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ORIGINAL PAPER

Synthesis of aryl-substituted or aryl-fused *N*-hydroxyethyl and *N*-hydroxymethypyrazole derivatives as potential ligands for the estrogen receptor

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Abstract A new series of *N*-hydroxyethylpyrazole (**12a–f**) and *N*-hydroxymethylpyrazole derivatives (**15a–f**) were designed for their estrogenic activities, having a 11.0 ± 0.5 Å distance between their two hydroxyl groups, aliphatic–OH and phenolic–OH similar to 17β-estradiol (E2) as an endogenous hormone. To synthesize the title compounds, the key intermediate 1,3-dicarbonyl derivatives (**2** and **8**), were treated with hydrazine hydrate to produce the pyrazole ring **5** and **9**. Further hydroxyalkylation of the latter produced the title pyrazoles. The position of hydroxyethyl or hydroxymethyl substituents in the products was determined through 2D NOE NMR spectroscopy.

Keywords 17β-Estradiol · Pyrazole · Estrogen receptor · 2D NOE NMR spectroscopy

Introduction

The estrogen receptors (ERs) are ligand-dependent transcription factors that exert their physiological effects by binding of endogenous steroid hormones, such as 17β-estradiol (E2) or synthetic estrogens. There are two subtypes of estrogen receptor, ERα and ERβ, which are members of the nuclear receptor (NR) that regulates many important physiological roles, such as maintenance of bone mineral density, cardiovascular health, neuroprotection, the development and function of the female reproduction system [1–3]. Recent evidences suggest that estrogen may also mediate non-reproductive events including learning and memory [1–3]. The most potent endogenous ligand for both estrogen receptors is 17β-estradiol (E2). The traditional utility of ER ligands has been reported for such therapies as hormone replacement therapy (HRT) and contraception that is mediated primarily via ERα [4].

The structure of high ER affinity synthetic estrogens, especially those of non-steroidal nature, generally consists of a phenolic functionality that mimics the phenol moiety of natural estradiol, and is tolerant to other target structural motifs that can be encompassed [5–7].

There are so many efforts to find a new series of safe and selective estrogenic compounds. In the course of investigations aimed at developing novel selective estrogen receptor modulators (SERMs) that possess high affinity and selectivity for an ER subtype, a broad variety of diverse ligands have been considered. In this work, the incorporation of a pyrazole moiety in the structures represents an intriguing case [8], since the propylpyrazoletriol (PPT) (Fig. 1), a 1,3,5-triaryl-4-alkyl-substituted pyrazole derivative, has been found to possess particularly high ERα selective binding affinity and potency [9–11], while cycloalkylpyrazoles (Fig. 1) have shown higher binding affinity for ERβ [12].

The affinity of ligand binding to either form of ER primarily reflects the presence of two hydroxyl groups with an O–O distance close to that between the 3- and 17β-hydroxyl groups of estradiol [12]. In general, it is thought that for optimum hydrogen bonding this distance should be 11.0 ± 0.5 Å [13]. Since the O–O distances for PPT are 12.3 and 13.1 Å, the rationale to design these molecules is

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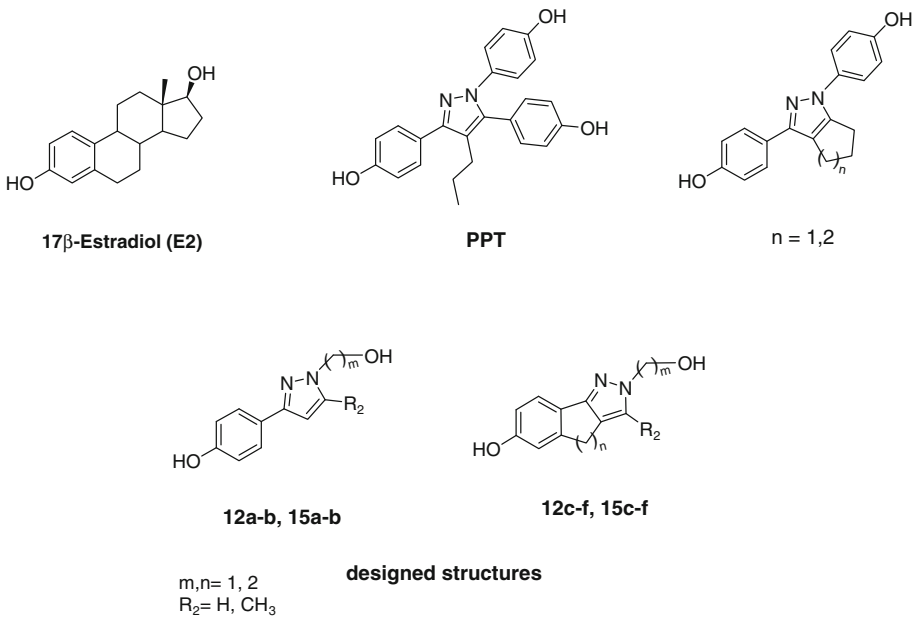


Fig. 1 17β-Estradiol (E2), Propylpyrazoletriol (*PPT*), cycloalkylpyrazoles and designed structures

to substitute one of the phenol rings with CH_2CH_2OH or CH_2OH in order to decrease the O–O distance of the hydroxyl groups according to the suitable range for optimum hydrogen binding. Therefore, herein we describe the synthesis of *N*-hydroxyethyl and *N*-hydroxymethypyrazole derivatives as potential ligands for the estrogen receptor.

Experimental

Commercially available chemicals were purchased from the Fluka, Aldrich or Merck Chemical Companies and used without further purification. Melting points were determined with a Reichert-Jung hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550-FT spectrometer. ^{1}H NMR spectra were measured on a Bruker 500 MHz spectrometer (Bruker, Rheinstatten, Germany), in $CDCl_3$, CD_3OD or DMSO-d_6 with TMS as the internal standard, where J (coupling constant) values are estimated in Hertz. Mass spectra were obtained with an Agilent Technologies 5975C spectrometer (Agilent Technologies, USA) at 70 eV.

General procedure A. Acylation of acetophenone, indanone and tetralone derivatives

A solution of appropriate starting material (**1** or **7**, 10 mmol) in methyl formate (for formylation) or methyl acetate (for acetylation) (25 ml) was added dropwise to a stirring suspension of freshly prepared sodium ethoxide (1 g, 15 mmol) in dry diethyl ether (25 ml) in an ice bath (0 °C), over a period of 30 min. The resulting mixture was warmed up to room temperature and stirred for further 1 h in this temperature and kept in 0 °C overnight. The precipitate was filtered and washed with diethyl ether and dissolved in water, neutralized with HCl and the precipitate was filtered and washed with water and dried to give acylated derivatives (**2** and **8**). The spectral data of **2a–c** and **2e–f** were similar with those reported [14–18].

2-Acetyl-5-methoxy-2,3-dihydro-1*H*-inden-1-one (**2d**): Yield 60 %; mp 89–91 °C; IR (KBr): ν 1,655 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 0.67H, H_7), 7.65 (d, J = 8.2 Hz, 0.33H, H_7), 6.96 (s, 1H, H_4), 6.93 (d, J = 8.2 Hz, 1H, H_6), 3.94 (dd, J = 3.2, 7.6 Hz, 0.33H, H_2), 3.89 (s, 3H, OCH_3), 3.67 (dd, J = 3.2, 17.5 Hz, 0.33H, H_3), 3.54 (s, 1.34H, H_3), 3.05 (dd, J = 7.6, 17.5 Hz, 0.33H, H_3), 2.48 (s, 1H), 2.12 ppm (s, 2H).

General procedure B. Preparation of pyrazole derivatives from 1,3-dicarbonyl compounds

To a solution of the appropriate 1,3-dicarbonyl compound (**2** or **8**, 1 mmol) in ethanol was added hydrazine monohydrate (4 mmol) and glacial acetic acid (4 mmol). The mixture was refluxed in an oil bath and the progress of the reaction was monitored by TLC. After cooling to room temperature the solution was poured into ice-water and the resulting precipitate was filtered, washed with cold water, dried and recrystallized from ethyl acetate to give **5** or **9** [19]. The spectral data of **5a–b** [20–23] and **5e** [24] were similar with those reported.

6-Methoxy-2,4-dihydroindeno[1,2-*c*]pyrazole (**5c**): Yield 80 %; mp 185–187 °C; IR (KBr): ν 3,129 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 1H, H_8), 7.52 (s, 1H, H_3), 7.08 (d, J = 2.3 Hz, 1H, H_5), 6.92 (dd, J = 2.3, 8.4 Hz, 1H, H_7), 3.86 (s, 3H, OCH_3), 3.67 ppm (s, 2H, H_4).

6-Methoxy-3-methyl-2,4-dihydroindeno[1,2-*c*]pyrazole (**5d**): Yield 83 %; mp 198–200 °C; IR (KBr): ν 3,145 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 7.65 (d, $J = 7.9$ Hz, 1H, H_8), 7.05 (s, 1H, H_5), 6.90 (d, $J = 7.9$ Hz, 1H, H_7), 3.86 (s, 3H, OCH_3), 3.54 (s, 2H, H_4), 2.3 ppm (s, 3H, CH_3).

7-Methoxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**5f**): Yield 90 %; mp 171–173 °C; IR (KBr): ν 3,170 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 7.66 (d, $J = 8.2$ Hz, 1H, H_9), 6.81 (d, $J = 8.2$ Hz, 1H, H_8), 6.80 (s, 1H, H_6), 3.82 (s, 3H, OCH_3), 2.92 (t, $J = 9.0$ Hz, 2H, H_5), 2.65 (t, $J = 9.0$ Hz, 2H, H_4), 2.26 ppm (s, 3H, CH_3).

