Mannich Bases as Synthetic Intermediates: Convenient Synthesis of Functionalized 1,2,4-Triazepines, 1,4-Diazepines and 1,5-Diazocines

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Transamination between the ketonic Mannich bases **1a**, **b** and primary arylamines gave a series of ketonic *sec*-Mannich bases **2a** – **h**. A variety of tetrahydro-1,2,4-triazepines **3a** – **f** have been synthesized by treating the arylhydrazones of **2** with formaldehyde. A similar reaction with the benzenesulfonylhydrazone of **2b** afforded **4**. The 3-styryl-2*H*-1,2,4-triazepine **5** was obtained from the phenylhydrazone of **2a** and cinnamaldehyde. Treatment of arylhydrazones of the 4-methoxystyryl keto base **7** with formaldehyde and cinnamaldehyde afforded the 3,4,5,6-tetrahydro-2*H*-1,2,4-triazepines **8a**, **b**. Mannich reaction with 4-(*p*-hydroxyphenyl)-tetrahydro-1,2,4-triazepine **3d** afforded the Mannich bases **9**, **10** and **11**.

The reaction of **1b** with *o*-phenylenediamine leads to the 1,5-benzodiazepine **13**. The new tetrahydro-1,4-diazepine and tetrahydro-1,5-diazocine Mannich bases **15** and **17** were obtained from **1b** and ethylenediamine or 1,3-diaminopropane, respectively. The bi(piperidine) derivative **19** was obtained from **1a** and 1,3-diaminopropane.

Key words: Mannich Bases, 1,2,4-Triazepines, 1,4-Diazepines, 1,5-Diazocines

Introduction

Mannich bases have been used extensively in the synthesis of heterocyclic systems [1 – 6] and of heterocycles having a potential basic side chain of alkaloidal nature [7 – 13]. In particular, ketonic *tert*-Mannich bases and their quaternary salts have been employed frequently as potential intermediates in the synthesis of a multitude of heterocycles of pharmaceutical interest, such as pyrazolines [9 – 11], pyridines [3], piperidines [14 – 16], 1,5-benzo- or 1,5-hetero-diazepines [16 – 19], and quinolines [20]. The use of *sec*-Mannich bases as synthetic intermediates has been reported in a limited number of cases for the synthesis of pyrimidines [21], quinolines [22, 23] and isoquinolines [24, 25], and recently we reported [16] the synthesis of the 2*H*-1,2,4-triazepine ring system starting with ketonic *sec*-amine bases.

In connection with our studies in the area of Mannich bases [4, 11 – 13, 16, 26] and in view of the widespread and increasing interest in the chemistry and biological activities of Mannich bases and related compounds, the synthetic potential of ketonic *sec*-Mannich bases as intermediates in heterocyclic synthesis was further investigated. We report here on the synthesis of some new functionalized tetrahydro-1,2,4-triazepines, tetrahydro-1,4-diazepines, tetrahydro-1,5-diazocines, and bi(piperidines), which possess considerable synthetic and pharmaceutical interest.

Results and Discussion

A series of ketonic *sec*-Mannich bases **2a** – **h** was prepared by transamination reaction between the ketonic *tert*-Mannich base hydrochloride **1a** or **1b** and the appropriate primary aromatic amine, according to an earlier report [27]. Compounds **2f** – **h** have been reported for the first time by this study. It was found that treatment of the ketonic *sec*-amines of the type **2** with *p*-nitrophenylhydrazine or phenylhydrazine, and subsequently with formaldehyde under mild conditions, afforded a series of 3,4,5,6-tetrahydro-2,4,7-triaryl-2*H*-1,2,4-triazepines (**3a** – **f**) with different substituents on the 1,2,4-triazepine ring (Scheme 1).

In line with this, the 2-benzenesulfonyl-tetrahydro-1,2,4-triazepine derivative **4** was obtained by treating **2b** with benzenesulfonyl hydrazide and formaldehyde. The synthesis of the 3-styryl-tetrahydro-1,2,4-triazepine **5** was achieved by treating the phenylhydrazone of **2a** with cinnamaldehyde. A practical advantage of the reactions leading to the 3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine derivatives **3** – **5** is that it is

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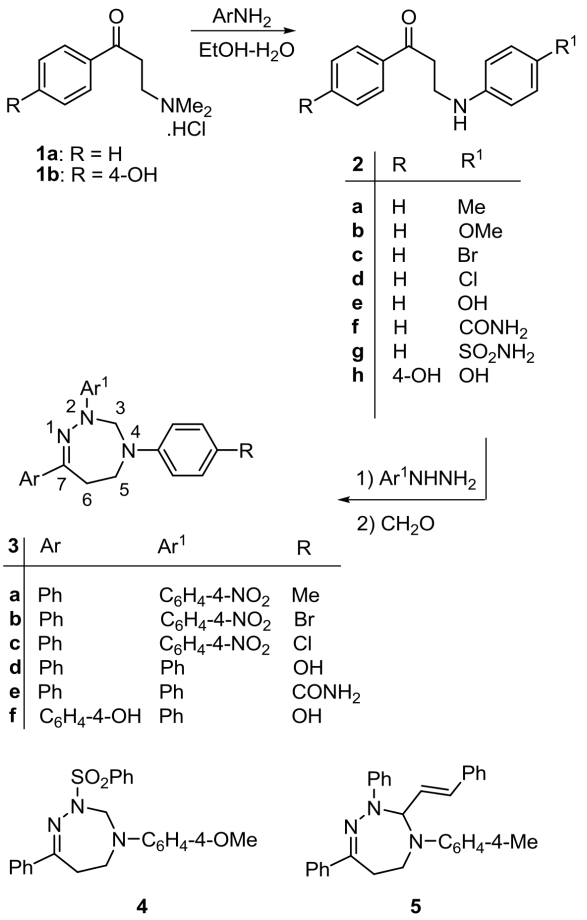
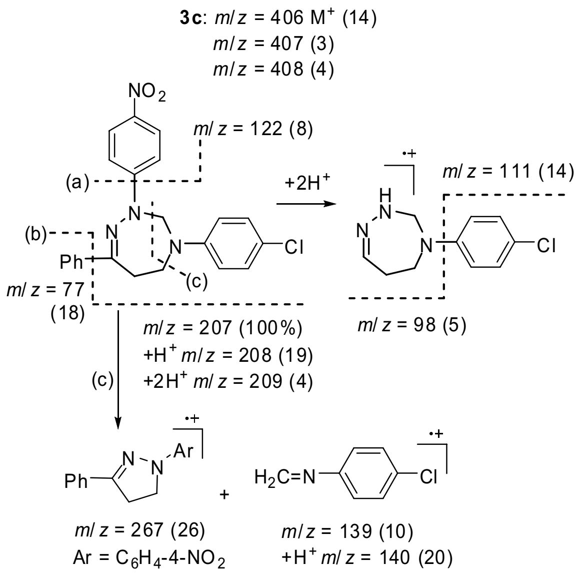


