HL
http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (4), 2014, 519-524

SYNTHESIS OF NOVEL DERIVATIVES OF PIPERIDINE

Vijay V Dabholkar*, Mustaqeem Mohammed A, Navnath.B Shinde, Omprakash G. Yadav

Organic Research Laboratory, Department of Chemistry,
Guru Nanak College, G.T.B Nagar, Mumbai-400 037.
E-mail: vijaydabholkar@gmail.com
mustaqeem19@gmail.com

Abstract:
The compound **(2)** was synthesized from 5, 6-Dimethoxy-2-piperidin-4-yl-methyl-indan-1-one **(1)** by treatment with Ethyl bromo acetate and tri ethyl amine in dichloromethane, which was further converted to its hydrazone derivative **(3)** by the action of hydrazine hydrate. **(3)** on further reaction with active methylene groups furnished respective pyrazoles, Oxadiazole, indazole & triazole. The structures of the synthesized compounds were confirmed by physico-chemical test and spectral techniques. The representative samples were also screened for their anti-microbial activity against gram positive and gram negative bacteria.

Introduction:

Heterocycles are abundant in nature and are of great significance to life because of their structural subunits exists in many natural products such as vitamins, hormones, antibiotics, alkaloids as well as pharmaceuticals, herbicidal, dyes and many more compounds[I]. Electron rich nitrogen and oxygen heterocycles like pyrazine, pyridine, imidazole, Piperidine, diazole etc[II]. are found to possess various diversified activities viz. antibacterial[III], antifungal[IV], antimycobacterial[V]. Pyrazole chemically known as 1, 2-diazole has become a popular topic due to its manifold uses[VI]. The chemistry of pyrazolone and its derivatives is particularly interesting because of their potential application in medicinal chemistry as analgesic[VII-VIII], anti-inflammatory[IX], antiparasitic[X] and enzyme inhibitory agents [XI].

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Bruker 600 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in ð ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis [4-(5,6-Dimethoxy-1oxo-indan-2-yl-methyl)-piperidin-1-yl]-acetic acid ethyl ester (2):

Equimolar mixture of **(1)** (1 mole), triethyl amine (1 mole) and ethyl bromoacetate (1mole), in dichloromethane was stirred for 2 hrs . The progress of the reaction was monitored by TLC, upon completion, the content was poured into cold water. The separated organic layer was washed with water to yield **(2).**

b.p =215-218 °C, yield = 68 %

Spectral Interpretation: (2)

IR (cm-1): 1760(C=O ester), 1700(C=O ketone), ^{1}H NMR (DMSO-d6, ð/ ppm): 1.32 (t, 3H), 1.40 (t, 2H, CH_2),1.46 (q, 4H,2× CH_2), 1.49 (m, 4H, CH), 2.24 (t, 4H,2× CH_2), 2.70 (d, 2H, CH_2), 3.32 (s, 2H, CH_2), 3.37 (m, 1H, CH),3.73(s, 6H, 2× OCH_3), 4.12 (s, 2H, CH_2),6.8-7.2 (s,2H,Ar-H) Anal.Calcd for $C_{21}H_{29}NO_5$, C,75.63; H, 6.03; N, 13.24% Found: C, 75.12; H, 5.69, N, 13.01 %

Synthesis of [4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl]-acetic acid hydrazide (3)

A mixture of **(2)** (1 mole) and hydrazine hydrate (1.2 mole) in methanol was refluxed for 7 hrs. The progress of reaction was monitored by TLC, upon completion, the reaction mass was cooled to 0 to 5 ºC. Yellow color solid thus obtained, was filtered and washed with cold methanol to yield **(3)**.

m.p = <300 °C, yield = 78%

IR (cm-1): 1720(C=O), 1680(C=O amide), ^{1}H NMR (DMSO-d_6, ð/ ppm): 1.40 (t, 2H, CH_2),1.46 (q, 4H,2× CH_2), 1.49 (m, 4H, CH), 2.24 (t, 4H,2× CH_2), 2.80 (d, 2H, CH_2), 3.37 (m, 1H, CH),3.73(s, 6H, 2× CH_3), 4.12 (s, 2H, CH_2), 5.0 (s, 2H, NH_2), 7.0-7.2 (s,2H,Ar-H), 9.0 (s, 1H, NH), Anal.Calcd for $C_{19}H_{27}N_3O_4$, C,63.14; H, 7.47; N, 11.63% Found: C, 63.30; H, 7.01, N, 11.25 %

Synthesis of 4 & 5

A mixture of carbohydazide **(3)** (1 mole) and acetyl acetone (1.25 mole) was refluxed for 6 hrs in presence of ethanol as a solvent & acetic acid as a catalyst. The progress of reaction was monitored on TLC. Upon completion, the reaction mass was cooled to RT. The product thus obtained was filtered and washed with ethanol, followed by recrystallization to afford respective (**4)**. Similar procedure was adopted for synthesis of **(5)**.