General procedure C. Preparation of *N*-hydroxylethylpyrazoles

To a stirred mixture of protected pyrazole (**5** or **9**, 1 mmol), sodium hydroxide (1.5 mmol), dioxane (50 ml) and benzyltriethylammonium chloride (0.05 mmol) was dropwise added to 2-bromoethanol (1 mmol) within 1 h at 80 °C. The reaction mixture was stirred for further 1.5 h then the mixture was then cooled, filtered and the solid were washed with dioxane (3 × 10 ml). The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC to give **3**, **4**, **10** or **11** [25].

2-[3-(4-Methoxyphenyl)pyrazol-1-yl]ethanol (**3a**): mp 79–80 °C; IR (KBr): ν 3,269 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.67 (d, $J = 8.5$ Hz, 2H, $H_{2,6}$), 7.60 (d, $J = 1.6$ Hz, 1H, H_5), 6.94 (d, $J = 8.5$ Hz, 2H, $H_{3,5}$), 6.53 (d, $J = 1.6$ Hz, 1H, H_4), 4.15 (t, $J = 4.5$ Hz, 3H, $\underline{CH_2}CH_2OH$), 4.01 (t, $J = 4.5$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.84 ppm (s, 3H, OCH_3).

2-[3-(4-Methoxyphenyl)-5-methylpyrazol-1-yl]ethanol (**3b**): mp 128–129 °C; IR (KBr): ν 3,284 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.69 (d, $J = 8.5$ Hz, 2H, $H_{2,6}$), 6.92 (d, $J = 8.5$ Hz, 2H, $H_{3,5}$), 6.28 (s, 1H, H_4), 4.16 (t, $J = 4.4$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.05 (t, $J = 4.4$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.83 (s, 3H, OCH_3), 2.31 ppm (s, 3H, CH_3).

2-(6-Methoxyindeno[1,2-*c*]pyrazol-2(4*H*)-yl)ethanol (**3c**): mp 149–151 °C; IR (KBr): ν 3,250 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.63 (d, $J = 7.9$ Hz, 1H, H_8), 7.25 (s, 1H, H_3), 7.03 (s, 1H, H_5), 6.88 (d, $J = 7.9$ Hz, 1H, H_7), 4.29 (t, $J = 4.5$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.03 (t, $J = 4.5$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.84 (s, 3H, OCH_3), 3.59 ppm (s, 2H, H_4).

2-(6-Methoxy-3-methylindeno[1,2-*c*]pyrazol-2(4*H*)-yl)ethanol (**3d**): mp 123–125 °C; IR (KBr): ν 3,257 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.62 (d, $J = 8.0$ Hz, 1H, H_8), 7.04 (s, 1H, H_5), 6.89 (d, $J = 8.0$ Hz, 1H, H_7), 4.19 (t, $J = 5.2$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.05 (t, $J = 5.2$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.85 (s, 3H, OCH_3), 3.52 (s, 2H, H_4), 2.33 ppm (s, 3H, CH_3).

2-(7-Methoxy-4,5-dihydro-2*H*-benzo[*g*]indazol-2-yl)ethanol (**3e**): mp 135–137 °C; IR (KBr): ν 3,203 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.73 (d, $J = 7.8$ Hz, 1H, H_9), 7.18 (s, 1H, H_3), 6.81 (d, $J = 7.8$ Hz, 1H, H_8), 6.78 (s, 1H, H_6), 4.22 (t, $J = 5.2$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.01 (t, $J = 5.2$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.83 (s, 3H, OCH_3), 2.90 (t, $J = 7.0$ Hz, 2H, H_5), 2.75 ppm (t, $J = 7.0$ Hz, 2H, H_4).

2-(7-Methoxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-2-yl)ethanol (**3f**): mp 123–125 °C; IR (KBr): ν 3,227 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.71 (d, $J = 8.0$ Hz, 1H, H_9), 6.81 (d, $J = 8.0$ Hz, 1H, H_8), 6.78 (s, 1H, H_6), 4.13 (t, $J = 4.6$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.03 (t, $J = 4.6$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.82 (s, 3H, OCH_3), 2.90 (t, $J = 7.4$ Hz, 2H, H_5), 2.64 (t, $J = 7.4$ Hz, 2H, H_4), 2.21 ppm (s, 3H, CH_3).

2-[5-(4-Methoxyphenyl)pyrazol-1-yl]ethanol (**4a**): mp 135–137 °C; IR (KBr): ν 3,269 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.47 (d, $J = 1.6$ Hz, 1H, H_3), 7.33 (d, $J = 8.8$ Hz, 2H, $H_{2,6}$), 6.95 (d, $J = 8.8$ Hz, 2H, $H_{3,5}$), 6.22 (d, $J = 1.6$ Hz, 1H, H_4), 4.21 (t, $J = 5.1$ Hz, 2H, $\underline{CH_2}CH_2OH$), 3.97 (t, $J = 5.1$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.85 ppm (s, 3H, OCH_3).

2-[5-(4-Methoxyphenyl)-3-methylpyrazol-1-yl]ethanol (**4b**): mp 149–151 °C; IR (KBr): ν 3,289 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.30 (d, $J = 8.0$ Hz, 2H, $H_{2,6}$), 6.96 (d, $J = 8.0$ Hz, 2H, $H_{3,5}$), 6.05 (s, 1H, H_4), 4.12 (t, $J = 4.7$ Hz, 2H, $\underline{CH_2}CH_2OH$), 3.93 (t, $J = 4.7$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.84 (s, 3H, OCH_3), 2.29 ppm (s, 3H, CH_3).

2-(6-Methoxyindeno[1,2-*c*]pyrazol-1(4*H*)-yl)ethanol (**4c**): mp 142–144 °C; IR (KBr): ν 3,277 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.44 (d, $J = 8.2$ Hz, 1H, H_8), 7.39 (s, 1H, H_3), 7.07 (s, 1H, H_5), 6.87 (d, $J = 8.2$ Hz, 1H, H_7), 4.47 (t, $J = 4.4$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.10 (t, $J = 4.4$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.85 (s, 3H, OCH_3), 3.53 ppm (s, 2H, H_4).

2-(6-Methoxy-3-methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)ethanol (**4d**): mp 165–166 °C; IR (KBr): ν 3,293 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.40 (d, $J = 8.2$ Hz, 1H, H_8), 7.07 (s, 1H, H_5), 6.86 (d, $J = 8.2$ Hz, 1H, H_7), 4.39 (t, $J = 4.4$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.06 (t, $J = 4.4$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.84 (s, 3H, OCH_3), 3.45 (s, 2H, H_4), 2.29 ppm (s, 3H, H_3).

2-(7-Methoxy-4,5-dihydro-2*H*-benzo[*g*]indazol-1-yl)ethanol (**4e**): mp 109–110 °C; IR (KBr): ν 3,211 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.48 (d, $J = 8.4$ Hz, 1H, H_9), 7.36 (s, 1H, H_3), 6.89 (d, $J = 2.8$ Hz, 1H, H_6), 6.82 (dd, $J = 2.8$, 8.4 Hz, 1H, H_8), 4.48 (t, $J = 4.6$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.14 (t, $J = 4.6$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.84 (s, 3H, OCH_3), 2.87 (t, $J = 7.0$ Hz, 2H, H_5), 2.68 ppm (t, $J = 7.0$ Hz, 2H, H_4).

2-(7-Methoxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-1-yl)ethanol (**4f**): mp 108–110 °C; IR (KBr): ν 3,220 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.44 (d, $J = 8.4$ Hz, 1H, H_9), 6.88 (d, $J = 2.4$ Hz, 1H, H_6), 6.80 (dd, $J = 2.4$, 8.4 Hz, 1H, H_8), 4.42 (t, $J = 4.8$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.09 (t, $J = 4.8$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.83 (s, 3H, OCH_3), 2.86 (t, $J = 7.2$ Hz, 2H, H_5), 2.57 (t, $J = 7.2$ Hz, 2H, H_4), 2.22 ppm (s, 3H, H_3).

General procedure D. Demethylation with BBr_3

To a stirred solution of methyl protected pyrazole (**3a–f**, 1 mmol) in dry CH_2Cl_2 (35 mL) at −78 °C, a solution of BBr_3 (1 *M* in dry CH_2Cl_2; 10–15 eq) was added dropwise. After complete addition of BBr_3, the reaction was maintained at −78 °C for 1 h and then the temperature was allowed to rise to room temperature and stirred for 16 h in this temperature. The mixture was cooled to 0 °C and carefully quenched with H_2O. The product was then extracted with EtOAc (3 × 20 ml) and the organic layers were dried over Na_2SO_4. After evaporation of the solvent the residue was purified by chromatography (EtOAc/*n*-hexane, 1:1) to give (**6a–f**).

1-(2-Bromoethyl)-3-(4-hydroxyphenyl)pyrazole (**6a**): Yield 96 %; mp 109–110 °C; IR (KBr): *v* 3,235 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 7.36 (d, $J = 8.6$ Hz, 2H, $H_{2,6}$), 7.29 (d, $J = 2.3$ Hz, 1H, H_5), 6.61 (d, $J = 8.6$ Hz, 2H, $H_{3,5}$), 6.21 (d, $J = 2.3$ Hz, 1H, H_4), 4.28 (t, $J = 6.2$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.54 ppm (t, $J = 6.2$ Hz, 2H, $CH_2\underline{CH_2}Br$); MS *m/z* (%): 268 (M^++2, 90), 266 (M^+, 90), 239 (3), 237 (3), 219 (6), 190 (12), 173 (100), 161 (92), 131 (57), 107 (51), 77 (34), 51 (12).