2	R	R^1
a	H	Me
b	H	OMe
c	H	Br
d	H	Cl
e	H	OH
f	H	$CONH_2$
g	H	SO_2NH_2
h	4-OH	OH

3	Ar	Ar^1	R
a	Ph	C_6H_4-4-NO_2	Me
b	Ph	C_6H_4-4-NO_2	Br
c	Ph	C_6H_4-4-NO_2	Cl
d	Ph	Ph	OH
e	Ph	Ph	$CONH_2$
f	C_6H_4-4-OH	Ph	OH

Scheme 1.

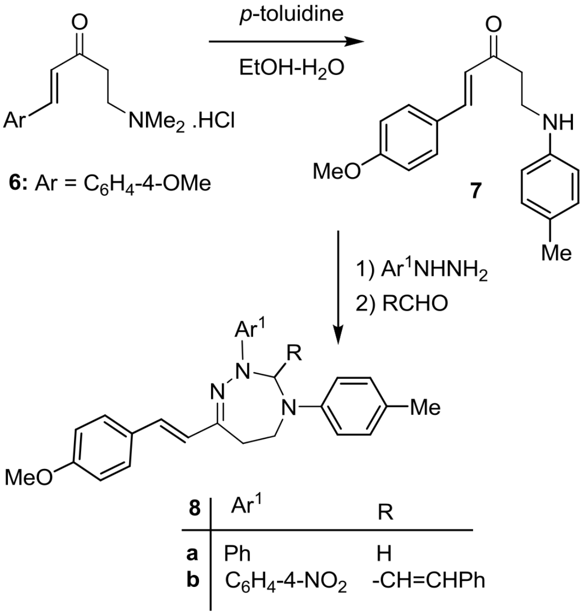
often unnecessary to isolate the arylhydrazone intermediates of the ketonic *sec*-Mannich bases. The mass and ^1H NMR spectra of compounds **3**–**5** are consistent with their structures. The main characteristic features of the ^1H NMR spectrum of **3a** are a singlet at δ = 5.35 assignable to 3-H_2 and two triplets at δ = 3.65 (5-H_2) and 3.38 (6-H_2), and a singlet at δ = 2.33 (Ar-CH_3). The mass spectra of **3a**–**f**, **4** and **5** contain peaks of the respective molecular ions, and fragmentation patterns which supported their structures. As an example the fragmentation pattern of **3c** is depicted in Scheme 2.



Scheme 2.

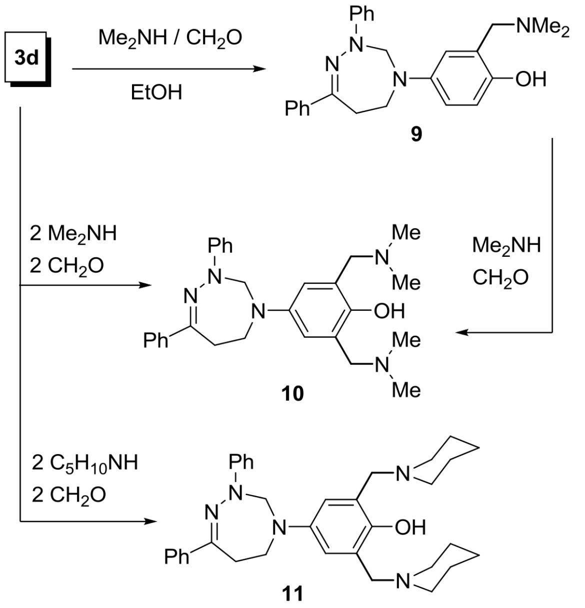
The scope of the above reaction has been broadened by treatment of the arylhydrazones derived from 1-(*p*-anisyl)-5-(*p*-tolylamino)-1-penten-3-one (**7**) with formaldehyde or cinnamaldehyde to afford 7-(4-methoxystyryl)-tetrahydro-2-phenyl-4-(*p*-tolyl)-2*H*-1,2,4-tiazepine (**8a**) and 7-(4-methoxystyryl)-3-styryl-tetrahydro-2*H*-1,2,4-triazepine (**8b**), respectively (Scheme 3). The analytical and spectral data of **8a** and **8b** are consistent with their structures.

The Mannich reaction of the 4-(*p*-hydroxyphenyl)-tetrahydro-2*H*-1,2,4-triazepine (**3d**) is of particular interest, because it provides access to tetrahydro-2*H*-1,2,4-triazepines having a phenolic Mannich base as a structural unit. This has been achieved by treating **3d** with dimethylamine or piperidine and formaldehyde to



8	Ar^1	R
a	Ph	H
b	C_6H_4-4-NO_2	-CH=CHPh

Scheme 3.



