fluorobenzylidene)-1,4-dihydro-1-phenylindeno[1,2-*c*]pyrazole-3-carbohydrazide 13** A mixture of **8** (0.29 g, 1 mmol) and 4-flurobenzaldehyde (0.12 g, 1 mmol) in absolute ethanol (30 ml) in the presence of few drops of glacial acetic acid was refluxed for 4 h. The formed solid was filtered off, washed with ethanol dried and crystallized from EtOH/DMF (3 : 1, v/v). IR (KBr) ν_{max}/cm^{-1} 3191 (NH), 1693 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.92 (s, 2H, indane-3-CH_2), 7.31—7.92 (m, 13H, ArH), 8.68 (s, 1H, –C<u>H</u>=N), 11.77 (s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%) 397 (M^++1, 23), 244 (100).

1,4-Dihydro-*N*-(1,3-dioxoisoindolin-2-yl)-1-phenylindeno[1,2-*c*]pyrazole-3-carboxamide 14 A mixture of **8** (0.29 g, 1 mmol) and phthalic anhydride (0.15 g, 1 mmol) in glacial acetic acid (20 ml) was refluxed for 8 h. The formed solid was filtered off, dried, and crystallized from AcOH/H_2O (3 : 1, v/v). IR (KBr) ν_{max}/cm^{-1} 3067 (NH), 1785, 1735, 1690 (3C=O); ^{1}H-NMR (DMSO-d_6) δ: 3.85 (s, 2H, indane-3-CH_2), 7.36—8.13 (m, 13H, ArH), 10.97 (s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%) 420 (M^+, 33), 259 (100).

Synthesis of the Bis-hydrazones 16a, b A mixture of **8** (0.29 g, 1 mmol) and appropriate hydrazonoyl chlorides **15a**, **b** (1 mmol) in absolute ethanol (30 ml) was refluxed for 4 h. The formed solid was filtered off, dried, and crystallized from EtOH/DMF (2 : 1).

N′-Phenyl-2-(2-(1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonyl)hydrazono)propanehydrazonoyl Chloride **16a**: IR (KBr) ν_{max}/cm^{-1} 3242—3055 (2NH), 1682 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.38 (s, 3H, CH_3), 3.95 (s, 2H, indane-3-CH_2), 7.28—7.69 (m, 14H, ArH), 10.16 (s, 1H, NH, D_2O-exchangeable), 10.49 (s, 1H, NH, D_2O-exchangeable).

N′-(4-Fluorophenyl)-2-(2-(1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonyl)hydrazono)propanehydrazonoyl Chloride **16b**: IR (KBr) ν_{max}/cm^{-1} 3246, 3159 (2NH), 1685 (C=O); ^{1}H-NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 3.90 (s, 2H, indane-3-CH_2), 7.26—7.71 (m, 13H, ArH), 10.21 (s, 1H, NH, D_2O-exchangeable), 10.52 (s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%) 486 (M^+, 5), 149 (100).

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