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Synthesis of Some New Bis(Mannich Bases) Related to Succinimide and Benzamide and Evaluation of Their Antibacterial and Antifungal Activities

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Abstract

Treatment of Succinimide (1) with the appropriate aldehyde and amine afforded Mannich bases 2a-f, 3 and 4 and the bis(Mannich bases) 5-8. The Mannich bases 2a-fwere used as precursors in synthesis of the new mixed bis(Mannich bases) 9a-c, 10a-c, 11a,b and 12a,b. Mannich reaction of benzamide (13) and the mixed diamide 17 with the appropriate aldehyde and amine gave the Mannich bases 14-16, 18 and 19. In addition, *N*-amidomethylation of tetrahydrocarbazole (21) and its benzo derivative 23 with the amidic Mannich bases 20a-c afforded compounds22a-c and 24a-c, respectively.

Keywords

Bis(Mannich Bases), Mixed Mannich Bases, Amidic Mannich Bases

1. Introduction

Mannich bases have an important interest in organic synthesis special in recent therapeutics research. The *N*-Mannich bases derived from *NH*-heterocycles and their derivatives have received significant attention due to their wide range of biological and pharmacological activities [1, 2, 3]. It has been reported that Mannich reaction of succinimide (pyrrolidine-2,5-dione) (1) with primary aromatic amines and formaldehyde was used for the synthesis of *N*-(arylaminomethyl)succinimides, which are useful for characterization of amines [4]. This reaction has been extended to *sec*. amines [5-7] and aliphatic primary amines [4, 8, 9].

A wide variety of *N*-Mannich bases of succinimide with different substitution patterns have been reported to possess anticonvulsant activity [10-12], whereas the literature survey indicates that the synthesis of mixed bis-Mannich bases was less widely synthesized, and has been reported in a limited number of cases which have antioxidant activity [13]. So the present work is concerned with attempts to extend the scope of the synthesis of a new series of bis(*N*-Mannich bases) and mixed bis(*N*-Mannich bases) related to succinimide and benzamide which have considerable synthetic and pharmaceutical interest.

2. Results and Discussion

The Mannich reaction of succinimide (pyrrolidine-2,5-dione) (1) with formaldehyde and the appropriate aromatic amine gave the corresponding1-(arylaminomethyl)pyrrolidine-2,5-diones (2a-f). In addition, the synthesis of *N*-Mannich bases of succinimide, based on its reaction with aromatic aldehyde and the appropriate amine, has been achieved by treating 1 with benzaldehyde

and aniline or morpholine to afford 1-(phenyl(phenylamino)-methyl)pyrroli-dine-2,5-dione (3) and 1-(morpholino(phenyl)-methyl)pyrrolidine-2,5-dione (4), respectively (Figure 1).

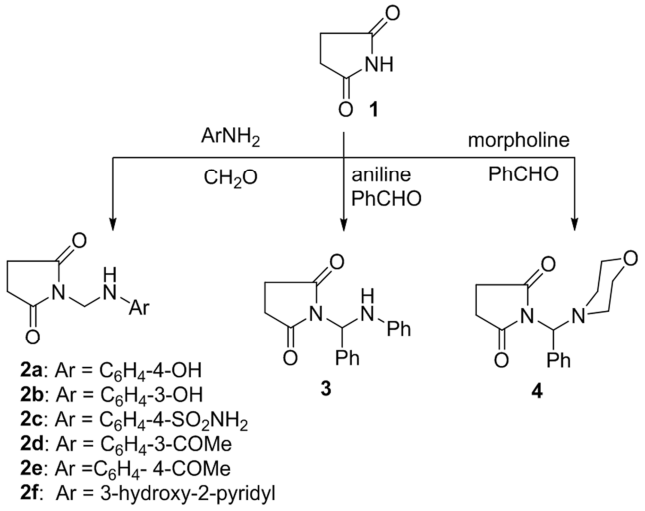


Figure 1. *Synthesis of different N-Mannich bases related to succinimide using different aromatic amines and also different type of aldehydes.*

The bis(Mannich base) *N,N'*-bis(pyrrolidine-2,5-dione-1-ylmethyl)-*p*-phenylenediamine (5) was obtained on using *p*-phenylenediamine in the Mannich reaction with 1. The possibility of using glyoxal in the Mannich reaction with 1 was also investigated as a route to bis(Mannich bases). Therefore, the synthesis of 1,1'-(1,2-bis(p-tolylamino)ethane-1,2-diyl)dipyrrolidine-2,5-dione (6) has been achieved by treating 1with *p*-toluidene and glyoxal in a molar ratio (2:2:1). Formulation of structures 5 and 6 was based on analytical and spectral data. Their mass spectra revealed molecular ion peaks at *m/z* = 330 and 434, respectively, and fragmentation patterns which indicated their structures (Figure 2).

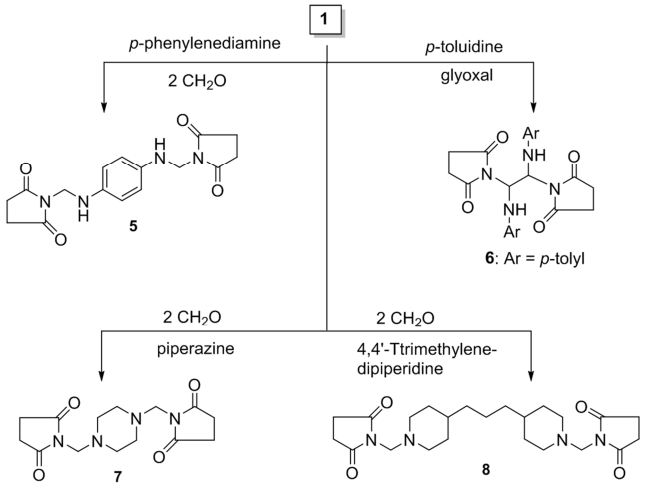


Figure 2. *Synthesis of N,N'-bis Mannich bases related to succinimide using different primary and secondary amines.*

The bis(Mannich base) 1,1'-(piperazine-1,4-diylbis(methylene))dipyrrolidine-2,5-dione (7) was obtained by Mannich reaction of 1 with piperazine and formaldehyde. A similar reaction takes place with 4,4'-trimethylene-dipiperidine, yielding the bis(Mannich base) (8).

The synthesis of mixed Mannich bases related to ketones was reported in a little number of cases [14-17]. Whereas, there is no report on the synthesis of mixed Mannich bases related to succinimide. In the present study, the Mannich bases 2a-e are used as precursors for the synthesis of certain mixed Mannich bases of pharmaceutical interest. Accordingly, Mannich reaction of the phenolic moiety of 2awith formaldehyde and the appropriate amine has been of considerable interest, because it provides access to the succinimido-phenolic hybrid Mannich bases 9a-c. Therefore, the synthesis of the mixed Mannich bases 9a-c has been achieved by treating 2a with formaldehyde and diethylamine and piperidine or morpholine, respectively. The structures of compounds 9a-c were supported by analytical and spectral data (Figure 3).

