

Article

Synthesis of Tricyclic Condensed Rings Incorporating the Pyrazole or Isoxazole Moieties Bonded to a 4-Piperidinyl Substituent

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Abstract: In this paper we report the synthesis of new compounds based on the pyrazole and isoxazole framework fused to a cycloalkene unit, and bearing as a substituent the 1-piperidinyl group as new examples of potential antipsychotic molecules. The general synthesis involves the acylation of a chloro-substituted cyclic ketone with a 1-substituted piperidine-4-carboxylate derivative, followed by heterocyclization of the formed 1,3-dioxo compound with a hydrazine or hydroxylamine.

Keywords: heterocyclization; hydrazine; hydroxylamine; tricyclic isoxazoles; tricyclic pyrazoles

1. Introduction

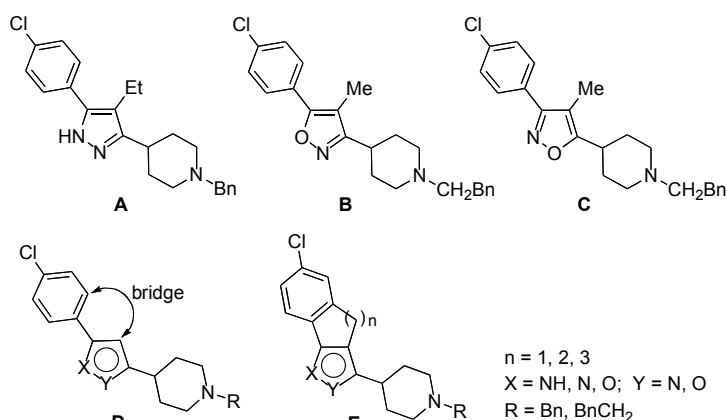
Among the compounds with antipsychotic properties [1] there are the heteropentalenes A–C [2], characterized by a pyrazole and isoxazole framework bonded to *p*-chlorophenyl and 4-piperidinyl substituents (Figure 1). In continuation of our interest in the field of the synthesis of biologically active

compounds [3], we have now devoted our attention to obtain tricyclic compounds **E** related to the heteropentalenes **A–C** as new potential antipsychotic compounds.

A well known strategy to affect the biological activity of organic compounds is to decrease their conformational flexibility. In fact, it has been proposed that appropriate structural constraints could restrict a pharmacophoric structural element to a sufficiently small region of conformational space thereby permitting the ligand to bind to its designated receptor with high affinity and selectivity [4,5]. A way to achieve this goal with heteropentalenes **A–C** could be to connect the unsubstituted central carbon of the heteropentalene and the α -carbon of the phenyl group with an alkylidene bridge (formula **D**, Figure 1).

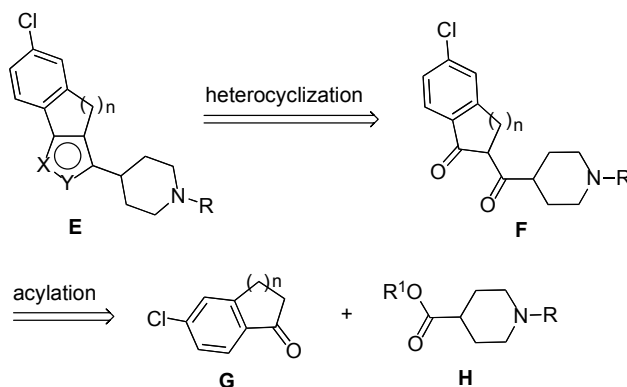
In this line, we have developed a practical and extensible method to build compounds with a tricyclic framework incorporating the pyrazole and isoxazole framework and with the central ring that can be modulated in size, namely compounds with the general formula **E** shown in Figure 1. These new compounds share with **A–C** the chlorine on the aryl ring and the 4-(1-benzyl)- or 4-(1-phenylethyl)-piperidinyl substituents on the isoxazole and pyrazole moieties (Figure 1).

Figure 1. Leads and target molecules.



The planned retrosynthesis of the derivatives **E** is shown in Scheme 1. In this approach, the final heterocyclization of the 1,3-dioxo compounds **F** with hydrazine or hydroxylamine is preceded by acylation of the chloro-substituted cyclic ketones **G** with the 1-substituted piperidine-4-carboxylate derivatives **H**.

Scheme 1. Retrosynthesis approach.

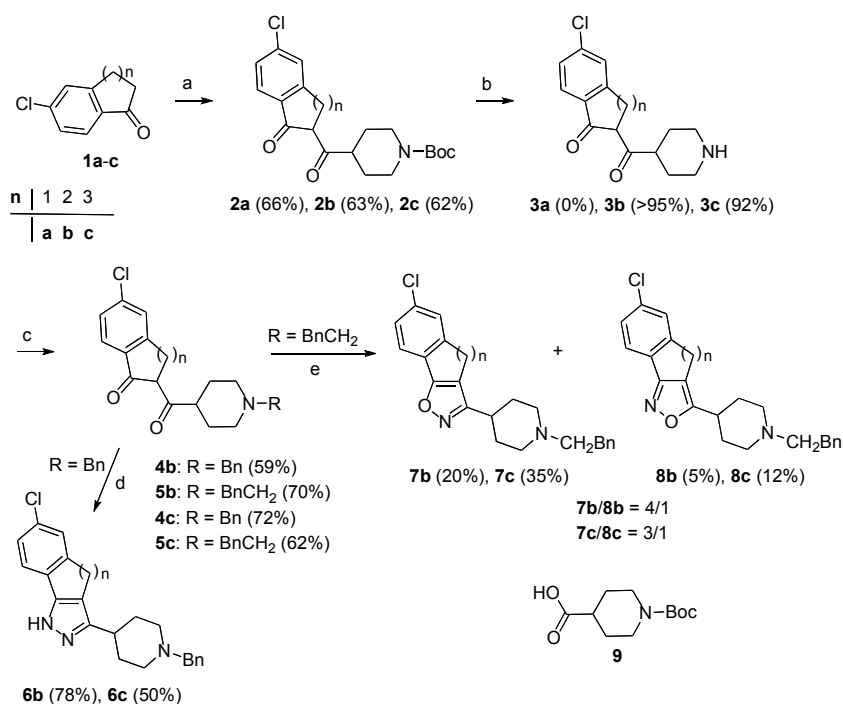


2. Results and Discussion

To begin the synthesis of the target derivatives **E** (Scheme 1), the known cyclic ketones **1a–c** [6,7] were acylated by reaction of the corresponding sodium enolate, obtained by reaction with sodium hydride, with the reagent formed by reaction of the *N*-Boc protected isonipecotic acid **9** with 1,1'-carbonyldiimidazole [8] (Scheme 2). In this way, 1,3-dicarbonyl derivatives **2a–c** were obtained in 62–63% yields. Next, these compounds were submitted to *N*-deprotection by treatment with trifluoroacetic acid in CH₂Cl₂. However, while **2b** and **2c** were easily deprotected giving compounds **3b** and **3c** in high yields (92–95%), the removal of the *N*-Boc group from **2a** failed. Further attempts to deprotect **2a** with HCOOH, 3N HCl in AcOEt, CF₃COOH and Et₃SiH, and SnCl₄ in AcOEt all failed unexpectedly, therefore, alternative approaches to the target compounds **6a**, **7a** and **8a** were investigated next (see below).

