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Aust. J. Chem.
http://dx.doi.org/10.1071/CH15526

Full Paper

Friedel–Crafts Chemistry. Part 46. Unprecedented Construction of Tricyclic Pyrazolo[3,4-*b*]quinolines, -[1,8]naphthyridines, -azepines, -azocines, -pyrido[3,2-*g*]azocines, and pyrazolo[3,4-*b*]azonines via Friedel–Crafts Ring Closures

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A series of keto-substituted pyrazolo[3,4-*b*]quinolines, pyrazolo[3,4-*b*][1,8]naphthyridines, benzo[*e*]pyrazolo[3,4-*b*]azepines, benzo[*g*]pyrazolo[3,4-*b*]azocines, pyrazolo[3,4-*b*]pyrido[3,2-*g*]azocines, and benzo[*g*]pyrazolo[3,4-*b*]azonines scaffolds were synthesized via a Friedel–Crafts cyclialkylation approach. The precursor acids were obtained by utilizing the modified Ullman coupling reactions of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid with different aryl amines followed by ring closures in the presence of $AlCl_3/CH_3NO_2$ or P_2O_5 or polyphosphoric acid catalysts. Particular attention is given to the novel structures especially in regard to the promising pharmaceutical and therapeutic values associated with their skeletons.

Manuscript received: 9 August 2015.
Manuscript accepted: 12 October 2015.
Published online: 6 November 2015.

Introduction

Numerous medium-sized heterocyclic rings, particularly azepines, azocines, and azonines and their benzo derivatives (Fig. 1), form parts of the structures of a large variety of biologically active natural products[1] and pharmacological agents.[2] Moreover, their polyfunctionalized scaffolds are noted for their diverse industrial applications in dyes,[3] semiconductors,[4] and polymers.[5]

Owing to their interesting biological activities and unique structural features, syntheses of such ring systems have become an attractive research field for the development of new pharmacological compounds.[6] Despite the unfavourable enthalpy and entropy factors, as well as transannular interactions[7] associated with the classical synthetic methods for medium-sized rings that pose significant restrictions in the ring formation, the last three decades have witnessed an upsurge in research for the construction of such ring systems. Consequently, a comprehensive review of azepine, azocine, and azonine derivatives surveying their occurrence, synthetic strategies, and biological activities has been attempted.[8]

However, among different fused nitrogen heterocycles, pyrazole-based compounds occupy a special place in the history of *N*-heterocycles not only owing to their wide range of biological activity,[9] but also to their pharmacological effects.[10] Pyrazole derivatives have wide applications in the agrochemicals industry as herbicides,[11] fungicides,[12] pesticides,[13] dyestuffs,[14] and insecticides.[15] Although pyrazoles are rare in nature, the first natural pyrazole (1-pyrazolyl-alanine) was isolated in 1959 from seeds of watermelons.[16]

In particular, fused pyrazole derivatives are important substructures of compounds with biological activity and, since the past two decades, have been found in some well-known drug molecules (Fig. 2) such as Allopurinol (pyrazolo[3,4-*d*]pyrimidin-4-one),[17] Sildenafil (pyrazolo[4,3-*d*]pyrimidine),[18] Zaleplon (pyrazolo[1,5-*a*]pyrimidine),[19] and Zolazepam (pyrazolo[3,4-*e*][1,4]diazepine)[20] as well as examples of polyfunctionalized drugs such as Celecoxib and Rimonabant.[21] Moreover, several fused pyrazoles possessing interesting biological activities have recently been synthesized, such as thieno[2,3-*c*]pyrazoles,[22] pyrazolo[4,3-*c*]quinolones,[23] and pyrazolo[5,1-*a*]isoquinolines.[24] Despite the discovery of pyrazole[25] as an antipyretic agent dating back to 1884, interest in its preparation, structural modification, and pharmaceutical application continues unabated.

A full literature survey for applied methodologies in the synthesis of fused pyrazolo-quinoline, naphthyridine, azepine, azocine, and azonine systems revealed that more attention has been given to accessing pyrazolo[3,4-*b*]quinolines than other skeletons and a limited number of synthetic strategies currently exist in the literature. Some of the important reported strategies for the synthesis of pyrazolo[3,4-*b*]quinolines are summarized in the following.

In 1928, the first synthesis of pyrazoloquinoline described in the literature was obtained by Friedländer condensation from anthranilic aldehydes and substituted pyrazolone.[26] Tomasik et al.[27] have recently reported the utility of the Friedländer methodology[28] for the synthesis of pyrazoloquinoline derivatives from the acid-catalyzed condensation between 2-aminobenzophenones and pyrazolin-5-ones.

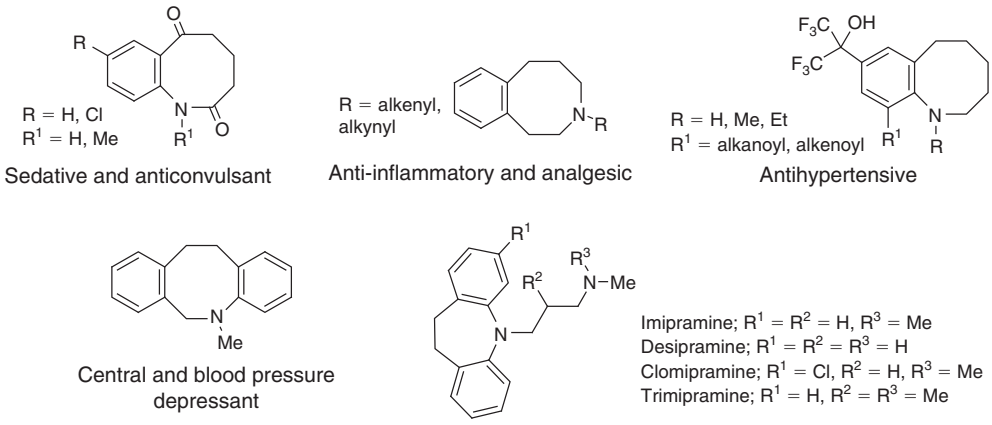


Fig. 1. Medium-sized nitrogen heteropolycycle-containing drugs.

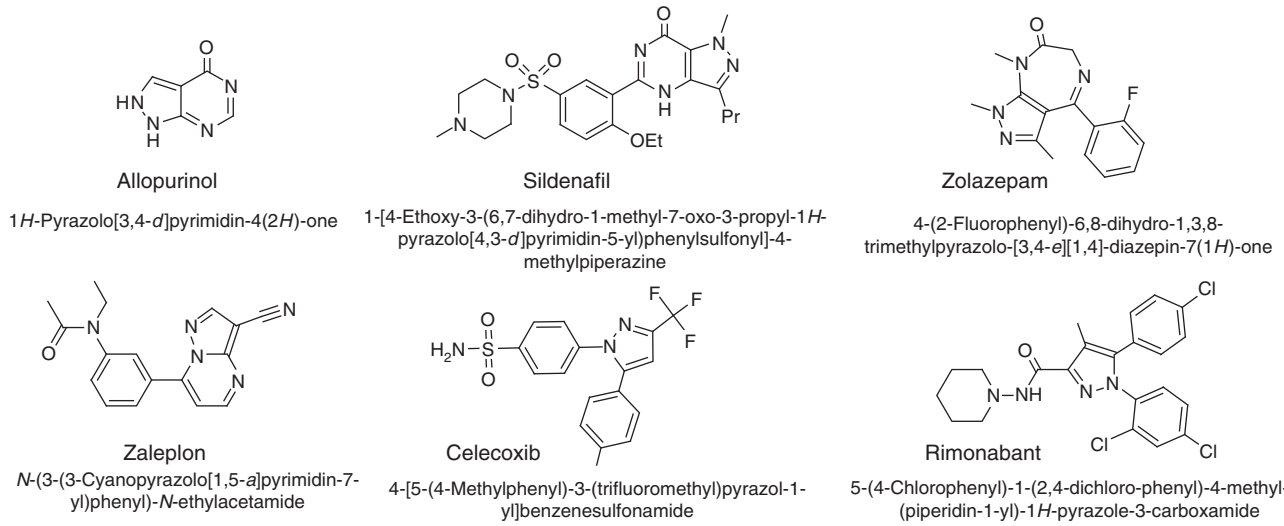


Fig. 2. Pyrazole heteropolycycle-containing pharmaceutical drugs.

