ISSN 2321-807X

Exocyclic enaminones as building blocks for synthesis of bioactive polyheterocyclic compounds

Magda A. Abdallah[a], Thoraya A. Farghaly[a,b*] and Mohamed R. Abdel Aziz[a]

[a)] Department of Chemistry, Faculty of Science, Cairo University, Giza, 12613, Egypt.

[b)] Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia.

e.mail: thoraya-f@hotmail.com

ABSTRACT

The reaction of exocyclic enaminones namely, 2-(dimethylaminomethylene)-3,4-dihydro-2*H*-naphthalen-1-one, 3-(dimethylaminomethylene)-thiochroman-4-one and 2-(dimethyl-aminomethylene)-indane-1,3-dione, each with heterocyclic diazonium salts afforded the respective hydrazones which undergo either *in situ* dehydrative cyclization or cyclized by heating with acetic acid to give polycyclic compounds. The structure of all the newly synthesized products were confirmed by elemental and spectral (IR, ^{1}H NMR, Mass) data. Also, the biological activity of some of the prepared compounds was tested against some microorganisms and promising results were obtained.

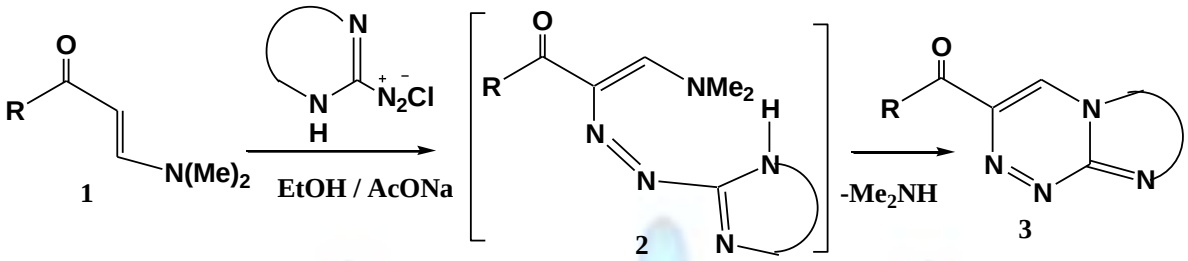
Keywords

Exocyclic enaminones; heterocyclic diazonium salts; polycyclic compounds; biological activity.

ISSN 2321-807X

INTRODUCTION

Literature reports indicate that enaminones constitute an important class of useful precursors in organic synthesis, in pharmaceutical development and in heterocyclic synthesis [1-6]. Since enaminones have two reactive sites, they are able to react with both electrophiles and nucleophiles [7-11] to give a variety of bioactive products. Several reports indicate that reaction of acyclic enaminones as nucleophiles with heterocyclic diazonium salts give the azo compounds which undergo *in situ* cyclization *via* elimination of dimethylamine to give the respective cyclized products [12,13] (Scheme 1). On the other hand, literature survey indicate that only one report [14] was found about reaction of exocyclic enaminones with heterocyclic diazonium salts.



Scheme 1

On the basis of these findings, we report herein a facile method for synthesizing tetra- and penta-heterocyclic ring systems *via* coupling reaction of a number of different exocyclic enaminones with heterocyclic diazonium salts. Our objective from this study is to investigate the reactivity of these exocyclic enaminones towards a variety of heterocyclic diazonium salts. Also, the activity of the products obtained from this reaction against a number of bacteria and fungi species was studied.

Experimental

Materials

Melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in potassium bromide using Pye Unicam SP-1000 spectrophotometer. ^{1}HNMR spectra were recorded in DMSO-d_6 using a varian Em-300 MHz Spectrometer and TMS as internal reference. Mass spectra were recorded on AEIMS30 mass spectrometer operating at 70ev. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Antimicrobial activity was carried out at the Regional Center for Mycology and Biotechnology (RCMB) at Al-Azhar University, Cairo, Egypt. The enaminones **4a,b** and **5** were reported as described before [15-17].

*Coupling of the enaminones **4a,b** and **5** with heterocyclic amines*

General procedure: To a stirred solution of the appropriate enaminones **4a,b** or **5** (10 mmol) in ethanol (50 ml) was added sodium hydroxide (0.4 g, 10 mmol) and the mixture was cooled in an ice bath to 0–5 ºC. To the resulting solution, while being stirred, was added dropwise over a period of 20 min a solution of the appropriate heterocyclic diazonium salt, prepared as usual by diazotizing the respective heterocyclic amine (2-amino-[1,2,4]-triazole, 2-amino-benzimidazole or 5-amino-3-phenyl-pyrazole) (10 mmol) in hydrochloric acid (6 M, 6 ml) or in nitric acid with sodium nitrite (1 M, 10 ml). The whole mixture was then left in a refrigerator overnight. The precipitated solid formed was collected, washed with water and finally crystallized from ethanol to give the respective hydrazone **8b**, **12b**, **14**, **16**, **18** or the cyclized compounds **9a, 11a,b** and **12a**, respectively.

*Cyclization of hydrazones **8b**, **12b**, **14**, **16** and **18***

A solution of hydrazones **8b, 12b, 14, 16** or **18** (1 mmole) in glacial acetic acid (10 mL) was refluxed for 15 h. After cooling, the solution was then poured into ice and sodium acetate and the precipitate formed was filtered off and crystallized from the appropriate solvent to give compounds **9b, 13b, 15, 17** and **19**, respectively.

