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SYNTHESIS OF SOME NOVEL PIPERIDINE DERIVATIVES FROM SUBSTITUTED BENZOSUBERONES

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Abstract:
8-(4-Methoxy-phenyl)-2-methyl-12-piperidin-1-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalenederivatives (**4a-e & 5a-e**) are obtained by the condensation of 2-Amino-4-(4-methoxy-phenyl)-10-methyl-4,5,6,7-tetrahydro-1-oxa-dibenzo[a,c]cycloheptene-3-carbonitrile derivatives**3**withphosphorus oxy chloride in dimethyl formamide and piperidine. The structuresof the compounds**5a-e** were confirmed by the spectral analysis.

Keywords: benzosuberones; piperidine; carbonitrile.

Introduction:

Piperidine containing compounds represent one of the most important synthetic medicinal blocks for drugs construction, and their synthesis has long been widespread. It can be unequivocally stated that heterocyclic compounds play a significant part in the pharmaceutical industry, and one of the most common in their structure is the piperidine cycle. Its derivatives are used in over twenty drug classes [I], including anticancer agents [II] - [VII], drugs for Alzheimer's disease therapy [VIII], antibiotics [IX], analgesics [X] [XI], antipsychotics [XII]-[XIV], antioxidants [XV] [XVI], etc. Moreover, piperidines are also a part of many alkaloids showing biological activity. For example, the well-known atropine (used clinically for the treatment of vomiting, nausea, and bradycardia [XVII]; an effective agent for slowing the development of myopia [XVIII]) and morphine analgesic for severe pain relief [XIX]; used as a third-line therapy in the treatment of neuropathic pain [XX]) contain a fused piperidine ring.

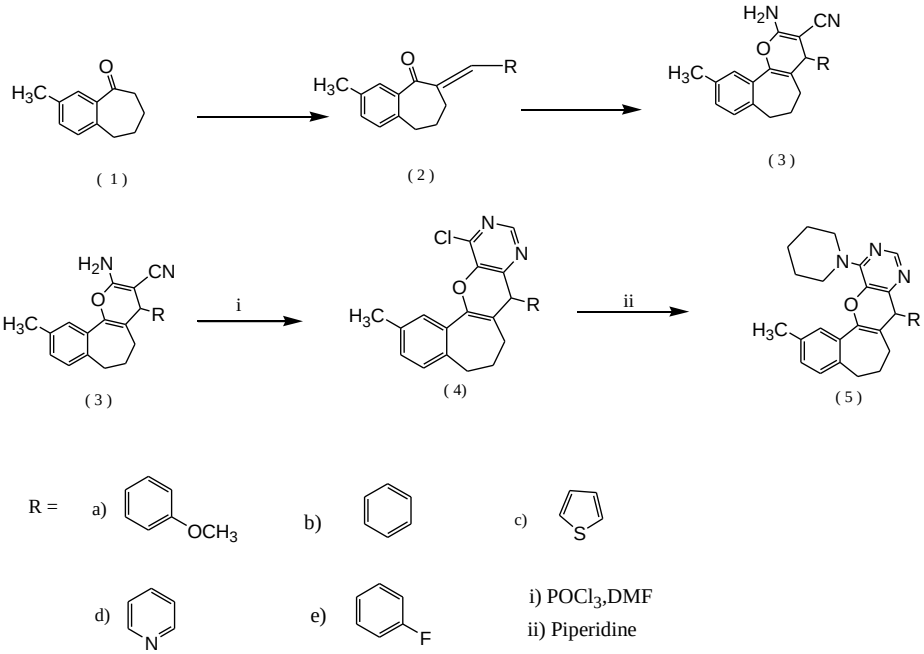
Piperidine, a derivative of piperidine and the main active chemical component of black pepper, is attracting more and more attention from researchers, despite the fact that it was discovered more than 200 years ago. It is believed that piperine has a broad scope of beneficial biological properties, from antibacterial to anticancer [XXI]-[XXV]. Febrifugine and its synthetic analog halofuginone are efficiently used as anti-parasitic drugs [XXVI]. Along with

already known drugs, the scientific community constantly proposes new biologically active piperidine scaffolds. Further, researchers will discuss recent discoveries in the biological evaluation of synthetic potential drugs containing the piperidine moiety.