Spectral Interpretation:

2-{1-[2-(3,5-Dimethyl-pyrazol-1-yl)-2-oxo-ethyl]-piperidin-4-ylmethyl}-5,6-dimethoxy-indan-1-one(4): M.P =206-208 °C, yield = 75%, IR (cm-1): 1720(C=O), 1680(N-C=O), ^{1}H NMR (DMSO-d6, ð/ ppm): 1.2 (m, 1H, CH_2), 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.24 (s, 4H, 2x CH_2), 2.24 (s, 4H, 2x CH_2), 2.5 (s, 1H,CH), 3.33(t, H, CH), 3.6(s, 1H,NH),3.76 (s, 6H, 2x OCH_3), 5.2 (s, 2H, CH_2), 5.6 (s, 1H, CH), 7.12-7.36 (d, 2H, Ar -H). ^{13}C NMR (DMSO-d_6, ð/ ppm): 13.5(CH_3), 15.5(CH_3), 19.10 (2×CH_2) ,25.5(CH), 30.50 (2×CH_2) ,35.00 (2×CH_2) , 38.25 (CH_2), 42.25 (CH_2) ,55(2× OCH_3), 104(CH), 121-150 (Ar-C and C=C), 165.22 (C=O), LCMS; m/z: 425; Anal.Calcd for $C_{23}H_{29}N_3O_5$, C,67.76 H, 7.29; N, 9.88% Found: C, 64.06; H, 7.52, N, 9.45 %

1-{2-[4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl]-acetyl}-5-methyl-1,2-dihydro-pyrazol-3-one (5): M.P =77 °C, yield = 70%, IR (cm-1): 1725(C=O), 1685(N-C=O), ^{1}H NMR (DMSO-d_6, ð/ ppm): 1.2 (m, 1H, CH_2), 2.1 (s, 3H, CH_3), 2.24 (s, 4H, 2x CH_2), 2.24 (s, 4H, 2x CH_2), 2.5 (s, 1H,CH), 3.33(t, 2H, CH), 3.6(s, 1H,NH),3.76 (s, 6H, 2x OCH_3), 5.2 (s, 2H, CH_2), 5.6 (s, 1H, CH), 7.12-7.36 (d, 2H, Ar -H). ^{13}C NMR (DMSO-d6, ð/ ppm): 13.5(CH_3), 19.10 (2×CH_2) ,25.5(CH), 30.50 (2×CH_2) ,35.00 (2×CH_2) , 38.25 (CH_2), 42.25 (CH_2) ,55(2×OCH_3), 104(CH), 121-150 (Ar-C and C=C), 165.22 (C=O), 186.5 (C=O).LCMS; m/z: 423; Anal.Calcd for $C_{23}H_{29}N_3O_5$, C,64.63 H, 6.79; N, 9.83% Found: C, 64.06; H, 6.52, N, 9.45 %

Synthesis of 6 & 7

A mixture of carbohydazide **(3)** (1 mole) and Meldrum's acid or dimedone (1.25 mole) was refluxed for 6 hrs in presence of ethanol as a solvent & acetic acid as a catalyst. The progress of reaction was monitored on TLC. Upon completion, the reaction mass was cooled to RT. The product thus obtained was filtered and washed with ethanol, followed by recrystallization to afford respective (**6**). Similar procedure was adopted for synthesis of **(7).**

Spectral Interpretation:

[4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl]-acetic acid(6-hydroxy-2,2-dimethyl-[1,3]dioxin-4-ylidene)-hydrazide. (6):