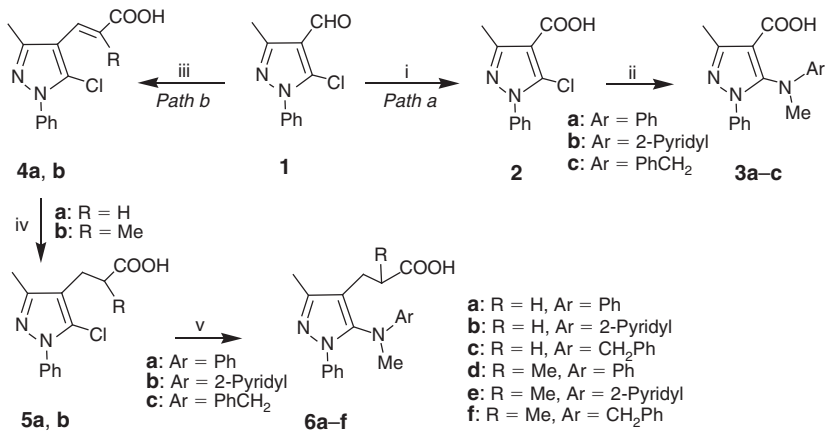
Chaczatrian and coworkers[29] reported that several pyrazoloquinoline derivatives were obtained via condensation reactions either by reaction of 5-aminopyrazoles and aromatic aldehydes in the presence of $ZnCl_2$ or by reactions of 4-benzylidenepyrazolones and aromatic amines in ethylene glycol. The latter approach led to the development of single-step synthetic procedures.

Martini and coworkers[30] described an efficient synthesis of pyrazoloquinolines by the condensation of 2-acetonyl-4*H*-3,1-benzoxazin-4-one with arylhydrazines, affording the corresponding *N*-(1-aryl-3-methylpyrazol-5-yl)anthranilic acids followed by ring-closure with polyphosphoric acid providing the 3,9-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-ones.

A unique strategy[31] based on consecutive reaction steps for the formation of various pyrazoloquinolines has been developed by Kumar et al. This strategy depends on the base-catalyzed K_2CO_3-promoted alkylation of halosubstituted benzoic acids with 5-aminopyrazoles in DMF in the presence of a catalytic amount of $Cu(OAc)_2$, giving the required anthranilic acid derivatives. The latter anthranilic acids underwent ring closure with $POCl_3$, providing unique access to pyrazoloquinolines in moderate yield. This methodology allowed the incorporation of a variety of substituent types at the 3- and 4-positions of the resulting pyrazoloquinoline ring system. Further, in 2010, Zhang et al.[32] reported the utility of the combination reactions to access pyrazolo[3,4-*b*]quinolinones from aromatic aldehydes and 5-amino-3-methyl-1-phenylpyrazole in the presence of Meldrum's acid (dimedone) in [BMIM][BF_4] (BMIM = 1-butyl-3-methylimidazolium) under thermal or microwave condition.

Other widely used methodologies that have been successfully applied in the synthesis of pyrazoloquinoline[33] share a common substrate of 2-chloroquinoline-3-carboxaldehyde and intermediates in such a way that it can be said they are interconnected. Although considerable attention has been directed towards the synthesis of pyrazoloquinoline derivatives owing to their broad spectrum in chemical, biological, and industrial applications, the search for new methods for simple, direct, economical, and efficient construction of this class of heterocycles still constitutes a major challenge in organic synthesis.

In recent years, we directed part of our Friedel–Crafts ring-closure[34] research to developing facile methods for the synthesis of known and new condensed heteropolycycles[35] of promising pharmacological value. In our previous works of this series,[36,37] we developed a synthetic methodology for the



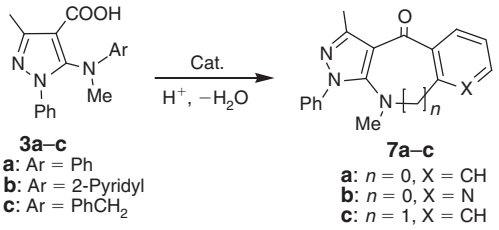
Scheme 1. Reagents and conditions: (i) $KMnO_4/H_2O$/*t*-butanol, 70–80°C, 40 min; (ii) and (v) aromatic amines (PhNHMe or 2-methylaminopyridine or $MeNHCH_2Ph$), K_2CO_3/CuO/DMSO, 140–150°C, 8 h; (iii) Ac_2O/AcONa or Pr_2O/PrONa, 120–130°C, 8–10 h; (iv) Na/Hg (2.5 %), NaOH, 3 h, room temperature.

synthesis of a series of 5*H*-dibenz[*b*,*f*]azepines (iminodibenzyls), 5*H*-dibenz[*b*,*f*]azocines, 11*H*-benzo[*f*]pyrido[2,3-*b*]azepines, 6*H*-benzo[*g*]pyrido[2,3-*c*]azocines, dibenzoazepines, -azocines, -azonines, and -azecines. In another paper,[38] we introduced facile syntheses for nine substituted indeno[1,2-*c*]pyrazoles, 2*H*-benzo[*g*]indazoles, and benzo[6,7]cyclohepta[1,2-*c*]pyrazoles. This prompted us to apply the same procedures for the universal construction of fused tricyclic pyrazoloquinoline, -naphthyridine, -azepine, -azocine, and -azonine scaffolds via Friedel–Crafts ring closure of nitrogen-containing carboxylic acids precursors.

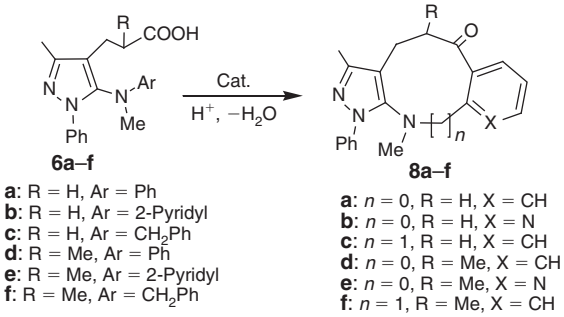
Results and Discussion

Our synthetic routes to the desired heterocyclic acid precursors **3a**–**c** and **6a**–**f** are outlined in Scheme 1. The synthesis of heteroaryl acids was planned from easily obtained 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**)[39] via two different synthetic pathways. *Path a* included oxidation of the aldehyde following a standard literature procedure with $KMnO_4$ solution to afford 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid (**2**).[40] The resulting halo-acid **2** was then used in the catalyzed Ullmann[41] *N*-coupling reaction with different *N*-methylaromatic amines. The reaction was carried out in DMSO solution and in the presence of K_2CO_3 to give the corresponding *N*-aryl acids (**3a**–**c**) in good overall yields (77–82 %).