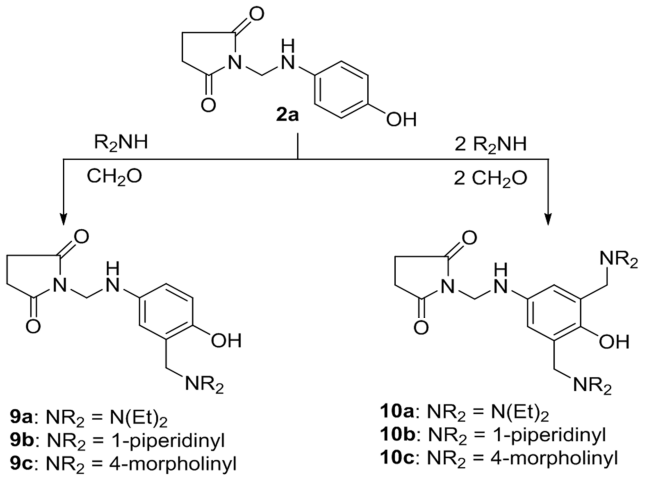


Figure 3. *Synthesis of mixed Mannich bases and mixed bis-Mannich bases using Mannich base related to succinimide.*

In addition, Mannich reaction of 2awith formaldehyde and diethylamine in a molar ratio (1:2:2) afforded 1-((3,5-bis((diethylamino)methyl)-4-hydroxyphenyl-amino)methyl)-pyrrolidine-2,5-dione (10a). A similar reaction of 2a with piperidine and morpholine led to the formation of the mixed Mannich bases 10b and 10c, incorporating a phenolic bis(Mannich base). The mass spectra of compounds 10a-ccontain peaks of the respective molecular ions.

In connection with this study, it was found that application of Mannich reaction to (2c) using formaldehyde and piperidine or morpholine, afforded 4-((2,5-dioxopyrrolidin-1-yl)methylamino)-*N*-(piperidin-1-ylmethyl)benzenesulfonamide (11a) and the *N*-(morpholinomethyl) analogue 11b, respectively. The scope of the synthesis of mixed Mannich bases has been extended by using 2e [4] in the Mannich reaction with piperidine and morpholine hydrochlorides to give 1-((4-(3-(piperidin-1-yl)propanoyl)phenylamino)-methyl)pyrrolidine-2,5-dione hydrochloride (12a) and the (3-morpholinopropanoyl) analogue 12b (Figure 4). The formation of the hybridized bis(Mannich bases) 9a-c, 10a-c and 12a-b is of particular interest, because the chemistry and biological activity of phenolic and ketonic Mannich bases has received considerable interest.

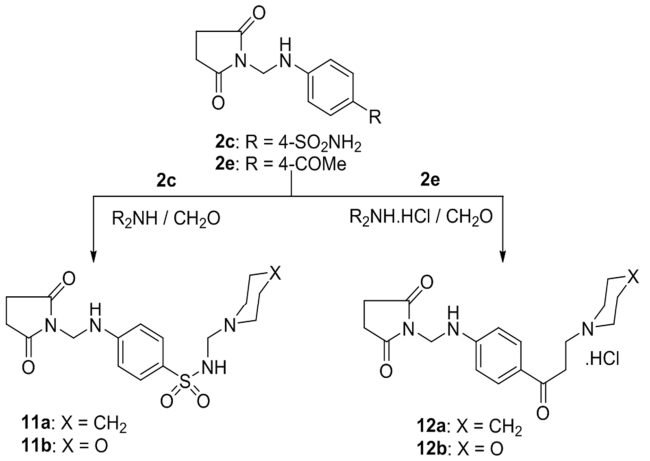


Figure 4. *Synthesis of hydrochloride mixed Mannich bases and sulfonamide mixed Mannich bases using Mannich base related to succinimide.*

In the course of this study, some new Mannich bases of alkaloidal nature incorporating benzamide as a structural unit were synthesized. Therefore, treating benzamide (13) with pyridine-3-carboxaldehyde and piperidine gave *N*-(piperidin-1-yl(pyridin-3-yl)methyl)benzamide (14). A similar reaction with piperazine afforded *N,N′*-(piperazine-1,4-diylbis(pyridin-3-ylmethylene))dibenzamide (15). The bis(Mannich base) 16 was obtained from 13, morpholine and terephthalaldehyde (Figure 5).

In addition, the mixed diamide 2-(morpholine-4-carbonyl)benzamide (17) [18] was subjected to Mannich reaction with piperidine and formaldehyde to give 2-(morpholine-4-carbonyl)-*N*-(piperidin-1-ylmethyl)benzamide (18). Whereas, *N,N′*-methylene bis(2-(morpholine-4-carbonyl)benzamide) (19) was obtained from 17 and formaldehyde (Figure 6).

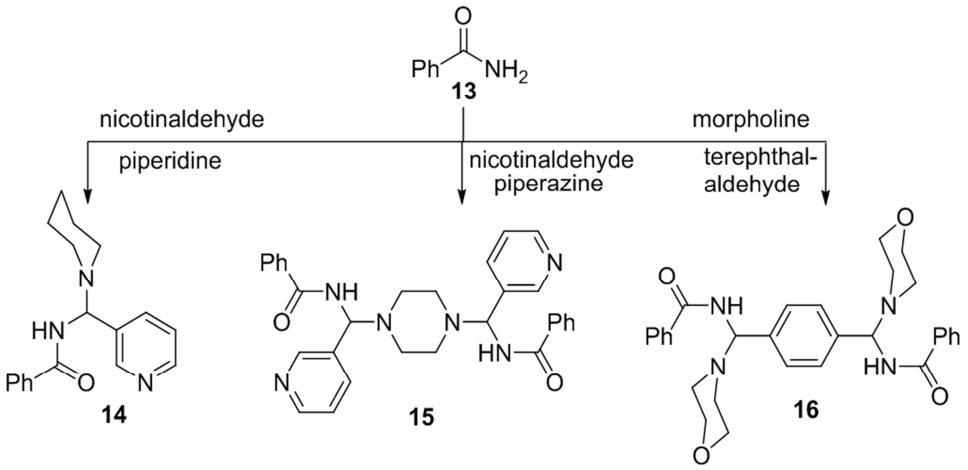


Figure 5. *Synthesis of mixed Mannich base and mixed bis-Mannich bases related to benzamide.*