Cancer is one of the biggest health problems worldwide, with nearly 10 million deaths reported in 2020 according to WHO. A lot of resources are spent on the development of new drugs for fighting cancer, but despite all efforts, innate and acquired resistance mechanisms are often observed [XXVII]. Therefore, screening for new developments and breakthroughs in this area is very important and relevant.

It was thought worthwhile to prepare the title compounds with the hope that these new ring systems may prove to be biologically active. we report in this paper the conversion of 2-Amino-4-(4-methoxy-phenyl)-10-methyl-1-oxo-4,5,6,7-tetrahydro-1*H*-dienzo[a,c]cycloheptene-3-carbonitrile

Derivatives [XXVIII] **(3a-e)** into derivatives of a new heterocyclic system containing piperidine moiety **(5a-e)**



Results and Discussion

6-(4-Methoxy-benzylidene)-3-methyl-6,7,8,9-tetrahydro-benzocyclohepten-5-one (**2a-e**)were obtained by the condensation of 3-Methyl-6,7,8,9-tetrahydro-benzocyclohepten-5-one (**1**) with appropriate aromatic aldehydes. Cyclizaion of **2a-e** with malononitrile in dimethyl formamide yielded 2-Amino-4-(4-methoxy-phenyl)-10-methyl-1-oxo-4,5,6,7-tetrahydro-1*H*-dienzo[a,c]cycloheptene-3-carbonitrile derivatives (**3a-e).** The compound **4a-e** obtained from **3a-e** with the addition of Phosphorous oxychloride in dimethyl formamide at 0^0 C then it was stirred for 24 hours at 80^0C and worked up as usual. This crude compound (**4a-e)** was treated with piperidine at 70^0C for 2 hours and after work up it was purified by column chromatography yielded **5a-e** and confirmed by spectral analysis.

Experimental:

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; 1H NMR in CDCl3 on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micro mass 7070H

mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapour as visualizing agent.

12-Chloro-8-(4-methoxy-phenyl)-2-methyl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (4a-e) General procedure:0.6 ml of phosphorous oxy chloride was added slowly at 0^{o}C to a well stirred solution of 0.02 ml of dimethyl formamide, it was stirred for 30 minutes then 0.1 gr of compound (**3a-e**) was added to it and it was slowly increases to 80^{o}C, the reaction mixture was stirred for 24 hrs at this temperature . After completion of the reaction it was worked up in the usual way to give crude compound (**4a-e**).

8-(4-Methoxy-phenyl)-2-methyl-12-piperidin-1-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (5a-e) General procedure:0.0012 moles (0.5 grs)of the crude compound (**4a-e**) was mixed with 1 ml of piperidine and it was stirred for 2 hrs at 70^{0} C. Then the mixture was concentrated to dryness in vacuum and the residue was dissolved in water extracted with chloroform. The organic layer was worked up in the usual way to give gummy compound which was purified by column chromatography using silica gel with ethyl acetate-petroleum ether as eluent (2:8) afforded **5a**: Yield: 60%; m.p. 60-62^{0}C; IR (KBr): 1259 1657 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.48-1.52 (6H, m, Piperdin-CH_2) 1.64-1.70 (2H, m, 6-CH_2), 1.94-2.10 (2H, m, 7-CH_2), 2.34 (3H, s, 2-CH_3), 2.54-2.60 (2H, m, 5-CH_2), 2.69-2.71 (4H, m, N-CH_2), 3.71 (3H, s, OCH_3), 4.68 (1H, s, 8-CH), 6.64-7.05 (7H, m, Ar-CH) and 7.64 (1H, s, N-CH); MS: m/z 453 ($M^{+\cdot}$); Anal. Found: C, 76.80; H, 6.82; N, 9.25, O, 7.04 $C_{29}H_{31}N_3O_2$ requires C, 76.82; H, 6.84; N, 9.27; O, 7.06 %.

2-Methyl-8-phenyl-12-piperidin-1-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (5b): Yield: 61%; m.p. 218-220^{0}C (decomposed); IR (KBr): 1657 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.47-1.52 (6H, m, Piperdin-CH_2) 1.64-1.66 (2H, m, 6-CH_2), 1.95-2.10 (2H, m, 7-CH_2), 2.35 (3H, s, 2-CH_3), 2.54-2.59 (2H, m, 5-CH_2), 2.68-2.71 (4H, m, N-CH_2), 4.73 (1H, s, 8-CH), 6.64-7.15 (8H, m, Ar-CH) and 7.65 (1H, s, N-CH); MS: m/z 423 ($M^{+\cdot}$); Anal. Found: C, 79.40; H, 6.83; N, 9.90 O, 3.76. $C_{28}H_{29}N_3O$ requires C, 79.43; H, 6.85; N, 9.92O, 3.78 %.