Scheme 4.

give the mono-(Mannich base) **9** or the bis-(Mannich bases) **10** and **11** depending on the molar ratio of the reactants (Scheme 4).

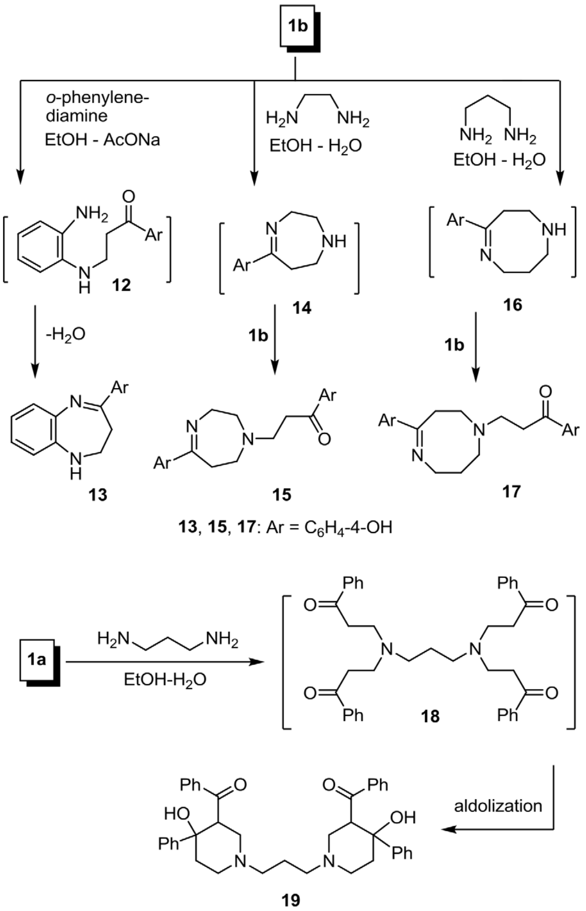
The structures of compounds **9**–**11** are supported by analytical and spectral data. The ^{1}H NMR specrum of **9** displays four singlets at δ = 2.38 (NMe_2), 3.67 (Ar-CH_2N), 5.17 (3-H$_2$), and 6.71 (ArOH), and two triplets at δ = 3.62 (5-H$_2$) and 3.34 (6-H$_2$). The mass spectra of **9**, **10** and **11** revealed molecular ion peaks at m/z = 400, 458 [M+1]$^+$ and 537, respectively, and fragmentation patterns which supported their structures.

In connection with the present study, the transamination reaction between **1b** and *o*-phenylenediamine afforded the 2,3-dihydro-4-(*p*-hydroxyphenyl)-1*H*-1,5-benzodiazepine **13**. It is believed that the initially formed intermediate **12** readily undergoes cyclodehydration to give **13**, as confirmed by analytical and spectral data (Scheme 5).

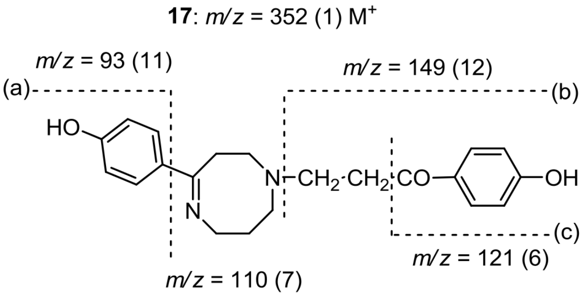
On the other hand, the reaction of **1b** with ethylenediamine led to the formation of 2,3,6,7-tetrahydro-1-(β-4-hydroxybenzoylethyl)-5-(4-hydroxyphenyl)-1*H*-1,4-diazepine (**15**) rather than the tetrahydro-1,4-diazepine **14**, which would be the expected product. Obviously, **15** was formed *via* the intermediacy of the non-isolable tetrahydro-1,4-diazepine **14**, resulting from the cyclocondensation reaction of ethylenediamine with **1b**, which readily reacts further with a second molecule of **1b** *via* transamination to afford the new Mannich base **15**. The reaction of **1b** with 1,3-diaminopropane proceeded quite analogously to afford 3,4,7,8-tetrahydro-1-(β-4-hydroxybenzoylethyl)-6-(4-hydroxyphenyl)-2*H*-1,5-diazocine (**17**). The reaction of **1b** with ethylenediamine and 1,3-diaminopropane is of particular interest, because it offers access with good yields to the new tetrahydro-1,4-diazepine and tetrahydro-1,5-diazocine Mannich bases **15** and **17**, respectively.

The mass spectrum of **17** exhibited a molecular ion peak at m/z = 352 [M]$^+$ and a peak at m/z = 110 due to the tetrahydro-1,5-diazocine unit. The side chain can be identified by two peaks at m/z = 121 and 149 (Scheme 6). The formation of **15** and **17** is in line with our recent report [16] on the reaction of bis-ketonic Mannich bases with ethylenediamine.

On the other hand, the reaction of **1a** with 1,3-diaminopropane in a molar ratio of 4 : 1 takes a different course. The reaction proceeded smoothly to



Scheme 5.



Scheme 6.

give 1,3-bis(3-benzoyl-4-hydroxy-4-phenylpiperidin-1-yl)propane (**19**), *via* the intermediacy of *N*,*N*,*N′*,*N′*-tetra(*β*-benzoylethyl)-1,3-diaminopropane (**18**), which undergoes intramolecular aldolization to give **19** as the end product. The identity of the product as the bi-(piperidinol) **19**, and not the isomeric tetraketo base **18**, was shown by the IR spectrum which displayed a strong OH band at 3421 cm^{-1} as well as the absorption band at 1629 cm^{-1} for C=O. The tendency of primary alkyl amines to undergo double *N*-alkylation with ketonic Mannich bases, and subsequent aldolization of the resulting bis-(ketonic Mannich bases) to *N*-alkyl piperidinols, has been previously reported [14–16]. Attempts to isolate the intermediate tetraketo base **18** were unsuccessful due to the ease with which such bases undergo aldolization even at r. t.