Compounds **3b,c** were converted in 59–72% yields into the related *N*-benzyl and *N*-phenylethyl derivatives **4b,c** and **5b,c** by reaction with benzyl chloride and 2-phenyl-1-iodoethane, respectively. With the key 1,3-dicarbonyl derivatives **4b,c** and **5b,c** in hand, their conversion into the desired derivatives **E** was pursued according to the planned retrosynthetic scheme. Compounds **4b,c** and hydrazine in methanol were stirred at room temperature to afford the pyrazole derivatives **6b** and **6c** in good yields (78% and 50%, respectively). Treatment of **5b,c** with hydroxylamine hydrochloride in EtOH/AcOH at 80 °C gave isoxazoles **7b,c** and **8b,c** as mixtures of regioisomers in moderate to good yields. With **5b** isoxazoles **7b** and **8b** were obtained in a 4/1 ratio, while **5c** gave isoxazoles **7c** and **8c** in a 3.2/1 ratio [9].

Scheme 2. Synthesis of compounds **6b**, **6c**, **7b**, **7c**, **8b** and **8c**.

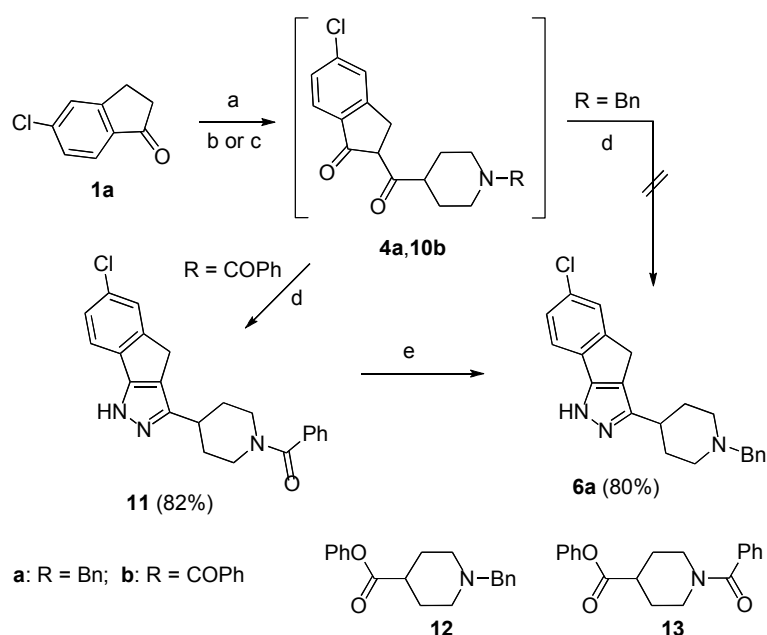


Reagents and conditions: (a) (i) NaH, DMF, rt; (ii) **9**, 1,1'-carbonyldiimidazole, DMF, rt, 45 min; (iii) 120 °C, 6 h; (b) CF₃COOH, CH₂Cl₂, rt, 2 h; (c) BnCl or BnCH₂I, DMF, *i*-Pr₂NEt, 25–60 °C, 12h; (d) H₂N-NH₂, MeOH, rt, 12 h; (e) NH₂OH, EtOH, AcOH, 80 °C, 12 h.

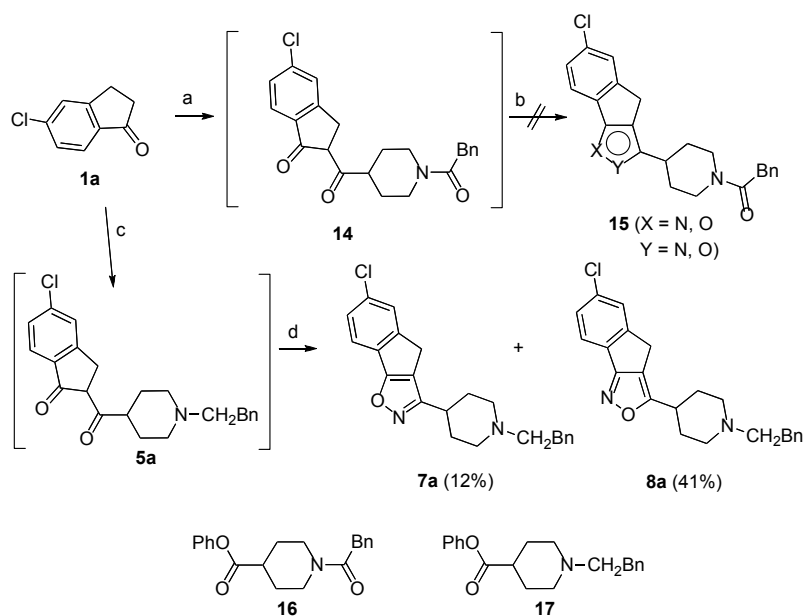
To obtain compound **6a** the synthetic routes outlined in Scheme 3 were followed. Firstly, the sodium enolate of the ketone **1a** was reacted with phenyl 1-benzylpiperidine-4-carboxylate **12**, but the 1,3-dicarbonyl intermediate **4a** failed to give the expected pyrazole **6a** by treatment with hydrazine in AcOH/MeOH at 80 °C. However, when the same enolate was treated with phenyl 1-(phenylcarbonyl)-piperidine-4-carboxylate **13** [10], obtained by esterification with phenol of the parent acid (Scheme 5), the formed 1,3-dicarbonyl **10b** afforded by treatment with hydrazine in AcOH/MeOH at 80 °C the substituted pyrazole **11** in 82% yield. Finally, LiAlH₄ reduction of the carbonyl group to the methylene unit afforded the target pyrazole **6a** in 80% yield (66% overall yield from **1a**).