1-(2-Bromoethyl)-3-(4-hydroxyphenyl)-5-methylpyrazole (**6b**): Yield 90 %; mp 153–154 °C; IR (KBr): *v* 3,341 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 7.28 (t, $J = 8.0$ Hz, 2H, $H_{2,6}$), 6.92 (d, $J = 8.0$ Hz, 2H, $H_{3,5}$), 6.05 (s, 1H, H_4), 4.38 (t, $J = 5.8$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.68 (t, $J = 5.8$ Hz, 2H, $CH_2\underline{CH_2}Br$), 2.32 ppm (s, 3H, CH_3); MS *m/z* (%): 282 (M^++2, 64), 280 (M^+, 64), 248 (4), 201 (11), 188 (51), 174 (100), 146 (34), 115 (36), 91 (12), 65 (10).

2-(2-Bromoethyl)-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**6c**): Yield 68 %; mp 144–146 °C; IR (KBr): *v* 3,251 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.57 (d, $J = 8.1$ Hz, 1H, H_8), 7.32 (s, 1H, H_3), 7.00 (s, 1H, H_5), 6.83 (dd, $J = 2.3$, 8.1 Hz, 1H, H_7), 4.57 (t, $J = 6.2$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.77 (t, $J = 6.2$ Hz, 2H, $CH_2\underline{CH_2}Br$), 3.59 ppm (s, 2H, H_4); MS *m/z* (%): 280 (M^++2, 71), 278 (M^+, 71), 201 (15), 185 (100), 173 (23), 158 (17), 135 (13), 115 (29), 89 (13), 63 (11).

2-(2-Bromoethyl)-3-methyl-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**6d**): Yield 70 %; mp 235–236 °C; IR (KBr): *v* 3,290 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.57 (d, $J = 8.2$ Hz, 1H, H_8), 6.99 (d, $J = 2.0$ Hz, 1H, H_5), 6.81 (dd, $J = 2.0$, 8.2 Hz, 1H, H_7), 4.49 (t, $J = 5.2$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.78 (t, $J = 5.2$ Hz, 2H, $CH_2\underline{CH_2}Br$), 3.52 (s, 2H, H_4), 2.38 ppm (s, 3H, CH_3); MS *m/z* (%): 294 (M^++2, 86), 292 (M^+, 86), 213 (20), 199 (100), 186 (46), 172 (28), 158 (19), 145 (17), 128 (58), 107 (16), 77 (22), 43 (19).

2-(2-Bromoethyl)-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**6e**): Yield 72 %; mp 119–121 °C; IR (KBr): *v* 3,230 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.68 (d, $J = 8.4$ Hz, 1H, H_9), 7.23 (s, 1H, H_3), 6.72 (m, 2H, $H_{6,8}$), 4.49 (t, $J = 6.2$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.74 (t, $J = 6.2$ Hz, 2H, $CH_2\underline{CH_2}Br$), 2.87 (t, $J = 7.2$ Hz, 2H), 2.74 ppm (t, $J = 7.2$ Hz, 2H); MS *m/z* (%): 294 (M^++2, 63), 292 (M^+, 63), 230 (52), 199 (100), 187 (36), 169 (14), 147 (16), 128 (23), 107 (31), 91 (20), 77 (22), 41 (18).

2-(2-Bromoethyl)-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**6f**): Yield 65 %; mp 224–226 °C; IR (KBr): *v* 3,250 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 9.35 (bs, 1H, OH), 7.44 (d, $J = 8.2$ Hz, 1H, H_9), 6.65 (d, $J = 2.2$ Hz, 1H, H_6), 6.62 (dd, $J = 2.2$, 8.2 Hz, 1H, H_8), 4.39 (t, $J = 6.3$ Hz, 2H, $\underline{CH_2}CH_2Br$), 3.81 (t, $J = 6.3$ Hz, 2H, $CH_2\underline{CH_2}Br$), 2.76 (t, $J = 7.2$ Hz, 2H, H_5), 2.55 ppm (t, $J = 7.2$ Hz, 2H, H_4); MS *m/z* (%): 308 (M^++2, 19), 306 (M^+, 19), 279 (24), 227 (5), 212 (28), 200 (29), 167 (84), 149 (100), 128 (54), 115 (35), 104 (22), 83 (35), 78 (55), 57 (66), 43 (36).

3-(4-Benzyloxyphenyl)-3-oxopropanal (**8a**): It was prepared according to "General procedure A" and was completely enolized to 1-(4-benzyloxyphenyl)-3-hydroxy-2-propen-1-one. Yield 67 %, mp 80–83 °C; IR (KBr): *v* 3,289 (OH), 1,633 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 15.35 (bs, 1H, OH), 8.15 (d, $J = 4.0$ Hz, 1H, H_3-vinylic), 7.89 (d, $J = 8.2$ Hz, 2H, $H_{2,6}$), 7.50–7.28 (m, 5H, Ph), 7.02 (d, $J = 8.2$ Hz, 2H, $H_{3,5}$), 6.16 (d, $J = 4.0$ Hz, 1H, H_2-vinylic), 5.14 (s, 2H, CH_2).

1-(4-Benzyloxyphenyl)butane-1,3-dione (**8b**): It was prepared according to "General procedure A" and was partially enolized. Yield 73 %, mp 100–102 °C; IR (KBr): *v* 3,346 (OH), 1,712 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.91 (d, $J = 8.4$ Hz, 0.4H, $H_{2,6}$), 7.86 (d, $J = 8.4$ Hz, 1.6H, $H_{2,6}$), 7.45–7.30 (m, 5H, Ph), 7.01 (d, $J = 8.4$ Hz, 2H, $H_{3,5}$), 6.12 (s, 0.8H, H-vinylic), 5.13 (s, 2H, CH_2), 4.01 (s, 0.4H, CH_2), 2.17 ppm (s, 3H, CH_3).

6-Benzyloxy-3-hydroxy-1*H*-indene-2-carbaldehyde (**8c**): It was prepared according to "General procedure A" and was partially enolized to 5-benzyloxy-2-hydroxymethylene-2,3-dihydroinden-1-one. Yield 72 %; mp 145–147 °C; IR (KBr): *v* 3,307 (OH), 1,685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.77 (d, $J = 8.8$ Hz, 0.67H, H_7), 7.69 (d, $J = 8.8$ Hz, 0.33H, H_7), 7.44–7.32 (m, 6H, Ph, H-vinylic), 7.04–6.98 (m, 2H, $H_{4,6}$), 5.15 (s, 2H, CH_2-Ph), 3.55 ppm (s, 2H, H_3).

2-Acetyl-5-benzyloxy-2,3-dihydroinden-1-one (**8d**): It was prepared according to "General procedure A" and was partially enolized. Yield 76 %; mp 132–134 °C; IR (KBr): *v* 3,320 (OH), 1,660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.75 (d, $J = 8.5$ Hz, 0.67H, H_7), 7.65 (d, $J = 8.5$ Hz, 0.33H, H_7), 7.45–7.35 (m, 5H, Ph), 7.03–6.96 (m, 2H, $H_{4,6}$), 5.14 (s, 2H, $\underline{CH_2}$–Ph), 3.94 (dd, $J = 3.2$, 7.6 Hz, 0.33H, H_2), 3.67 (dd, $J = 3.2$, 17.5 Hz, 0.33H, H_3), 3.54 (s, 1.34H, H_3), 3.05 (dd, $J = 7.6$, 17.5 Hz, 0.33H, H_3), 2.48 (s, 1H, CH_3), 2.12 ppm (s, 2H, CH_3).

6-Benzyloxy-1-hydroxy-3,4-dihydronaphthalene-2-carbaldehyde (**8e**): It was prepared according to "General procedure A" and was comletely enolized to

6-benzyloxy-2-hydroxymethylene-3,4-dihydronaphthalen-1(2*H*)-one. Yield 69 %; mp 88–90 °C; IR (KBr): *ν* 3,400 (OH), 1,643 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): *δ* 14.66 (s, 1H, OH), 7.94 (d, $J = 8.6$ Hz, 1H, H_8), 7.49–7.33 (m, 6H, Ph, H-vinylic), 6.93 (dd, $J = 2.2$, 8.6 Hz, 1H, H_7), 6.81 (d, $J = 2.2$ Hz, 1H, H_5), 5.12 (s, 2H, $\underline{CH_2}$-Ph), 2.86 (t, $J = 7.0$ Hz, 2H, H_4), 2.55 ppm (t, $J = 7.0$ Hz, 2H, H_3).

2-Acetyl-6-benzyloxy-3,4-dihydronaphthalen-1(2*H*)-one (**8f**): It was prepared according to "General procedure A" and was partially enolized. Yield 75 %; mp 118–120 °C; IR (KBr): *ν* 3,310 (OH), 1,600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): *δ* 7.91 (d, $J = 8.6$ Hz, 1H, H_9), 7.43–7.33 (m, 5H, Ph), 6.91 (dd, $J = 2.4$, 8.6 Hz, 1H, H_8), 6.78 (d, $J = 2.4$ Hz, 1H, H_6), 5.11 (s, 2H, $\underline{CH_2}$–Ph), 2.84 (t, $J = 7.2$ Hz, 2H, H_5), 2.61 (t, $J = 7.2$ Hz, 2H, H_4), 2.19 ppm (s, 3H, CH_3).