2-Methyl-12-piperidin-1-yl-8-thiophen-2-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (5C): Yield: 54%; m.p. 65-67^{0}C; IR (KBr): 1657 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.48-1.52 (6H, m, Piperdin-CH_2) 1.64-1.66 (2H, m, 6-CH_2), 1.97-2.00 (2H, m, 7-CH_2), 2.35 (3H, s, 2-CH_3), 2.54-2.58 (2H, m, 5-CH_2), 2.67-2.71 (4H, m, N-CH_2), 4.73 (1H, s, 8-CH), 6.71-7.06 (7H, m, Ar-CH), and 7.66 (1H, s, N-CH); MS: m/z 429 ($M^{+\cdot}$); Anal. Found: C, 72.70; H, 6.27; N, 9.77;O, 3.70; S, 7.43. $C_{26}H_{27}N_3OS$ requires C, 72.72; H, 6.29; N, 9.79;O, 3.72; S, 7.45 %.

2-Methyl-12-piperidin-1-yl-8-pyridin-2-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (5d) : Yield: 57%; m.p. 60-64^{0}C; IR (KBr): 1657 (C=N) cm^{-1}; ^{1}H NMR (CO, 7.06 DCl_3): δ 1.48-1.52 (6H, m, Piperdin-CH_2) 1.63-1.66 (2H, m, 6-CH_2), 1.99-2.10 (2H, m, 7-CH_2), 2.36 (3H, s, 2-CH_3), 2.54-2.59 (2H, m, 5-CH_2), 2.67-2.70 (4H, m, N-CH_2), 4.73 (1H, s, 8-CH), 6.64-7.74 (6H, m, Ar-CH), 7.66 (1H, s, N-CH and 8.65-8.68 (1H, d, Py-N-CH); MS: m/z 424 ($M^{+\cdot}$); Anal. Found: C, 76.39; H, 6.58; N, 13.18; O,3.75. $C_{27}H_{28}N_4O$ requires C, 76.41; H, 6.60; N, 13.20; O,3.77 %.

8-(4-Fluoro-phenyl)-2-methyl-12-piperidin-1-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene (5e) : Yield: 55%; m.p. 61-63^{0}C; IR (KBr): 1657 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.49-1.53 (6H, m, Piperdin-CH_2) 1.63-1.70 (2H, m, 6-CH_2), 1.95-2.08 (2H, m, 7-CH_2), 2.34 (3H, s, 2-CH_3), 2.53-2.61 (2H, m, 5-CH_2), 2.69-2.72 (4H, m, N-CH_2), 4.73 (1H, s, 8-CH), 6.84-7.15 (7H, m, Ar-CH) and 7.66 (1H, s, N-CH); MS: m/z 441 ($M^{+\cdot}$); Anal. Found: C, 76.17; H, 6.32; N, 9.50; O,3.60; F, 4.28. $C_{28}H_{28}N_3OF$ requires C, 76.19; H, 6.34; N, 9.52; O,3.62; F, 4.30 %.

2-Methyl-12-piperidin-1-yl-8-thiophen-2-yl-5,6,7,8-tetrahydro-13-oxa-9,11-diaza-benzo[3,4]cyclohepta[1,2-b]naphthalene: Yield: 54%; m.p. 65-67^{0}C; IR (KBr): 1657 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.48-1.52 (6H, m, Piperdin-CH_2) 1.64-1.66 (2H, m, 6-CH_2), 1.97-2.00 (2H, m, 7-CH_2), 2.35 (3H, s, 2-CH_3), 2.54-2.58 (2H, m, 5-CH_2), 2.67-2.71 (4H, m, N-CH_2), 4.73 (1H, s, 8-CH), 6.71-7.06 (7H, m, Ar-CH), and 7.66 (1H, s, N-CH); MS: m/z 429 ($M^{+\cdot}$); Anal. Found: C, 72.70; H, 6.27; N, 9.77;O, 3.70; S, 7.43. $C_{26}H_{27}N_3OS$ requires C, 72.72; H, 6.29; N, 9.79;O, 3.72; S, 7.45 %.

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