This satisfactory result appeared to open a way to isoxazoles **7a** and **8a** by simple replacing of the piperidine derivative **13** with the analogue **16** (Scheme 4). However, the treatment of the 1,3-dicarbonyl intermediate **14**, obtained in turn by reaction of **1a** with **16**, with hydroxylamine hydrochloride in EtOH/AcOH at 80 °C failed to afford the expected isoxazoles **15**. This unexpected result prompted us to verify another route based on the use of the *N*-benzylpiperidine **17** that was obtained by esterification with phenol of the parent acid (Scheme 5). We were pleased to find that the 1,3-dicarbonyl intermediate **5a**, formed by reaction of the enolate of the ketone **1a** with **17**, could be directly converted in the usual way into a mixture of isoxazoles **7a** and **8a** in 41% and 12% yield, respectively (Scheme 4).

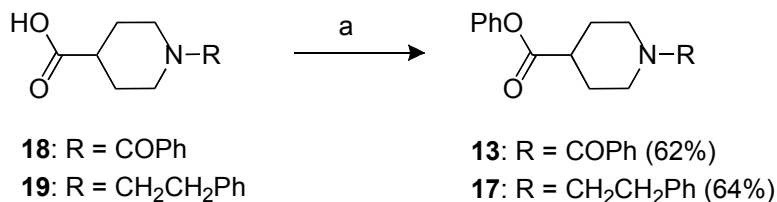
Scheme 3. Synthesis of compound **6a**.



Reagents and conditions: (a) (i) NaH, benzene, rt, (b) **12**, reflux, 3.5 h; (c) **13**, reflux, 3.5 h; (d) H₂N-NH₂, AcOH, EtOH, 80 °C, 4 h; (e) LiAlH₄, THF, rt, 12 h.

Scheme 4. Synthesis of compounds **7a** and **8a**.

Reagents and conditions: (a) (i) NaH, benzene, rt, (ii) **16**, reflux; (b) NH₂OH, AcOH, EtOH, 80 °C; (c) (i) NaH, benzene, rt, (ii) **17**, reflux, 4 h; (b) NH₂OH, AcOH, EtOH, 80 °C, 7 h.

Scheme 5. Synthesis of compounds **13** and **17**.

Reagents and conditions: (a) PhOH, EDC, DMAP, CH₂Cl₂, 40 °C, 14 h.

3. Experimental

3.1. General

All reagents and solvents were purchased from commercial suppliers and used as received. Low boiling petroleum ether corresponds to the fraction collected between 40 and 60 °C. THF was distilled from sodium-benzophenone ketyl and degassed thoroughly with dry nitrogen directly before use. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-460 plus equipment. The NMR spectra were obtained with a Varian VXR-300 spectrometer at 200 MHz for ¹H and 50 MHz for ¹³C. Chemical shifts are reported in ppm downfield from internal Me₄Si in CDCl₃. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), triplet (t), multiplet (m) and broad resonances (br). Elemental analyses were performed on a Perkin-Elmer 240 B analyser. TLC was performed on Merck silica gel 60 TLC plates F254 and visualized using UV or phosphomolibdic acid. Flash chromatography was carried out on silica gel (40–60 mesh). The chloroketone **1a** was a commercial compound. 6-Chloro-3,4-dihydronaphthalen-1-one (**1b**) [6], 7-chloro-2,3,4,5-tetrahydrobenzocyclo-

heptan-1-one (**1c**) [7], *N*-Boc-nipecotic acid [8] and the piperidines **18** [10] and **19** [11] were obtained following the corresponding literature procedures.

3.2. General Procedure for the Synthesis of the Compounds **2a–2c**

A solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (**9**, 2.85 g, 12.45 mmol) and 1,1'-carbonyldiimidazole (2.29 g, 14.11 mmol) in DMF (3 mL) was stirred at room temperature for 45 min. This solution was added dropwise to a solution prepared by stirring for 20 min the suitable ketone **1a**, **1b** or **1c** (7.64 mmol) with NaH (60% in oil, 0.93 g, 23.20 mmol) in DMF (20 mL). The resulting mixture was heated for the appropriate time. After cooling, H₂O was added and the mixture was extracted with Et₂O (3 × 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

tert-Butyl 4-(5-chloro-1-oxo-2,3-dihydro-1H-indene-2-carbonyl)piperidine-1-carboxylate (**2a**). According to the general procedure, the reaction between **1a** and **9** was carried out at 30 °C for 7 h. The residue was purified by flash chromatography (petroleum ether/EtOAc = 9:1) affording **2a**: yield 66%; red solid; Mp 102–103 °C. *R_f* = 0.10 (petroleum ether/AcOEt = 9:1). ¹H-NMR: δ 1.48 (s, 9H), 1.60–1.95 (m, 4H), 2.40–2.64 (m, 1H), 2.64–2.98 (m, 2H), 3.62 (s, 2H), 4.13–4.33 (m, 2H), 7.40 (d, 1H, *J* = 8.0 Hz), 7.48 (s, 1H), 7.74 (d, 1H, *J* = 8.0 Hz), 13.80 (brs, 1H). ¹³C-NMR: δ 27.9 (CH₂), 28.4 (3 × CH₃), 29.8 (2 × CH₂), 41.8 (CH), 43.4 (2 × CH₂), 79.7 (C), 108.8 (C), 124.2 (CH), 126.0 (CH), 128.1 (CH), 136.7 (C), 139.1 (C), 148.6 (C), 154.7 (CO), 182.7 (CO), 191.3 (COH). IR: (nujol) ν 1703 (CO), 1655 (CO), 1605 (CO) cm⁻¹. Anal. Calcd for C₂₀H₂₄ClNO₄: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.65; H, 6.49; N, 3.81.

tert-Butyl 4-(6-chloro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbonyl)piperidine-1-carboxylate (**2b**). According to the general procedure, the reaction between **1b** and **9** was carried out at 110 °C for 7 h. The residue was purified by flash chromatography (petroleum ether/EtOAc = 8:2) affording **2b**: yield 63%; red solid; Mp 120–121 °C. *R_f* = 0.43 (petroleum ether/AcOEt = 8:2). ¹H-NMR: δ 1.47 (s, 9H), 1.59–1.87 (m, 5H), 2.67 (d, 2H, *J* = 7.4 Hz), 2.80–2.88 (m, 4H), 4.18 (d, 2H, *J* = 7.4 Hz), 7.24 (d, 1H, *J* = 10.2 Hz), 7.31 (s, 1H), 7.87 (d, 1H, *J* = 8.2 Hz), 16.65 (s, 1H). ¹³C-NMR: δ 21.9 (CH₂), 27.8 (CH₂), 28.4 (3 × CH₃), 29.3 (2 × CH₂), 41.4 (CH), 43.3 (2 × CH₂), 79.6 (C), 104.6 (C), 126.2 (CH), 127.2 (CH), 127.3 (CH), 127.5 (C), 136.7 (C), 142.2 (C), 157.3 (CO), 179.0 (CO), 197.8 (COH). IR: (nujol) ν 1707 (CO), 1650 (CO), 1611 (CO) cm⁻¹. Anal. Calcd for C₂₁H₂₆ClNO₄: C, 64.36; H, 6.69; N, 3.57. Found: C, 64.88; H, 6.65; N, 3.59.