M.P =49 °C, yield = 68%, IR (cm-1): 1745(C=O ester), 1680(N-C=O), ^{1}H NMR (DMSO-d_6, ð/ ppm): 1.76(s, 6H,2x CH_3), 2.24 (s, 4H, 2x CH_2), 2.24 (s, 4H, 2x CH_2), 2.5 (s, 1H,CH), 3.33(t, 2H, CH_2), 3.6(s, 1H,NH), 4.16 (s, 6H, 2x OCH_3), 4.50 (s, 2H, CH_2), 7.12-7.36 (d, 2H, Ar -H),8.9 (s, 1H,CH), 9.80(s, 1H,OH), 10.00(s,1H, OH) ^{13}C NMR (DMSO-d_6, ð/ ppm): 20.50 (2xCH_3), 25.5(CH), 30.50 (2×CH_2) , 32.45(tetrahedral C), 35.00 (2×CH_2) , 38.25 (CH_2), 42.25 (CH_2) ,55(OCH_3), 104(CH), 109(=C), 121-135 (Ar-C),155(C=N) 165.22 (C=O), 210.20 (C=O), LCMS; m/z: 454; Anal.Calcd for $C_{25}H_{32}N_3O_5$, C, 66.05 H, 7.04; N, 9.25% Found: C,66.25 H, 7.44; N, 9.45%

[4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl]-acetic acid(3-hydroxy-5,5-dimethyl-cyclohex-2-enylidene)-hydrazide. (7):

M.P =55 °C, yield = 69%C , IR (cm-1): 1722(C=O ketone), 1680(N-C=O), ^{1}H NMR (DMSO-d_6, ð/ ppm): 1.12(s, 6H,2x CH_3), 2.09 (s, 2H, CH_2), 2.24 (s, 4H, 2x CH_2), 2.24 (s, 4H, 2x CH_2), 2.5 (s, 1H,CH), 3.33(t, 2H, CH_2), 3.6(s, 1H,NH), 4.16 (s, 6H, 2x OCH_3), 4.50 (s, 2H, CH_2), 7.12-7.36 (d, 2H, Ar -H),8.9 (s, 1H,CH), 9.80(s, 1H,OH), 9.50(s,1H, OH) ^{13}C NMR (DMSO-d_6, ð/ ppm): 15.50 (2xCH_3), 25.5(CH), 25.50(CH_2) ,29.50 (2×CH_2) ,30.50 (2×CH_2) , 32.45(tetrahedral C), 35.00 (2×CH_2) , 38.25 (CH_2), 42.25 (CH_2) ,55(OCH_3), 104(CH), 109(=C), 121-135 (Ar-C),155(C=N) 165.22 (C=O), 210.20 (C=O), LCMS; m/z: 450; Anal.Calcd for $C_{27}H_{36}N_3O_3$, C, 72.05 H, 8.04; N, 9.30% Found: C,72.25 H, 8.44; N, 9.45%

Antimicrobial and antifungal activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in table.

Table: 1

Antimicrobial activities of some newly synthesized compounds.

Compds	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
4	17	15	18	21	18	09	9
5	17	18	16	20	18	11	8
6	15	14	18	18	14	11	9
7	15	15	15	16	17	12	10
DMSO	0	0	0	0	0	0	0
Ampicilin®	24	20	19	22	24	14	14

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. Albicans = candida Albicans.

The sensitivity of microorganisms to the tested compounds is identified in the following manner*;