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^1H and ^{13}C NMR data were obtained in $CDCl_3$ or $[D_6]DMSO$ solution on a Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a GC-MS QP-1000 EX Shimadzu instrument. The course of the reaction and the purity of the synthesized compounds were monitored by TLC using EM science silica gel-coated plates with visualization by irradiation with an ultraviolet lamp. Compounds **3f**, **8b**, **17**, and **19** are of limited solubility in common ^1H NMR solvents. Compounds **1b** [28], **2a**–**d** [27], **2c** and **e** [16], **3d** [16], and **6** [9] were prepared as previously described.

*β-Arylaminopropiophenones **2f**–**h***

A mixture of **1a** (2.13 g, 10 mmol) or **1b** (2.29 g, 10 mmol) and the appropriate amine (10 mmol) in 50 % aqueous ethanol (80 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **2f**–**h**.

*4-(3-Oxo-3-phenylpropylamino)benzamide (**2f**)*

M. p. 198 °C. Yield 75 % (colorless crystals). – IR (KBr): ν = 3399 (NH), 3360 (CONH), 1666 (CO), 1592, 1388, 1326, 1060 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.46 (t, 2H, $COCH_2CH_2N$), 3.31 (t, 2H, $COCH_2CH_2N$), 4.40 (s, 1H, ArN*H*), 7.19–7.73 (m, 9H, aromatic), 8.11 (br. s, 2H, $CONH_2$). – MS (EI, 70 eV): *m*/*z* (%) = 268 (18) $[M]^+$, 267 (2) $[M–1]^+$, 149 (100) $[CH_2NH\text{-}C_6H_4\text{-}CONH_2]^+$, 136 (7), 133 (3), 132 (12), 120 (11), 105 (37), 77 (32). – $C_{16}H_{16}N_2O_2$ (268.31): calcd. C 71.62, H 6.01, N 10.44; found C 71.59, H 5.58, N 10.21.

*4-(3-Oxo-3-phenylpropylamino)benzenesulfonamide (**2g**)*

M. p. 220 °C. Yield 60 % (colorless crystals). – IR (KBr): ν = 3410 (NH), 3380 (SO_2NH), 1671 (CO), 1469, 1330, 1226, 1145 cm^{-1}. – MS (EI, 70 eV): *m*/*z* (%) = 304 (14) $[M]^+$, 305 (3) $[M+1]^+$, 303 (2) $[M–1]^+$, 185 (100) $[CH_2NH\text{-}C_6H_4\text{-}SO_2NH_2]^+$, 172 (10), 156 (6), 133 (4), 119 (10) $[PhCOCH_2]^+$, 105 (56) $[PhCO]^+$, 77 (39). – $C_{15}H_{16}N_2O_3S$ (304.36): calcd. C 59.19, H 5.30, N 9.20; found C 59.09, H 5.21, N 9.11.

*3-(4-Hydroxyphenylamino)-1-(4-hydroxyphenyl)propan-1-one (**2h**)*

M. p. 185 °C. Yield 57 % (yellow crystals). – IR (KBr): ν = 3439 (OH), 3366 (NH), 1664 (CO), 1492, 1338, 1226, 1120 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.34 (t, 2H, $COCH_2CH_2N$), 3.42 (t, 2H, $COCH_2CH_2N$), 4.46 (s, 1H, ArN*H*), 7.11–7.82 (m, 8H, aromatic), 11.77 (s, 2H, 2× O*H*). – MS (EI, 70 eV): *m*/*z* (%) = 257 (10) $[M]^+$, 148 (37) $[HO\text{-}C_6H_4\text{-}COCH{=}CH_2]^+$, 121 (100) $[HO\text{-}C_6H_4\text{-}CO]^+$, 109 (43), 93 (25). – $C_{15}H_{15}NO_3$ (257.28): calcd. C 70.02, H 5.88, N 5.44; found C 69.95, H 5.82, N 5.31.

*3,4,5,6-Tetrahydro-2,4,7-triaryl-2H-1,2,4-triazepines **3a**–**f***

A solution of the appropriate *β*-(arylamino)propiophenone (**2a**–**h**) (5 mmol) and *p*-nitrophenylhydrazine (0.77 g, 5 mmol) or phenylhydrazine (0.54 g, 5 mmol) in ethanol (30 mL) was heated on a steam bath for 20 min, then formalin (37 %, 0.6 mL, 8 mmol) and acetic acid (0.1 mL) were added. The reaction mixture was heated for 5 min, and the product obtained on cooling was filtered and crystallized from the appropriate solvent to give **3a**–**f**.

*3,4,5,6-Tetrahydro-2-(p-nitrophenyl)-7-phenyl-4-p-tolyl-2H-1,2,4-triazepine (**3a**)*

M. p. 196 °C (ethanol). Yield 71 % (yellow crystals). – IR (KBr): ν = 1610 (C=N), 1520, 1365, 1238, 1210, 870 cm^{-1}. – ^{1}H NMR (CDCl$_3$): δ = 2.33 (s, 3H, Ar*Me*), 3.38 (t, 2H, 6-*H*$_2$), 3.65 (t, 2H, 5-*H*$_2$), 5.35 (s, 2H, 3-*H*$_2$), 6.88 – 8.08 (m, 13H, aromatic). – ^{13}C NMR (CDCl$_3$): δ = 20.51 (CH$_3$), 30.98 (C-6), 45.64 (C-5), 71.62 (C-3), 112.88, 116.60, 126.40, 128.54, 129.14, 130.12, 132.47, 138.10, 140.03, 146.01, 152.31 (all Ar-*C*), 154.94 (C-7). – MS (EI, 70 eV): m/z (%) = 386 (3) [M]$^+$, 387 (1) [M+1]$^+$, 268 (17), 309 (5), 236 (100) [M–(NO$_2$-C$_6$H$_4$-N=CH$_2$)]$^+$, 218 (11), 173 (3), 150 (4), 122 (12), 119 (62) [Me-C$_6$H$_4$-N=CH$_2$]$^+$, 120 (31), 105 (54), 91 (79), 77 (36). – $C_{23}H_{22}N_4O_2$ (386.45): calcd. C 71.48, H 5.74, N 14.50; found C 71.40, H 5.68, N 14.44.