However, the second route (*Path b*) involved the elongation reactions of acid precursors **4a**, **b**. These acids were smoothly obtained through the Perkin-type reaction[42] of aldehyde **1** with acid anhydrides and the corresponding sodium salts of acids to give substituted 3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)acrylic acids (**4a**, **b**). The resulting acids **4a**, **b** were reduced with sodium amalgam[43] (2.5 %) in NaOH solution to afford reduced acids **5a**, **b**. The latter acids were converted to the *N*-aryl acids **6a**–**f** by reaction with aromatic amines in pyridine (Scheme 1). Examination of the ^{1}H NMR data of the synthesized acids precursors reveals that, for example, the ^{1}H NMR spectrum for substituted pyrazol-4-propanoic acid **5a** displays five signals, including a CH_2 protons triplet at δ 2.55 ppm and a methyl group attached to the pyrazole ring as one singlet at δ 2.70 ppm. The second CH_2 protons appear as a triplet at 2.80 ppm and aromatic protons appear as multiplets at δ 6.30–7.75 ppm, while the fifth singlet proton at δ 11.3 ppm was assigned to the carboxyl group proton. However, in the IR



Scheme 2. Cycliacylations of acids **3a**–**c** under Friedel–Crafts conditions (Table 1).



Scheme 3. Cycliacylations of acids **6a**–**f** under Friedel–Crafts conditions (Table 2).

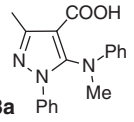
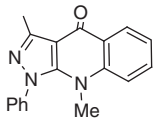
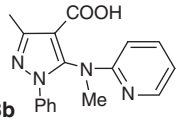
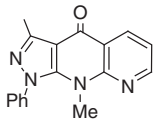
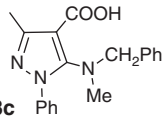
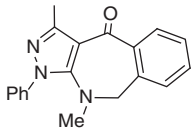
spectra, the characteristic peaks of the alkene proton were absent.

Our synthetic protocol allows access to functionalized fused tricyclic pyrazolo[3,4-*b*]quinolines, -[1,8]naphthyridines, -azepines, -azocines, -pyrido[3,2-*g*]azocines, and -azonines by means of the Friedel–Crafts cycliacylations of the key intermediate heterocyclic acids **3a**–**c** and **6a**–**f**.

Subsequently, we carried out the ring closures of acids **3a**–**c** and **6a**–**f**, which were smoothly effected in the presence of $AlCl_3/CH_3NO_2$ or P_2O_5 or polyphosphoric acid (PPA) catalysts under different reaction conditions to provide substituted azatricyclic ketones **7a**–**c** and **8a**–**f** (Schemes 2 and 3; Tables 1 and 2) in overall high reaction yields. The structures of all products were confirmed from both analytical and spectral data.

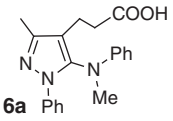
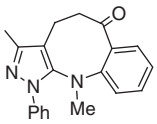
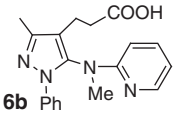
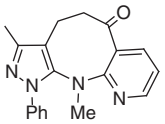
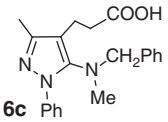
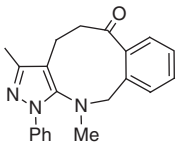
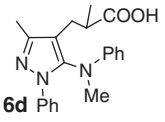
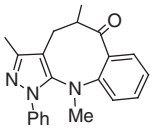
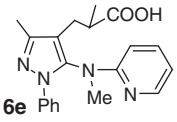
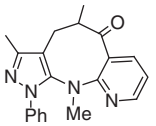
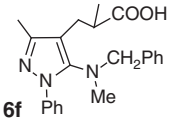
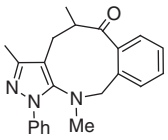
The ^{1}H NMR data affirm clearly the formation of cyclic heterocyclic products. Owing to the diastereotopic groups

Table 1. Friedel–Crafts cycliacylations of pyrazole-containing carboxylic acids 3a–c

Entry	Substrate	Product	Conditions	Product (%)[A]
1	 **3a**		$AlCl_3/CH_3NO_2$[B], DCM[C], 10 h, rt P_2O_5[D], toluene, 6 h, reflux PPA[E], 6 h, 160–170°C	**7a** (81) **7a** (86) **7a** (75)
2	 **3b**		$AlCl_3/CH_3NO_2$, DCM, 10 h, rt P_2O_5, toluene, 9 h, reflux PPA, 4 h, 160–170°C	**7b** (90) **7b** (84) **7b** (74)
3	 **3c**		$AlCl_3/CH_3NO_2$, DCM, 12 h, rt P_2O_5, toluene, 8 h, reflux PPA, 5 h, 160–170°C	**7c** (91) **7c** (86) **7c** (77)

[A]Isolated yields are relative to the substrate.
[B]With $AlCl_3/CH_3NO_2$ catalyst, reactant proportions were: carboxylic acid (0.002 mol), $AlCl_3$ (0.0024 mol), CH_3NO_2 (0.024 mol), solvent (10 mL).
[C]Dichloromethane.
[D]With P_2O_5 catalyst, reactant proportions were: acid (0.4 g) and P_2O_5 (4 g) in anhydrous toluene (15 mL).
[E]With polyphosphoric acid (PPA) catalyst, reactant proportions were: acid (0.5 g) and PPA (5 g).

Table 2. Friedel–Crafts cycliacylations of pyrazole containing carboxylic acids 6a–f

Entry	Substrate	Product	Conditions	Product (%)[A]
4	 **6a**		$AlCl_3/CH_3NO_2$[B], DCM[C], 5 h, rt P_2O_5[D], toluene, 9 h, reflux PPA[E], 2 h, 160–170°C	**8a** (87) **8a** (83) **8a** (75)
5	 **6b**		$AlCl_3/CH_3NO_2$, DCM, 6 h, rt P_2O_5, toluene, 8 h, reflux PPA, 1 h, 160–170°C	**8b** (84) **8b** (89) **8b** (76)
6	 **6c**		$AlCl_3/CH_3NO_2$, DCM, 5 h, rt P_2O_5, toluene, 5 h, reflux PPA, 2 h, 160–170°C	**8c** (87) **8c** (86) **8c** (73)
7	 **6d**		$AlCl_3/CH_3NO_2$, DCM, 6 h, rt P_2O_5, toluene, 5 h, reflux PPA, 3 h, 160–170°C	**8d** (92) **8d** (90) **8d** (80)
8	 **6e**		$AlCl_3/CH_3NO_2$, DCM, 5 h, rt P_2O_5, toluene, 7 h, reflux PPA, 2 h, 160–170°C	**8e** (88) **8e** (84) **8e** (78)
9	 **6f**		$AlCl_3/CH_3NO_2$, DCM, 8 h, rt P_2O_5, toluene, 8 h, reflux PPA, 2 h, 160–170°C	**8f** (86) **8f** (92) **8f** (81)

[A]Isolated yields are relative to the substrate.
[B]With $AlCl_3/CH_3NO_2$ catalyst, reactant proportions were: carboxylic acid (0.002 mol), $AlCl_3$ (0.0024 mol), CH_3NO_2 (0.024 mol), solvent (10 mL).
[C]Dichloromethane.
[D]With P_2O_5 catalyst, reactant proportions were: acid (0.4 g) and P_2O_5 (4 g) in anhydrous toluene (15 mL).
[E]With polyphosphoric acid (PPA) catalyst, reactant proportions were: acid (0.5 g) and PPA (5 g).