*3-[(2H-[1,2,4]Triazol-3-yl)-hydrazono]-thiochroman-4-one (**8b**)*

Yellow solid, (81% yield), mp 210-212ºC (EtOH); IR (KBr) ν_{max} 3330, 3237 (2NH), 1668 (CO), 1567 (C=N), ^{1}H NMR (DMSO-d_6) δ 5.48 (s, 2H, CH_2), 7.54-8.56 (m, 4H, ArH), 8.88 (s, 1H, triazole-H), 12.21 (s, 1H, NH), 14.0 (s, 1H, NH). MS m/z (%) 259 (M^+, 54), 258 (29), 177 (86), 176 (34), 149 (35), 136 (59), 84 (100), 76 (33), 57 (59). Anal. Calcd. For $C_{11}H_9N_5OS$ (259.29): C, 50.95; H, 3.50; N, 27.01. Found: C, 50.78; H, 3.37; N, 26.94%.

*6,7-Dihydro-1,3,4,5,11c-pentaaza-cyclopenta[c]phenanthrene (**9a**)*

Redish brown powder, (70% yield), mp 72-74 ºC (EtOH / Dioxane); IR (KBr) ν_{max} 1632 (C=N), ^{1}H NMR (DMSO-d6) δ 3.10 (t, *J* = 7 Hz, 2H, CH_2), 3.29 (t, *J* = 7 Hz, 2H, CH_2), 7.23-7.78 (m, 4H, ArH), 8.31 (s, 1H, triazole-H). MS m/z (%) 224 (M^++1, 45), 223 (M^+, 19), 222 (26), 115 (52), 63 (100). Anal. Calcd. For $C_{12}H_9N_5$ (223.23): C, 64.56; H, 4.06; N, 31.37. Found: C, 64.35; H, 4.19; N, 31.26%.

*6H-7-Thia-1,3,4,5,11c-pentaaza-cyclopenta[c]phenanthrene (**9b**)*

Dark brown crystals, (67% yield), mp 150-152 ºC (EtOH); IR (KBr) ν_{max} 1564 (C=N), ^{1}H NMR (DMSO-d_6) δ 4.25 (s, 2H, CH_2), 7.29-7.90 (m, 4H, ArH), 9.25 (s, 1H, triazole-H). MS m/z (%) 242 (M^++1, 61), 241 (M^+, 64), 240 (62), 237 (55), 236 (52), 233 (55), 221 (54), 218 (54), 180 (60), 162 (87), 136 (75), 108 (85), 76 (100). Anal. Calcd. for $C_{11}H_7N_5S$ (241.27): C, 54.76; H, 2.92; N, 29.03. Found: C, 54.57; H, 2.86; N, 29.11%.

*2-Phenyl-6,7-dihydro-1,4,5,11c-tetraaza-cyclopenta[c]phenanthrene (**11a**)*

Orange solid, (77% yield), mp 210-212 ºC (EtOH/Dioxane); IR (KBr) ν_{max} 1630 (C=N), ^{1}H NMR (DMSO-d_6) δ 3.14 (t, *J* = 7 Hz, 2H, CH_2), 3.41 (t, *J* = 7 Hz,2H, CH_2), 7.50-7.54 (m, 5H, ArH), 7.55-7.89 (m, 4H, ArH), 7.89 (s, 1H, pyrazole-H). MS m/z (%) 298 (M^+, 100), 297 (36), 154 (49), 77 (57). Anal. Calcd. for $C_{19}H_{14}N_4$ (298.34): C, 76.49; H, 4.73; N, 18.78. Found: C, 76.30; H, 4.67; N, 18.58%.

*2-Phenyl-6H-7-thia-1,4,5,11c-tetraaza-cyclopenta[c]phenanthrene **(11b**)*

Brown powder, (70% yield), mp 130-132 ºC (Dioxane); IR (KBr) ν_{max} 1590(C=N), ^{1}H NMR (DMSO-d_6) δ 4.57 (s, 2H, CH_2), 7.40-8.22 (m, 9H, ArH), 7.98 (s, 1H, pyrazole-H). MS m/z (%) 316 (M^+, 36), 315 (18), 185 (32), 155 (16), 145 (21), 101 (19), 77 (42). Anal. Calcd. For $C_{18}H_{12}N_4S$ (316.38): C, 68.33; H, 3.82; N, 17.71. Found: C, 68.24; H, 3.66; N, 17.59%.

*3-[(1H-Benzimidazol-2-yl)-hydrazono]-thiochroman-4-one (**12b**)*

Brown powder, (77% yield), mp 136-138 ºC (EtOH/Dioxane); IR (KBr) ν_{max} 3377, 3114 (2NH), 1680 (CO), 1593 (C=N). ^{1}H NMR (DMSO-d_6) δ 4.29 (s, 2H, CH_2), 7.16-7.97 (m, 8H, ArH), 10.19 (s, 1H, NH), 12.82 (s, 1H, NH). MS m/z (%) 308 (M^+, 0.3), 133 (100), 132 (23), 77 (5). Anal. Calcd. For $C_{16}H_{12}N_4OS$ (308.36): C, 62.32; H, 3.92; N, 18.17. Found: C, 62.18; H, 3.78; N, 18.01%.

*5,6-Dihydro-7,8,9,13b-tetraaza-indeno[2,1-c]phenanthrene **(13a)***

Brown powder, (70% yield), mp 270ºC (EtOH/Dioxane); IR (KBr) ν_{max}1634 (C=N), ^{1}H NMR (DMSO-d_6) δ 2.72 (t, 2H, CH_2), 3.14 (t, 2H, CH_2), 7.25-7.59 (m, 8H, ArH). MS m/z (%) 272 (M^+, 30), 253 (29), 214 (23), 149 (43), 58 (100). Anal. Calcd. For $C_{17}H_{12}N_4$ (272.30): C, 74.98; H, 4.44; N, 20.58. Found: C, 74.85; H, 4.21; N, 20.34 %.