tert-Butyl 4-(2-chloro-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carbonyl)piperidine-1-carboxylate (**2c**). According to the general procedure the reaction between **1c** and **9** was carried out at 70 °C for 7 h. The residue was purified by flash chromatography (petroleum ether/EtOAc = 9:1) affording **2c**: yield 63%; yellow solid; Mp 134–136 °C. *R_f* = 0.31 (petroleum ether/AcOEt = 9:1). ¹H-NMR: δ 1.48 (s, 9H), 1.53–1.92 (m, 7H), 1.92–2.13 (m, 1H), 2.18 (t, 2H, *J* = 6.8 Hz), 2.55–2.90 (m, 3H), 4.10–4.31 (m, 2H), 7.21 (s, 1H), 7.27–7.42 (m, 1H), 7.57 (d, 1H, *J* = 8.2 Hz), 16.78 (s, 1H). ¹³C-NMR: δ 22.7 (CH₂), 28.3 (3 × CH₂), 28.5 (CH₃), 31.1 (CH₂), 31.3 (2 × CH₂), 40.9 (CH), 43.2 (2 × CH₂), 79.5 (C), 108.2 (C), 126.8 (CH), 128.7 (CH), 129.0 (CH), 131.0 (C), 136.4 (C), 141.4 (C),

154.5 (CO), 186.2 (CO), 194.4 (COH). IR: (nujol) ν 1706 (CO), 1652 (CO), 1613 (CO) cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{ClNO}_4$: C, 65.10; H, 6.95; N, 3.45. Found: C, 66.08; H, 6.98; N, 3.42.

3.3. General Procedure for the Synthesis of Compounds **3b**, **3c**

A solution of CF_3COOH (1.46 g, 12.8 mmol) in CH_2Cl_2 (4.6 mL) was added dropwise to a solution of the 1,3-dicarbonyl compound **2b** or **2c** (1.28 mmol) in CH_2Cl_2 (9.2 mL). After stirring 2 h at room temperature, CH_2Cl_2 was added. The resulting mixture was washed two times with a 10% solution of K_2CO_3 and then with H_2O . The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

6-Chloro-2-(piperidine-4-carbonyl)-3,4-dihydronaphthalen-1(2H)-one (3b). Compound **2b** was converted into the title product **3b** according to the general procedure. The residue was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH} = 8:2$) affording **3b**: yield 63%; yellow solid; Mp 150–154 °C. $R_f = 0,10$ ($\text{CHCl}_3/\text{MeOH} 8:2$); $^1\text{H-NMR}$: δ 2.62–2.85 (m, 4H), 2.58–2.77 (m, 4H), 2.80–2.95 (m, 4H), 3.10–3.34 (m, 2H), 7.21 (s, 1H), 7.32 (d, 1H, $J = 8.2$ Hz), 7.86 (d, 1H, $J = 8.2$ Hz), 8.52–9.20 (brs, 1H). $^{13}\text{C-NMR}$: δ 21.9 (CH_2), 27.5 (CH_2), 31.3 ($2 \times \text{CH}_2$), 42.0 (CH), 45.1 ($2 \times \text{CH}_2$), 109.2 (C), 126.3 (CH), 127.4 (CH), 129.1 (CH), 137.0 (C), 137.2 (C), 144.5 (C), 189.0 (CO), 192.4 (COH) IR: (nujol) ν 3453 (NH), 1701 (CO), 1680 (CO) cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{ClNO}_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.56; H, 6.26; N, 4.83.

2-Chloro-6-(piperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (3c). Compound **2c** was converted into the title product **3c** according to the general procedure. The residue was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH} = 8:2$) affording **3c**: yield 63%; white solid; Mp 138–142 °C. $R_f = 0,11$ ($\text{CHCl}_3/\text{MeOH} = 8:2$); $^1\text{H-NMR}$: δ 1.60–1.92 (m, 4H), 1.92–2.10 (m, 2H), 2.18 (t, 2H, $J = 6.2$ Hz), 2.58–2.85 (m, 5H), 2.90–2.98 (m, 1H), 3.12–3.28 (m, 2H), 7.21 (s, 1H), 7.33 (d, 1H, $J = 8.0$ Hz), 7.56 (d, 1H, $J = 8.0$ Hz), 8.00–9.00 (brs, 1H). $^{13}\text{C-NMR}$: δ 22.8 (CH_2), 28.7 (CH_2), 31.1 ($2 \times \text{CH}_2$), 31.5 (CH), 40.6 (CH_2), 45.1 ($2 \times \text{CH}_2$), 108.2 (C), 126.8 (CH), 128.7 (CH), 129.0 (CH), 136.0 (C), 136.8 (C), 141.5 (C), 188.0 (CO), 194.4 (COH). IR: (nujol) ν 3,430 (NH), 1,703 (CO), 1,680 (CO) cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{ClNO}_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 67.37; H, 6.64; N, 4.53.