3-(4-Benzyloxyphenyl)-1*H*-pyrazole (**9a**): It was prepared according to "General procedure B". Yield 73 %; mp 113–115 °C; IR (KBr): *ν* 3,425 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.66 (d, $J = 8.4$ Hz, 2H, $H_{2,6}$), 7.60 (s, 1H, H_5-pyrazole), 7.45 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.40 (t, $J = 7.2$ Hz, $H_{3',5'}$), 7.34 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.02 (d, $J = 8.4$ Hz, 2H, $H_{3,5}$), 6.54 (s, 1H, H_4-pyrazole), 5.11 (s, 2H, CH_2), 2.35 (s, 3H, CH_3).

3-(4-Benzyloxyphenyl)-5-methyl-1*H*-pyrazole (**9b**): It was prepared according to "General procedure B". Yield 87 %; mp 149–150 °C; IR (KBr): *ν* 3,381 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.64 (d, $J = 8.5$ Hz, 2H, $H_{2,6}$), 7.44 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.39 (t, $J = 7.2$ Hz, 2H, $H_{3',5'}$), 7.32 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.00 (d, $J = 8.5$ Hz, 2H, $H_{3,5}$), 6.29 (s, 1H, H_4-pyrazole), 5.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3).

6-Benzyloxy-2,4-dihydroindeno[1,2-*c*]pyrazole (**9c**): It was prepared according to "General procedure B". Yield 84 %; mp 189–191 °C; IR (KBr): *ν* 3,129 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.64 (d, $J = 8.4$ Hz, 1H, H_8), 7.47–7.32 (m, 6H, Ph, H_3), 7.16 (d, $J = 2.4$ Hz, 1H, H_5), 6.98 (dd, $J = 2.4$, 8.4 Hz, 1H, H_7), 5.11 (s, 2H, $\underline{CH_2}$–Ph), 3.63 ppm (s, 2H, H_4).

6-Benzyloxy-3-methyl-2,4-dihydroindeno[1,2-*c*]pyrazole (**9d**): It was prepared according to "General procedure B". Yield 83 %; mp 198–200 °C; IR (KBr): *ν* 3,114 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.64 (d, $J = 8.3$ Hz, 1H, H_8), 7.46–7.32 (m, 5H, Ph), 7.14 (d, $J = 2.2$ Hz, 1H, H_5), 6.93 (dd, $J = 2.4$, 8.3 Hz, 1H, H_7), 5.11 (s, 2H, $\underline{CH_2}$–Ph), 3.53 (s, 2H, H_4), 2.36 ppm (s, 3H, CH_3).

7-Benzyloxy-4,5-dihydro-2*H*-benzo[*g*]indazole (**9e**): It was prepared according to "General procedure B". Yield 89 %; mp 152–154 °C; IR (KBr): *ν* 3,270 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.62 (d, $J = 7.4$ Hz, 1H, H_9), 7.45–7.33 (m, 6H, Ph, H_3), 6.89 (s, 1H, H_6), 6.87 (d, $J = 8.6$ Hz, 1H, H_8), 5.12 (s, 2H, $\underline{CH_2}$–Ph), 2.92 (t, $J = 7.2$ Hz, 2H, H_5), 2.78 ppm (t, $J = 7.2$ Hz, 2H, H_4).

7-Benzyloxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**9f**): It was prepared according to "General procedure B". Yield 82 %; mp 141–142 °C; IR (KBr): *ν* 3,219 cm^{-1} (NH); ^1H NMR ($CDCl_3$): *δ* 7.66 (d, $J = 8.0$ Hz, 1H, H_9), 7.45–7.31 (m, 5H, Ph), 6.88 (m, 2H, $H_{6,8}$), 5.08 (s, 2H, $\underline{CH_2}$–Ph), 2.91 (t, $J = 7.2$ Hz, 2H, H_5), 2.65 (t, $J = 7.2$ Hz, 2H, H_4), 2.26 ppm (s, 3H, CH_3).

2-[3-(4-Benzyloxyphenyl)pyrazol-1-yl]ethanol (**10a**): It was prepared according to "General procedure C". Yield 77 %; mp 117–119 °C; IR (KBr): *ν* 3,248 cm^{-1} (OH); ^1H NMR ($CDCl_3$): *δ* 7.71 (d, $J = 8.7$ Hz, 2H, $H_{2,6}$), 7.45 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.41 (d, $J = 2.2$ Hz, 1H, H_5-pyrazole), 7.39 (t, $J = 7.2$ Hz, 2H, $H_{3',5'}$), 7.33 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.01 (d, $J = 8.7$ Hz, 2H, $H_{3,5}$), 6.48 (d, $J = 2.2$ Hz, 1H, H_4-pyrazole), 5.10 (s, 2H, CH_2), 4.25 (t, $J = 4.5$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.02 ppm (t, $J = 4.5$ Hz, 2H, $CH_2\underline{CH_2}OH$).

2-[3-(4-Benzyloxyphenyl)-5-methylpyrazol-1-yl]ethanol (**10b**): It was prepared according to "General procedure C". Yield 72 %; mp 104–106 °C; IR (KBr): *ν* 3,306 cm^{-1} (OH); ^1H NMR ($CDCl_3$): *δ* 7.68 (d, $J = 8.7$ Hz, 2H, $H_{2,6}$), 7.44 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.39 (t, $J = 7.2$ Hz, 2H, $H_{3',5'}$), 7.32 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 6.99 (d, $J = 8.7$ Hz, 2H, $H_{3,5}$), 6.27 (s, 1H, H_4-pyrazole), 5.09 (s, 2H, CH_2), 4.13 (t, $J = 4.4$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.05 (t, $J = 4.4$ Hz, 2H, $CH_2\underline{CH_2}OH$), 2.30 ppm (s, 3H, CH_3).

2-(6-Benzyloxyindeno[1,2-*c*]pyrazol-2(4*H*)-yl)ethanol (**10c**): It was prepared according to "General procedure C". Yield 27 %; mp 118–120 °C; IR (KBr): *ν* 3,415 cm^{-1} (OH); ^1H NMR ($CDCl_3$): *δ* 7.63 (d, $J = 8.2$ Hz, 1H, H_8), 7.48–7.32 (m, 6H, Ph, H_3), 7.16 (s, 1H, H_5), 6.96 (d, $J = 8.2$ Hz, 1H, H_7), 5.11 (s, 2H, $\underline{CH_2}$-Ph), 4.30 (t, $J = 4.7$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.03 (t, $J = 4.7$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.55 ppm (s, 2H, H_4).

2-(6-Benzyloxy-3-methylindeno[1,2-*c*]pyrazol-2(4*H*)-yl)ethanol (**10d**): Yield 3 %; mp 128–130 °C; IR (KBr, cm^{-1}): *ν* 3,320 (OH); ^1H NMR ($CDCl_3$): *δ* 7.65 (d, $J = 8.4$ Hz, 1H, H_8), 7.46–7.34 (m, 5H, Ph), 7.10 (d, $J = 2.4$ Hz, H_5), 6.94 (dd, $J = 2.4$, 8.4 Hz, 1H, H_7), 5.10 (s, 2H, CH_2-Ph), 4.18 (t, $J = 4.8$ Hz, 2H, $\underline{CH_2}CH_2OH$), 4.04 (t, $J = 4.8$ Hz, 2H, $CH_2\underline{CH_2}OH$), 3.48 (s, 2H, H_4), 2.32 ppm (s, 3H, CH_3).

2-(7-Benzyloxy-4,5-dihydro-2*H*-benzo[*g*]indazol-2-yl) ethanol (**10e**): It was prepared according to "General procedure C". Yield 43 %; mp 112–114 °C; IR (KBr): *ν* 3,203 cm^{-1} (OH); ^1H NMR ($CDCl_3$): *δ* 7.73 (d, $J = 8.1$ Hz, 1H, H_9), 7.47–7.32 (m, 5H, Ph), 7.17 (s, 1H, H_3), 6.89–6.87 (m, 2H, $H_{6,8}$), 5.07 (s, 2H, $\underline{CH_2}$–Ph), 4.20 (t, $J = 4.7$ Hz, 2H, $\underline{CH_2}CH_2OH$), 3.99 (t, $J = 4.7$ Hz, 2H, $CH_2\underline{CH_2}OH$), 2.89 (t, $J = 7.2$ Hz, 2H, H_5), 2.74 ppm (t, $J = 7.2$ Hz, 2H, H_4).

2-(7-Benzyloxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol -2-yl)ethanol (**10f**): It was prepared similar to "General procedure C". Yield 37 %; mp 123–125 °C; IR (KBr): *ν*

3,227 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.72 (d, $J = 8.0$ Hz, 1H, H_9), 7.46–7.33 (m, 5H, Ph), 6.88 (m, 2H, $H_{6,8}$), 5.09 (s, 2H, CH_2–Ph), 4.12 (t, $J = 4.6$ Hz, 2H, CH_2CH_2OH), 3.96 (t, $J = 4.6$ Hz, 2H, CH_2CH_2OH), 2.90 (t, $J = 7.2$ Hz, 2H, H_5), 2.64 (t, $J = 7.2$ Hz, 2H, H_4), 2.10 ppm (s, 3H, CH_3).