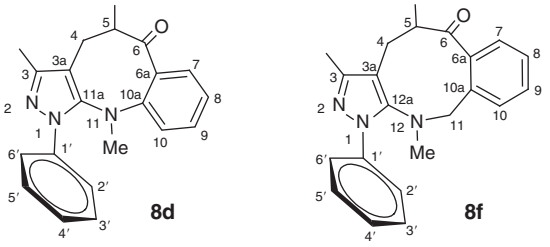


Fig. 3. Diastereotopic protons contained in condensed pyrazole heteropolycycles.

presenting unresolved signals, the ^{1}H NMR spectra of compounds **8d**–**f** characterized by the appearance of the diastereotopic hydrogens of the CH_2 group directly bonded to the pyrazole ring showed a large change in chemical shifts.

Thus, the ^{1}H NMR spectrum of tricyclic azocinone **8d** (Fig. 3) shows the chemical shifts of the CH_2 protons of the azocine ring (H4a and H4b) characteristic of the A_2B system and is characterized by the presence of apparent quartet signals near δ 2.42 ppm with a coupling constant of 6.4 Hz for one proton and a triplet near δ 2.81 ppm with a coupling constant of 6.2 Hz for the other proton. In comparison with compound **8d**, the ^{1}H NMR spectrum of tricyclic azoninone **8f** shows the chemical shifts for CH_2 protons (H4a and H4b) as a characteristic apparent triplet for H*a* at an average of δ 2.51 ppm with a coupling constant of 6.3 Hz and a triplet for Hb near δ 2.84 ppm with a coupling constant of 6.0 Hz.

Conclusions

In summary, we have developed a convergent protocol for the synthesis of unprecedented fused pyrazolequinolines, -naphthyridines, -azepines, -azocines, -azocines, and -azonines by Friedel–Crafts cycliacylations with good yields of suitable synthesized carboxylic acids substrates. Particular attention will be given to the novel structures identified to date and the promising pharmaceutically and therapeutic values associated with their tricyclic skeletons. The chemistry described and the results obtained confirm the significant and wide versatility of Friedel–Crafts ring-closure reactions in the synthesis of heteropolycycles.

Experimental

General

All reagents were purchased from Merck, Sigma–Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu 470 infrared spectrophotometer using KBr wafer and thin film techniques (ν, cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on Jeol LA 400 MHz Fourier-transform (FT)-NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C) and on Varian NMR (90 MHz) spectrometers using $CDCl_3$ solvent with TMS as internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz respectively. Elemental analyses were performed on a PerkinElmer 2400 Series II analyser. Reactions were monitored by thin-layer chromatography (TLC) using precoated silica plates visualized with UV light. Flash column chromatography was performed on silica gel or basic alumina.

5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid (*2*)

To a solution of aldehyde **1**[38] (8.4 g, 30 mmol) in aqueous *t*-butanol (*t*-butanol/H_2O, 1 : 1, 50 mL) was added a solution of $KMnO_4$ (6.6 g, 42 mmol) in H_2O (30 mL) at 70–80°C over a period of 40 min. Afterwards, the reaction mixture was basified with KOH (10 %, 50 mL) at room temperature and the whole mixture was filtered under suction. The clear filtrate was acidified with HCl (40 mL, 30 %). The resulting precipitate was filtered off, washed with water, dried, and crystallized from ethanol to give 7.9 g (88 %) of pure acid **2** as white crystals, mp 219–221°C (lit. mp 217–219°C[39]). ν_{max} (KBr)/cm^{-1} 3105, 2560, 1684, 1620, 1585, 1473, 1440, 1360, 1140, 755. δ_H (90 MHz, [D6] DMSO) 2.4 (3H, s, CH_3), 6.80–7.70 (5H, m, Ar–H), 12.80 (s, 1H, COOH). Anal. Calc. for $C_{11}H_9ClN_2O_2$ (236.5): C 55.81, H 3.80, N 11.83, Cl 15.01. Found: C 64.52, H 3.72, N 9.33, Cl 11.80 %.

General Procedure for N-Arylation of Chloropyrazole-4-carboxylic Acid *2* with Different Aromatic Amines

A mixture of chloro-acid **2** (4.2 g, 18 mmol), K_2CO_3 (4.1 g, 30 mmol), aryl amine (PhNHMe or 2-methyl-2-pyridylamine or $MeNHCH_2Ph$) (20 mmol), and CuO (0.3 g) in anhydrous DMSO (20 mL) was heated with continuous stirring for 8 h at 140–150°C. After the mixture was cooled, NaOH solution (50 mL, 10 %) and decolorizing carbon (3 g) were added and the mixture was heated for 20 min, then filtered by suction. The resulting cold filtrate was acidified with HCl solution (40 mL, 20 %) and the crude precipitate was filtered and recrystallized from ethanol gave the pure acids **3a**–**c**. The yields and spectral data are given in the following.

5-(N-methyl-N-phenylamino)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid (*3a*)

White plates; 80 %; mp 182–184°C (ethanol). ν_{max} (KBr)/cm^{-1} 3090, 2984, 2524, 1690, 1605, 1580, 1475, 1430, 1355, 1143, 758. δ_H (90 MHz, $CDCl_3$) 2.65 (3H, s, *N*-CH_3), 2.80 (3H, s, CH_3), 6.40–7.70 (10H, m, Ar–H), 11.3 (s, 1, COOH). *m*/*z* (EI, 70 eV) (%), 308 ($M^+ + 1$, 12), 307 (M^+, 29), 294 (62), 292 (71), 291 (40), 277 (25), 262 (100), 247 (62), 230 (53), 215 (36), 199 (29), 166 (74), 154 (17), 122 (30), 105 (16), 90 (12), 78 (8). Anal. Calc. for $C_{18}H_{17}N_3O_2$ (307): C 70.35, H 5.53, N 13.68. Found: C 70.54, H 5.72, N 13.38 %.

5-(N-methyl-N-(pyridin-2-yl)amino)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid (*3b*)

Brownish crystals; 77 %; mp 157–159°C (benzene). ν_{max} (KBr)/cm^{-1} 3110, 2565, 1695, 1600, 1590, 1460, 1445, 1330, 1120, 760. δ_H (90 MHz, [D6]DMSO) 2.50 (3H, s, *N*-CH_3), 2.75 (3H, s, CH_3), 6.45–7.85 (9H, m, Ar–H), 11.4 (s, 1, COOH). *m*/*z* (EI, 70 eV) (%), 308 (M^+, 40), 307 (19), 291 (62), 278 (31), 263 (54), 248 (27), 233 (19), 231 (38), 216 (28), 200 (33), 170 (15), 168 (63), 156 (42), 124 (42), 104 (11), 91 (16), 77 (10). Anal. Calc. for $C_{17}H_{16}N_4O_2$ (308): C 66.23, H 5.19, N 18.18. Found: C 66.16, H 5.42, N 17.95 %.