*3,4,5,6-Tetrahydro-4-(p-bromophenyl)-2-(p-nitrophenyl)-7-phenyl-2H-1,2,4-triazepine (**3b**)*

M. p. 188 °C (ethanol). Yield 60 % (reddish crystals). – IR (KBr): ν = 1615 (C=N), 1529, 1355, 1218, 1110, 875 cm^{-1}. – ^{1}H NMR (CDCl$_3$): δ = 3.32 (t, 2H, 6-*H*$_2$), 3.57 (t, 2H, 5-*H*$_2$), 5.15 (s, 2H, 3-*H*$_2$), 7.17 – 8.24 (m, 13H, aromatic). – MS (EI, 70 eV): m/z (%) = 451 (14) [M]$^+$, 452 (9) [M+1]$^+$, 301 (100), 300 (93) [M–(NO$_2$-C$_6$H$_4$-N=CH$_2$)]$^+$, 267 (38) [M–(Br-C$_6$H$_4$-N=CH$_2$)]$^+$, 220 (27), 207 (73), 184 (25), 156 (12), 77 (43). – $C_{22}H_{19}BrN_4O_2$ (451.32): calcd. C 58.55, H 4.24, N 12.41; found C 58.48, H 4.18, N 12.21.

*3,4,5,6-Tetrahydro-4-(p-chlorophenyl)-2-(p-nitrophenyl)-7-phenyl-2H-1,2,4-triazepine (**3c**)*

M. p. 190 °C (ethanol). Yield 65 % (reddish crystals). – IR (KBr): ν = 1617 (C=N), 1537, 1326, 1209, 1100, 855 cm^{-1}. – ^{1}H NMR (CDCl$_3$): δ = 3.28 (t, 2H, 6-*H*$_2$), 3.51 (t, 2H, 5-*H*$_2$), 4.86 (s, 2H, 3-*H*$_2$), 7.21 – 8.12 (m, 13H, aromatic). – MS (EI, 70 eV): m/z (%) = 406 (14) [M]$^+$, 407 (3) [M+1]$^+$, 408 (4) [M+2]$^+$, 267 (26), 208 (19), 207 (100) [M–(Ph+C$_6$H$_4$-NO$_2$)]$^+$, 139 (10), 122 (8), 111 (14), 77 (16). – $C_{22}H_{19}ClN_4O_2$ (406.86): calcd. C 64.94, H 4.71, N 13.77; found C 64.88, H 4.60, N 13.65.

*4-(2,3,5,6-Tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)-benzamide (**3e**)*

M. p. 215 °C (DMF). Yield 53 % (pale-yellow crystals). – IR (KBr): ν = 3359 (CONH$_2$), 1645 (CO), 1610 (C=N), 1517, 1436, 1225, 1142, 879 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.26 (t, 2H, 6-*H*$_2$), 3.87 (t, 2H, 5-*H*$_2$), 5.43 (s, 2H, 3-*H*$_2$), 6.66 (br. s, 2H, CON*H*$_2$), 7.25 – 7.84 (m, 14H, aromatic). – MS (EI, 70 eV): m/z (%) = 370 (4) [M]$^+$, 371 (2) [M+1]$^+$, 369 (1) [M–1]$^+$, 265 (100) [M–PhN=N]$^+$, 222 (65), 221 (93), 149 (53), 105 (35), 77 (81). – $C_{23}H_{22}N_4O$ (370.45): calcd. C 74.57, H 5.99, N 15.12; found C 74.50, H 6.01, N 15.04.

*3,4,5,6-Tetrahydro-4,7-di(p-hydroxyphenyl)-2-phenyl-2H-1,2,4-triazepine (**3f**)*

M. p. 199 °C (washed with boiling ethanol). Yield 50 % (dark-brown powder). – IR (KBr): ν = 3410–3329 (OH), 1610 (C=N), 1523, 1456, 1215, 1112, 956 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 360 (51) [M+1]$^+$, 238 (62) [M–(HO-C$_6$H$_4$-N=CH$_2$)]$^+$, 173 (58), 121 (33) [HO-C$_6$H$_4$-N=CH$_2$]$^+$, 97 (100), 96 (67), 95 (56), 93 (83), 77 (15). – $C_{22}H_{21}N_3O_2$ (359.42): calcd. C 73.52, H 5.89, N 11.69; found C 73.49, H 5.80, N 11.62.