2-[3-(5-Benzyloxyphenyl)pyrazol-1-yl]ethanol (**11a**): It was prepared according to "General procedure C". Yield 12 %; mp 138–140 °C; IR (KBr): ν 3,282 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.70 (d, $J = 8.8$ Hz, 2H, $H_{2,6}$), 7.54 (d, $J = 2.2$ Hz, 1H, H_5-pyrazole), 7.47 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.39 (t, $J = 7.2$ Hz, 2H, $H_{3',5'}$), 7.35 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.04 (d, $J = 8.8$ Hz, 2H, $H_{3,5}$), 6.27 (d, $J = 2.2$ Hz, 1H, H_4-pyrazole), 5.12 (s, 2H, CH_2–Ph), 4.20 (t, $J = 4.7$ Hz, 2H, CH_2CH_2OH), 3.97 ppm (t, $J = 4.7$ Hz, 2H, CH_2CH_2OH).

2-[3-(5-Benzyloxyphenyl)-5-methylpyrazol-1-yl]ethanol (**11b**): It was prepared according to "General procedure C". Yield 19 %; mp 137–139 °C; IR (KBr): ν 3,265 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.69 (d, $J = 8.7$ Hz, 2H, $H_{2,6}$), 7.45 (d, $J = 7.2$ Hz, 2H, $H_{2',6'}$), 7.37 (t, $J = 7.2$ Hz, 2H, $H_{3',5'}$), 7.30 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.03 (d, $J = 8.7$ Hz, 2H, $H_{3,5}$), 6.05 (s, 1H, H_4-pyrazole), 5.11 (s, 2H, CH_2-Ph), 4.18 (t, $J = 4.4$ Hz, 2H, CH_2CH_2OH), 3.95 (t, $J = 4.4$ Hz, 2H, CH_2CH_2OH), 2.29 ppm (s, 3H, CH_3).

2-(6-Benzyloxyindeno[1,2-*c*]pyrazol-1(4*H*)-yl)ethanol (**11c**): It was prepared according to "General procedure C". Yield 45 %; mp 128–130 °C; IR (KBr): ν 3,300 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.45–7.32 (m, 7H, Ph, $H_{3,8}$), 7.15 (dd, $J = 2.3$, 8.4 Hz, H_7), 5.11 (s, 2H, CH_2–Ph), 4.47 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 4.10 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 3.54 ppm (s, 2H, H_4).

2-(6-Benzyloxy-3-methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)ethanol (**11d**): Yield 83 %; mp 116–118 °C; IR (KBr): ν 3,320 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.45–7.33 (m, 6H, Ph, H_8), 7.14 (d, $J = 2.3$ Hz, 1H, H_5), 6.94 (dd, $J = 2.3$, 8.3 Hz, 1H, H_7), 5.10 (s, 2H, CH_2–Ph), 4.39 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 4.06 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 3.45 (s, 2H, H_4), 2.29 ppm (s, 3H, CH_3).

2-(7-Benzyloxy-4,5-dihydro-2*H*-benzo[*g*]indazol-1-yl)ethanol (**11e**): It was prepared according to "General procedure C". Yield 30 %; mp 87–89 °C; IR (KBr): ν 3,203 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.73 (d, $J = 8.1$ Hz, 1H, H_9), 7.46–7.30 (m, 6H, Ph, H_3), 6.97 (d, $J = 2.4$ Hz, 1H, H_6), 6.88 (dd, $J = 2.4$, 8.1 Hz, 1H, H_8), 5.09 (s, 2H, CH_2–Ph), 4.46 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 4.12 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 2.85 (t, $J = 7.2$ Hz, 2H, H_5), 2.66 ppm (t, $J = 7.2$ Hz, 2H, H_4).

2-(7-Benzyloxy-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-1-yl)ethanol (**11f**): It was prepared according to "General procedure C". Yield 37 %; mp 123–125 °C; IR (KBr): ν 3,227 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 7.71 (d, $J = 8.2$ Hz, H_9), 7.45–7.34 (m, 5H, Ph), 6.97 (d, $J = 2.6$ Hz, 1H, H_6), 6.87 (dd, $J = 2.6$, 8.2 Hz, 1H, H_8), 5.09 (s, 2H, CH_2–Ph), 4.42 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 4.09 (t, $J = 4.8$ Hz, 2H, CH_2CH_2OH), 2.86 (t, $J = 7.0$ Hz, 2H, H_5), 2.57 (t, $J = 7.0$ Hz, 2H, H_4), 2.23 ppm (s, 3H, CH_3).

General procedure E. Hydrogenolysis of benzyl-protected pyrazoles

N-Hydroxylethylpyrazole derivatives (**10a–f**, 0.2 mmol) in MeOH–AcOH (5:1, 20 ml) were hydrogenated over 10 % Pd/C (10 mg) at 60 psi and the progress of the reaction was monitored by TLC. When the reaction was complete, the resulting mixture was filtered through Celite, and concentrated under reduced pressure to give debenzylated residues (**12a–f**) [12].

2-(3-(4-Hydroxyphenyl)pyrazol-1-yl)ethanol (**12a**): Yield 89 %; mp 152–153 °C; IR (KBr): ν 3,229 cm^{-1} (OH); ^1H NMR (CD_3OD): δ 7.61 (d, $J = 2.2$ Hz, 1H, H_5-pyrazole), 7.59 (d, $J = 8.5$ Hz, 2H, $H_{2,6}$), 6.81 (d, $J = 8.5$ Hz, 2H, $H_{3,5}$), 6.49 (d, $J = 2.2$ Hz, 1H, H_4-pyrazole), 4.25 (t, $J = 4.5$ Hz, 2H, CH_2CH_2OH), 3.91 ppm (t, $J = 4.5$ Hz, 2H, CH_2CH_2OH); MS *m/z* (%): 204 (M^+, 72), 173 (100), 161 (40), 146 (20), 119 (12), 91 (10), 77 (10), 65 (12).

2-(3-(4-Hydroxyphenyl)-5-methylpyrazol-1-yl)ethanol (**12b**): Yield 92 %; mp 123–125 °C; IR (KBr): ν 3,227 cm^{-1} (OH); ^1H NMR (CD_3OD): δ 7.57 (d, $J = 9.0$ Hz, 2H, $H_{2,6}$), 6.83 (d, $J = 9.0$ Hz, 2H, $H_{3,5}$), 6.40 (s, 1H, H_4-pyrazole), 4.22 (t, $J = 5.5$ Hz, 2H, CH_2CH_2OH), 3.90 (t, $J = 5.5$ Hz, 2H, CH_2CH_2OH), 3.28 ppm (s, 3H, CH_3); MS *m/z* (%): 218 (M^+, 72), 187 (100), 173 (55), 146 (33), 127 (10), 107 (34), 86 (32), 77 (22), 57 (20).

2-(2-Hydroxyethyl)-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**12c**): Yield 72 %; mp 216–218 °C; IR (KBr): ν 3,229, 3,218 cm^{-1} (OH); ^1H NMR (CD_3OD): δ 7.50 (d, $J = 8.2$ Hz, 1H, H_8), 7.35 (s, 1H, H_3), 6.96 (s, 1H, H_5), 6.77 (d, $J = 8.2$ Hz, 1H, H_7), 4.24 (t, $J = 5.3$ Hz, CH_2CH_2OH), 3.90 (t, $J = 5.3$ Hz, CH_2CH_2OH), 3.55 ppm (s, 2H, H_4); MS *m/z* (%): 216 (M^+, 85), 185 (100), 172 (76), 141 (34), 77 (42), 85 (31).

2-(2-Hydroxyethyl)-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**12e**): Yield 65 %; mp 202–204 °C; IR (KBr): ν 3,203, 3,118 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.35 (s, 1H, Ph–OH), 7.44 (d, $J = 8.2$ Hz, 1H, H_9), 7.42 (s, 1H, H_3), 6.63–6.61 (m, 2H, $H_{6,8}$), 4.88 (t, $J = 5.0$ Hz, 1H, CH_2CH_2OH), 4.07 (t, $J = 5.0$ Hz, 2H, CH_2CH_2OH), 3.70 (q, $J = 5.0$ Hz, 2H, CH_2CH_2OH), 2.73 (t, $J = 7.2$ Hz, 2H, H_5), 2.61 ppm (t, $J = 7.2$ Hz, 2H, H_4); MS *m/z* (%): 230 (M^+, 87), 199 (100), 186 (15), 128 (9), 115 (10).

2-(2-Hydroxyethyl)-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**12f**): Yield 68 %; mp 209–211 °C; IR (KBr): ν 3,313, 3,120 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.31 (bs, 1H, Ph–OH), 7.59 (d, $J = 8.2$ Hz, 1H, H_9), 6.63 (d, $J = 2.4$ Hz, 1H, H_6), 6.60 (dd, $J = 2.4$, 8.2 Hz, 1H, H_8), 4.48 (t, $J = 5.6$ Hz, 2H, CH_2CH_2OH), 4.02 (t,

$J = 5.6$ Hz, 2H, $\underline{CH_2}CH_2OH$), 3.68 (q, $J = 5.6$ Hz, 2H, $CH_2\underline{CH_2}OH$), 2.73 (t, $J = 7.4$ Hz, 2H, H_5), 2.61 (t, $J = 7.4$ Hz, 2H, H_4), 2.18 ppm (s, 3H, CH_3); MS *m/z* (%): 244 (M^+, 74), 213 (96), 200 (100), 159 (24), 131 (16), 115 (25), 77 (12).