5-(N-benzyl-N-methylamino)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid (*3c*)

White crystals; 82 %; mp 120–122°C (ethanol). ν_{max} (KBr)/cm^{-1} 3060, 2973, 2550, 1695, 1605, 1580, 1465, 1440, 1335, 1254, 745. δ_H (90 MHz, $CDCl_3$) 2.55 (3H, s, *N*-CH_3), 2.70 (3H, s, CH_3), 4.45 (2H, s, *N*-CH_2), 6.30–7.85 (10H, m, Ar–H), 11.2 (s, 1, COOH). *m*/*z* (EI, 70 eV) (%), 322 ($M^+ + 1$, 8), 321 (M^+, 27), 304 (63), 306 (17), 291 (26), 276 (100), 274 (69), 246 (22), 244 (36), 214 (11), 199 (20), 168 (58), 155 (36), 121 (18), 104 (14), 90 (17), 78 (10). Anal. Calc. for $C_{19}H_{19}N_3O_2$ (321): C 71.02, H 5.91, N 13.08. Found: C 70.81, H 9.12, N 13.20 %.

General Perkin-Type Procedure for the Synthesis of Acrylic Acids

A mixture of aldehyde **1** (3.5 g, 15 mmol), acid anhydride (ethanoic or propanoic anhydride) (18 mmol), and sodium salt of the corresponding acid (18 mmol) was heated in an oil bath at 120–130°C with occasionally stirring for 8–10 h. After reaction completion, the warm mixture was poured with stirring into ice-cold water (50 mL), basified with Na_2CO_3 solution (20 mL, 30 %), and extracted with diethyl ether (2 × 20 mL). The ether extracts were discarded and the resulting solution was heated with decolorizing carbon (2 g), filtered while hot, then poured with stirring into concentrated HCl mixed with ice (50 mL). The precipitated acid **13a** or **b** was filtered, washed successively with water, and left to dry. Purifications, yields and spectral data are given in the following.

3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)acrylic Acid (**4a**)

White needles; 74 %; mp 149–151°C (methanol). ν_{max} (KBr)/cm^{-1} 3110, 2945, 2545, 1705, 1600, 1585, 1460, 1445, 1350, 1140, 747. δ_H (90 MHz, $CDCl_3$) 2.75 (3H, s, CH_3), 2.75 (3H, s, CH_3), 6.20 (H, d, *J* 6, CH), 6.45–7.70 (6H, m, Ar–H; CH), 11.35 (s, 1, COOH). Anal. Calc. for $C_{13}H_{11}ClN_2O_2$ (262.5): C 59.42, H 4.19, N 10.66, Cl 13.52. Found: C 59.45, H 4.07, N 10.84, Cl 13.37 %.

3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-methylacrylic Acid (**4b**)

Pale yellow crystals; 83 %; mp 172–174°C (cyclohexane). ν_{max} (KBr)/cm^{-1} 3084, 2965, 2625, 1700, 1580, 1455, 1440, 1365, 1245, 1080, 749. δ_H (90 MHz, $CDCl_3$) 1.90 (3H, s, CH_3), 2.75 (3H, s, CH_3), 6.30–7.75 (6H, m, Ar–H, =CH), 10.9 (s, 1, COOH). Anal. Calc. for $C_{14}H_{13}ClN_2O_2$ (276.5): C 60.75, H 4.70, N 10.12, Cl 12.83. Found: C 60.44, H 4.93, N 10.23, Cl 12.64 %.

General Procedure for Reduction of Acids **4a, b**

A solution of acid **4a** or **b** (10 mmol) in NaOH solution (15 mL, 1 N) was treated with sodium amalgam (25 g, 2.5 %) in small portions over a period of 20 min with vigorous stirring. The reaction mixture was stirred for an additional 3 h at room temperature and then the mercury was separated, washed with water, and the washings were added to the main solution. The whole solution was acidified with concentrated HCl (10 mL) and the crude acid **5a** or **5b** was filtered, washed, and dried. Yields and spectral data are given in the following.

3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) propanoic Acid (**5a**)

Pale yellow crystals; 90 %; mp 167–168°C (benzene). ν_{max} (KBr)/cm^{-1} 3046, 2990, 2520, 1725, 1605, 1585, 1450, 1435, 1365, 1280, 1070, 760. δ_H (90 MHz, $CDCl_3$) 2.55 (2H, t, *J* 6, CH_2), 2.70 (3H, s, CH_3), 2.80 (2H, t, *J* 6, CH_2), 6.30–7.75 (5H, m, Ar–H), 11.3 (s, 1, COOH). Anal. Calc. for $C_{13}H_{13}ClN_2O_2$ (264.5): C 58.97, H 4.91, N 10.58, Cl 13.42. Found: C 58.79, H 4.82, N 10.35, Cl 13.20 %.

2-((5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methyl)propanoic Acid (**5b**)

White crystals; 83 %; mp 155–157°C (ethanol). ν_{max} (KBr)/cm^{-1} 3035, 2952, 2610, 1718, 1600, 1578, 1450, 1445, 1370, 1035, 749. δ_H (90 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.5, CH_3), 2.65–2.94 (3H, m, CH–CH_2), 2.75 (3H, s, CH_3), 6.35–7.70 (5H, m, Ar–H), 10.8 (s, 1, COOH). Anal. Calc. for $C_{14}H_{15}ClN_2O_2$ (278.5): C 60.32, H 5.38, N 10.05, Cl 12.74. Found: C 60.38, H 5.22, N 10.26, Cl 12.64 %.

General Procedure for N-Arylation of Substituted Pyrazole-4-propionic Acid

The titled acids were obtained by repeating the Ullmann *N*-coupling reaction with the same procedure as described for *N*-aryl acids **3a**–**c** with different aromatic amines. The yields and spectral data are given in the following.

3-(5-(N-methyl-N-phenylamino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)propanoic Acid (**6a**)

Greenish plates; 74 %; mp 222–224°C (ethanol). ν_{max} (KBr)/cm^{-1} 3030, 2980, 2590, 1730, 1590, 1550, 1440, 1435, 1335, 1260, 755. δ_H (90 MHz, $CDCl_3$) 2.45 (2H, t, *J* 7.5, CH_2), 2.60 (3H, s, *N*-CH_3), 2.70 (3H, s, CH_3), 2.95 (2H, t, *J* 6, CH_2), 6.40–7.75 (6H, m, Ar–H), 11.2 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 335 (M^+, 27), 318 (24), 290 (100), 275 (52), 360 (35), 258 (74), 245 (17), 232 (25), 213 (32), 204 (16), 180 (62), 178 (19), 168 (64), 105 (22), 90 (12), 78 (7). Anal. Calc. for $C_{20}H_{21}N_3O_2$ (335): C 71.64, H 6.26, N 12.53. Found: C 71.72, H 6.28, N 12.68 %.