*6H-5-Thia-7,8,9,13b-tetraaza-indeno[2,1-c]phenanthrene **(13b**)*

Reddish brown powder (72% yield), mp 60-62 ºC (EtOH); IR (KBr) ν_{max} 1584 (C=N). ^{1}H NMR (DMSO-d_6) δ 5.57 (s, 2H, CH_2), 7.60-8.48 (m, 8H, ArH). MS m/z (%) 290 (M^+, 2), 213 (13), 158 (42), 117 (12), 102 (100), 77 (32). Anal. Calcd. for $C_{16}H_{10}N_4S$ (290.34): C, 66.19; H, 3.47; N, 19.30. Found: C, 66.05; H, 3.28; N, 19.11%.

*2-[(5-Phenyl-2H-pyrazol-3-yl)-hydrazono]-indan-1,3-dione **(14**)*

Orange crystal, (65% yield), mp 120-122 ºC (EtOH); IR (KBr) ν_{max} 3390 (NH), 3151 (NH), 1713 (CO), 1670 (CO), 1593 (C=N). ^{1}H NMR (DMSO-d_6) δ 7.37-7.86 (m, 9H, ArH), 7.90 (s, 1H, pyrazole-H), 13.34 (s, 2H, 2NH). MS m/z (%) 317 (M^++1, 38), 316 (54), 285 (40), 228 (48), 149 (100), 107 (40), 57 (80). Anal. Calcd. For $C_{18}H_{12}N_4O_2$ (316.31): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.20; H, 3.65; N, 17.53%.

*2-Phenyl-1,4,5,10c-tetraaza-cyclopenta[c]fluoren-6-one (**15**)*

Brown powder, (61% yield), mp 158-160 ºC (EtOH); IR (KBr) ν_{max} 1726 (CO). ^{1}H NMR (DMSO-d_6) δ 7.57-8.59 (m, 9H, ArH), 8.19 (s, 1H, pyrazole-H). MS m/z (%) 299 (M^++1, 48), 298 (92), 251 (62), 195 (50), 167 (56), 77 (100), 76 (78). Anal. Calcd. For $C_{18}H_{10}N_4O$ (298.30): C, 72.48; H, 3.38; N, 18.78. Found: C, 72.27; H, 3.23; N, 18.56%.

*2-[(2H-[1,2,4]Triazol-3-yl)-hydrazono]-indan-1,3-dione (**16**)*

Yellow powder, (65% yield), mp 274-276 ºC (EtOH/Dioxane); IR (KBr) ν_{max} 3116 (NH), 1718, 1679 (CO), 1531 (C=N). ^{1}H NMR (DMSO-d_6) δ 7.42-8.12 (m, 4H, ArH), 8.51 (s, 1H, Triazole-H), 13.07 (s, 1H, NH), 14.15 (s, 1H, NH). MS m/z (%) 242 (M^+, 13), 241 (30), 158 (61), 105 (25), 102 (100) ,76 (79), 75 (56). Anal. Calcd. For $C_{11}H_7N_5O_2$ (242.21): C, 54.77; H, 2.93; N, 29.03. Found: C, 54.54; H, 2.68; N, 28.89%.

*1,3,4,5,10c-Pentaaza-cyclopenta[c]fluoren-6-one (**17**)*

Yellow powder, (60% yield), mp 290-292 ºC (EtOH/Dioxane); IR (KBr) ν_{max} 1719 (CO), 1533 (C=N). ^{1}H NMR (DMSO-d_6) δ 7.15-7.99 (s, 4H, ArH), 8.64 (s, 1H, triazole-H). MS m/z (%) 224 (M^++1, 7), 223 (51), 158 (32), 114 (43), 102 (77), 79 (100), 75 (33). Anal. Calcd. For $C_{11}H_5N_5O$ (223.19): C, 59.20; H, 2.26; N, 31.38. Found: C, 59.07; H, 2.13; N, 31.16%.

*2-[(1H-Benzimidazol-2-yl)-hydrazono]-indan-1,3-dione (**18**)*

Yellow crystal (68% yield), mp > 300 ºC (Dioxane); IR (KBr) ν_{max}; 3412, 3254 (2NH), 1715, 1690 (2CO), 1524 (C=N). ^{1}H NMR (DMSO-d_6) δ 7.10-7.89 (m, 8H, ArH), 9.28 (s, 1H, NH), 10.57 (s, 1H, NH). MS m/z (%) 291 (M^++1, 26), 290 (36), 272 (43), 188 (42), 149 (73), 136 (41), 71 (55), 58 (100), 57 (78). Anal. Calcd. for $C_{16}H_{10}N_4O_2$ (290.28): C, 66.20; H, 3.47; N, 19.30. Found: C, 66.05; H, 3.24; N, 19.16%.

ISSN 2321-807X

*5,6,7,12c-Tetraaza-indeno[2,1-c]fluoren-8-one (**19**)*

Brown crystal, (65% yield), mp 152ºC (EtOH); IR (KBr) ν_{max} 1720 (CO), 1534 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.98-7.59 (m, 8H, ArH). MS m/z (%) 273 (M^++1, 18), 191(20), 160 (20), 127 (20), 98 (21), 80 (100), 76 (19). Anal. Calcd. For $C_{16}H_8N_4O$ (272.26): C, 70.58; H, 2.96; N, 20.58. Found: C, 70.31; H, 2.78; N, 20.34%.