3.4. General Procedure for the Synthesis of the Compounds **4b**, **4c** and **5b**, **5c**

To a solution of the 1,3-dicarbonyl compound **3b** or **3c** (3.27 mmol) in DMF (18.25 mL) was added *i*-Pr₂NEt (0.59 g, 4.58 mmol) and then the appropriate halide (1.1 eq). The mixture was then stirred at room temperature or heated under reflux for the necessary time. Water was added and the mixture was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

2-(1-Benzylpiperidine-4-carbonyl)-6-chloro-3,4-dihydronaphthalen-1(2H)-one (4b). A solution of the ketone **3b** and benzyl chloride in DMF was stirred at room temperature for 12 h. After workup the residue was purified by flash chromatography (petroleum ether/EtOAc = 1:1) affording **4b**: yield 59%; brown oil; $R_f = 0.46$ (petroleum ether/EtOAc = 1:1); $^1\text{H-NMR}$: δ 1.51–1.80 (m, 4H), 1.90 (d, 2H,

$J = 11$ Hz), 2.03 (d, 2H, $J = 13.2$ Hz), 2.58–2.76 (m, 1H), 2.84 (t, 2H, $J = 7.4$ Hz), 3.00 (d, 2H, $J = 9.6$ Hz), 3.55 (s, 2H), 7.20 (s, 1H), 7.29–7.40 (m, 6H), 7.86 (d, 1H, $J = 8.6$ Hz), 16.68 (s, 1H). $^{13}\text{C-NMR}$: δ 22.8 (CH₂), 28.6 (CH₂), 32.1 (2 \times CH₂), 33.5 (CH), 45.1 (2 \times CH₂), 64.5 (CH₂), 118.4 (C), 126.7 (CH), 126.9 (CH), 127.5 (CH), 128.3 (2 \times CH), 128.6 (CH), 128.9 (CH), 129.1 (C), 129.3 (CH), 131.2 (C), 139.6 (C), 142.3 (C), 184.9 (CO), 195.3 (COH) IR: (nujol) ν 1,710 (CO), 1,682 (CO) cm^{-1} . Anal. Calcd for C₂₃H₂₄ClNO₂: C, 72.34; H, 6.33; N, 3.67. Found: C, 72.41; H, 6.38; N, 3.75.

6-(1-Benzylpiperidine-4-carbonyl)-2-chloro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (4c). A solution of the ketone **3c** and benzyl chloride in DMF was stirred at room temperature for 12 h. After workup, the residue was purified by flash chromatography (petroleum ether/EtOAc = 1:1) affording **4c**: yield 72%; brown oil; $R_f = 0.37$ (petroleum ether/EtOAc = 1:1); $^1\text{H-NMR}$: δ 1.61–2.24 (m, 8H), 2.53–2.76 (m, 2H), 2.76–3.11 (m, 5H), 3.54 (s, 2H), 7.00–7.48 (m, 6H), 7.55 (d, 1H, $J = 8.2$ Hz), 8.00 (s, 1H), 16.8 (s, 1H). $^{13}\text{C-NMR}$: δ 22.9 (CH₂), 28.5 (CH₂), 31.0 (2 \times CH₂), 31.4 (CH₂), 31.6 (CH), 52.8 (2 \times CH₂), 62.9 (CH₂), 108.4 (C), 126.6 (CH), 126.8 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.3 (2 \times CH), 128.7 (CH), 129.3 (C), 131.0 (C), 139.6 (C), 145.1 (C), 194.9 (CO), 195.3 (COH). Anal. IR: (nujol) ν 1,705 (CO), 1,682 (CO) cm^{-1} . Calcd for C₂₄H₂₆ClNO₂: C, 72.81; H, 6.62; N, 3.54. Found: C, 72.21; H, 6.65; N, 3.57.

6-Chloro-2-(1-phenethylpiperidine-4-carbonyl)-3,4-dihydronaphthalen-1(2H)-one (5b). A solution of the ketone **3b** and phenylethyl iodide in DMF was heated at 60 °C for 12 h. After workup, the residue was purified by flash chromatography (petroleum ether/EtOAc = 2:8) affording **5b**: yield 70%; brown oil; $R_f = 0.42$ (petroleum ether/EtOAc = 1:1); $^1\text{H-NMR}$: δ 1.26–2.53 (m, 11H), 2.54–2.75 (m, 2H), 2.75–2.99 (m, 2H), 3.04–3.23 (m, 2H), 7.08–7.45 (m, 6H), 7.49 (m, 1H), 7.71 (d, 1H, $J = 9.0$ Hz), 14.27 (s, 1H). $^{13}\text{C-NMR}$: δ 22.8 (CH₂), 28.7 (CH₂), 32.1 (CH₂), 32.6 (2 \times CH₂), 33.5 (CH), 45.3 (2 \times CH₂), 64.5 (CH₂), 117.9 (C), 126.6 (CH), 128.3 (CH), 128.8 (CH), 128.9 (2 \times CH), 129.1 (2 \times CH), 129.2 (CH), 131.2 (C), 139.6 (C), 141.5 (C), 142.3 (C), 194.9 (CO), 195.3 (COH) Anal. IR: (nujol) ν 1,700 (CO), 1,681 (CO) cm^{-1} . Calcd for C₂₄H₂₆ClNO₂: C, 72.81; H, 6.62; N, 3.54. Found: C, 72.11; H, 6.66; N, 3.58.

2-Chloro-6-(1-phenethylpiperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (5c). A solution of the ketone **3c** and phenylethyl iodide in DMF was heated at 60 °C for 12 h. After workup, the residue was purified by flash chromatography (CHCl₃/acetone = 9:1) affording **5c**: yield 62%; brown oil; $R_f = 0.33$ (CHCl₃/acetone = 9:1); $^1\text{H-NMR}$: δ 1.72–1.89 (m, 3H), 1.95–2.28 (m, 7H), 2.53–2.92 (m, 7H), 3.12 (d, 2H, $J = 9.6$), 7.20 (s, 1H), 7.23–7.25 (m, 6H), 7.56 (d, 1H, $J = 8.4$ Hz), 16.7 (s, 1H). $^{13}\text{C-NMR}$: δ 22.8 (CH₂), 28.8 (CH₂), 31.2 (CH₂), 31.7 (2 \times CH₂), 33.5 (CH₂), 41.0 (CH), 53.2 (2 \times CH₂), 60.7 (CH₂), 108.3 (CH), 126.0 (CH), 126.6 (CH), 126.8 (CH), 127.5 (2 \times CH), 128.3 (CH), 128.6 (2 \times CH), 128.7 (C), 129.1 (C), 131.0 (C), 141.5 (C), 187.9 (CO), 195.3 (COH). IR: (nujol) ν 1,699 (CO), 1,676 (CO) cm^{-1} . Anal. Calcd for C₂₅H₂₈ClNO₂: C, 73.25; H, 6.88; N, 3.42. Found: C, 73.76; H, 6.84; N, 3.46.