3-(5-(N-methyl-N-(pyridin-2-yl)amino)-)-3-methyl-1-phenyl-1H-pyrazol-4-yl)propanoic Acid (**6b**)

Pale yellowish crystals; 75 %; mp 157–159°C (acetone). ν_{max} (KBr)/cm^{-1} 3054, 2942, 2670, 1724, 1600, 1590, 1440, 1435, 1311, 1263, 760. δ_H (90 MHz, $CDCl_3$) 2.45 (3H, s, *N*-CH_3), 2.60 (2H, t, *J* 6, CH_2), 2.75 (3H, s, CH_3), 2.95 (2H, t, *J* 6, CH_2), 6.40–7.95 (9H, m, Ar–H), 10.7 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 337 ($M^+ + 1$, 14), 336 (M^+, 44), 317 (20), 291 (100), 275 (32), 361 (52), 259 (41), 246 (10), 233 (20), 214 (12), 205 (12), 182 (74), 179 (25), 169 (86), 105 (13), 92 (7), 78 (6). Anal. Calc. for $C_{19}H_{20}N_4O_2$ (336): C 67.85, H 5.95, N 16.66. Found: C 67.62, H 6.11, N 16.81 %.

3-(5-(N-benzyl-N-methylamino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)propanoic Acid (**6c**)

White crystals; 68 %; mp 184–186°C (ethanol). ν_{max} (KBr)/cm^{-1} 3020, 2972, 2560, 1720, 1605, 1590, 1455, 1445, 1365, 1230, 765. δ_H (90 MHz, $CDCl_3$) 2.35 (3H, s, *N*-CH_3), 2.50 (2H, t, *J* 6, CH_2), 2.70 (3H, s, CH_3), 2.85 (2H, t, *J* 6, CH_2), 6.40–7.95 (10H, m, Ar–H), 11.4 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 351 ($M^+ + 2$, 4), 350 ($M^+ + 1$, 14), 349 (M^+, 38), 332 (10), 304 (100), 289 (64), 274 (33), 260 (68), 246 (13), 227 (41), 206 (11), 199 (26), 191 (29), 181 (50), 178 (14), 168 (77), 105 (22), 91 (35), 78 (9). Anal. Calc. for $C_{21}H_{23}N_3O_2$ (349): C 72.20, H 6.59, N 12.03. Found: C 72.25, H 6.63, N 12.27 %.

2-((5-(N-methyl-N-phenylamino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)propanoic Acid (**6d**)

Pale yellow needles; 84 %; mp 144–146°C (acetone). ν_{max} (KBr)/cm^{-1} 3045, 2970, 2630, 1735, 1595, 1570, 1455, 1440, 1336, 1020, 745. δ_H (90 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.5, CH_3), 2.50–2.95 (3H, m, CH–CH_2), 2.60 (3H, s, *N*-CH_3), 2.75 (3H, s, CH_3), 6.40–7.75 (10H, m, Ar–H), 11.0 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 350 ($M^+ + 1$, 8), 349 (M^+, 42), 332 (26), 304 (100), 289 (52), 288 (14), 274 (17), 358 (82), 261 (32), 246 (21), 227 (44), 206 (16), 198 (42), 191 (17), 180 (64), 179 (10), 167 (65), 104 (14), 90 (14), 78 (4). Anal. Calc. for $C_{21}H_{23}N_3O_2$ (349): C 72.20, H 6.59, N 12.03. Found: C 72.35, H 6.38, N 12.12 %.

*2-(5-(N-methyl-N-(pyridin-2-yl)amino)-)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)propanoic Acid (**6e**)*

Greenish crystals; 82 %; mp 110–112°C (benzene). ν_{max} (KBr)/cm^{-1} 3020, 2955, 2595, 1720, 1605, 1596, 1455, 1440, 1355, 1035, 755. δ_H (90 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.5, CH_3), 2.45 (3H, s, *N*-CH_3), 2.50–2.95 (3H, m, CH–CH_2), 2.70 (3H, s, CH_3), 6.45–7.75 (9H, m, Ar–H), 10.8 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 350 (M^+, 48), 349 (15), 333 (14), 305 (100), 290 (25), 275 (24), 273 (12), 261 (64), 228 (56), 205 (20), 199 (17), 190 (12), 181 (72), 179 (14), 167 (81), 106 (21), 90 (10), 78 (12). Anal. Calc. for $C_{20}H_{22}N_4O_2$ (350): C 68.54, H 6.28, N 16.00. Found: C 68.72, H 6.04, N 15.82 %.

*2-((5-(N-benzyl-N-methylamino)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)propanoic Acid (**6f**)*

Yellow crystals; 65 %; mp 128–130°C (benzene). ν_{max} (KBr)/cm^{-1} 3010, 2940, 2517, 1722, 1595, 1584, 1460, 1440, 1335, 1265, 1020, 745. δ_H (90 MHz, $CDCl_3$) 1.15 (3H, d, *J* 7.5, CH_3), 2.40 (3H, s, *N*-CH_3), 2.50–3.10 (3H, m, CH–CH_2), 2.75 (3H, s, CH_3), 4.20 (2H, s, CH_2), 6.35–7.70 (10H, m, Ar–H), 10.8 (s, 1, COOH). *m/z* (EI, 70 eV) (%), 363 (M^+, 27), 346 (23), 318 (100), 303 (44), 288 (21), 274 (26), 260 (39), 241 (15), 227 (36), 205 (11), 198 (27), 180 (60), 179 (11), 168 (62), 105 (13), 91 (26), 78 (14). Anal. Calc. for $C_{22}H_{25}N_3O_2$ (363): C 72.72, H 6.88, N 11.57. Found: C 72.78, H 6.65, N 11.81 %.

Friedel–Crafts Cycliacylation Procedures

Early procedures[34,35] describing ring closure of heteroaryl acids with $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA were followed. In all reactions, the crude solid products were purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane 3 : 1) and following crystallization from an appropriate solvent, gave the pure products **7a**–**c** and **8a**–**f**. The conditions and yields for the tricyclic products are shown in Tables 1 and 2, whereas the physical constants and spectral data are given in the following.

*3,9-Dimethyl-1-phenyl-1H-pyrazolo[3,4-b]quinolin-4(9H)-one (**7a**)*

Yellow crystals; 82 %; mp 228–230°C (benzene). ν_{max} (KBr)/cm^{-1} 3030, 2985, 1685, 1585, 1470, 1450, 1374, 1265, 1149, 1073, 746. δ_H (90 MHz, $CDCl_3$) 2.55 (3H, s, CH_3), 2.85 (3H, s, CH_3), 6.55–7.40 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 16.0 (1C, –CH_3), 46.7 (1C, *N*-CH_3), 108.6 (1C, C-3a), 114.6 (1C, Ar, C-4a), 116.6 (1C, Ar, C-8), 120.3 (1C, Ar, C-6), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 132.4 (2C, Ar, C-3′, C-5′), 133.5 (1C, Ar, C-5), 136.5 (1C, Ar, C-7), 141.7 (1C, Ar, C-1′), 147.2 (1C, Ar, C-8a), 149.5 (1C, C-9a), 150.8 (1C, C-3), 185.2 (1C, C=O, C-4). *m/z* (EI, 70 eV) (%), 290 ($M^+ + 1$, 17), 289 (M^+, 100), 274 (53), 261 (42), 259 (27), 212 (15), 205 (32), 182 (54), 167 (72), 139 (15), 105 (8), 90 (20), 76 (9). Anal. Calc. for $C_{18}H_{15}N_3O$ (289): C 74.74, H 5.19, N 14.53. Found: C 74.82, H 5.23, N 14.44 %.