*3,4,5,6-Tetrahydro-4-(p-methoxyphenyl)-2-benzenesulfonyl-7-phenyl-2H-1,2,4-triazepine (**4**)*

A solution of **2b** (0.64 g, 2.5 mmol) and benzenesulfonyl hydrazide (0.43 g, 2.5 mmol) in ethanol (30 mL) was heated on a steam bath for 20 min. After standing at r. t. for 2 h, formalin (37 %, 0.3 mL, 4 mmol) and acetic acid (0.1 mL) were added. The reaction mixture was heated for 5 min, and the product obtained on cooling was filtered and crystallized from ethanol to give **4**. M. p. 134 °C. Yield 60 % (pale-yellow crystals). – IR (KBr): ν = 1614 (C=N), 1515, 1478, 1362, 1165, 849 cm^{-1}. – ^{1}H NMR (CDCl$_3$): δ = 3.22 (t, 2H, 6-*H*$_2$), 3.52 (t, 2H, 5-*H*$_2$), 3.83 (s, 3H, O*Me*), 5.51 (s, 2H, 3-*H*$_2$), 7.12 – 7.77 (m, 14H, aromatic). – ^{13}C NMR (CDCl$_3$): δ = 54.67 (OMe), 29.97 (C-6), 46.76(C-5), 72.78 (C-3), 111.98, 116.10, 126.34, 128.14, 129.10, 130.11, 132.17, 138.11, 146.22, 152.41 (all Ar-*C*), 156.44 (C-7). – MS (EI, 70 eV): m/z (%) = 421 (2) [M]$^+$, 422 (1) [M+1]$^+$, 252 (40), 251 (100), 173 (48), 174 (18), 142 (30), 107 (16) [C$_6$H$_4$-OMe)]$^+$, 97 (8), 77 (59). – $C_{23}H_{23}N_3O_3S$ (421.51): calcd. C 65.54, H 5.50, N 9.97; found C 65.48, H 5.47, N 9.88.

*3,4,5,6-Tetrahydro-2,7-diphenyl-3-styryl-4-p-tolyl-2H-1,2,4-triazepine (**5**)*

This compound was obtained from **2a** (0.60 g, 2.5 mmol) and phenylhydrazine (0.27 g, 2.5 mmol) in the manner described for the synthesis of **3a** – **f**, except for the use of cinnamaldehyde (0.40 g, 3 mmol) instead of formaldehyde. The product was crystallized from ethanol to give **5**. M. p. 180 °C. Yield 65 % (pale-yellow crystals). – IR (KBr): ν = 1610 (C=N), 1577, 1458, 1322, 1222, 1145, 870 cm^{-1}. – ^{1}H NMR (CDCl$_3$): δ = 2.31 (s, 3H, Ar*Me*), 3.36 (t, 2H, 6-*H*$_2$), 3.58 (t, 2H, 5-*H*$_2$), 4.87 (d, 2H, 3-*H*$_2$), 6.22 (d, 1H, -C*H*=CH-Ph), 6.61 (d, 1H, -CH=C*H*-Ph), 6.83–7.68 (m, 19H, aromatic). – ^{13}C NMR (CDCl$_3$): δ = 21.81 (Me), 31.10 (C-6), 47.56 (C-5), 72.18 (C-3), 113.44, 114.36, 117.18, 124.44 (Ph-CH=*CH*), 127.12, 128.11, 129.12, 131.22 (Ph-*CH*=CH), 134.44, 138.33, 142.63, 147.41 (all Ar-*C*), 157.27 (C-7). – MS (EI, 70 eV): m/z (%) = 443 (58) [M]$^+$, 442 (50) [M–1]$^+$, 350 (59) [M–(p-tolyl)]$^+$, 264 (55), 131 (29), 119 (100) [PhC(=NH)Me]$^+$, 117 (88), 103 (47), 91 (45) [C$_6$H$_4$-

Me]$^+$. – $C_{31}H_{29}N_3$ (443.58): calcd. C 83.94, H 6.59, N 9.47; found C 83.88, H 6.56, N 9.39.

*1-(p-Anisyl)-5-(p-tolylamino)-1-penten-3-one (**7**)*

A mixture of **6** (2.15 g, 8 mmol) and *p*-toluidine (0.85 g, 8 mmol) in 50 % aqueous ethanol (80 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **6**. M. p. 110 °C. Yield 85 % (yellow crystals). – IR (KBr): ν = 3382 (NH), 1653 (CO), 1605, 1557, 1460, 1319, 1209, 1105, 868 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3H, Ar*Me*), 2.96 (t, 2H, COC*H*$_2$CH$_2$N), 3.52 (t, 2H, COCH$_2$C*H*$_2$N), 3.52 (s, 3H O*Me*), 6.64 (s, 1H, ArN*H*), 6.59 (d, 2H, Ar-CH=C*H*-CO), 6.93 (d, 2H, Ar-C*H*=CH-CO), 7.12 – 7.58 (m, 8H, aromatic). – $C_{19}H_{21}NO_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.18, H 7.10, N 4.69.

*7-(4-Methoxystyryl)-3,4,5,6-tetrahydro-2-phenyl-4-p-tolyl-2H-1,2,4-triazepine (**8a**)*

This compound was obtained from equimolar amounts of **6**, phenylhydrazine and formaldehyde (5 mmol) in ethanol (40 mL), following the procedure described for the synthesis of **3a** – **f**. The product was crystallized from ethanol to give **8a**. M. p. 184 °C. Yield 55 % (yellow crystals). – IR (KBr): ν = 1617 (C=N), 1597, 1489, 1308, 1229, 1114, 1082, 847 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 3H, Ar*Me*), 3.42 (t, 2H, 6-*H*$_2$), 3.60 (s, 3H, O*Me*), 3.94 (t, 2H, 5-*H*$_2$), 4.58 (s, 2H, 3-*H*$_2$), 6.89 (d, 2H, Ar-CH=C*H*-), 6.96 (d, 2H, Ar-C*H*=CH-), 7.02–7.33 (m, 8H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 22.11 (Me), 32.18 (C-6), 48.44 (C-5), 54.23 (OMe), 79.89 (C-3), 113.33, 114.28, 116.88, 127.14, 129.44, 130.10, 136.47 (Ar-CH=*CH*), 138.33 (Ar-*CH*=CH), 142.63, 146.41, 156.10, 158.31 (all Ar-*C*), 154.77 (C-7). – $C_{26}H_{27}N_3O$ (397.51): calcd. C 78.56, H 6.85, N 10.57; found C 78.50, H 6.77, N 10.49.