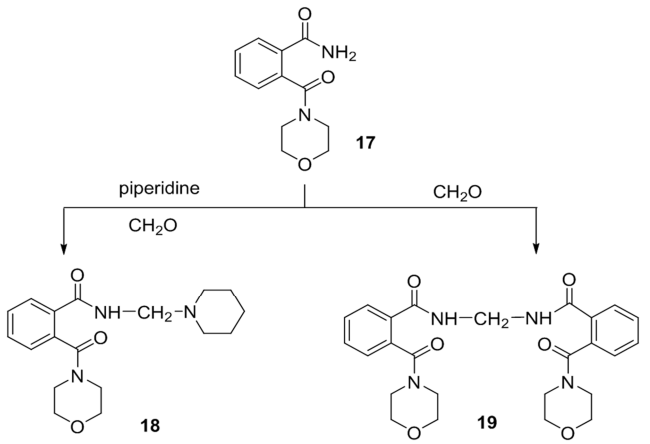


Figure 6. *Mannich reaction of the mixed diamide benzamide to afford amidic Mannich base and its reaction with formaldehyde only.*

On the other hand, *N*-amidomethylation of tetrahydrocarbazole (21) with the amidic Mannich bases 20a[19], 20b [20] and 20c [21] afforded the corresponding Mannich bases 22a-c, respectively. A similar reaction with 5,6-dihydro-11*H*-benzo[*a*]carbazole (23) [22] led to the formation of compounds 24a-c (Figure 7).

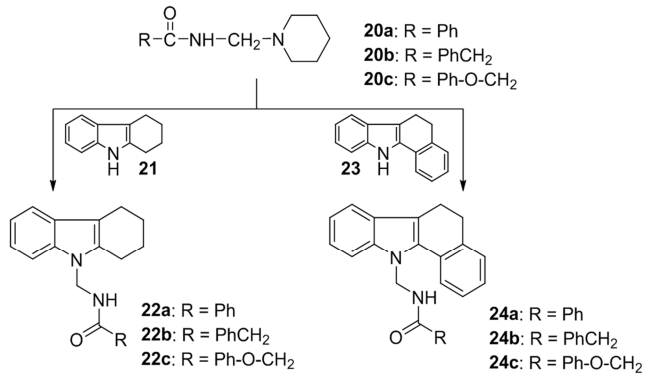


Figure 7. *Mannich reaction using tetrahydrocarbazole and benzo-carbazole as secondary amines.*

3. Experimental

The overall uncorrected melting points were measured on a (Gallenkamp electric melting point apparatus). Elemental microanalyses and Mass spectra were recorded at the Science Faculty, Azhar University, on a GC-MS QP-1000 EX Shimadzu instrument. Infrared spectra were determined on a Nicolet ISIO FTIR spectrometer. ^{1}H NMR and ^{13}C NMR data

were estimated in $CDCl_3$ or DMSO-d_6 solution on a JNM-ECA 500II(500 MHz) instrument using TMS as internal standard at Nuclear Magnetic Resonance Unit, Science Faculty, Mansoura University. Chemical shifts (δ) were recorded in ppm downfield from internal TMS. The chemicals and solvents were commercially purchased and used without any purification. The time of the reaction and the purity of the new compounds were monitored by TLC using irradiation with an ultraviolet lamp. Compounds 2b, 9a-c, 10a-c, 14, 22a-c and 24a-c are of limited solubility in ^{1}H-NMR solvents.

N-((Aryl amino)methyl)succinimides (2a- 2f)

A mixture of succinimide (0.5 g, 5 mmol) in EtOH (15 mL), formalin 36% (0.4 mL, 5 mmol) and the appropriate aromatic amine (5 mmol) was boiled under reflux for the appropriate time. The obtained material that precipitated on cooling was purified*via* crystallization from ethanol.

N-((4-Hydroxy phenyl amino)methyl)succinimide (2a)

M.p. 165-168°C. Yield 95% (dark brown powder); IR (KBr): υ = 3422 (OH), 3326 (NH), 1768, 1687 (CO), 1518, 1346, 1243 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 8.58 (s, 1H, O*H*), 6.47-6.64 (m, 4H, aromatic), 5.07 (s, 1H, N*H*), 4.67 (d, 2H, N-CH_2-NH), 2.58 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 222 (0.1) $[M+2]^+$, 221 (1) $[M+1]^+$, 220 (15) $[M]^+$, 121 (100), 109 (37), 99 (64). $C_{11}H_{12}N_2O_3$ (220.25): calcd. C 59.93%, H 5.45%, N 12.71%; found C 59.80%, H 5.38%, N 12.68%.

N-((3-Hydroxy phenyl amino)methyl)succinimide (2b)

M.p. > 300°C (washed with boiling ethanol). Yield 72% (deep yellow powder); IR (KBr): υ = 3377 (OH), 1771, 1703 (CO), 1620, 1511, 1183 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 220 (1) $[M]^+$, 218 (12) $[M-2]^+$, 217 (1) $[M-3]^+$, 149 (100), 91 (77). $C_{11}H_{12}N_2O_3$ (220.25): calcd. C 59.93%, H 5.45%, N 12.71%; found C 59.80%, H 5.38%, N 12.68%.

N-((4-Sulfanilamido)phenyl amino methyl)succinimide (2c)

M.p. 170°C. Yield 73% (white powder); IR (KBr): υ = 3376 (NH), 1775, 1699 (CO), 1603, 1154, 1094 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 7.93 (s, 2H, NH_2), 6.98 (s, 1H, N*H*), 6.73-7.63 (m, 4H, aromatic), 4.77 (d, 2H, N-CH_2-NH), 2.72 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 285 (1) $[M+2]^+$, 284 (1) $[M+1]^+$, 283 (7) $[M]^+$,184 (68), 168 (53), 104 (38), 99 (100), 92 (79). $C_{11}H_{13}N_3O_4S$ (283.30): calcd. C 46.59%, H 4.59%, N 14.83%; found C 46.40%, H 4.48%, N 14.73%.

N-((3-Acetyl phenyl amino)methyl)succinimide (2d)

M.p. 108°C. Yield 67% (brown powder); IR (KBr): υ = 3375 (NH), 1770, 1695, 1683 (CO), 1596, 1439, 1354, 1311, 1200 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.99-7.42 (m, 4H, aromatic), 5.80 (s, 1H, N*H*), 5.01 (s, 2H, N-CH_2-NH), 2.67 (s, 4H, 2 × CH_2 of succinimide), 2.56 ppm (s, 3H, CH_3); MS (EI, 70 eV): *m/z* (%) = 248 (1) $[M+2]^+$, 247 (6) $[M+1]^+$, 246 (40) $[M]^+$, 245 (28) $[M-1]^+$, 148 (45), 147 (100), 104 (60). $C_{13}H_{14}N_2O_3$ (246.29): calcd. C 63.34%, H 5.68%, N 11.37%; found C 63.20%, H 5.58%, N 11.33%.