*3,9-Dimethyl-1-phenyl-1H-pyrazolo[3,4-b][1,8]naphthyridin-4(9H)-one (**7b**)*

Pale green plates; 85 %; mp 184–186°C (cyclohexane). ν_{max} (KBr)/cm^{-1} 3065, 2940, 1690, 1605, 1590, 1475, 1440, 1380, 1270, 1130, 750. δ_H (90 MHz, $CDCl_3$) 2.50 (3H, s, CH_3), 2.75 (3H, s, CH_3), 6.50–7.55 (8H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 16.4 (1C, –CH_3), 46.7 (1C, *N*-CH_3), 109.6 (1C, C-3a), 116.9 (1C, Ar, C-6), 119.8 (1C, Ar, C-4a), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 133.4 (2C, Ar, C-3′, C-5′), 141.0 (1C, Ar, C-5), 142.7 (1C, Ar, C-1′), 148.5 (1C, C-9a), 151.8 (1C, C-3), 155.6 (1C, Ar, C-7), 167.5 (1C, Ar, C-8a), 188.2 (1C, C=O, C-4). *m/z* (EI, 70 eV) (%), 290 ($M^+ + 1$, 17), 289 (M^+, 100), 274 (53), 261 (42), 259 (27), 212 (15), 205 (32), 182 (54), 167 (72), 139 (15), 105 (8), 90 (20), 76 (9). Anal. Calc. for $C_{17}H_{14}N_4O$ (290): C 70.34, H 4.82, N 19.31. Found: C 70.52, H 4.83, N 19.35 %.

*3,10-Dimethyl-4,9-dihydro-1-phenyl-benzo[e]pyrazolo[3,4-b]azepin-4(10H)-one (**7c**)*

Amber crystals; 78 %; mp 164–166°C (benzene). ν_{max} (KBr)/cm^{-1} 3063, 2960, 1702, 1595, 1473, 1440, 1385, 1266, 1132, 1075, 745. δ_H (90 MHz, $CDCl_3$) 2.50 (3H, s, CH_3), 2.75 (3H, s, CH_3), 4.20 (2H, s, CH_2), 6.45–7.40 (8H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 17.2 (1C, –CH_3), 42.7 (1C, *N*-CH_3), 60.3 (1C, –CH_2–, C-9), 106.6 (1C, C-3a), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (2C, Ar, C-4a, C-4′), 130.2 (1C, Ar, C-6), 132.1 (1C, Ar, C-8), 133.4 (2C, Ar, C-3′, C-5′), 134.5 (1C, Ar, C-5), 137.5 (2C, Ar, C-7, C-8a), 142.7 (1C, Ar, C-1′), 150.8 (1C, C-3), 154.4 (1C, C-10a), 190.6 (1C, C=O, C-4). *m/z* (EI, 70 eV) (%), 304 ($M^+ + 1$, 22), 303 (M^+, 100), 288 (19), 275 (37), 273 (12), 260 (61), 245 (20), 226 (12), 211 (7), 182 (70), 168 (84), 151 (22), 106 (10), 91 (12), 78 (7). Anal. Calc. for $C_{19}H_{17}N_3O$ (303): C 75.24, H 5.61, N 13.86. Found: C 75.37, H 5.49, N 13.62 %.

*3,11-Dimethyl-4,5,6-trihydro-1-phenyl-benzo[g]pyrazolo[3,4-b]azocin-6(11H)-one (**8a**)*

Yellow crystals; 88 %; mp 158–160°C (acetone). ν_{max} (KBr)/cm^{-1} 3020, 2985, 1735, 1600, 1584, 1459, 1443, 1375, 1270, 1135, 755. δ_H (400 MHz, $CDCl_3$) 2.53 (3H, s, *N*-CH_3), 2.62 (2H, t, *J* 7.5, CH_2), 2.74 (3H, s, CH_3), 2.93 (2H, t, *J* 7.5, CH_2), 6.52–7.43 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 16.5 (1C, –CH_3), 19.3 (1C, –CH_2–, C-4), 46.2 (1C, –CH_2–, C-5), 48.0 (1C, *N*-CH_3), 109.1 (1C, C-3a), 115.4 (1C, Ar, C-10), 118.4 (1C, Ar, C-6a), 121.1 (1C, Ar, C-8), 124.2 (2C, Ar, C-2′, C-6′), 130.3 (1C, Ar, C-4′), 133.4 (2C, Ar, C-3′, C-5′), 134.6 (1C, Ar, C-7), 137.0 (1C, Ar, C-9), 142.7 (1C, Ar, C-1′), 147.3 (1C, Ar, C-10a), 151.3 (1C, C-3), 157.0 (1C, C-11a), 205.4 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 319 ($M^+ + 2$, 5), 318 ($M^+ + 1$, 18), 317 (M^+, 100), 289 (25), 275 (42), 273 (10), 261 (68), 246 (14), 231 (19), 212 (13), 181 (84), 167 (91), 150 (16), 105 (14), 90 (10), 77 (5). Anal. Calc. for $C_{20}H_{19}N_3O$ (317): C 75.70, H 5.99, N 13.24. Found: C 75.72, H 5.81, N 13.34 %.

*3,11-Dimethyl-4,5,6-trihydro-1-phenyl-1H-pyrazolo[3,4-b]pyrido[3,2-g]azocin-6(11H)-one (**8b**)*

Yellow crystals; 80 %; mp 210–212°C (ethanol). ν_{max} (KBr)/cm^{-1} 3055, 2958, 1740, 1600, 1485, 1440, 1373, 1265, 1134, 1082, 747. δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, *N*-CH_3), 2.71 (2H, t, *J* 6.2, CH_2), 2.73 (3H, s, CH_3), 2.84 (2H, t, *J* 6.2, CH_2), 6.52–7.39 (8H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 16.1 (1C, –CH_3), 18.4 (1C, –CH_2–, C-4), 45.9 (1C, –CH_2–, C-5), 47.0 (1C, *N*-CH_3), 108.1 (1C, C-3a), 115.2 (1C, Ar, C-8), 122.5 (1C, Ar, C-6a), 125.2 (2C, Ar, C-2′, C-6′), 128.3 (1C, Ar, C-4′), 132.4 (2C, Ar, C-3′, C-5′), 140.5 (1C, Ar, C-7), 141.7 (1C, Ar, C-1′), 149.3 (1C, C-3), 151.2 (1C, Ar, C-9), 152.0 (1C, Ar, C-11a), 167.6 (1C, Ar, C-10a), 200.4 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 319 ($M^+ + 1$, 12), 318 (M^+, 100), 290 (38), 275 (14), 273 (12), 260 (42), 245 (34), 213 (34), 180 (69), 168 (63), 152 (10), 105 (22), 91 (14), 77 (9). Anal. Calc. for $C_{19}H_{18}N_4O$ (318): C 71.69, H 5.66, N 17.61. Found: C 71.62, H 5.52, N 17.74 %.