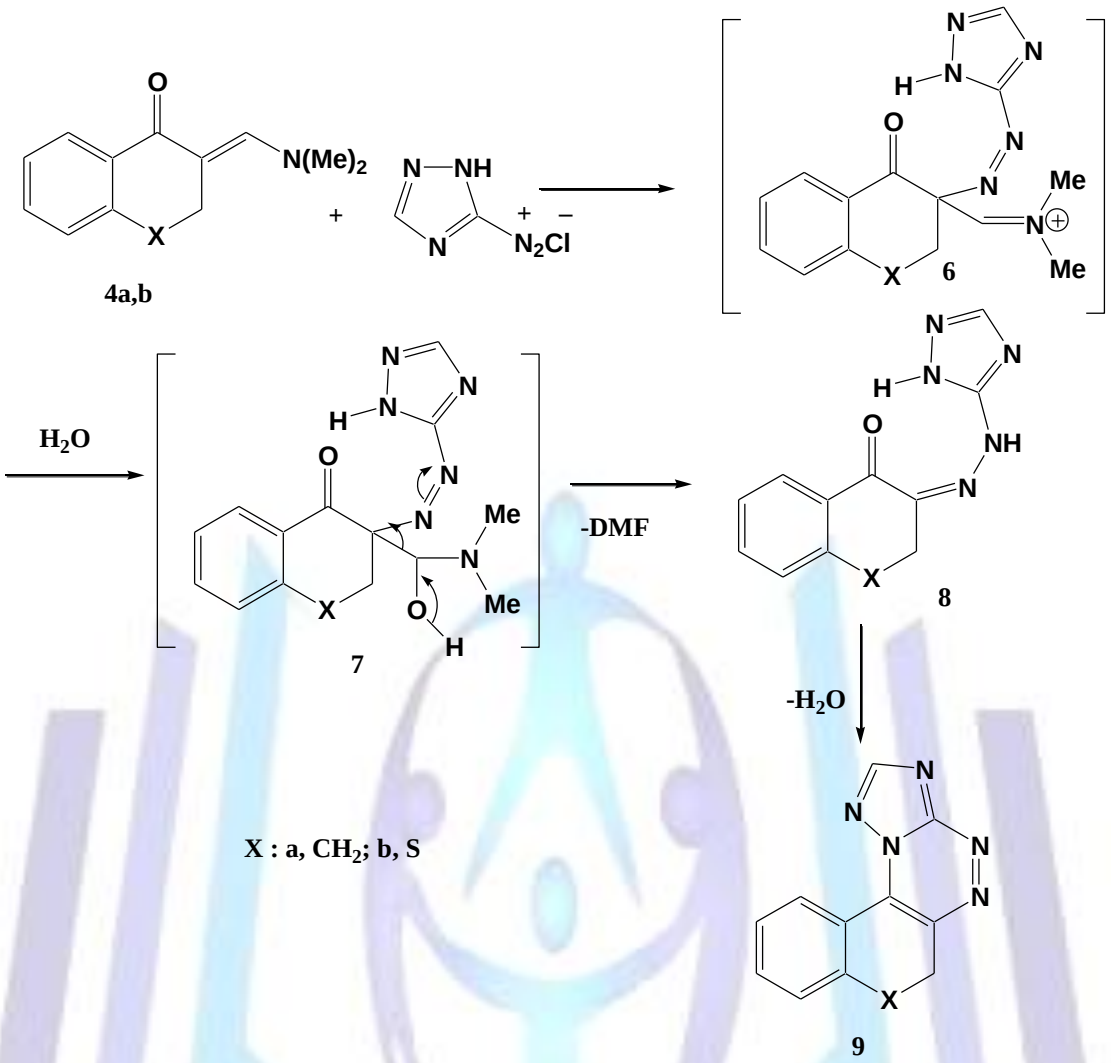
Microorganism's strains and preparation of inoculum: A. Fumigatus (RCMB 02568), S. Racemosum (RCMB 05922), G. Candidum (RCMB 05097), C. Albicans (RCMB 05036), S. Pneumoniae (RCMB 010010), B. Subtilis (RCMB 010067), P. Aeruginosa (RCMB 010043) and E. Coli (RCMB 010052). strains were used in this study. The microbial suspension equivalent to the turbidity of 0.5 McFarland (10^8 CFU/ml) standard was prepared from a fresh subculture of tested bacteria in Mueller Hinton Broth (MHB) and tested fungi in Sabouraud dextrose Broth (SDB) then this suspension was diluted to 10^6 CFU/ml using MHB for bacteria and Sabouraud dextrose Broth (SDB) for tested fungi. The adjusted microbial inoculum (100 µl) were added to each well of sterile 96-well flat-bottomed microtiter plate containing the tested concentration of tested samples (100 µl/well). As a result, last inoculum concentration of 5×10^5 CFU/ml was obtained in each well. Three wells containing microbial suspension with no sample using DMSO employed for dissolving the tested compound (Growth control) and two wells containing only media (background control) were included in this plate. Optical densities were measured after 24 hours at 37°C for bacteria and after 48 hours at 28°C for fungi using a multi-detection microplate reader at The Regional Center for Mycology and Biotechnology (Sun Rise –Tecan, USA) at 600 nm. Ampicillin, Gentamicin and Amphotericin B were used as standards for Gram positive bacteria, Gram negative bacteria and fungi respectively.

For the determination of MIC of tested samples by the micro-broth kinetic assay, the percentage of growth at each sample concentration was calculated with the following equation: % growth = [(OD600 of wells containing the sample/OD600 of the sample-free well) x 100] after substraction of background ODs (ODs of microorganism-free wells)[18].