N-((3-Hydroxy pyridin-2-yl amino)methyl)succinimide (2f)

M.p. > 300°C. Yield 55% (black powder); IR (KBr): υ = 3395 (OH), 1771, 1703 (CO), 1623 (C=N), 1515, 1184 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 8.12 (S, 1H, O*H*), 7.35 (s, 1H, N*H*), 6.28-7.49 (m, 3H, aromatic), 5.04 (d, 2H, N-CH_2-NH), 2.08 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 221 (5) [M]+, 220 (1) [M-1]+, 123 (13), 110 (71), 99 (61). $C_{10}H_{11}N_3O_3$ (221.24): calcd. C 54.24%, H 4.97%, N 18.98%; found C 54.20%, H 4.88%, N 18.90%.

N-((Phenyl amino)benzyl)succinimide (3)

Succinimide (1 g, 10 mmol) in EtOH (10 mL), benzaldehyde (1 mL, 10 mmol) and aniline (0.9 mL, 10 mmol) was stirred at r.t. and kept for 2 days; water (30 mL) was added for precipitation. The precipitate was filtered and crystallized from ethanol. M.p. 100-102°C. Yield 65% (pale brown plates); IR (KBr): υ = 3334 (NH), 1765, 1691 (CO), 1181, 693 cm-1; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1H, N*H*), 7.16-7.91 (m, 10H, aromatic), 6.74 (d, 1H, N-C*H*-NH), 2.76 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 181 (75), 180 (100), 77 (47). $C_{17}H_{16}N_2O_2$ (280.35): calcd. C 72.77%, H 5.71%, N 9.99%; found C 72.68%, H 5.66%, N 9.90%.

N-((Morpholino)benzyl)succinimide (4)

Succinimide (0.5 g, 5 mmol) in EtOH (10 mL), benzaldehyde (0.5 mL, 5 mmol) and morpholine (0.44 mL, 5 mmol) was boiled under reflux for 5 hrs, water (30 mL) was added for precipitation. The precipitate was crystallized from ethanol. M.p. 180°C. Yield 43% (fine white powder); IR (KBr): υ = 1776, 1705 (CO), 1329, 1112, 1007 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.25-7.88 (m, 5H, aromatic), 5.99 (s, 1H, N-C*H*-N), 3.78 (t, 4H, 2-H_2, 6-H_2 of morpholine), 2.99 (t, 4H, 3-H_2, 5-H_2 of morpholine), 2.75 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 276 (0.2) $[M+2]^+$, 275 (1) $[M+1]^+$, 274 (4) $[M]^+$, 273 (1) $[M-1]^+$, 188 (58), 176 (51), 105 (27), 86 (100). $C_{15}H_{18}N_2O_3$ (274.35): calcd. C 65.61%, H 6.56%, N 10.21%; found C 65.58%, H 6.45%, N 10.11%.

N,N′-Bis(pyrrolidine-2,5-dione-1-ylmethyl)-*p*-phenylenediamine (5)

A mixture of succinimide (0.4 g, 4 mmol) in EtOH (25 mL), formalin 36% (0.3 mL, 4 mmol) and *p*-phenylenediamine (0.2 g, 2 mmol) was boiled under reflux for 2 hrs. The material that precipitated during reflux was filtered and purified via crystallization from ethanol. M.p. 242°C. Yield 93% (gray powder); IR (KBr): υ = 3354 (NH), 1768, 1692 (CO), 1521, 1354, 1288, 1249, 1207, 827 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 6.46-6.84 (m, 4H, aromatic), 4.65 (d, 4H, 2 × N-CH_2-NH), 2.57 ppm (s, 8H, 4 × CH_2 of 2 × succinimide); MS (EI, 70 eV): *m/z* (%) = 330 (0.1) $[M]^+$, 327 (0.1) $[M-3]^+$, 231 (50), 99 (100), 77 (32). $C_{16}H_{18}N_4O_4$ (330.38): calcd. C 58.11%, H 5.45%, N 16.95%; found C 58.01%, H 5.36%, N 16.89%.

1,1'-(1,2-Bis(*p*-tolylamino)ethane-1,2-diyl)dipyrrolidine-2,5-dione (6)

A mixture of succinimide(0.5 g, 5 mmol) in EtOH (25 mL), Glyoxal 40% solution (0.5 mL, 3 mmol) and *p*-toluidine (0.54 g, 5 mmol) was boiled under reflux for 4 hrs. The obtained material was filtered and purified *via* crystallization from ethanol. M.p. 250-252°C. Yield 28% (faint pink

powder); IR (KBr): υ = 3349 (NH), 1773, 1708 (CO), 1523, 1349, 1274, 1171, 814 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 6.15-7.13 (m, 8H, aromatic), 5.77 (d, 2H, 2 × N-C*H*-NH), 2.48 (s, 8H, 4 × CH_2 of 2 × succinimide), 2.12 ppm (s, 6H, 2 × CH_3); ^{13}C-NMR (500 MHz, DMSO): δ = 179.47 (CO of succinimide), 147.20, 143.01, 137.63, 129.94, 126.99, 129.46, 121.51, 113.82 (all Ar-C), 61.43 (2 × CHNH), 29.53 (C-3, C-4 of succinimide), 20.73 ppm (CH_3); MS (EI, 70 eV): *m/z* (%) = 435 (0.1) $[M+1]^+$, 434 (0.4) $[M]^+$, 222 (10), 217 (79), 119 (18), 99 (37), 91 (100). $C_{24}H_{26}N_4O_4$ (434.54): calcd. C 66.28%, H 5.98%, N 12.89%; found C 66.21%, H 5.86%, N 12.68%.

Bis-Mannich bases 7 and 8

A mixture of succinimide (0.5 g, 5 mmol) in EtOH (10 mL), formalin 36% (0.63 mL, 7.5 mmol) and the appropriate *sec*-amine (2.5 mmol) was boiled under reflux for the appropriate time. The material that precipitated on cooling was filtered and crystallized from ethanol.

1,4-(Succinimidomethyl)piperazine (7)

M.p. 300 -302°C (washed with boiling ethanol). Yield 69% (white brilliant powder); IR (KBr): υ = 1766, 1697 (CO), 1324, 1285, 1200, 1166, 1081, 1012 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 4.16 (s, 4H, 2 × N-CH_2-N), 2.63 (s, 8H, 4 × CH_2 of 2 × succinimide), 2.40 ppm (s, 8H, N-*(*CH_2CH_2*)*$_2$-N of piperazine); MS (EI, 70 eV): *m/z* (%) = 310 (2) $[M+2]^+$, 309 (14) $[M+1]^+$, 308 (79) $[M]^+$, 307 (2) $[M-1]^+$, 210 (19), 112 (39), 84 (53). $C_{14}H_{20}N_4O_4$ (308.38): calcd. C 54.48%, H 6.49%, N 18.16%; found C 54.34%, H 6.36%, N 18.02%.