Highly Sensitive = Inhibition zone: 15-20 mm

Moderately Sensitive = Inhibition zone: 10-15 mm

Slightly Sensitive = Inhibition zone: 5-10 mm

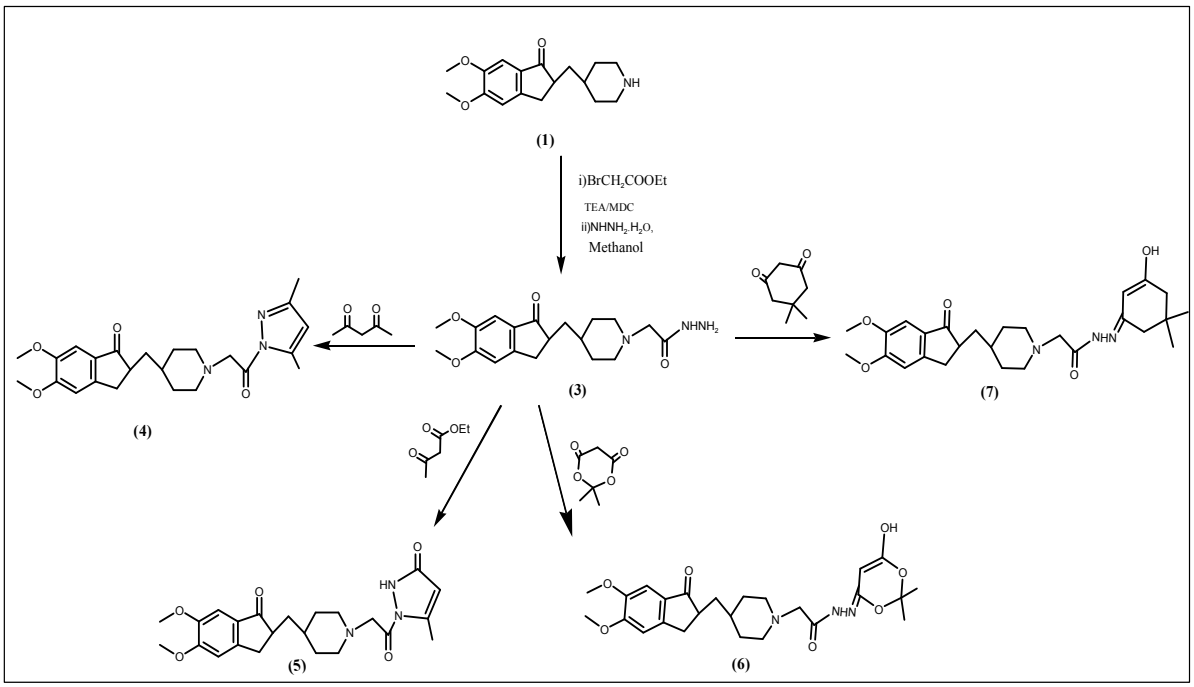
Not Sensitive = Inhibition zone: 0 mm

* Each result represents the average of triplicate readings.

Acknowledgement:

Authors are thankful to the Management of Guru Nanak College, G.T.B. Nagar, Mumbai for constant encouragement and providing necessary facilities. Authors are also thankful to, The Director, TIFR Mumbai for spectral data.

REACTION SCHEME



References:

[I] J.U. Yuhong, R.S. Verma, *J. Org. Chem.* 71, **2006,** 135.

[II] Donald J. Abraham, "*Berger's Medicinal Chemistry & drug discovery"*, John Willey and Sons, Inc. New York 5, **2003**, 19.

[III] GÜrsoy A; Demiravak S; Capan G; Erol K, Vural K; *Eur J Med Chem*. 35, **2003**, 59.

[IV] Amir M.; Kumar H.,; Khan. S.A.; *Bioorg Med Chem Lett*.18, **2008**, 918-922.

[V] Kuettel S.; Zambon A.; Kaiser A.; Brun R.; Scapozza L.; Perozzo R.*; J Med Chem*., 50, **2007**, 5833.

[VI] Li J, DeMello KM, Cheng H, Sakya SM, Bronk BS, Rafka RJ, Jaynes BH, Ziegler CB, *Bioorg Med Chem Lett.* 14, **2004**, 95.

[VII] Regan J; Capolino A;Cirillo PF; Gilmore T; Graham AG; Hickey E; Kroe RR; Madwed J; Moriak M; Nelson R; Pargellis CA; Swinamer A; Torcellini C; Tsang M, Moss N. (BIRB 796*). J Med Chem*. 46, **2003**, 4676.

[VIII] V. H. Bhaskar, P. B. Mohite; *Journal of Optoelectronics and Biomedical Materials* 3(1), **2011**, 7– 16.

[IX] Singh, V.; Srivastava, V.K.; Palit, G.; Shanker, K.; Coumarin congeners as antidepressants. *Arzneim-Forsch. Drug. Res*. 42, **1992**, 993-996.

[X] Kömürcü, □.G.; Rollas S.; Ülgen M.; Gorrod J.W; Çevikba□ A. Evaluation of Some Arylhydrazones of p-Aminobenzoic acid hydrazide as Antimicrobial Agents and Their *in- vitro*Hepatic Microsomal Metabolism. *Boll. Chim. Farm.* 134, **1995**, 375-379.

[XI] Ülgen M.; Durgun, B.B.; Rollas, S.; Gorrod, J.W. The in vitro hepatic microsomal metabolism of benzoic acid benzylidenehydrazide.*Drug Metab. Interact.* 13, **1997***,* 285-294.

Received on September 6, 2014.