General procedure F. Demethylation of methyl protected pyrazoles with HBr

Pyrazole derivatives (**5a–f**, 5 mmol) were boiled in aqueous 48 % hydrobromic acid (25 ml) for 12 h under nitrogen. The mixture was then cooled and filtered. The precipitate was dissolved in sodium hydroxide (20 ml, 6 %). The solution was neutralized with sodium bicarbonate solution (10 %) and filtered, dried and recrystallized to give **14a–f**. The spectral data of **14e** were similar with those reported [11].

3-(4-Hydroxyphenyl)-1*H*-pyrazole (**14a**): Yield 93 %; mp 184–185 °C; IR (KBr): *v* 3,396 (OH), 3,263 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 9.60 (bs, 1 H, Ph–$\underline{OH}$), 7.59 (d, $J = 8.0$ Hz, 2H, $H_{2,6}$), 7.55 (d, $J = 1.6$ Hz, 1H, H_5), 6.88 (d, $J = 8.0$ Hz, 2H, $H_{3,5}$), 6.45 ppm (d, $J = 1.6$ Hz, 1H, H_4).

3-(4-Hydroxyphenyl)-5-methyl-1*H*-pyrazole (**14b**): Yield 95 %; mp > 300 °C; IR (KBr): *v* 3,310 (OH), 3,255 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 9.53 (bs, 1 H, OH), 7.53 (d, $J = 8.3$ Hz, 2H, $H_{2,6}$), 6.77 (d, $J = 8.3$ Hz, 2H, $H_{3,5}$), 6.31 (s, 1H, H_4), 2.22 ppm (s, 3H, CH_3).

2,4-Dihydroindeno[1,2-*c*]pyrazol-6-ol (**14c**): Yield 60 %; mp 171–173 °C; IR (KBr): *v* 3,300 (OH), 3,225 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 12.43 (bs, 1H, NH), 9.37 (bs, 1H, OH), 7.50 (s, 1H, H_3), 7.38 (d, $J = 8.1$ Hz, 1H, H_8), 6.92 (s, $J = 2.1$ Hz, 1H, H_5), 6.72 (dd, $J = 2.1, 8.1$ Hz, 1H, H_7), 3.50 ppm (s, 2H, H_4).

3-Methyl-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**14d**): Yield 67 %; mp 299–301 °C; IR (KBr): *v* 3,300 (OH), 3,243 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 12.08 (bs, 1H, NH), 9.32 (bs, 1H, OH), 7.32 (d, $J = 8.0$ Hz, 1H, H_8), 6.88 (d, $J = 2.2$ Hz, 1H, H_5), 6.69 (dd, $J = 2.2$, 8.0 Hz, 1H, H_7), 3.40 (s, 2H, H_4), 2.23 ppm (s, 3H, CH_3).

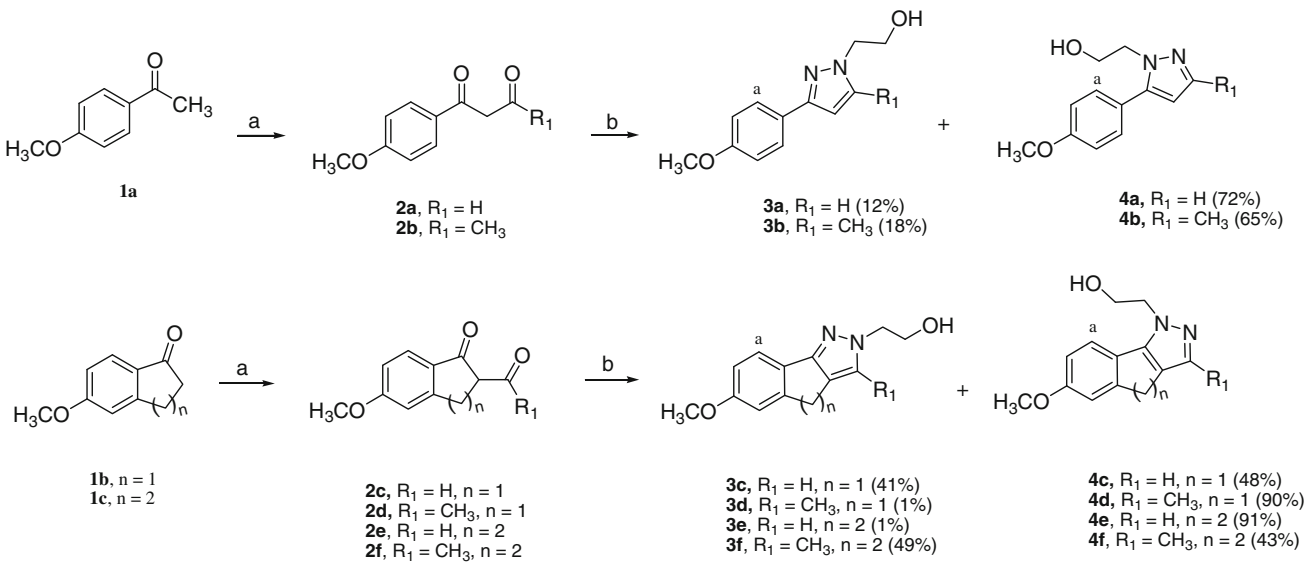
3-Methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**14f**): Yield 70 %; mp 250–252 °C; IR (KBr): *v* 3,300 (OH), 3,252 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 12.18 (bs, 1H, NH), 9.32 (bs, 1H, OH), 7.40 (d, $J = 8.2$ Hz, 1H, H_9), 6.64 (s, 1H, H_6), 6.61 (d, $J = 8.2$ Hz, 1H, H_8), 2.74 (t, $J = 7.2$ Hz, 2H, H_5), 2.51 (t, $J = 7.2$ Hz, 2H, H_4), 2.10 ppm (s, 3H, CH_3).

General procedure G. Preparation of *N*-hydroxymethylpyrazoles (**15a–f**)

Demethylated-pyrazole derivatives (**14a–f**, 1 mmol) and paraformaldehyde (1.3 mmol) were placed under nitrogen. The interior of the flask was flushed with dry nitrogen three times. Dry THF (30 ml) was added to give a suspension. The suspension was kept well stirred at 45 °C until the starting material disappeared by TLC control. Evaporation of THF under reduced pressure gave residues which were recrystallized from ethyl acetate to give **15a–f** [14].

1-Hydroxymethyl-3-(4-hydroxyphenyl)pyrazole (**15a**): Yield 84 %; mp 177–178 °C; IR (KBr): *v* 3,280, 3,230 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.56 (bs, 1H, Ph–$\underline{OH}$), 7.23 (d, $J = 2.5$ Hz, 1H, H_5), 7.22 (d, $J = 8.7$ Hz, 2H, $H_{2,6}$), 6.43 (d, $J = 8.7$ Hz, 2H, $H_{3,5}$), 6.09 (d, $J = 2.5$ Hz, 1H, H_4), 5.06 ppm (s, 2H, $\underline{CH_2}OH$); MS *m/z* (%): 190 (M^+, 3), 160 (100), 131 (96), 103 (25), 77 (42), 51 (21).

1-Hydroxymethyl-3-(4-hydroxyphenyl)-5-methyl-pyrazole (**15b**): Yield 98 %; mp >300 °C; IR (KBr): *v*



Scheme 1 Reagents and conditions: *a* R_1COOCH_3, C_2H_5ONa, 0 °C to r.t.; *b* $NH_2NHCH_2CH_2OH$, THF, DMF (1:1), reflux