1,1'-(4,4'-(Propane-1,3-diyl)bis(piperidine-4,1-diyl))bis(methylene) dipyrrolidine-2,5-dione (8)

M.p. 158°C (ethanol). Yield 51% (fine white needles); IR (KBr): υ = 1771, 1700 (CO), 1332, 1280, 1132, 1073, 666 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.45 (s, 4H, 2 × N-CH_2-N), 3.71 (t, 8H, 2-H_2, 6-H_2 of 2 × piperidine), 2.74 (s, 8H, 4 × CH_2 of 2 × succinimide), 2.16 (t, 8H, 3-H_2, 5-H_2 of 2 × piperidine), 1.14-1.62 ppm (m, 6H, trimethylene); MS (EI, 70 eV): *m/z* (%) = 435 (0.3) $[M+3]^+$, 432 (1) $[M]^+$, 334 (12), 112 (12), 43 (100). $C_{23}H_{36}N_4O_4$ (432.63): calcd. C 63.80%, H 8.32%, N 12.94%; found C 63.74%, H 8.26%, N 12.82%.

Synthesis of Mannich bases 9a-9c

A mixture of compound 2a (1.1 g, 5mmol) in EtOH (10 mL), formalin 36% (0.4 mL, 5 mmol) and the appropriate *sec*-amine (5 mmol) was boiled under reflux for the appropriate time. The obtained material was filtered and washed with boiling ethanol.

1-((3-((Diethylamino)methyl)-4-hydroxyphenylamino)methyl) pyrrolidine-2,5-dione (9a)

M.p. >300°C. Yield 26% (brown powder); IR (KBr): υ = 3436 (OH), 1771, 1702 (CO), 1623, 1494, 1278, 1225 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 305 (2) $[M]^+$, 301 (1) $[M-4]^+$, 246 (12), 176 (36), 87 (17). $C_{16}H_{23}N_3O_3$ (305.42): calcd. C 62.86%, H 7.53%, N 13.75%; found C 62.74%, H 7.46%, N 13.68%.

1-((3-Piperidinomethyl)-4-hydroxyphenylamino)methyl)succinimide (9b)

M.p. > 300°C. Yield 16% (brown powder); IR (KBr): υ = 3446 (OH), 1699, 1625 (CO), 1491, 1285, 1143, 820 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 317 (4) $[M]^+$, 316 (1) $[M-1]^+$, 315 (3) $[M-2]^+$, 300 (5), 98 (21), 84 (100). $C_{17}H_{23}N_3O_3$ (317.43): calcd. C 64.27%, H 7.25%, N 13.23%; found C 64.16%, H 7.18%, N 13.13%.

1-((3-(Morpholinomethyl)-4-hydroxyphenylamino)methyl) succinimide (9c)

M.p. >300°C. Yield 23% (brown powder); IR (KBr): υ = 3445 (OH), 1772, 1700 (CO), 1624, 1491, 1281, 1114, 818 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 320 (1) $[M+1]^+$, 112 (10), 98 (26), 86 (7). $C_{16}H_{21}N_3O_4$ (319.36): calcd. C 60.12%, H 6.58%, N 13.15%; found C 60.06%, H 6.49%, N 13.03%.

Synthesis of bis(Mannich bases) 10a-10c

A mixture of compound 2a (1.1 g, 5mmol) in EtOH (10 mL), formalin 36% (1 mL, 12 mmol) and the appropriate *sec*-amine (12 mmol) was boiled under reflux for the appropriate time. The obtained material that precipitated on cooling was filtered and washed with boiling ethanol.

1-((3,5-Bis((diethylamino)methyl)-4-hydroxyphenylamino)methyl)-pyrrolidine-2,5-dione (10a)

M.p. >300°C. Yield 36% (brown powder); IR (KBr): υ = 3435 (OH), 1780, 1624 (CO), 1495, 1275, 1229 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 390 (1) $[M]^+$, 112 (5), 98 (19), 87 (9), 57 (94), 43 (100). $C_{21}H_{34}N_4O_3$ (390.59): calcd. C 64.52%, H 8.70%, N 14.34%; found C 64.44%, H 8.61%, N 14.28%.

1-((3,5-Bis((piperidino)methyl)-4-hydroxyphenylamino)methyl)-pyrrolidine-2,5-dione (10b)

M.p. > 300°C. Yield 30% (brown powder); IR (KBr): υ = 3439 (OH), 1626 (CO), 1493, 1449, 1284, 820 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 414 (5) $[M]^+$, 413 (1) $[M-1]^+$, 412 (2) $[M-2]^+$, 411 (4) $[M-3]^+$, 316 (7), 112 (23), 98 (2), 97 (79). $C_{23}H_{34}N_4O_3$ (414.61): calcd. C 66.57%, H 8.20%, N 13.51%; found C 66.44%, H 8.01%, N 13.38%.

1-((3,5-Bis((morpholino)methyl)-4-hydroxyphenylamino)methyl)-pyrrolidine-2,5-dione (10c)

M.p. >300°C. Yield 50% (brown powder); IR (KBr): υ = 3439 (OH), 1771, 1703 (CO), 1624, 1491, 1287, 1115 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 419 (7) $[M+1]^+$, 318 (5), 100 (11), 98 (22), 86 (14). $C_{21}H_{30}N_4O_5$ (418.55): calcd. C 60.21%, H 7.17%, N 13.38%; found C 60.14%, H 7.09%, N 13.19%.

Synthesis of Mannich bases 11a and 11b

A mixture of compound 2c (0.6 g, 2 mmol) in EtOH (10 mL), formalin 36% (0.3 mL, 4 mmol) and the appropriate *sec*-amine (3 mmol) was boiled under reflux for 1-2 hrs. The viscous product that precipitated on cooling, was solidified by addition of water (30 mL), then it was filtered and purified *via* crystallization from EtOH:DMF (1:1).

4-((Succinimidomethyl)amino)-*N*-(piperidinomethyl)benzene sulfonamide (11a)

M.p. 178°C. Yield 75% (white powder); IR (KBr): υ = 3391, 3373 (NH), 1773, 1700 (CO), 1598, 1312, 1149, 1093 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 7.94 (s, 1H, N*H*SO_2), 6.56-7.88 (m, 4H, aromatic), 5.81 (s, 1H, N*H*), 4.55 (s, 2H, N-CH_2-N), 4.22 (s, 2H, CH_2-N), 2.88 (s, 4H, 2 × CH_2 of succinimide), 2.35 (t, 4H, 2-H_2, 6-H_2 of pipeidine), 2.29-2.31 (m, 4H, 3-H_2,5-H_2 of piperidine), 1.29-1.45 ppm (m, 2H, 4-H_2 of piperidine); MS (EI, 70 eV): *m/z* (%) = 379 (1) $[M-1]^+$, 376 (0.5) $[M-4]^+$, 112 (8), 83 (19). $C_{17}H_{24}N_4O_4S$ (380.46):

calcd. C 53.62%, H 6.31%, N 14.72%; found C 53.54%, H 6.19%, N 14.66%.