Results and discussion

The starting exocyclic enaminones **4a,b** and **5** were prepared in good yields as described before [15-17] *via* condensation of the corresponding cyclic ketones namely, tetralone, 4-thiochromanone or indane-1,3-dione, with dimethylformamide-dimethylacetal (DMF-DMA) in dry xylene (or toluene) under reflux for 6hrs. The reaction of enaminones **4a,b** each with a variety of diazonium salts of heterocyclic amines, namely, 3-amino-1,2,4-triazole, 2-aminobenzimidazole and 5-amino-3-phenyl-1*H*-pyrazole, was then investigated. Thus, reaction of enaminones **4a,b**, each with the diazonium salt of 3-amino-1,2,4-triazole at low temperature in ethanol and in the presence of sodium acetate afforded products **8b** and **9a** (Scheme 2). The structure assigned for the products **8b** and **9a** was confirmed based on elemental and spectral (IR, ^{1}HNMR and Mass) data (see Experimental). For example, the IR spectra for product **9a** revealed the absence of both the carbonyl and the N-H stretching bands. Also, ^{1}H NMR displayed only singlet signal at δ 9.25 ppm and multiplet signals in the region δ 7.29-7.90 ppm due to the triazole and aromatic protons, respectively. The mass spectra of **8a** and **9b** revealed in each case a molecular ion peak which is in agreement with the assigned structure. Based on the foregoing data, we can conclude that product **9b** were formed directly *via* in situ dehydrative cyclization of the respective hydrazone **8b** (Scheme 2).

ISSN 2321-807X

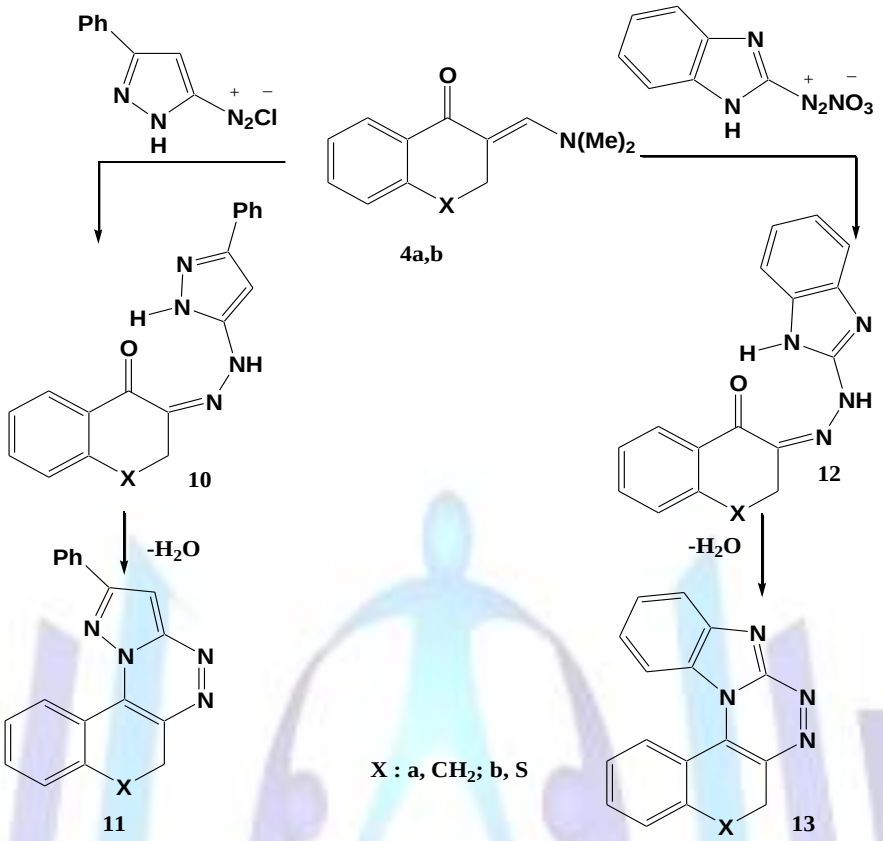


Scheme 2

Similarly, coupling reaction of **4a-b** each with the diazonium salt of 3-amino-5-phenyl-pyrazole or 2-aminobenzimidazole under the same reaction conditions afforded the respective pentacyclic products **11a,b**, **13a** and the hydrazone **12b.** The structure of the products was also identified on the basis of both elemental and spectral data (see Experimental). Treatment of the hydrazones **8b** and **12b** each with glacial acetic acid under reflux for 15hrs, gave the respective polycyclic compounds **9b** and **13b** (Scheme 2 and 3).

The structure assigned for the cyclized products **9b** and **13b** was established through the data obtained from both elemental and spectral analysis. For example, the IR spectrum of products revealed the absence of the characteristic bands due to the N-H groups. Also, the ^{1}H NMR spectrum of the same products displayed the expected peaks assigned for the aromatic protons and revealed the absence of the peaks attributed to the 2N-H protons.