*7-(4-Methoxystyryl)-3,4,5,6-tetrahydro-2-(4-nitrophenyl)3-styryl-4-p-tolyl-2H-1,2,4-triazepine (**8b**)*

This compound was obtained from equimolar amounts of **6**, *p*-nitrophenylhydrazine and cinnamaldehyde (5 mmol) in ethanol (80 mL), in the manner described for the synthesis of **3a** – **f**. The product obtained was filtered and washed with boiling ethanol (3 × 15 mL) to give **8b**. M. p. 265 °C. Yield 33 % (yellow powder). – IR (KBr): ν = 1622 (C=N), 1588, 1459, 1326, 1232, 1119, 1066, 865 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 530 (46) [M–Me]$^+$, 213 (67), 134 (52), 107 (6), 103 (61), 98 (70) [triazepine unit]$^+$, 84 (100) [triazepine unit–(CH$_2$)]$^+$. – $C_{34}H_{32}N_4O_3$ (544.64): calcd. C 74.98, H 5.92, N 10.29; found C 74.91, H 5.89, N 10.21.

*2-(Dimethylaminomethyl)-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (**9**)*

A solution of **3d** [16] (1.37 g, 4 mmol), formalin (37 %, 0.4 mL, 5 mmol) and dimethylamine (40 %, 0.56 mL, 5 mmol) in ethanol (50 mL) was refluxed for 6 h. After standing at r. t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **9**. M. p. 145 °C. – Yield 72 % (colorless crystals). – IR (KBr): ν = 3373 (OH), 1605 (C=N), 1588, 1454, 1371, 1271, 1113, 1073 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 6H, N(*Me*)$_2$), 3.33 (t, 2H, 6-*H*$_2$), 3.60 (t, 2H, 5-*H*$_2$), 3.67 (s, 2H, C*H*$_2$N), 5.17 (s, 2H, 3-*H*$_2$), 12.01 (s, 1H, O*H*), 6.88 – 7.85 (m, 13H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 30.98 (C-6), 44.21 (C-5), 46.61 (NMe), 62.44 (CH$_2$N), 74.89 (C-3), 115.32, 117.12, 118.89, 119.42, 120.54, 126.11, 126.29, 128.29, 128.56, 128.84, 139.42, 141.74, 148.33, (all Ar-*C*), 152.09 (C-7). – MS (EI, 70 eV): m/z (%) = 400 (4) [M]$^+$, 401 (1) [M+1]$^+$, 250 (59) [M–(C$_6$H$_3$-OH+CH$_2$Me$_2$)]$^+$, 251 (13), 93 (7), 77 (100), 58 (15) [CH$_2$NMe$_2$]$^+$. – $C_{25}H_{28}N_4O$ (400.52): calcd. C 74.97, H 7.05, N 13.99; found C 74.91, H 6.97, N 13.90.

*2,6-Bis-(dimethylaminomethyl)-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (**10**)*

Procedure A: This compound was obtained from equimolar amounts of **9**, formalin and dimethylamine (5 mmol) in ethanol (50 mL), following the procedure described for the synthesis of **9**. The product was crystallized from ethanol to give **10**. M. p. 190 °C. Yield 55 % (colorless crystals). – IR (KBr): ν = 3370 (OH), 1612 (C=N), 1577, 1446, 1335, 1221, 1108, 1079 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 12H, 2× *NMe*$_2$), 3.34 (t, 2H, 6-*H*$_2$), 3.96 (t, 2H, 5-*H*$_2$), 4.17 (s, 4H, 2× C*H*$_2$N), 5.31 (s, 2H, 3-*H*$_2$), 12.11 (s, 1H, O*H*), 6.94 – 7.75 (m, 12H, aromatic). – MS (EI, 70 eV): m/z (%) = 457 (6) [M]$^+$, 456 (18) [M–1]$^+$, 370 (6), 222 (40), 233 (27), 248 (10), 263 (100) [M–(Ph=N-NPh)]$^+$, 264 (75), 104 (23), 77 (19), 57 (34). – $C_{28}H_{35}N_5O$ (457.61): calcd. C 73.49, H 7.71, N 15.30; found C 73.41, H 7.69, N 15.22.

Procedure B: A solution of **3d** (1.37 g, 4 mmol), formalin (37 %, 0.8 mL, 10 mmol) and dimethylamine (40 %, 1.12 mL, 10 mmol) in ethanol (50 mL) was refluxed for 8 h. After standing at r. t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **10**. M. p. 190 – 192 °C. Yield 60 %. The structure was confirmed by a comparison of ^{1}H NMR data, m. p. and TLC with that from Procedure A.

*2,6-[Bis-(piperidin-1-ylmethyl)]-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (**11**)*

This compound was obtained from **3d** (1.37 g, 4 mmol), formalin (37 %, 1 mL, 12 mmol) and piperidine (1 g, 12 mmol), following the procedure described for the synthesis of **9**. The product was crystallized from ethanol to give **11**. M. p. 142 °C. Yield 49 % (colorless crystals). – IR (KBr): ν = 3377 (OH), 1618 (C=N), 1557, 1426, 1355, 1216, 1100, 1050 $\mathrm{cm^{-1}}$. – ^{1}H NMR ($CDCl_3$): δ = 1.52 – 1.67 [m, 12H, 2× (3-H_2, 4-H_2, 5-H_2) of piperidine], 2.55 (m, 4H, 2-H_2, 6-H_2 of piperidine), 3.35 (t, 2H, 6-H_2), 3.60 (t, 2H, 5-H_2), 3.68 (s, 4H, 2× CH_2N), 5.16 (s, 2H, 3-H_2), 11.11 (s, 1H, O*H*), 6.85 – 7.86 (m, 12H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 23.92 (C-3, C-4, C-5 of piperidine), 25.72 (C-6), 31.21 (C-5), 46.65 (C-2, C-6 of piperidine), 53.85 (CH_2N), 75.10 (C-3), 115.33, 118.82, 120.54, 126.12, 126.29, 128.28, 128.54, 128.82, 139.45, 142.45, 148.98 (all Ar-*C*), 150.54 (C-7). – MS (EI, 70 eV): m/z (%) = 537 (1) $[M]^+$, 440 (61) $[M–(CH_2NC_5H_{10})+H]^+$, 250 (100) $[M–(C_6H_2OH(CH_2NC_5H_{10})_2]^+$, 251 (22), 222 (16), 204 (10), 84 (4) $[NC_5H_{10}]^+$. – $C_{34}H_{43}N_5O$ (537.74): calcd. C 75.94, H 8.06, N 13.02; found C 75.91, H 7.98, N 12.97.