3.5. General Procedure for the Synthesis of Compounds **6b**, **6c**

A solution of the 1,3-dicarbonyl compound **4b** or **4c** (0.68 mmol) and hydrazine hydrate (0.32 g, 6.39 mmol) in MeOH (9 mL) was stirred overnight at room temperature. Water was added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

3-(1-Benzylpiperidin-4-yl)-7-chloro-4,5-dihydro-1H-benzo[g]indazole (6b). Compound **4b** was converted into the title product **6b** according to the general procedure. After workup, the residue was purified by flash chromatography (CHCl₃/acetone = 9:1) affording **6b**: yield 78%; yellow solid; Mp 173–174 °C; *R_f* = 0.51 (CH₂Cl₂/MeOH = 95:5); ¹H-NMR: δ 1.80–2.27 (m, 6H), 2.71–2.82 (m, 3H), 2.91 (t, 2H, *J* = 7.2 Hz), 3.01 (t, 2H, *J* = 7.2 Hz), 3.56 (s, 2H), 7.20–7.40 (m, 7H), 7.64–7.71 (m, 1H). ¹³C-NMR: δ 18.9 (CH₂), 29.6 (CH₂), 31.3 (2 × CH₂), 33.7 (CH), 53.6 (2 × CH₂), 63.3 (CH₂), 111.2 (C) 123.2 (CH), 126.9 (CH), 127.1 (CH), 127.4 (CH), 127.5 (C), 128.2 (2 × CH), 129.2 (2 × CH), 132.7 (C), 137.8 (C), 138.3 (C), 142.3 (CN), 142.8 (CN). Anal. Calcd for C₂₃H₂₄ClN₃: C, 73.10; H, 6.40; N, 11.12. Found: C, 73.91; H, 6.43; N, 11.07.

3-(1-Benzylpiperidin-4-yl)-8-chloro-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[2,1-c]pyrazole (6c). Compound **4c** was converted into the title product **6c** according to the general procedure. After elaboration, the residue was purified by flash chromatography (CHCl₃/acetone = 9:1) affording **6c**: yield 50%; yellow solid; Mp 165–166 °C; *R_f* = 0.51 (CH₂Cl₂/MeOH = 95:5); ¹H-NMR: δ 1.68–2.32 (m, 8H), 2.51–2.90 (m, 5H), 3.04 (d, 2H, *J* = 9.8 Hz), 3.59 (s, 2H), 7.10–7.42 (m, 7H), 7.60–7.72 (m, 1H), 9.10–10.01 (brs, 1H). ¹³C-NMR: δ 24.1 (CH₂), 26.9 (CH₂), 29.7 (CH₂), 31.0 (2 × CH₂), 34.8 (CH), 53.8 (2 × CH₂), 63.2 (CH₂), 112.5 (C), 125.7 (CH), 126.4 (CH), 127.1 (CH), 127.4 (CH), 127.5 (2 × CH), 128.2 (2 × CH), 129.3 (2 × C), 129.6 (C), 134.5 (C) 141.3 (CN), 142.8 (CN). Anal. Calcd for C₂₄H₂₆ClN₃: C, 73.55; H, 6.69; N, 10.72 Found: C, 73.25; H, 6.88; N, 10.42.

3.6. 1H-1-Oxa-2-aza-7-chloro-3-(1-phenethylpiperidin-4-yl)-4,5-dihydronaphtho[2,1-d]isoxazole (**7b**) and 1H-1-oxa-2-aza-8-chloro-3-(1-phenethylpiperidin-4-yl)-5,6-dihydro-4H-benzo[3,4]cyclohepta[1,2-d]isoxazole (**7c**)

A solution of the 1,3-dicarbonyl compound **5b** or **5c** (2.44 mmol) and hydroxylamine hydrochloride (1.02 g, 14.64 mmol) in EtOH (12.2 mL) containing 4 drops of AcOH was heated under reflux for 24 h. Water was added and the mixture was extracted with CHCl₃. The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CHCl₃/MeOH = 97:3) to give **7b** or **7c**.

Compound 7b. Yield 20%; brown solid; Mp 170–172 °C; *R_f* = 0.11 (CHCl₃/MeOH = 97:3); ¹H-NMR (DMSO-d₆): δ 1.50–1.80 (m, 9H), 1.42–2.10 (m, 4H), 2.48 (t, 2H, *J* = 7.0 Hz), 2.69 (t, 2H, *J* = 7.0 Hz), 7.12–7.42 (m, 8H). ¹³C-NMR: δ 28.4 (CH₂), 29.5 (CH₂), 32.7 (CH₂), 38.2 (2 × CH₂), 40.7 (CH), 52.7 (2 × CH₂), 59.7 (CH₂), 117.8 (C), 125.0 (CH), 125.4 (CH), 125.8 (CH), 126.5 (CH), 127.9 (2 × CH), 128.2 (2 × CH), 128.6 (C), 130.9 (C), 136.4 (C), 144.1 (C), 157.3 (CN), 166.1 (CO). Anal. Calcd for C₂₄H₂₅ClN₂O: C, 73.36; H, 6.41; N, 7.13. Found: C, 73.96; H, 6.44; N, 7.10.

Compound 7c. yield 35%; brown solid; Mp 114–117 °C; $R_f = 0.24$ ($\text{CHCl}_3/\text{MeOH} = 8:2$); $^1\text{H-NMR}$ (DMSO-d_6): δ 1.82–2.10 (m, 4H), 2.11–2.33 (m, 4H), 2.60–2.76 (m, 5H), 2.70–2.98 (m, 4H), 3.10–3.21 (m, 2H), 7.12–7.20 (m, 7H), 7.88 (d, 1H, $J = 8.2$ Hz). $^{13}\text{C-NMR}$: δ 23.9 (CH_2), 24.5 (CH_2), 29.8 (2 x CH_2), 33.6 (CH_2), 35.2 (CH), 53.5 (2 x CH_2), 60.7 (CH_2), 113.8 (C), 126.1 (CH), 126.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (2 x CH), 128.6 (2 x CH), 129.6 (C), 134.7 (C), 141.5 (C), 142.1 (C), 161.2 (CN), 166.6 (CO) Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$: C, 73.79; H, 6.69; N, 6.88. Found: C, 73.25; H, 6.71; N, 6.91.

3.7. *2H-1-Aza-2-oxa-7-chloro-3-(1-phenethylpiperidin-4-yl)-4,5-dihydronaphtho[1,2-c]isoxazole (8b)* and *2H-1-aza-2-oxa-8-chloro-3-(1-phenethylpiperidin-4-yl)-5,6-dihydro-4H-benzo[3,4]cyclohepta[2,1-c]isoxazole (8c)*

A solution of the 1,3-dicarbonyl compound **5b** or **5c** (2.44 mmol) and hydroxylamine hydrochloride (1.02 g, 14.64 mmol) in EtOH (12.2 mL) containing 15 drops of AcOH was heated under reflux for 24 h. After cooling, H_2O was added and the mixture was extracted with CHCl_3 . The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography ($\text{CHCl}_3/\text{acetone} = 8:2$) to give **8b** or **8c**.