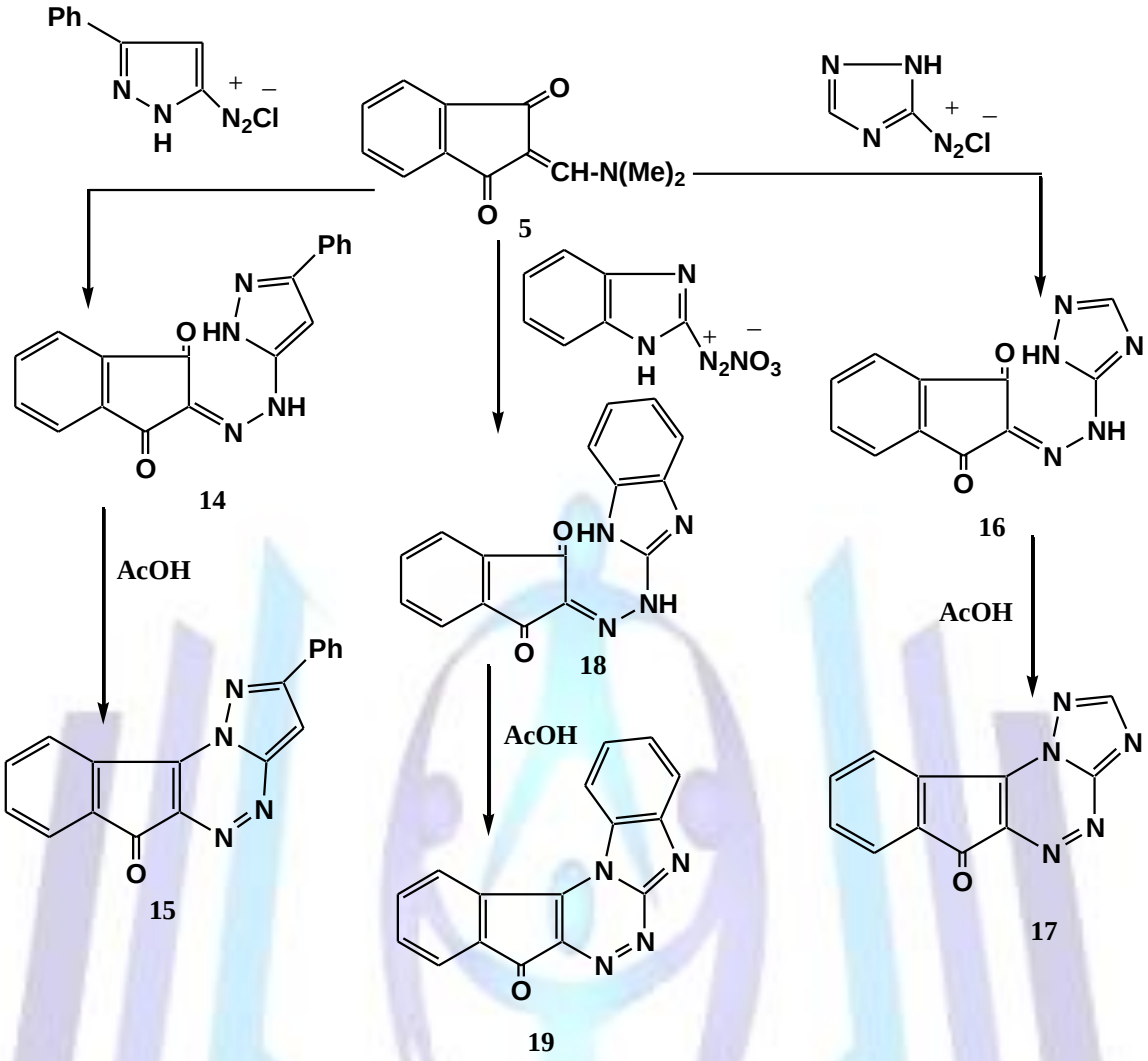
ISSN 2321-807X



Scheme 3

On the other hand, coupling reaction of exocyclic enaminone **5** with the same heterocyclic diazonium salts under the above mentioned conditions led to formation of the stable hydrazones **14**, **16** and **18**, which in turn cyclized by elimination of one molecule of water *via* heating with glacial acetic acid to give the final polycyclized products (Scheme 4).

The structure of the hydrazones **14**, **16** and **18** was also confirmed based on the data obtained from elemental and spectral analysis (see Experimental).



Scheme 4

Biological Screening :

Anti-microbial activity:

In vitro anti-microbial screening of some of the newly prepared compounds was carried out using four fungal strains , namely , Aspergillus fumigatus (RCMB 02568)(AF), Syncephalastrum racemosum (RCMB 05922)(SR), Geotricum candidum (RCMB 05097)(GC) and Candida albicans (RCMB 05036)(CA) and four bacteria species including Gram positive bacteria, Streptococcus pneumoniae (RCMB 010010)(SP), Bacillus subtilis (RCMB 010067)(BS), Gram negative bacteria, Pseudomonas aeruginosa (RCMB 010043)(PA) and Escherichia coli (RCMB10052)(EC). The results obtained showed that all the tested compounds especially compound **14** displayed high activity against most of the used microorganisms (fungi and bacteria) (see Table 1).The products **12b** and **16** have no activity against Candida albicans (CA). Also, the latter products together with products **8b** and **11b** have no activity against Pseudomonas aeruginosa (PA). Compound **14** showed higher potency against the fungus, namely, Syncephalastrum racemosum (SR) than the standard fungicide Amphotericin B (see Table 1)

ISSN 2321-807X

Table 1. Preliminary anti-microbial activity for tested compounds

Compd No.	Fungi				Gram positive bacteria		Gram negative bacteria	
	A. fumigatus	***S. racemosum***	***G. candidum***	***Candida albicans***	***S. Pneumoniae***	***B. subtilis***	***P. aeruginosa***	***E. coli***
8b	14.2 (±0.44)	15.3 (±0.58)	18.9 (±0.14)	16.2 (±0.25)	16.2 (±0.15)	19.8 (±0.42)	N.A.	15.9 (±0.37)
11b	16.1 (±0.33)	17.2 (±0.25)	19.4 (±0.34)	18.2 (±0.24)	17.3 (±0.63)	20.2 (±0.44)	N.A.	17.4 (±0.53)
12b	13.2 (±0.33)	14.1 (±0.25)	14.9 (±0.34)	N.A.	14.3 (±0.15)	15.2 (±0.42)	N.A.	12.4 (±0.53)
14	20.3 (±0.25)	22.4 (±0.44)	22.6 (±0.63)	19.4 (±0.58)	21.4 (±0.25)	22.4 (±0.63)	12.6 (±0.44)	18.6 (±0.44)
16	10.6 (±0.25)	11.7 (±0.34)	16.5 (±0.58)	N.A.	16.0 (±0.44)	18.3 (±0.67)	N.A.	13.0 (±0.46)
18	16.3 (±0.44)	18.4 (±0.58)	19.1 (±0.37)	15.2 (±0.58)	18.9 (±0.44)	20.3 (±0.58)	10.1 (±0.58)	19.8 (±0.63)
Amphotericin B	23.7 (±0.10)	19.7 (±0.2)	28.7 (±0.20)	25.4 (±0.1)	N.A.	N.A.	N.A.	N.A.
Ampicillin	N.A.	N.A.	N.A.	N.A.	23.8 (±0.2)	32.4 (±0.30)	N.A.	N.A.
Gentamicin	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	17.3 (±0.1)	19.9 (±0.30)

The test was done using the diffusion agar technique, well diameter: 6.0 mm (100 µl was tested), RCMB: Regional Center for Mycology and Bio-technology Antimicrobial unit test organisms NA: No activity, data are expressed in the form of mean± SD.