4-((Succinimidomethyl)amino)-*N*-(morpholinomethyl)benzene sulfonamide (11b)

M.p. 208°C. Yield 40% (fine white powder); IR (KBr): υ = 3376, 3258 (NH), 1772, 1697 (CO), 1337, 1158, 818, 544 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 6.96 (s, 1H, N*H*), 6.83-7.51 (m, 4H, aromatic), 4.77 (d, 4H, 2 × N-CH_2-NH), 4.35 (t, 4H, 2-H_2, 6-H_2 of morpholine), 3.43 (t, 4H, 3-H_2, 5-H_2 of morpholine), 2.62 ppm (s, 4H, 2 × CH_2 of succinimide); MS (EI, 70 eV): *m/z* (%) = 382 (5) $[M]^+$, 379 (2) $[M-3]^+$, 184 (12), 112 (29), 100 (15), 98 (44), 86 (14). $C_{16}H_{22}N_4O_5S$ (382.43): calcd. C 50. 21%, H 5.75%, N 14.64%; found C 50.14%, H 5.69%, N 14.56%.

Synthesis of Mannich bases 12a and 12b

A mixture of Mannich base 2e (0.5 g, 2 mmol) in EtOH (15 mL), paraformaldehyde (0.1 g, 3 mmol) and the appropriate *sec*-amine hydrochloride (3 mmol) was boiled under reflux for 5 hrs. The material that precipitated on cooling was filtered and crystallized from ethanol.

N-(((4-(3-Piperidino-1-propanoyl) phenyl)amino)methyl)succinimide-hydrochloride (12a)

M.p. > 300°C. Yield 59% (red powder); IR (KBr): υ = 3363 (NH), 1771, 1703, 1652 (CO), 1594, 1177 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 6.57-7.77 (m, 4H, aromatic), 6.06 (s, 1H, N*H*), 4.69 (s, 2H, N-CH_2-NH), 3.12-3.18 (m, 4H, COCH_2CH_2N), 2.62 (s, 4H, 2 × CH_2 of succinimide), 2.49 (t, 4H, 2-H_2, 6-H_2 of piperidine), 1.04-1.83 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine) ppm; MS (EI, 70 eV): *m/z* (%) = 381 (0.1) $[M+2]^+$, 379 (3) $[M]^+$, 378 (2) $[M-1]^+$, 120 (20), 119 (7), 98 (10), 84 (24), 76 (8), 57 (100). $C_{19}H_{26}N_3O_3Cl$ (379.93): calcd. C 60.01%, H 6.84%, N 11.05%; found C 59.94%, H 6.79%, N 10.96%.

N-(((4-(3-Morpholino-1-propanoyl)phenyl)amino)methyl)succinimide hydrochloride (12b)

M.p. 200°C. Yield 66% (white powder); IR (KBr): υ = 3329 (NH), 1767, 1696, 1661 (CO), 1603, 1276, 1184 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.79-7.91 (m, 4H, aromatic), 5.78 (s, 1H, *NH*), 5.02 (s, 2H, N-CH_2-NH), 3.69-3.73 (m, 4H, COCH_2CH_2N), 3.25 (t, 4H, 2-H_2, 6-H_2 of morpholine), 2.69 (s, 4H, 2 × CH_2 of succinimide), 2.61 ppm (t, 4H, 3-H_2, 5-H_2 of morpholine); MS (EI, 70 eV): *m/z* (%) = 384 (0.1) $[M+2]^+$, 383 (1) $[M+1]^+$, 382 (0.4) $[M]^+$, 253 (100), 147 (61), 119 (7). $C_{18}H_{24}N_3O_4Cl$ (381.86): calcd. C 56.57%, H 6.29%, N 11.00%; found C 56.44%, H 6.20%, N 10.96%.

N-(Piperidin-1-yl(pyridin-3-yl)methyl)benzamide (14)

A mixture of benzamide13 (1.5 g, 12.4 mmol) in MeOH (15 mL), pyridine-3-carboxaldehyde (1.2 mL, 12.4 mmol) and piperidine (1.2 mL, 12.4 mmol) was boiled under reflux for 12-16 hrs. The gummy material that precipitated on cooling was solidified by addition of ice cold water (30 mL), and then it was filtered and purified *via* crystallization from benzene or ethanol. M.p. 122°C. Yield 55% (white crystals); IR (KBr): υ = 3367 (NH), 1659 (CO), 1622, 1401, 1120, 633 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 297 (6) $[M+2]^+$, 296 (9) $[M+1]^+$, 295 (1) $[M]^+$, 267 (34), 77 (20), 43 (100). $C_{18}H_{21}N_3O$ (295.42):calcd. C 73.12%, H 7.11%, N 14.22%; found C 73.04%, H 7.01%, N 14.16%.

N,N′-(piperazine-1,4-diylbis(pyridin-3-ylmethylene))dibenzamide (15)

A mixture of benzamide13 (1.5 g, 12.4 mmol) in MeOH (15 mL), pyridine-3-carboxaldehyde (1.2 mL, 12.4 mmol) and piperazine (0.5 g, 6 mmol) was boiled under reflux for 12 hrs. The precipitated material was filtered and washed with boiling ethanol. M.p. 248°C. Yield 58% (white powder); IR (KBr): υ = 3373, 3303 (NH), 1641, 1600 (CO), 1525, 696 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 7.36-8.95 (m, 18H, aromatic), 8.65 (s, 2H, 2 × N*H*), 6.05 (d, 2H, 2 × N-C*H*-NH), 2.55 ppm (s, 8H, 2-H_2, 3-H_2, 5-H_2, 6-H_2 of piprazine); ^{13}C-NMR (500 MHz, DMSO): δ = 167.29 (C=O), 148.70, 135.12, 134.77, 134.07, 131.53, 128.22, 127.46, 123.31 (all Ar-C), 69.02 (2 × CH), 48.08 ppm (C_2, C_3, C_5, C_6 of piperazine); MS (EI, 70 eV): *m/z* (%) = 506 (1) $[M]^+$, 505 (0.4) $[M-1]^+$, 105 (39), 79 (7), 77 (70). $C_{30}H_{30}N_6O_2$ (506.66): calcd. C 71.05%, H 5.92%, N 16.58%; found C 70.98%, H 5.86%, N 16.49%.

N,N′-(1,4-Phenylenebis(morpholinomethylene))dibenzamide (16)

A mixture of benzamide 13 (1.5 g, 12.4 mmol) in MeOH (15 mL), terephthalaldehyde (0.8 g, 6 mmol) and morpholine (1.1 mL, 12.4 mmol) was boiled under reflux for 12 hrs. The obtained material was filtered and purified *via* crystallization from ethanol. M.p. 158°C. Yield 59% (white powder); IR (KBr): υ = 3296 (NH), 1698, 1638 (CO), 1520, 1114, 1005, 704, 660 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 8.11 (s, 2H, 2 × N*H*), 7.36-7.96 (m, 14H, aromatic), 6.01 (d, 2H, 2 × C*H*NH), 3.58-3.61 ppm (m, 16H, 2-H_2, 3-H_2, 5-H_2, 6-H_2 of 2 × morpholine); MS (EI, 70 eV): *m/z* (%) = 515 (1) $[M+1]^+$, 509 (2) $[M-6]^+$, 105 (97), 77 (100). $C_{30}H_{34}N_4O_4$ (514.68): calcd. C 69.95%, H 6.61%, N 10.88%; found C 69.88%, H 6.56%, N 10.79%.

