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Synthesis, Physico-chemical and Antimicrobial Studies of Diketones, Disemicarbazones and Pentaaza Dispiro Tetradecaenes

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A new class of piperidin-4,5-diones (**1a-3a**), disemicarbazones (**1b-3b**) and pentaaza dispiro tetradecadienes (**1c-2c**) have been synthesized and characterized by analytical and spectral data. All the compounds were also evaluated for their antimicrobial activity.

Key Words: Piperidin diones, Disemicarbazones, Pentaazadispirotetradecadienes, Selenium dioxide, Heterocyclization.

INTRODUCTION

Everyday a large number of organic compounds are synthesized, characterized and its applicability in different fields is tested. Synthesis of 1,2-diketones by selenium dioxide oxidation are well documented in literature[1,2]. Synthesis and stereo structure of spiro 1,3,4-oxadiazoline from semicarbazones are reported by Somogyi *et al.*[3]. During the past considerable evidence has been accumulated to demonstrate the efficacy of 1,3,4-oxadiazoles as antimicrobial[4] insecticidal[5] electron import materials for OLEDS[6,7] and as increased brain derived neutotropic factor[8] (BDNF). By progress of these observations, the synthesis of new heterocyclic 1,2-diketones (**1a-3a**), its disemicarbazones (**1b-3b**) and 1,2-dispiro compounds (**1c-2c**) are undertaken.

EXPERIMENTAL

Melting points reported are uncorrected and measured using Tempo apparatus. IR spectra are recorded in KBr pellets on a Perkin Elmer 577 IR spectrophotometer (ν_{max}, cm^{-1}) ^1H and ^{13}C NMR spectra were recorded on a Jeol GSX 400 model spectrophotometer in $CDCl_3$/DMSO-d_6 with TMS as internal standard.

General procedure

Synthesis of diaryl substituted piperdin-4,5-diones (1a-3a): Precursors carbomethoxy-2,6-diaryl substituted piperidin-4-ones (**1-3**) are synthesized by literature procedure[9]. 3-Carbomethoxy-2,6-diphenylpiperidin-4-one (0.01 m) and selenium dioxide (0.01 M) are refluxed in sufficient quantity of glacial acetic acid in a fume cupboard for 5 h. Clear filtrate after the separation of metallic selenium is neutralized with ammonia, filtered and recrystallized with alcohol to give orange red crystals (**1a**). Related compounds (**2a-3a**) are synthesized in a similar way from their corresponding precursors (**1, 2**).

Synthesis of 3-carbomethoxy-2,6-diarylpiperidin-4,5-disemicarbazones (1b-3b): 3-Carbomethoxydiarylpiperidin-4,5-diones (**1a-3a**) mixed with semicarbazide in the ratio 1:2 and refluxed in a water bath in an alcoholic medium for *ca.* 5 h. Clear filtrate diluted and filtered. Recrystallized and column chromatographed to get white crystals.

Substituted piperidinyldispiro-1,3,4-oxadiazoles (1c-2c)

3,13-Diacylamino-7,9-diphenyl-6-carbomethoxy-4,14-dioxa-1,2,8,11,12-pentaazadispiro[4.4.4]tetradeca-2,12-diene (1c): 3-Carbomethoxypiperidin-4,5-dione (**1b**) refluxed with acetic anhydride and conc. H_2SO_4 for *ca.* 5 h. Clear filtrate neutralized with ammonia, filtered and recrystallized to get brown colour solid.

3,13-Diacylamino-7,9-di(*p*-methoxyphenyl-6-carbomethoxy-4,14-dioxa-1,2,8,11,12-pentaaza dispiro[4.4.4]-tetradeca-2,12-diene (2c): Compound **2b** refluxed with acetic anhydride to get the title compound.

Structural characterization

3-Carbomethoxy-2,6-diphenylpiperidin-4,5-dione (1a): m.f. $C_{19}H_{17}NO_2$, m.p. 110 ºC, Yield (65 %): N %, found. (calcd.) 4.35 (4.33). IR (KBr, ν_{max}, cm^{-1}): 3443 (N-H), 1720, 1710, 1690 (CO of ring and ester); 3020, 1600, 1108, 767, 698 (aromatic); 2976, 2950 (C-H). ^1H NMR (δ ppm) 3.5 (s, 3H, $COOCH_3$), 7.2-7.7 (m, 10H, Ar-H) 3.3 (d, 1H, C_3(H) 3.8-4.2 (m, 2H, C_2(H), C_6(H)); 1.8 δ (bs, 1H, NH). ^{13}C NMR (δ ppm) 37, 46 ($COOCH_3$), 62, 70 (C_2, C_6), 77 (solvent) 127, 131, 142, 143, 144 (aromatic) 179 (CO of ester), 192, 198 (CO of ring).