*2,3-Dihydro-4-(p-hydroxyphenyl)-1H-1,5-benzodiazepine (**13**)*

A mixture of **1b** (1.14 g, 5 mmol), *o*-phenylenediamine (0.54 g, 5 mmol) and fused sodium acetate (1.5 g) in absolute ethanol (80 mL) was refluxed for 6 h. The crystalline product was filtered and washed with boiling ethanol-acetone (1 : 1) to give **13**. M. p. 134 °C. Yield 60 % (yellow crystals). – IR (KBr): ν = 3394 (OH), 3360 (NH), 1611 (C=N), 1513, 1493, 1344, 1144, 810 $\mathrm{cm^{-1}}$. – ^{1}H NMR ($CDCl_3$): δ = 3.11 (m, 2H, 3-H_2), 3.54 (m, 2H, 2-H_2), 6.16 (br. s, 1H, N*H*), 6.84 – 7.83 (m, 8H, aromatic), 8.22 (br. s, 1H, O*H*). – ^{13}C NMR ($CDCl_3$): δ = 32.16 (C-3), 47.11 (C-2), 113.44, 119.20, 123.24, 127.81, 130.35, 134.45 (all Ar-*C*), 138.11 (C-5a), 138.55 (C-5b), 168.11 (C-4). – MS (EI, 70 eV): m/z (%) = 238 (1) $[M]^+$, 222 (2), 210 (4), 121 (9), 120 (100), 119 (12), 107 (31), 106 (27), 92 (19), 77 (35). – $C_{15}H_{14}N_2O$ (238.28): calcd. C 75.61, H 5.92, N 11.76; found C 75.55, H 5.88, N 11.69.

*2,3,6,7-Tetrahydro-1-(β-4-hydroxybenzoylethyl)-5-(4-hydroxyphenyl)-1H-1,4-diazepine (**15**)*

A mixture of **1b** (1.14 g, 5 mmol) and ethylenediamine (0.3 g, 5 mmol) in 50 % aqueous ethanol (50 mL) was refluxed for 3 h. After standing at r. t. for 24 h, the product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **15**. M. p. 255 °C. Yield 52 % (pale-yellow powder). – IR (KBr): ν = 3422 (OH), 1610 (C=N), 1510, 1349, 1036, 1008, 814 $\mathrm{cm^{-1}}$. – ^{1}H NMR ([D_6] DMSO): δ = 2.48 (m, 2H, 7-H_2), 2.52 (m, 2H, COC$H_2$$CH_2$N), 2.64 (m, 2H, 2-$H_2$), 2.96 (m, 2H, COC$H_2CH_2$N), 3.28 (m, 2H, 6-$H_2$), 3.56 (m, 2H, 3-$H_2$), 6.78 – 7.77 (m, 8H, aromatic), 10.11 (br. s, 1H, O*H*). – $C_{20}H_{22}N_2O_3$ (338.40): calcd. C 70.99, H 6.55, N 8.28; found C 70.91, H 6.49, N 8.20.

*3,4,7,8-Tetrahydro-1-(β-4-hydroxybenzoylethyl)-6-(4-hydroxyphenyl)-2H-1,5-diazocine (**17**)*

This compound was obtained from equimolar amounts of **1b** and 1,3-diaminopropane (5 mmol), following the procedure described for the synthesis of **15**. The product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **17**. M. p. 260 °C. Yield 33 % (yellow powder). – IR (KBr): ν = 3940 (OH), 1619 (C=N), 1479, 1407, 1336, 1217, 1102 $\mathrm{cm^{-1}}$. – MS (EI, 70 eV): m/z (%) = 352 (1) $[M]^+$, 149 (12) $[HO\text{-}C_6H_4\text{-}COCH_2CH_2]^+$, 121 (6), 119, 110 (7), 109 (10), 111(11), 93 (11), 85 (28), 71 (43), 69 (100) $[(C_4H_7)N]^+$, 55 (69). – $C_{21}H_{24}N_2O_3$ (352.43): calcd. C 71.57, H 6.86, N 7.95; found C 71.50, H 6.79, N 7.87.

*1,3-Bis(3-benzoyl-4-hydroxy-4-phenylpiperidin-1-yl)propane (**19**)*

This compound was obtained from **1a** (3.83 g, 18 mmol) and 1,3-diaminopropane (0.33 g, 4.5 mmol), following the procedure described for the synthesis of **15**. The product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **19**. M. p. 256 °C. Yield 71 % (colorless powder). – IR (KBr): ν = 3421 (OH), 1629 (CO), 1600, 1483, 1407, 1216, 1102, 941 $\mathrm{cm^{-1}}$. – MS (EI, 70 eV): m/z (%) = 601 (58) $[M–1]^+$, 416 (47), 275 (57), 228 (48), 206 (63), 207 (39), 185 (83), 158 (58), 110 (100), 105 (27), 98 (87), 96 (60), 77 (35). – $C_{39}H_{42}N_2O_4$ (602.76): calcd. C 77.71, H 7.02, N 4.65; found C 77.70, H 6.98, N 4.58.

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