2-(Morpholine-4-carbonyl)-*N*-(piperidinomethyl)benzamide (18)

A mixture of 17 (1.2 g, 5 mmol) in EtOH (15 mL), formalin 36% (0.8 mL, 10 mmol) and piperidine (0.5 mL, 5 mmol) was boiled under reflux for 6 hrs. The product that solidified on cooling and addition of water (30 mL), was filtered and purified *via* crystallization from ethanol. M.p. 115°C. Yield 53% (white crystals); IR (KBr): υ = 3459 (NH), 1766, 1720 (CO), 1305, 1115, 736 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.72 (s, 1H, N*H*), 7.73-7.94 (m, 4H, aromatic), 5.49 (s, 2H, CH_2), 3.67 (t, 4H, 2-H_2, 6-H_2 of morpholine), 3.57 (t, 4H, 3-H_2, 5-H_2 of morpholine), 2.63 (t, 4H, 2-H_2, 6-H_2 of piperidine), 1.59 (br s, 4H, 3-H_2, 5-H_2 of piperidine), 1.35 ppm (br s, 2H, 4-H_2 of piperidine); MS (EI, 70 eV): *m/z* (%) = 245 (2), 84 (100), 98 (81), 160 (53), 86 (17). $C_{18}H_{25}N_3O_3$ (331.46): calcd. C 65.17%, H 7.54%, N 12.67%; found C 65.08%, H 7.46%, N 12.58%.

N,N′-methylene bis(2-(morpholine-4-carbonyl)benzamide) (19)

Mannich base 17 (3.1 g, 13 mmol) suspended in a solution containing saturated sodium sulphate, concentrated sulphuric acid (4 mL) and formalin 36% (0.7 mL, 8 mmol) was boiled

on water bath for 6 hrs. The obtained precipitate was filtered and purified *via* crystallization from ethanol. M.p. 200°C. Yield 52% (fine white powder); IR (KBr): υ = 3488 (NH), 1774, 1724 (CO), 1601, 1307, 1051, 713 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO): δ = 11.34 (s, 2H, 2 × N*H*), 7.82-7.90 (m, 8H, aromatic), 5.44 (s, 2H, CH_2), 3.46 (t, 8H, 2-H_2, 6-H_2 of 2 × morpholine), 2.49 ppm (t, 8H, 3-H_2, 5-H_2 of 2 × morpholine); MS (EI, 70 eV): *m/z* (%) = 306 (100), 161 (32), 104 (52), 77 (27), 76 (37). $C_{25}H_{28}N_4O_6$ (480.57): calcd. C 62.43%, H 5.83%, N 11.65%; found C 62.38%, H 5.74%, N 11.58%.

Mannich bases (22a-c)

A mixture of Mannich base 20a or20b or20c (2 mmol) and 1,2,3,4-tetrahydro-carbazole 21 (0.3 g, 2 mmol) in toluene (15 mL) containing NaOH (0.1 g) was heated under reflux for 3-4 hrs. The precipitate that obtained during reflux was filtered and washed with boiling ethanol.

N-(Benzamidomethyl)-1,2,3,4-tetrahydro-carbazole (22a)

M.p. > 300°C. Yield 62% (pale yellow powder); IR (KBr): υ = 3421 (NH), 1736 (CO), 1650, 1451, 867 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 305 (1) $[M+1]^+$, 304 (4) $[M]^+$, 300 (4) $[M-5]^+$, 262 (51), 120 (11), 77 (42), 76 (18), 57 (31). $C_{20}H_{20}N_2O$ (304.42): calcd. C 78.84%, H 6.57%, N 9.20%; found C 78.78%, H 6.48%, N 9.16%.

N-(Phenylacetamidomethyl)-1,2,3,4-tetrahydro-carbazole (22b)

M.p. > 300°C. Yield 42% (pale yellow powder); IR (KBr): υ = 3449 (NH), 1771 (CO), 1624, 1602, 1494, 755 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 319 (1) $[M+1]^+$, 318 (13) $[M]^+$, 316 (7) $[M-2]^+$, 184 (15), 170 (7), 71 (29), 57 (100). $C_{21}H_{22}N_2O$ (318.45): calcd. C 79.13%, H 6.91%, N 8.79%; found C 79.04%, H 6.82%, N 8.86%.

N-(Phenoxyacetamidomethyl)-1,2,3,4-tetrahydro-carbazole (22c)

M.p. > 300°C. Yield 68% (pale yellow powder); IR (KBr): υ = 3458 (NH), 1773 (CO), 1601, 1348, 610 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 334 (5) $[M]^+$, 197 (33), 169 (11), 137 (21), 93 (8), 87 (9). $C_{21}H_{22}N_2O_2$ (334.45): calcd. C 75.35%, H 6.58%, N 8.37%; found C 75.24%, H 6.52%, N 8.26%.

Mannich bases (24a-c)

A mixture of Mannich base 20a or 20b or 20c (2 mmol) and 1,2-benzo-3,4-dihydro-carbazole 23 (0.44 g, 2 mmol) in toluene (15 mL) containing NaOH (0.1 g) was heated under reflux for 3-4 hrs. The obtained material that precipitated during reflux, was filtered and washed with boiling ethanol.

N-(benzamidomethyl)-1,2-benzo-3,4-dihydro-carbazole) (24a)

M.p. > 300°C. Yield 82% (pale yellow powder); IR (KBr): υ = 3428 (NH), 1777 (CO), 1624, 1437, 881 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 355 (4) $[M+3]^+$, 352 (7) $[M]^+$, 351 (3) $[M-1]^+$, 347 (12) $[M-5]^+$, 314 (56), 224 (6), 134 (3), 77 (100). $C_{24}H_{20}N_2O$ (352.46): calcd. C 81.71%, H 5.67%, N 7.94%; found C 81.68%, H 5.58%, N 7.86%.

N-(Phenylacetamidomethyl)-1,2-benzo-3,4-dihydro-carbazole) (24b)

M.p. > 300°C. Yield 86% (pale yellow powder); IR (KBr): υ = 3424 (NH), 1733 (CO), 1636, 1574, 1503, 1470 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 368 (5) $[M+2]^+$, 367 (1) $[M+1]^+$, 366 (2) $[M]^+$, 365 (1) $[M-1]^+$, 233 (100), 232 (17), 77 (60). $C_{25}H_{22}N_2O$ (366.49): calcd. C 81.86%, H 6.00%, N 7.64%; found C 81.78%, H 5.91%, N 7.56%.