3-Carbomethoxy-2,6-di(*p*-methoxyphenyl)piperidin-4,5-dione (2a): m.f. $C_{21}H_{21}NO_6$, m.p. 160 ºC; yield (65 %); N %, found (calcd.) 3.65 (3.66). IR (KBr, ν_{max}, cm^{-1}): 3300 (N-H); 1725-1700 (CO of ring and ester); 3020, 1598, 1155, 826, 754, 700 (aromatic); 1247 (O-C of ester); 2984, 2976 (C-H). ^{1}H NMR (δ ppm); 3.5(s, 3H, $COOCH_3$); 7.2-7.7 (m, 8H, Ar-H); 3.8-3.9 (m, 4H,C_3(H), OCH_3); 4-4.25 (m, 2H, C_2(H), C_6(H)); 1.7 (bs, 1H, NH). ^{13}C NMR (δ ppm); 40, 44 ($COOCH_3$); 55 (OCH_3); 62, 84 (C_2, C_6), 77 (solvent), 126-132 (aromatic) 179, 180 ($COOCH_3$),198, 202 (CO of ring).

3-Carbomethoxy-2,6-di(*p*-N,N-dimethylaminophenyl) piperidin-4,5-dione (3a): m.f. $C_{22}H_{27}N_3O_4$; m.p. 150 ºC; yield (60 %): N %, found (calcd.) 9.92 (10.69), IR (KBr, ν_{max}, cm^{-1}): 3252 (N-H); 1745, 1710, 1690 (CO of ring and ester); ^{1}H NMR (δ ppm) 3.4 (s, 3H, $COOCH_3$); 2.9 (S, 6H, $N(CH_3)_2$); 6.8-7.8 (m,8H,Ar-H); 3.2 (d, 1H, C_3(H)); 4.0-4.2 (m, 2H, C_2(H), C_6(H)); 1.7 (bs, 1H, NH); ^{13}C NMR (δ ppm); 37, 46, 48 ($COOCH_3$, $N(CH_3)_2$); 60, 62 (C_2, C_6), 77 (solvent); 126, 128, 129, 130, 131, 143 (aromatic) 179 ($COOCH_3$), 190,192 (CO of ring).

3-Carbomethoxy-2,6-diphenylpiperidin-4,5-disemicarbazone (1b): m.f. $C_{21}H_{23}N_7O_4$; m.p. 120 ºC; yield (67 %): N %, found (calcd.) 22.33 (22.42), IR (KBr, ν_{max}, cm^{-1}): 3500-3300 (NH_2, NH), 1698 (CO of C=NNHCONH$_2$; 1720 (CO of ester); ^{1}H NMR (δ ppm); 2.1-2.4 (bs, 2H, C_3(H) and NH); 3.5-4.2 (m, 5H, $COOCH_3$, C_2(H), C_6(H)); 7.1-7.8 (Ar-H); 8.1, 8.4 (NH and NH_2). ^{13}C NMR (δ ppm); 46, 47, 60, 62, 126, 128, 129, 131, 134, 164, 168, 174, 178, 179, 180.

3-Carbomethoxy-2,6-di(*p*-methoxyphenyl)piperidin-4,5-disemicarbazone (2b): m.f. $C_{23}H_{27}N_7O_6$, m.p. 130 ºC, yield (73 %) N %, found (calcd.) (%) (19.72); IR (KBr, ν_{max}, cm^{-1}); 3456, 3254, 2948, 2947, 1720, 1685, 1604, 1512, 1429, 1106, 835, 732, ^{1}H NMR (δ ppm); 1.7-2.6 (overlapped signal, C_3(H), NH; 3.5-4.0 ($COOCH_3$, C_2(H), C_6(H), OCH_3); 6.8-7.8 (Ar-H), 8.4-8.7 (NH and NH_2), ^{13}C NMR (δ ppm); 40, 41, 43, 56, 62, 67, 121, 123, 126, 128, 172, 179, 180.