Minimum inhibition concentration MIC:

The minimum inhibition concentration and IC_{50} of four of the newly synthesized products **8b**, **11b**, **14** and **18** was examined against all the employed fungi and bacteria and the results obtained are depicted in the following Tables 2-5. These results indicated that the most reactive derivative is compound **14**.

Table 2. The minimum inhibition concentration and IC_{50} of compound **8b**

Sample concentration (µg/ml)	A. fumigatus Viability %	S. racemosum Viability %	G. candidum Viability %	C. albicans Viability %
125	86.33	64.35	33.22	49.22
62.5	100	89.22	49.22	72.44
31.25	100	100	63.25	88.22
15.63	100	100	72.14	100
7.81	100	100	83.52	100
3.9	100	100	100	100
1.95	100	100	100	100
0.98	100	100	100	100

0.49	100	100	100	100
IC 50-MIC	**>125-125**	**>125-62.5**	**60.8-7.81**	**98.3-25**
Amphotericin B	**<0.06-0.015**	**7.51-1.95**	**<0.06-0.015**	**0.5-0.06**

Table 2. The minimum inhibition concentration and IC_{50} of compound **8b**

Sample concentration (µg/ml)	**S. pneumoniae Viability %**	**B. subtilis Viability %**	**P. aeruginosa Viability %**	**E.coli Viability%**
125	42.11	10.32	100	62.58
62.5	55.44	18.33	100	86.25
31.25	83.58	42.55	100	100
15.63	100	66.88	100	100
7.81	100	82.44	100	100
3.9	100	100	100	100
1.95	100	100	100	100
0.98	100	100	100	100
0.49	100	100	100	100
IC_{50}-MIC	**88-31.25**	**15.2-6.25**	**0-0**	**>100-50**
Ampicillin	**<0.06-0.015**	**<0.06-0.007**		
Gentamicin			**115-15.63**	**8.85-1.95**

Table 3. The minimum inhibition concentration and IC_{50} of compound **11b**

Sample concentration (µg/ml)	**A. fumigates Viability %**	**S. racemosum Viability %**	**G. candidum Viability %**	**C. albicans viability %**
125	59.24	31.14	15.36	33.12
62.5	62.58	54.15	24.12	50.24
31.25	82.34	64.25	38.12	63.42
15.63	100	83.58	43.44	77.23
7.81	100	100	59.24	90.31
3.9	100	100	84.26	100
1.95	100	100	100	100
0.98	100	100	100	100
0.49	100	100	100	100
IC_{50}-MIC	**>125-25**	**73.8-15.63**	**12.4-3.9**	**63.4-7.81**
Amphotericin B	**<0.06-0.015**	**7.51-1.95**	**<0.06-0.015**	**0.5-0.06**

ISSN 2321-807X

Table 3. The minimum inhibition concentration and IC_{50} of compound **11b**

Sample concentration (µg/ml)	**S. pneumonia viability %**	**B. subtilis Viability %**	**P. aeruginosa viability %**	**E.coli Viability%**
125	33.25	17.26	100	36.25
62.5	56.24	28.66	100	52.44
31.25	63.25	37.35	100	68.33
15.63	82.34	49.36	100	89.57
7.81	100	54.32	100	100
3.9	100	76.25	100	100
1.95	100	87.35	100	100
0.98	100	100	100	100
0.49	100	100	100	100
IC_{50}-MIC	**79.5-15.63**	**14.6-1.95**	**0-0**	**71.9-15.63**
Ampicillin	**<0.06-0.015**	**<0.06-0.007**		
Gentamicin			**115-15.63**	**8.85-1.95**

Table 4. The minimum inhibition concentration and IC_{50} of compound **14**

Sample concentration (µg/ml)	**A. fumigates Viability %**	**S. racemosum Viability %**	**G. candidum Viability %**	**C. albicans Viability %**
125	10.12	9.13	8.22	17.25
62.5	31.66	22.77	19.23	24.16
31.25	43.22	30.66	28.33	31.28
15.63	51.66	43.25	32.25	43.28
7.81	62.44	53.14	46.77	62.55
3.9	73.25	62.11	56.67	83.44
1.95	88.22	76.33	71.72	100
0.98	100	86.22	80.25	100
0.49	100	100	100	100
IC_{50}-MIC	**18.7-1.95**	**10.3-0.98**	**6.53-0.98**	**12.9-3.9**
Amphotericin B	**<0.06-0.015**	**7.51-1.95**	**<0.06-0.015**	**0.5-0.06**

ISSN 2321-807X

Table 4. The minimum inhibition concentration and IC_{50} of compound **14**

Sample concentration (µg/ml)	**S. pneumonia Viability %**	**B. subtilis Viability %**	**P. aeruginosa Viability %**	**E. coli Viability%**
125	11.63	10.22	90.33	20.34
62.5	36.25	25.76	100	30.66
31.25	49.28	40.67	100	39.28
15.63	57.99	59.27	100	50.66
7.81	69.25	66.34	100	72.29
3.9	78.39	74.26	100	83.42
1.95	89.44	86.25	100	100
0.98	100	93.22	100	100
0.49	100	100	100	100
IC_{50}-MIC	**30-1.95**	**23.4-0.98**	**>125-125**	**16.5-3.9**
Ampicillin	**<0.06-0.015**	**<0.06-0.007**		
Gentamicin			**115-15.63**	**8.85-1.95**