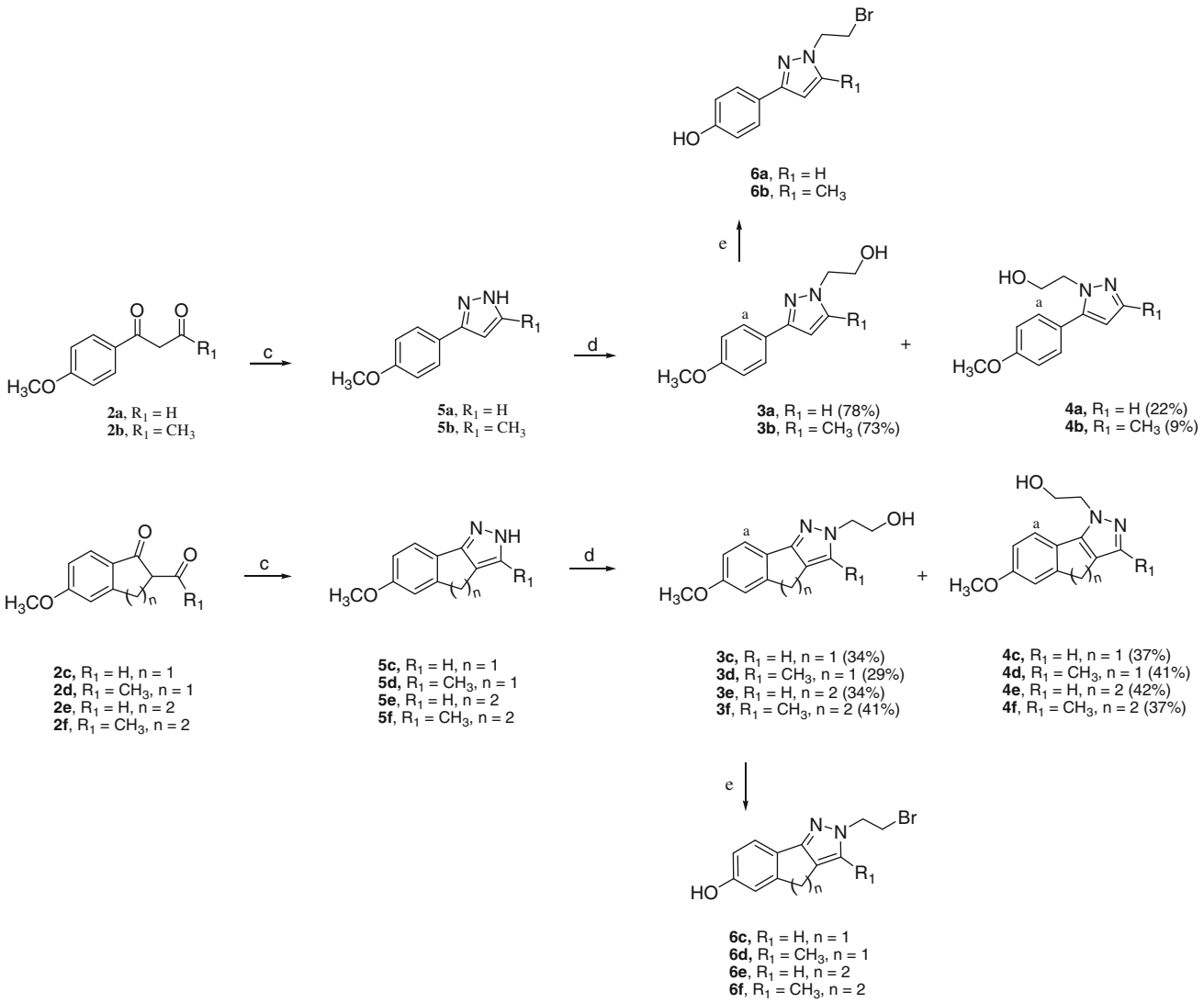
3,226 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.46 (bs, 1H, Ph–OH), 7.56 (d, $J = 8.2$ Hz, 2H, $H_{2,6}$), 6.76 (d, $J = 8.2$ Hz, 2H, $H_{3,5}$), 6.35 (s, 1 H, H_4), 5.32 (s, 2H, CH_2OH), 2.31 ppm (s, 3H, CH_3); MS *m/z* (%): 204 (M^+, 4), 174 (100), 145 (40), 131 (60), 115 (83), 91 (31), 77 (12), 63 (23), 42 (23).

2-Hydroxymethyl-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**15c**): Yield 84 %; mp 170–172 °C; IR (KBr): *v* 3,232 cm^{-1} (OH). ^1H NMR (DMSO-d_6): δ 9.46 (bs, 1H, Ph–OH), 7.60 (bs, 1H, H_3), 7.38 (d, $J = 7.7$ Hz, 1H, H_8), 6.91 (s, 1H, H_5), 6.72 (d, $J = 7.7$ Hz, 1H, H_7), 6.64 (t, $J = 7.4$ Hz, 1H, CH_2-OH), 5.36 (d, $J = 7.4$ Hz, 2H, CH_2–OH), 3.50 ppm (s, 2H, H_4). MS *m/z* (%): 202 (M^+, 4), 172 (100), 145 (82), 115 (62), 89 (82), 63 (50).

2-Hydroxymethyl-3-methyl-2,4-dihydroindeno[1,2-*c*]pyrazol-6-ol (**15d**): Yield 85 %; mp 283–285 °C; IR (KBr): *v* 3,414, 3,206 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.43 (bs, 1H, Ph–OH), 7.35 (d, $J = 8.0$ Hz, 1H, H_8), 6.90 (d, $J = 1.7$ Hz, 1H, H_5), 6.71 (dd, $J = 1.7$, 8.0 Hz, 1H, H_7), 6.47 (t, $J = 7.3$ Hz, CH_2–OH), 5.33 (d, $J = 7.3$ Hz, 2H, CH_2–OH), 3.44 (s, 2H, H_4), 2.32 ppm (s, 3H, CH_3); MS *m/z* (%): 216 (M^+, 5), 186 (100), 171 (74), 145 (64), 116 (27), 89 (37), 42 (25).

2-Hydroxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**15e**): Yield 80 %; mp 203–205 °C; IR (KBr): *v* 3,392, 3,262 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.39 (bs, 1H, Ph–OH), 7.51 (bs, 1H, H_3), 7.46 (d, $J = 8.2$ Hz, 1H, H_9), 6.63 (m, 3H, $H_{6,8}$ and CH_2–OH), 5.30 (s, 2H, CH_2–OH), 2.75 (t, $J = 7.2$ Hz, 2H, H_5), 2.63 ppm (t, $J = 7.2$ Hz, 2H, H_4). MS *m/z* (%): 216 (M^+, 3), 186 (100), 185 (95), 158 (80), 131 (55), 103 (33), 84 (57), 66 (29).

2-Hydroxymethyl-3-methyl-4,5-dihydro-2*H*-benzo[*g*]indazol-7-ol (**15f**): Yield 70 %; mp 248–250 °C; IR (KBr): *v*



Scheme 2 Reagents and conditions: *c* $NH_2NH_2{\cdot}H_2O$, CH_3COOH, C_2H_5OH, reflux; *d* $BrCH_2CH_2OH$, NaOH, benzyltriethylammonium chloride, dioxane, 80 °C; *e* BBr_3, CH_2Cl_2, −78 °C

3,300 cm^{-1} (OH); ^1H NMR (DMSO-d_6): δ 9.34 (bs, 1H, Ph–OH), 7.45 (d, $J = 8.2$ Hz, 1H, H_9), 6.63 (m, 3H, $H_{6,8}$ and CH_2–OH), 5.31 (s, 2H, CH_2–OH), 2.76 (t, $J = 7.2$ Hz, 2H, H_5), 2.55 (t, $J = 7.2$ Hz, 2H, H_4), 2.26 ppm (s, 3H, CH_3); MS *m/z* (%): 230 (M^+, 4), 200 (100), 199 (95), 158 (55), 131 (58), 115 (60), 77 (76), 42 (58).

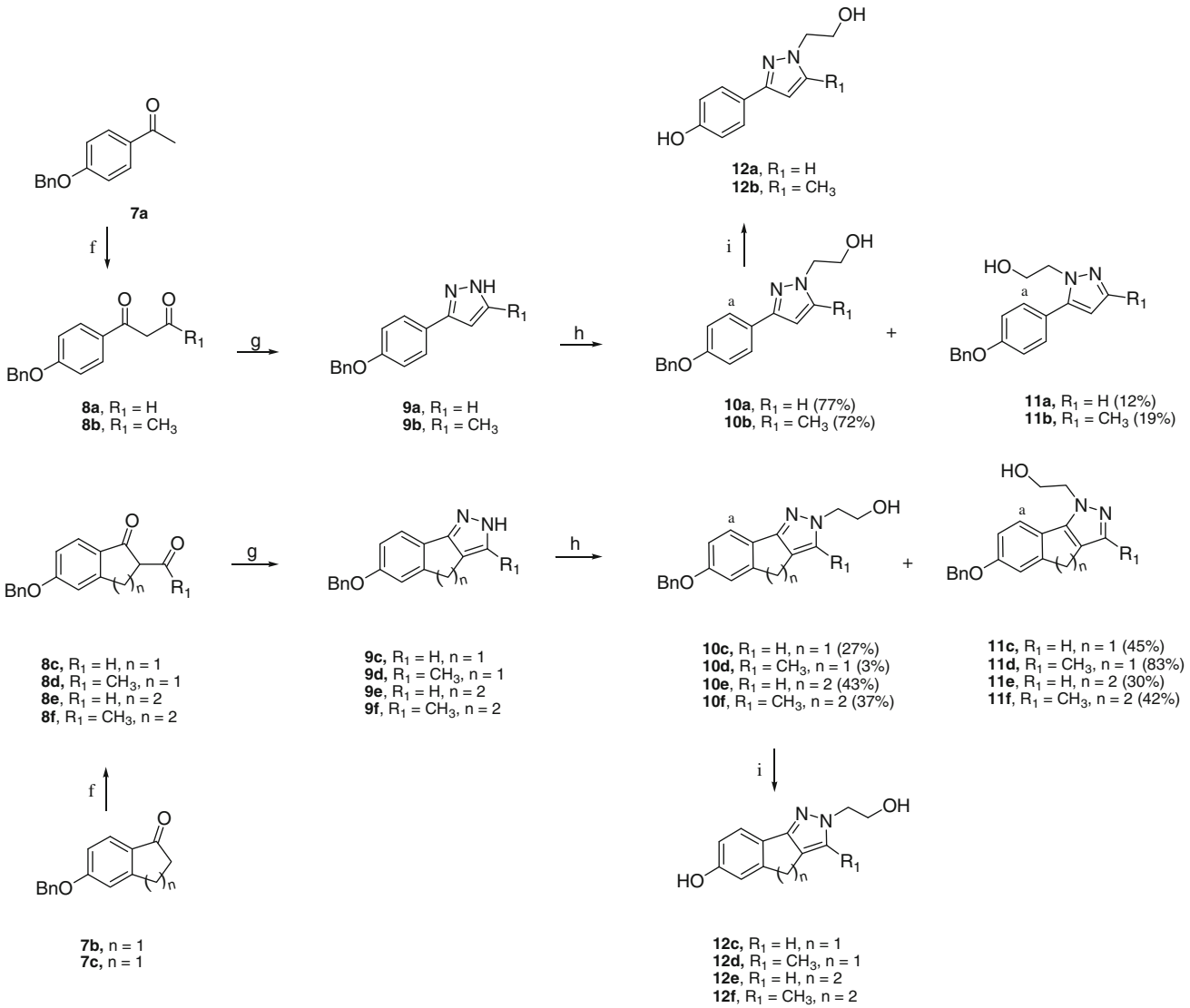
Results and discission

The synthetic reactions used for the preparation of *N*-hydroxyethyl (**12a–f**) and *N*-hydroxymethylpyrazole derivatives (**15a–f**) are illustrated in Schemes 1, 2, 3 and 4.