3-Carbomethoxy-2,6-di(*p*-N,N-dimethylaminophenyl) piperidin-4,5-disemicarbazone (3b): m.f. $C_{25}H_{33}N_7O_4$, m.p. 116 ºC, yield (66 %):N %, found (calcd.) 19.26 (19.87), IR (KBr, ν_{max}, cm^{-1}): 3500-3200, 2948, 2930, 1721, 1686, 1604, 1513, 1428, 1107, 836, 735, ^{1}H NMR (δ ppm): 3.4 (s, 3H, $COOCH_3$), 2.9 (S, 6H, $N(CH_3)_2$), 6.8-7.6 (m, 8H, Ar-H) 3.2 (d, 1H, C_3(H) and NH); 4.0-4.2 (m, 2H, C_2(H), C_6(H)); ^{13}C NMR (δ ppm): 37, 47, 63, 69, 77, 127, 132, 143, 144, 168, 172, 178.

3,13-Diacylamino-7,9-diphenyl-6-carbomethoxy-4,14-dioxa-1,2,8,11,12-pentaazadispiro[4.4.4]tetradeca-2,12-diene (1c): m.f. $C_{25}H_{27}N_7O_6$, m.p. 160 ºC, yield (62 %): N %, found (calcd.) 17.98 (18.81), IR (KBr, ν_{max}, cm^{-1}): 1729-1700 (CO of $NHCOCH_3$ and ester), 3018, 1602, 1113, 767, 698 (aromatic), 2950, 2976 (C-H); ^{1}H NMR (δ ppm): 7.2-7.5 (aromatic); 8.17-8.572 ($NHCOCH_3$ of two oxadiazoles rings) 3.54, 3.58, 3.81 (CH_3 of ester and $NHCOCH_3$); 2.12-2.26 (bs, 2H, C_3H and NH); 4.13-4.24 (m, 2H, C_2H and C_6H); ^{13}C NMR (δ ppm): 22, 37, 49 ($COOCH_3$, spiro carbon), 62, 64 (C_2, C_6), 77 (solvent) 121, 122, 126, 128, (aromatic), 159, 161 (C=N) 174, 187 ($COOCH_3$ and $NHCOCH_3$).

3,13-Diacylamino-7,9-di(*p*-methoxy phenyl-6-carbomethoxy-4,14-dioxa-1,2,8,11,12-pentaaza dispiro[4.4.4] tetra deca-2,12-diene (2c): m.f. $C_{25}H_{27}N_7O_6$ m.p. 160 ºC, yield (62 %): N %, found (calcd.) 17.98 (18.81), IR (KBr, ν_{max}, cm^{-1}): 1729-1700 (CO of $NHCOCH_3$ and ester), 3018, 1602, 1113, 767, 698 (aromatic), 2976, 2950 (aliphatic C-H); ^{1}H NMR (δ ppm); 7.27-7.52 (aromatic), 8.1-8.7 (NH of $NHCOCH_3$); 3.6-3.8 (overlapped signal methyl of $NHCOCH_3$, OCH_3); 1.9 (bs, NH); 2.2 (C_3H)); 4.0-4.2 (m, 2H, C_2(H) and C_6(H)); ^{13}C NMR (δ ppm); 3950 ($COOCH_3$, spiro carbon), 60, 64 (C_2, C_6), 77 (solvent) 119-128 (aromatic) 159, 161 (C=N) 174, 187 ($COOCH_3$ and $NHCOCH_3$).

Antimicrobial studies: All the compounds are screened for their antimicrobial activity against *Escherichia coli* and *Candida albicans* using ciprofloxacin as standard drug. Nutrient agar is used as culture medium. Test solutions and standard drug having100 µg/mL concentration are prepared in DMSO and used for testing growth inhibition by cup-plate method.

RESULTS AND DISCUSSION

Precursors diaryl substituted piperidin-4-ones (**1-3**) are prepared in high yields by following literature[9] procedure. New class of heterocyclic-1,2-diketones (**1a-3a**), disemicarbazones (**1b-3b**) and dispiro piperidinyl 1,3,4-oxadiazolines (**1c-2c**) are synthesised as per **Scheme-I**.