Compound 8b. Yield 5%; brown solid; Mp 165–166 °C; $R_f = 0.24$ ($\text{CHCl}_3/\text{acetone} = 97:3$); $^1\text{H-NMR}$ ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 1.43–1.70 (m, 4H), 1.71–1.93 (m, 4H), 1.95–2.10 (m, 1H), 2.42–2.65 (m, 4H), 2.52 (t, 2H, $J = 7.2$ Hz), 2.65 (t, 2H, $J = 7.2$ Hz), 7.05–7.38 (m, 5H), 7.42–7.84 (m, 2H), 8.32 (d, 1H, $J = 9.2$ Hz). $^{13}\text{C-NMR}$ ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 28.3 (CH_2), 29.5 (CH_2), 32.6 (CH_2), 38.2 (2 x CH_2), 40.7 (CH), 53.1 (2 x CH_2), 59.8 (CH_2), 118.0 (C), 120.2 (CH), 124.1 (CH), 125.4 (CH), 125.0 (CH), 125.8 (2 x CH), 127.9 (2 x CH), 128.6 (C), 131.2 (C), 134.8 (C), 140.3 (C), 161.2 (CN), 167.9 (CO). Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{ClN}_2\text{O}$: C, 73.36; H, 6.41; N, 7.13. Found: C, 72.86; H, 6.44; N, 7.01.

Compound 8c. Yield 12%; light brown solid; Mp 125–126 °C; $R_f = 0.47$ ($\text{CHCl}_3/\text{acetone} = 8:2$); $^1\text{H-NMR}$: δ 1.95–2.38 (m, 8H), 2.52–2.78 (m, 5H) 2.78–3.01 (m, 4H), 3.15 (d, 2H, $J = 9.6$ Hz), 7.08–7.40 (m, 7H), 7.89 (d, 1H, $J = 8.4$ Hz). $^{13}\text{C-NMR}$: δ 20.7 (CH_2), 27.0 (CH_2), 29.2 (CH_2), 33.0 (2 x CH_2), 33.2, (CH_2), 39.3 (CH), 53.1 (2 x CH_2), 60.4 (CH_2), 111.2 (C), 126.3 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.5 (2 x CH), 128.7 (2 x CH_2), 129.2 (C), 129.7 (C), 135.2 (C), 142.7 (C), 161.8 (CN), 170.4 (CO). Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$: C, 73.79; H, 6.69; N, 6.88. Found: C, 73.19; H, 6.62; N, 6.83.

(4-(6-Chloro-1,4-dihydroindeno[1,2-c]pyrazol-3-yl)piperidin-1-yl)(phenyl)metanone (11). 5-Chloro-2,3-dihydro-1H-inden-1-one **1a** (0.2 g, 1.23 mmol) and NaH (60% in oil, 0.12 g, 3.08 mmol) were added in sequence to a solution of phenyl 1-(phenylcarbonyl)piperidine-4-carboxylate **13** (0.33 g, 1.23 mmol) and the resulting mixture was heated under reflux for 3.5 h. After cooling a 50% aqueous solution of acetic acid was added and the resulting mixture was concentrated under reduced pressure. The residue was taken up in EtOH (4 mL) and AcOH (0.21 mL, 3.69 mmol). Hydrazine hydrate (0.09 mL, 1.85 mmol) was added and the resulting mixture was heated under reflux for 4 h. After cooling, the solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 . The organic phase was dried over Na_2SO_4 , filtered and the solvent removed under reduced pressure.

The residue was purified by flash chromatography (CHCl₃/acetone = 95:5) affording **11**: yield 82%; yellow solid; Mp 167–170 °C; *R_f* = 0,24 (CHCl₃/MeOH = 95:5); ¹H-NMR: δ 1.58–2.21 (m, 6H), 2.90–3.21 (m, 3H), 3.63 (s, 2H), 7.33 (d, 1H, *J* = 8.0 Hz), 7.37–7.50 (m, 6H), 7.6 (d, 1H, *J* = 8.0 Hz). ¹³C-NMR: δ 27.3 (CH₂), 29.1 (2 × CH₂), 29.4 (CH), 34.2 (2 × CH₂), 120.7 (C), 126.2 (CH), 126.9 (CH), 127.3 (CH), 128.5 (2 × CH), 129.8 (2 × CH₂), 129.9 (CH), 132.1(C), 132.7 (C), 133.8 (C), 141.6 (C), 150.1 (CN) 157.3 (CN), 170.5 (CO). Anal. Calcd for C₂₂H₂₀ClN₃O: C, 69.93; H, 5.33; N, 11.12. Found: C, 70.34; H, 5.31; N, 11.17.

3-(1-Benzylpiperidin-4-yl)-6-chloro-1,4-dihydroindeno[1,2-*c*]pyrazole (6a). A solution of the amide **11** (0.14 g, 0.37 mmol) in THF (2 mL) was added dropwise to a suspension of LiAlH₄ (56.0 mg, 1.48 mmol) in THF (2 mL) at 0 °C. After stirring at room temperature for 12 h the mixture was diluted with Et₂O (2,5 mL) and then NaOH (1 M, 0.1 mL) e H₂O (0.3 mL) were added. The formed solid was filtered and diluted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CHCl₃/acetone = 95:5) affording **6a**: yield 80%; yellow solid; Mp 146–148 °C; *R_f* = 0.25 (CHCl₃/MeOH 95:5); ¹H-NMR: 1.75–2.16 (m, 6H), 2.60–2.80 (m, 1H), 2.95 (m, 2H), 3.50 (m, 1H), 3.53 (s, 2H), 3.59 (s, 2H), 7.17–7.37 (m, 6H), 7.42 (s, 1H), 7.61 (d, 1H, *J* = 8.0 Hz), 9.25–10.35 (brs, 1H). ¹³C-NMR: δ 28.7 (CH₂), 30.3 (2 × CH₂), 31.0 (CH), 52.5 (2 × CH₂), 62.3 (CH₂), 119.7(C), 125.3 (CH), 126.2 (CH), 126.6 (CH), 127.6 (2 × CH), 128.8 (2 × CH), 130.8 (CH), 133.0 (C), 136.5 (C), 141.1 (C), 141.4 (C) 143.6 (CN) 149.7 (CN). Anal. Calcd for C₂₂H₂₂ClN₃: C, 72.62; H, 6.09; N, 11.55. Found: C, 72.70; H, 6.15; N, 11.59.