N-(Phenoxyamidomethyl)-1,2-benzo-3,4-dihydro-carbazole) (24c)

M.p. > 300°C. Yield 88% (pale yellow powder); IR (KBr): υ = 3425 (NH), 1608 (CO), 1439, 1241, 751 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 382 (8) $[M]^+$, 378 (7) $[M-4]^+$, 376 (9), 163 (13), 148 (11), 135 (10), 77 (21). $C_{25}H_{22}N_2O_2$ (382.49): calcd. C 78.43%, H 5.75%, N 7.32%; found C 78.38%, H 5.68%, N 7.26%.

4. Antibacterial and Antifungal Activities Using Filter Paper Disc Method

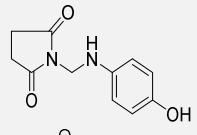
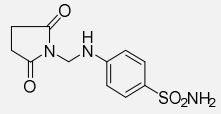
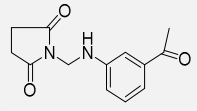
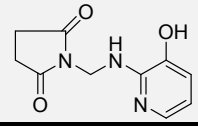
The method was according to the filter paper disc method [23]. Diameters of inhibition zone were estimated (mm) after 18-24 hours (table 1).

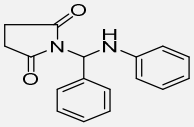
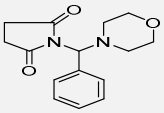
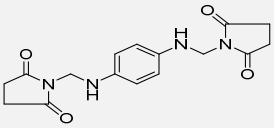
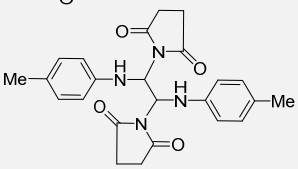
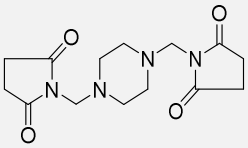
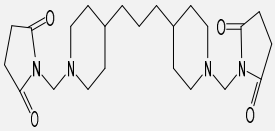
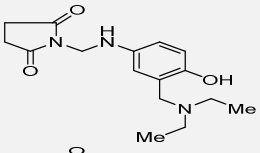
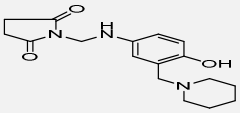
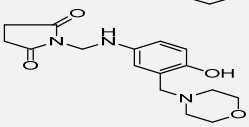
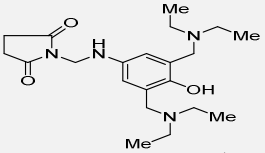
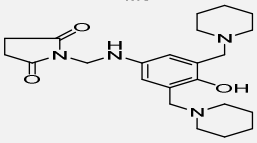
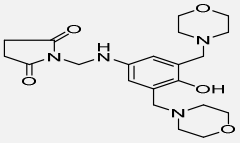
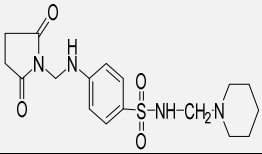
Tested organisms:

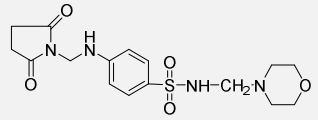
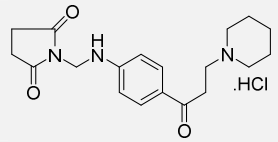
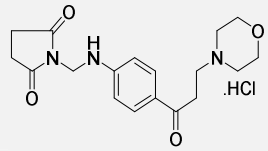
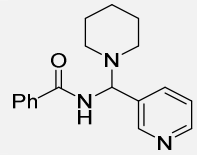
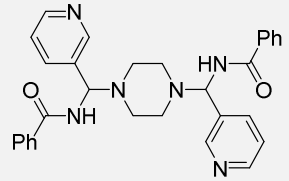
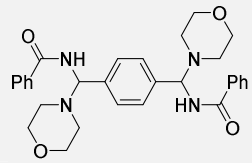
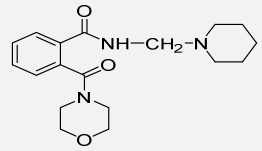
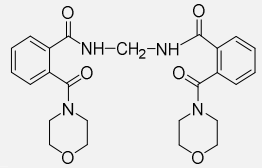
Bacteria: *Erwinia carotovora, Bacillus subtilis.*

Fungi: *Candida albicans.*

Table 1. *Indicate the diameter clear zone which confirm the antimicrobial activity to each compound.*

No.	Compounds	*Erwinia carotovora* [G –ve]	*Bacillus subtillis* [G+ve]	*Candida albicans* [Fungus]
2a		+ve [17 mm]	+ve [17 mm]	+ve [22 mm]
2c		-ve	-ve	+ve [11 mm]
2d		+ve [17.6 mm]	+ve [10 mm]	+ve [16 mm]
2f		-ve	-ve	-ve

No.	Compounds	*Erwinia carotovora* [G –ve]	*Bacillus subtillis* [G+ve]	*Candida albicans* [Fungus]
3		+ve [8 mm]	+ve [7.5 mm]	-ve
4		+ve [8 mm]	+ve [8 mm]	-ve
5		+ve [12 mm]	+ve [10 mm]	+ve [14.6 mm]
6		-ve	+ve [7 mm]	-ve
7		+ve [11 mm]	+ve [10 mm]	+ve [14.6 mm]
8		+ve [12 mm]	+ve [10 mm]	+ve [12 mm]
9a		-ve	-ve	-ve
9b		-ve	-ve	-ve
9c		-ve	-ve	-ve
10a		-ve	-ve	-ve
10b		-ve	-ve	-ve
10c		-ve	-ve	-ve
11a		-ve	-ve	-ve

No.	Compounds	*Erwinia carotovora* [G –ve]	*Bacillus subtillis* [G+ve]	*Candida albicans* [Fungus]
11b		-ve	-ve	-ve
12a		-ve	-ve	-ve
12b		-ve	-ve	-ve
14		-ve	-ve	-ve
15		+ve [7 mm]	+ve [8.3 mm]	+ve [8.3 mm]
16		+ve [8.3 mm]	+ve [10 mm]	+ve [9 mm]
18		+ve [12.6 mm]	+ve [12 mm]	+ve [16.6 mm]
19		+ve [7.5 mm]	+ve [7 mm]	-ve
	DMSO	-ve	-ve	-ve
	Standard Antibiotic (Streptomycin)	18 mm	15 mm	13 mm

Compounds 2a and 2d showed high antimicrobial activity. Compounds 7, 8 and 18 have moderate antimicrobial activity. Compounds 2c, 3, 4, 6, 15, 16 and 19 showed low antimicrobial activities, while the remaining compounds gave none antimicrobial activity.

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