All the synthesized compounds were characterized by elemental analysis and spectral data. IR spectrum of compound **1a** displayed bands characteristic of two CO's of piperidin ring, ester CO, phenyl ring and NH group. ^{13}C NMR data also proves the presence of two keto groups at 198 and 202 δ. Compound **1b** showed bands corresponding to C=N group in the ^{13}C NMR spectrum and absence of bands above 190 δ. Corresponding dispiro compound showed bands characteristic of spiro carbon, $NHCOCH_3$ and C=N in their spectrum. Elemental analysis also well agreed with their molecular formula. Related compounds **2a-2c** and **3a-3b** also showed bands and signals indicative of those compounds. All the compounds were screened for antimicrobial activity (Table-1). They showed mild activity against *E. coli* and *Candida albicans*.

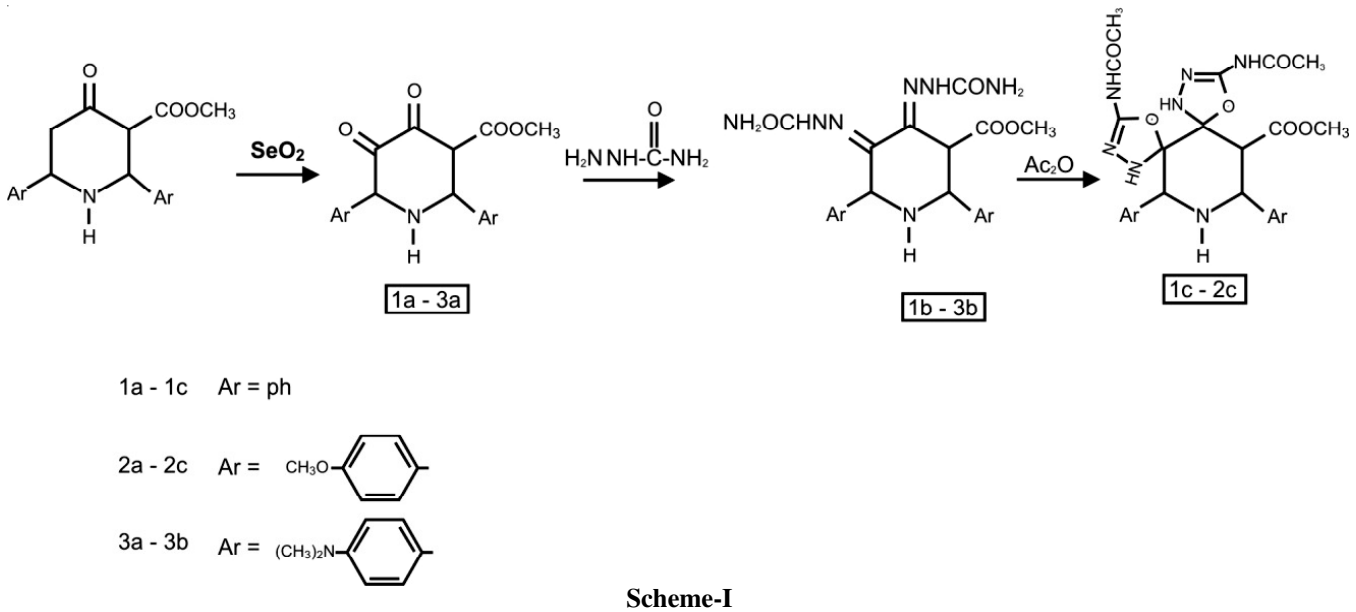
TABLE-1

Compounds	Zone of inhibition (mm)	
	Escherichia coli	*Canida albicans*
1a	13	–
2a	15	–
3a	10	5
1b	7	6
2b	4	6
3b	8	6
1c	4	6
2c	4	5
Ciprofloxan	24	13

All showed mild activity against *E. coli* and *C. albicans*

Conclusion

Synthesis, characterization and antimicrobial studies of diaryl substituted piperdin-4,5-diones, 3-carbomethoxy-2,6-diaryl piperidin-4,5-disemicarbazones and 3,13-diacylamino-7,9-diphenyl-6-carbomethoxy-4,14-dioxa-1,2,8,11,12-pentaazadispiro[4.4.4]tetradeca-2,12-diene were reported.



Scheme-I

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