*3,12-Dimethyl-4,5,6,11-tetrahydro-1-phenyl-benzo[g]pyrazolo[3,4-b]azonin-6(12H)-one (**8c**)*

Yellow plates; 86 %; mp 140–142°C (cyclohexane). ν_{max} (KBr)/cm^{-1} 3065, 2940, 1742, 1605, 1590, 1475, 1440, 1383, 1270, 1135, 750. δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, *N*-CH_3), 2.71 (2H, t, *J* 7.5, CH_2), 2.78 (3H, s, CH_3), 2.98 (2H, t, *J* 7.5, CH_2), 4.24 (2H, s, CH_2), 6.42–7.48 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 12.2 (1C, –CH_2–, C-4), 15.3 (1C, –CH_3), 43.6 (1C, *N*-CH_3), 45.5 (1C, –CH_2–, C-5), 62.6 (1C, –CH_2–, C-11), 106.1 (1C, C-3a), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 130.4 (2C, Ar, C-8, C-10), 131.6 (1C, Ar, C-7), 132.4 (2C, Ar, C-3′, C-5′), 134.4 (1C, Ar, C-10a), 137.0 (2C, Ar, C-9, C-6a), 142.7 (1C, Ar, C-1′), 149.3 (1C, C-3), 152.4 (1C, C-12a), 202.5 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 332 ($M^+ + 1$, 9), 331 (M^+, 100), 303 (42), 288 (23), 273 (40), 260 (14), 245 (12), 225 (52), 211 (25), 181 (57), 168 (82), 150 (12), 104 (15), 90 (10), 77 (4). Anal. Calc. for $C_{21}H_{21}N_3O$ (331): C 76.13, H 6.34, N 12.68. Found: C 76.20, H 6.25, N 12. 81 %.

*3,5,11-Trimethyl-4,5,6-trihydro-1-phenyl-benzo[g]pyrazolo[3,4-b]azocin-6(11H)-one (**8d**)*

Yellow crystals; 82 %; mp 184–186°C (acetone). ν_{max} (KBr)/cm^{-1} 3040, 2963, 1744, 1595, 1485, 1440, 1380, 1275, 1122, 1064, 755. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.3, CH_3), 2.42 (1Ha, app. q, *J* 6.4, CH_2), 2.62 (3H, s, *N*-CH_3), 2.75 (3H, s, CH_3), 2.81 (1Hb, t, *J* 6.2, CH_2), 3.61 (2H, m, CH), 6.44–7.50 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 17.4 (1C, –CH_3), 21.5 (1C, (C-5–*C*H_3), 25.2 (1C, –CH_2–, C-4), 47.0 (1C, *N*-CH_3), 52.6 (1C, C-5), 110.3 (1C, C-3a), 116.4 (1C, Ar, C-10), 117.4 (1C, Ar, C-6a), 120.1 (1C, Ar, C-8), 124.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 130.4 (2C, Ar, C-3′, C-5′), 131.6 (1C, Ar, C-7), 137.0 (1C, Ar, C-9), 142.7 (1C, Ar, C-1′), 146.3 (1C, Ar, C-10a), 149.3 (1C, C-3), 153.0 (1C, C-11a), 212.4 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 331 (M^+, 29), 330 (100), 304 (37), 288 (15), 275 (20), 259 (52), 245 (16), 228 (33), 211 (15), 180 (27), 168 (74), 151 (10), 105 (12), 91 (18), 78 (7). Anal. Calc. for $C_{21}H_{21}N_3O$ (331): C 76.13, H 6.34, N 12.60. Found: C 76.30, H 6.29, N 12.52 %.

*3,5,11-Trimethyl-4,5,6-trihydro-1-phenyl-1H-pyrazolo[3,4-b]pyrido[3,2-g]azocin-6(11H)-one (**8e**)*

Yellow needles; 76 %; mp 165–167°C (benzene/*n*-hexane). ν_{max} (KBr)/cm^{-1} 3017, 2949, 1745, 1604, 1595, 1480, 14450 1375, 1245, 1133, 750. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.2, CH_3), 2.42 (3H, s, *N*-CH_3), 2.63 (1Ha, app. quintet, *J* 6.2, CH_2), 2.78 (3H, s, CH_3), 2.92 (1Hb, t, *J* 6.2, CH_2), 3.14 (1H, m, CH), 6.35–7.47 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 14.0 (1C, –CH_3), 19.4 (1C, (C-5–*C*H_3), 23.8 (1C, –CH_2–, C-4), 45.0 (1C, *N*-CH_3), 53.3 (1C, C-5), 108.1 (1C, C-3a), 116.2 (1C, Ar, C-8), 120.5 (1C, Ar, C-6a), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 131.4 (2C, Ar, C-3′, C-5′), 139.5 (1C, Ar, C-7), 140.7 (1C, Ar, C-1′), 148.3 (1C, C-3), 151.2 (1C, Ar, C-9), 154.0 (1C, C-11a), 165.6 (1C, Ar, C-10a), 210.2 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 333 ($M^+ + 1$, 17), 332 (M^+, 41), 331 (100), 304 (23), 289 (44), 275 (52), 260 (47), 255 (22), 225 (17), 210 (15), 182 (53), 169 (51), 152 (41), 105 (18), 90 (14), 77 (4). Anal. Calc. for $C_{20}H_{20}N_4O$ (332): C 72.28, H 6.02, N 16.86. Found: C 72.22, H 6.14, N 16.64 %.

*3,5,12-Trimethyl-4,5,6,11-tetrahydro-1-phenyl-benzo[g]pyrazolo[3,4-b]azonin-6(12H)-one (**8f**)*

Yellow crystals; 81 %; mp 117–119°C (benzene). ν_{max} (KBr)/cm^{-1} 3035, 2972, 1736, 1600, 1590, 1475, 1445, 1383, 1270, 1130, 759. δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.2, CH_3), 2.44 (3H, s, *N*-CH_3), 2.51 (1Ha, app. t, *J* 6.3, CH_2), 2.73 (3H, s, CH_3), 2.84 (1Hb, t, *J* 6.0, CH_2), 3.58 (2H, m, CH), 6.38–7.44 (9H, m, Ar–H). δ_C (100 MHz, $CDCl_3$) 15.3 (1C, –CH_3), 18.7 (1C, –CH_2–, C-4), 20.5 (1C, (C-5–*C*H_3), 44.6 (1C, *N*-CH_3), 49.9 (1C, C-5), 62.6 (1C, –CH_2–, C-11), 110.3 (1C, C-3a), 123.2 (2C, Ar, C-2′, C-6′), 129.3 (1C, Ar, C-4′), 130.0 (2C, Ar, C-8, C-10), 131.6 (1C, Ar, C-7), 133.4 (2C, Ar, C-3′, C-5′), 135.4 (1C, Ar, C-10a), 137.0 (2C, Ar, C-9, C-6a), 142.7 (1C, Ar, C-1′), 152.3 (1C, C-3), 155.5 (1C, C-12a), 202.0 (1C, C=O, C-6). *m/z* (EI, 70 eV) (%), 346 ($M^+ + 1$, 24), 345 (M^+, 51), 344 (100), 317 (42), 302 (12), 287 (31), 272 (48), 268 (54), 253 (17), 240 (20), 224 (9), 181 (45), 169 (39), 152 (20), 105 (14), 91 (9), 77 (8). Anal. Calc. for $C_{22}H_{23}N_3O$ (345), C 76.52, H 6.66, N 12.17. Found: C 76.48, H 6.72, N, 12.30 %.

Acknowledgements

The authors are grateful for the financial support and all the facilities while performing and writing this work from the Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.

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