3.8. 1H-1-Oxa-2-aza-6-chloro-3-(1-phenethylpiperidin-4-yl)-1,4dihydroindeno[2,1-*d*]isoxazole (7a) and 2H-1-aza-2-oxa-6-chloro-3-(1-phenethylpiperidin-4-yl)-1,4dihydroindeno[1,2-*c*]isoxazole (8a)

To a solution of phenyl 1-(phenylethyl)piperidine-4-carboxylate **17** (0.50 g, 1.23 mmol) were added in sequence 5-chloro-2,3-dihydro-1H-inden-1-one **1a** (0.2 g, 1.23 mmol) and NaH (60% in oil, 0.12 g, 3.08 mmol). The resulting mixture was heated under reflux for 4 h. After cooling a 50% aqueous solution of acetic acid was added and the resulting mixture was concentrated under reduced pressure. To the residue was taken up in EtOH (5 mL), AcOH (0.21 mL, 3.69 mmol) and hydroxylamine hydrochloride (0.128 mg, 1.85 mmol) was added. The resulting mixture was heated under reflux for 8 h. The solvent was evaporated under reduced pressure and the residue was taken up in CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (CHCl₃/acetone = 8:2) to give **7a** and **8a**.

Compound 7a. Yield 12%; brown solid; Mp 149–151 °C; *R_f* = 0,20 (CHCl₃/acetone = 8:2); ¹H-NMR: δ 1.60–2.04 (m, 9H), 2.49 (t, 2H, *J* = 7.2 Hz), 2.62 (t, 2H, *J* = 7.2 Hz), 3.55 (s, 2H) 7.23–7.42 (m, 8H). ¹³C-NMR: δ 28.8 (CH₂), 30.6 (CH₂), 31.1 (2 × CH₂), 31.7 (CH), 52.5 (2 × CH₂), 62.4 (CH₂), 119.7 (C), 125.4 (CH), 126.2 (CH), 126.7 (CH), 127.8 (2 × CH), 128.8 (2 × CH), 130.9 (CH), 134.0 (C), 136.0 (C), 142.5 (C), 153.7 (C), 161.0 (CN), 166.4 (CO). Anal. Calcd for C₂₃H₂₃ClN₂O: C, 72.91; H, 6.12; N, 7.39. Found: C, 73.12; H, 6.10; N, 7.43.

Compound 8a. Yield 41%; brown solid; Mp 157–160 °C; $R_f = 0.41$ (CHCl₃/MeOH 8:2); ¹H-NMR (DMSO-d₆): δ 1.82–2.10 (m, 5H), 2.11–2.33 (m, 4H), 2.60–2.70 (m, 2H), 2.73–2.88 (m, 2H), 3.57 (s, 2H), 7.12–7.28 (m, 8H). ¹³C-NMR: δ 28.8 (CH₂), 30.5 (CH₂), 31.2 (2 × CH₂), 31.4 (CH), 53.2 (2 × CH₂), 62.3 (CH₂), 119.6 (C), 125.3 (CH), 126.5 (CH), 126.6 (CH), 127.8 (2 × CH₂), 128.8 (2 × CH₂), 130.9 (CH) 134.1 (C), 136.5 (C), 142.4 (C), 151.9 (C), 162.3 (CN) 169.2 (CO). Anal. Calcd for C₂₃H₂₃ClN₂O: C, 72.91; H, 6.12; N, 7.39. Found: C, 73.10; H, 6.14; N, 7.46.

3.9. Phenyl 1-benzoylpiperidine-4-carboxylate (**13**) and phenyl 1-phenethylpiperidine-4-carboxylate (**17**)

A mixture of the acid **18** or **19** (2.19 mmol) in CH₂Cl₂ (40 ml), 1-3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.84 g, 4.38 mmol), dimethylaminopiperidine (0.54 g, 4.38 mmol) and phenol (0.62 g, 6.57 mmol) was heated under reflux for 14 h. After cooling, the reaction mixture was diluted with CH₂Cl₂ and washed with a saturated NH₄Cl solution (3 × 20 mL). The separated organic phase was dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography affording the product **13** or **17**.

Compound 13. purified by flash chromatography by using as the eluent petroleum ether/EtOAc = 1:1; yield 62%; yellow oil; $R_f = 0.46$ (petroleum ether/EtOAc = 1:1); ¹H-NMR: δ 1.65–2.10 (m, 6H), 2.70–2.90 (m, 1H), 3.10–3.25 (m, 2H), 7.00–7.45 (m, 10H). ¹³C-NMR: δ 28.2 (2 × CH₂), 41.1 (CH), 46.8 (2 × CH₂), 121.3 (2 × CH), 125.9 (CH), 126.8 (2 × CH), 128.4 (2 × CH), 129.4 (2 × CH), 129.6 (CH), 135.8 (C), 150.4 (C), 170.4 (CO), 172.6 (CO). IR: (nujol) ν 1,752 (CO), 1,628 (CO) cm⁻¹. Anal. Calcd for C₁₉H₁₉NO₃: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.85; H, 6.25; N, 4.46.

Compound 17. purified by flash chromatography by using as the eluent CHCl₃/MeOH = 9:1; yield 64%; yellow oil; $R_f = 0.27$ (CHCl₃/MeOH = 9:1); ¹H-NMR: δ 1.80–2.20 (m, 4H), 2.56–2.65 (m, 2H), 2.80–2.90 (m, 3H), 3.00–3.15 (m, 2H), 3.43 (t, 2H, $J = 5.4$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz), 7.20–7.42 (m, 8H). ¹³C-NMR: δ 28.2, (2 × CH₂) 33.8 (CH₂), 41.1 (CH), 46.8 (2 × CH₂), 57.4 (CH₂), 122.5 (2 × CH), 126.9 (2 × CH), 127.3 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 129.5 (CH), 135.9 (C), 151.4 (C), 170.4 (CO). IR: (nujol) ν 1,750 (CO) cm⁻¹. Anal. Calcd for C₂₀H₂₃NO₂: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.75; H, 7.42; N, 4.58.

4. Conclusion

In conclusion, we have reported a practical synthesis of the tricyclic heterocycles **E** incorporating the pyrazole or isoxazole framework (Figure 1). These new products share with the antipsychotic compounds **A–C** two substituents, namely the chlorine on the aryl ring and the 4-(1-benzyl)- or 4-(1-phenylethyl)piperidinyl group on the isoxazole and pyrazole moieties. The antipsychotic activity of these new compounds will be determined, thus indicating which further structural modifications should be pursued to advantageously modify their biological activity.

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Conflict of Interest

The authors declare no conflict of interest.

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