A general route to access the target pyrazole derivatives is via acylation of the corresponding substrates **1a–c** and subsequent condensation with the appropriate hydrazine derivative.

The first pathway involved the acylation of methoxy-substituted acetophenone (**1a**), indanone (**1b**) and tetralone (**1c**) which afforded the 1,3-dicarbonyl compounds (**4a–f**) [7–10]. Sunsequent condensation of the latters with hydroxyethylhydrazine furnished for some derivatives (**4a**, **4b**, **4d** and **4e**) predominantly the hydroxylethylpyrazoles **4** (Scheme 1) [26]. However, it is noteworthy that the main goal of this synthetic route was the preparation of **3a–f**.

The configuration of the pyrazole products was elucidated through 2D NOE NMR spectroscopy. More specifically, the assigned regiochemistry of compounds **4a–f** were consistent with the observed strong cross peak between H_a and the ethyl group. On the contrary, for compounds

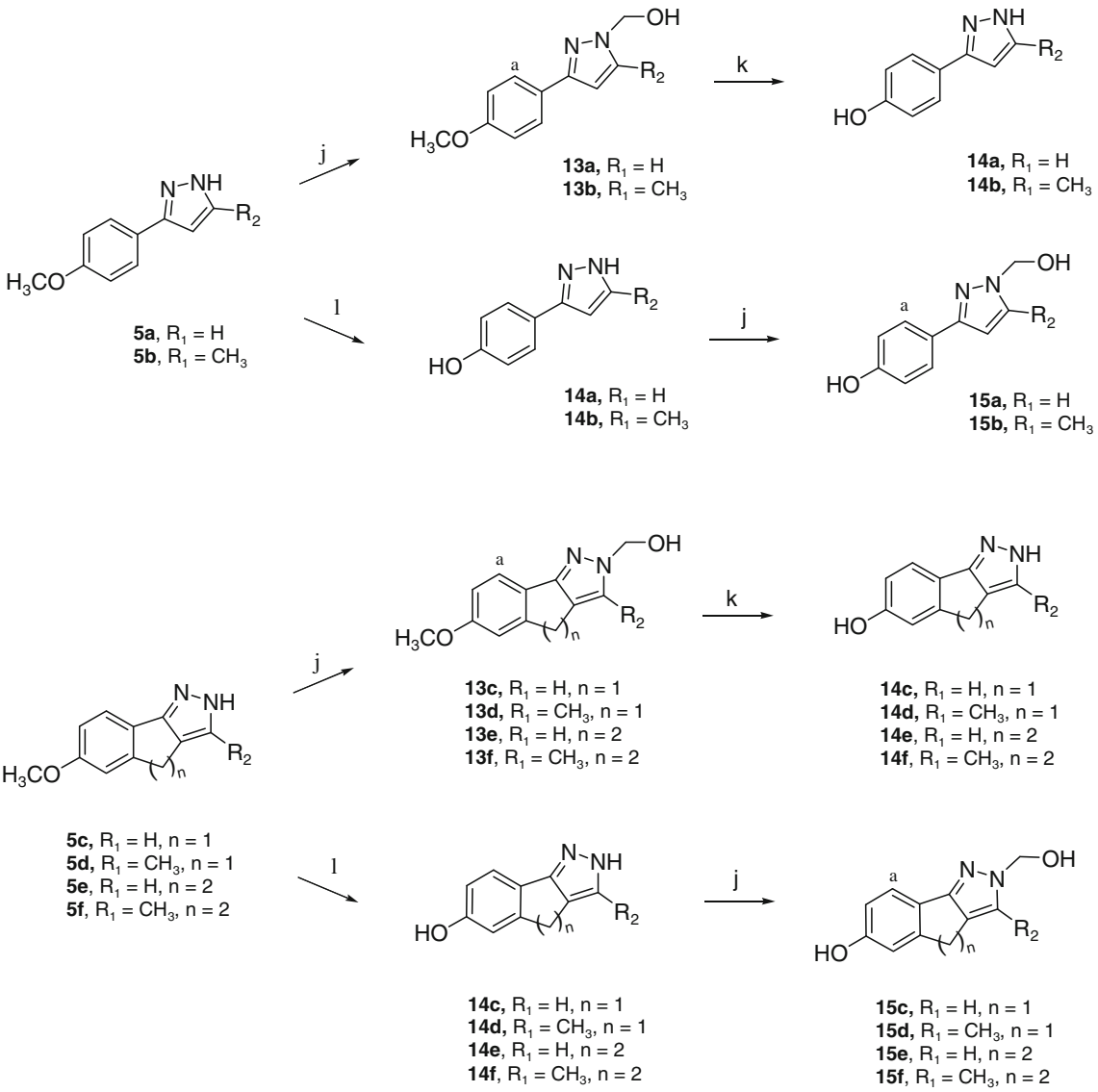


Scheme 3 Reagents and conditions: *f* R_1COOCH_3, C_2H_5ONa, 0 °C to r.t.; *g* $NH_2NH_2.H_2O$, CH_3COOH, C_2H_5OH, reflux; *h* $BrCH_2CH_2OH$, NaOH, benzyltriethylammonium chloride, dioxane, 80 °C; *i* Pd/C, H_2 (60 psi), MeOH–AcOH, r.t

3a–f the observed enhancement of the ethyl protons corresponds to R_1 hydrogens (H or methyl) substituted on pyrazole ring (Scheme 1).

The second pathway involved the condensation of the 1,3-dicarbonyl compounds (**2a–f**) with hydrazine hydrate in the presence of acetic acid which produced the pyrazole compounds **5a–f** (Scheme 2) [8–13]. The substitution reaction of pyrazole with 2-bromoethanol in basic media in the presence of benzyltriethylammonium chloride furnished a mixture of **3a–f** and their regioisomer **4a–f**, which were separated by preparative TLC. Finally, removal of the methoxy protecting groups of **3a–f** promoted by BBr_3 resulted in compounds **6a–f**, as depicted in Scheme 2, which their characterization by mass spectrometry showed that as well as demethylation, the aliphatic hydroxyl group was displaced with bromine. This can be rationalized considering that the hydroxyl groups on aliphatic chains in the presence of a lewis acid would be susceptible for substitution with bromide as a nucleophile.

The third synthetic route refers to the use of benzyl substituent as the protecting group of phenol moiety to avoid the latter substitution of hydroxyl with bromine. Similarly, the acylation of benzyloxy-substituted acetophenone (**7a**), indanone (**7b**) and tetralone (**7c**) afforded the 1,3-dicarbonyl compounds (**8a–f**). Subsequent condensation of the latters with hydrazine hydrate and further alkylation of the resulted pyrazole with 2-bromoethanol furnished a mixture of regioisomers **10a–f** and **11a–f**, which were separated by preparative TLC. Final hydrogenolysis of **10a–f** for removal of the benzyloxy-protecting groups produced in good yields of the title hydroxyethylpyrazoles **12a–f**.



Scheme 4 Reagents and conditions: *j* paraformaldehyde, THF, 45 °C; *k* BBr_3, CH_2Cl_2, −78 °C; *l* HBr 48 %, reflux

The fourth synthetic route, which is presented in Scheme 4, involves the hydroxymethylation of pyrazole compounds **5a–f** [27]. The condensation of latter pyrazoles with paraformaldehyde led to the exclusive formation of the pyrazole regioisomers **13a–f**. The regioselectivity of compound **13** was confirmed to be in accordance with the previously described spectroscopy experiments. More specifically, 2D NOE showed a strong cross peak between the methylene group (of CH_2OH) and the R_1 (H or methyl) substituents on pyrazole ring, as well as the absence of enhancement with H_a, are indicative of the assigned regiochemistry (Scheme 4). However, in subsequent demethylation promoted by BBr_3, the hydroxymethyl moiety was removed. Finally, prior removal of methoxy-protecting group of pyrazole **5a–f** [17], followed by hydroxymethylation by paraformaldehyde afforded the title hydroxymethylpyrazoles **15a–f**.

Finally as previously reported, ERα and ERβ are known to bind with high affinity steroidal and non-steroidal compounds having two hydroxyl groups with an O–O distance similar or even higher than estradiol (10.8 Å) such as propylpyrazoletriol (PPT) and 1,3-diarylcyclopentapyrazole that reportedly possess particularly high ERα and ERβ selective binding affinity and potency, respectively [8–12]. The O–O distance of the OH pair of compounds **12a–f** and **15a–f** estimated was equal to 10.7 and 9.6 Å, respectively, while the compounds **11a–f** does not provide suitable distance. The compounds **11a–f** were differentiated from **10a–f** (precursor of **12a–f**) by 2D NOE NMR spectroscopy (see above). However, compound **15** might provide suitable distance by help of a water molecule as a bridge. So, compounds **12** and **15** deserve to be evaluated as possible estrogen receptor ligands.

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