Table 5. The minimum inhibition concentration and IC_{50} of compound **18**

Sample concentration (µg/ml)	**A. fumigates Viability %**	**S. racemosum Viability %**	**G. candidum Viability %**	**C. albicans Viability %**
125	53.44	20.73	7.38	62.57
62.5	76.25	40.66	13.97	86.42
31.25	82.44	59.42	49.35	100
15.63	100	73.25	58.64	100
7.81	100	86.44	68.25	100
3.9	100	100	83.25	100
1.95	100	100	100	100
0.98	100	100	100	100
0.49	100	100	100	100
IC_{50}-MIC	**>125-31.25**	**46.9-7.81**	**30.2-3.9**	**>125-62.5**
Amphotericin B	**<0.06-0.015**	**7.51-1.95**	**<0.06-0.015**	**0.5-0.06**

Table 5. The minimum inhibition concentration and IC_{50} of compound **18**

Sample concentration (µg/ml)	S. pneumonia Viability %	B. subtilis Viability %	P. aeruginosa Viability %	E. coli Viability %
125	16.25	18.37	87.32	22.36
62.5	20.67	33.26	100	35.68
31.25	50.67	49.27	100	53.26
15.63	59.25	62.58	100	78.32
7.81	73.44	70.25	100	86.34
3.9	91.34	79.34	100	89.16
1.95	100	89.25	100	93.25
0.98	100	100	100	100
0.49	100	100	100	100
IC_{50}-MIC	**31.9-3.9**	**30.4-1.95**	**>125-125**	**37-1.95**
Ampicillin	**<0.06-0.015**	**<0.06-0.007**		
Gentamicin			**115-15.63**	**8.85-1.95**

Conclusion:

In the present paper, we described a facile method for synthesis of tetra- and pentacyclic compounds *via* coupling reaction of a number of exocyclic enaminones with some heterocyclic diazonium salts. The tetra-and pentacyclic compounds were obtained either by in situ dehydrative cyclization of the initially formed hydrazones or by thermal treatment of the respective hydrazones with glacial acetic acid. Also, some of the newly synthesized products were tested against some fungi and bacteria and the results obtained indicate that all the tested compounds have high activity against most of the employed microorganisms. Moreover, compound **14** showed promising results since it has a higher potency against the fungus Syncephalastrum racemosum than the standard employed fungicide Amphotericin B.

REFERENCES

[1] G. Palmieri, Cimarelli, Arkivoc, vi (2006)104.

[2] J. Svete, Arkivoc, vii (2006) 35.

[3] I. O. Edafiogho; et al , J. Pharm. Sci., 96 (2007) 2509.

[4] Kh. D. Khalil, H. M. Al-Matar, D. M. Al-Dorri, M. H. Elnagdi. Tetrahedron 65(2009) 9421–9427.

[5] S. M. Riyadh, I. A.Abdelhamid, H. M.Al-Matar, N. M.Hilmy, M. H. Elnagdi, Heterocycles , 75 (2008) 1849.

[6] F. A. Abu Shanab; S. M.; Sherif, S. A., Mousa J. Heterocycl. Chem., 46 (2009) 801.

[7] P. A.; Derbyshire, G. A.; Hunter, M.; McNab, L. C. Monahan, J. Chem. Soc., Perkin Trans. 1 (1993) 2017.

[8] V. K.; Ahluwalia, P.; Sharma, B. Goyal, Indian J. Chem., 36B (1997) 169.

[9] Abdel-Khalik, M. M.; Agamy, S. M.; Elnagdi, M. H. Z. Naturforsch 55b (2000) 1211.

[10] B.; Al-Saleh, N.; Al-Awadi, H.; Al-Kandari, M. M.; Abdel-Khalik, M. H. Elnagdi, J. Chem. Res.(s) (2000)16.

[11] S.; Strah, B. Stanovnik, J. Heterocycl. Chem. 34(1997) 263.

[12] A. S. Shawali, A. J, Haboub, J. Chem. Res. (2011)341.

[13] A. S. Shawali, T. A. Farghaly, A. I. R. Aldahshoury, Arkivoc, (ix) (2009) 19.

[14] T. A., Farghaly, M. M., Abdalla, Bioorg. Med. Chem., 17(2009) 8012-8019.

[15] R. M.; Wagner, Chem. Ber., 104 (1971) 2975-2983.

[16] S. Eiden,; Arch. Pharmazie, 311(1978) 867-873.

[17] J. C. Zhuo, Magnetic Resonance in Chem.; 35 (1977) 432-440.

[18] E. G. Kaya, H. Özbilge, S. Albayrak, Determination of the effect of gentamicin against staphylococcus aureus by using microbroth kinetic system, Ankem Derg 23(3) (2009)110-114.

Author' biography with Photo

Thoraya Abd Elreheem Farghaly was born in Cairo, Egypt in 1974. She received her B.Sc. (1996); M.Sc. (2002) and Ph.D. (2005) degrees from University of Cairo. At present, She is Associate Professor of organic chemistry in the Chemistry Department, Faculty of Science, University of Cairo. She joined the scientific school of Prof. A. S. Shawali in 1997 and conducted several research projects in the area of the chemistry of hydrazonoyl halides, enaminones and heterocyclic chemistry. She synthesized many bioactive heterocyclic compounds. She published 65 papers including one review article.