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SYNTHESIS AND CHARACTERIZATION OF NOVEL BENZIMIDAZOLE CONNECTED PYRAZOLES AS NOVEL ANTIBACTERIAL AGENTS

B. Pullarao[1], S. D. Khasim Sharif[1], D. Ravi Kumar[2] and D. Ramachandran[1]*

[1]Department of Chemistry, Acharya Nagajuna University, Nagarjuna Nagar, Guntur-522 510, India.
[2]Department of Chemistry, Krishna University, Dr. MRAR PG centre, Nuzvid-521 201, India.

***Corresponding Author: D. Ramachandran**
Department of Chemistry, Acharya Nagajuna University, Nagarjuna Nagar, Guntur-522 510, India.

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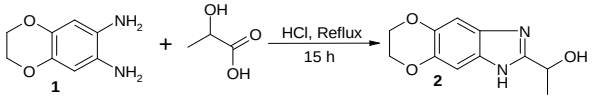
ABSTRACT
A facile and convenient method has been reported for the synthesis of six novel 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naph-thalene and its derivatives **(5a-f)** from 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-3-phenyl-propenones **(4a-f)** by involving 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-ethanol **(2)** and 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthaene-2-yl)-ethanone **(3)** as intermediates and 2,3-dihydro-benzo[1,4]dioxine-6,7-diamine **(1)** as starting compound. The chemical structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR, mass spectral study and elemental analysis. All the synthesized hybrids were evaluated for their *in vitro* antibacterial activity against different bacterial strains.

KEYWORDS: Pyrazoles, antibacterial activity.

INTRODUCTION
As with many other five-membered heterocyclic compounds, pyrazoles and their derivatives attract increasing attention in the fields of pharmacology and medicine because of their various bioactivities, including antifungal[1], anti-inflammatory[2], antiviral[3], antioxidant[4], cytotoxic[5], antihypertensive[6], A3 adenosine receptor antagonistic[7], antibacterial[8], tranquilizing, psychoanaleptic, muscle-relaxant, hypnotic, antidepressant, ulcerogenic and analgesic activities.[9] They are also highly significant in agrichemistry and many of these compounds have been widely used, given their fungicidal[10], insecticidal[11] and herbicidal activities.[12] Pyrazole carboxamide derivatives are important heterocyclic compounds in the development of medicines and pesticides because of their broad spectrum of biological activities, including insecticidal[13], fungicidal[14] and acaricidal activity.[15]

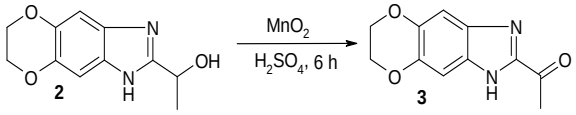
In the present work as continuation of our active research in the area of heterocyclic compounds, we planned to develop a novel series of 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8- dioxa-1,3-diaza-cyclopenta[*b*]naph-thalenes (5a-f), because of the important biological properties associated with this moiety. The reaction sequences used for the synthesis of target compounds are shown in scheme 1-4. The chemical structure of all compounds will be identified by different techniques, such as elemental analysis, Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS).

Thus, the raw material, 2,3-dihydro-benzo[1,4]dioxine-6,7-diamine (1) was reacted with lactic acid in presence of hydrochloric acid solution at reflux temperature for 15 h with uniform stirring on water bath to give the initial intermediate, 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-ethanol (2) in good yield. The structure of this intermediate was characterized by IR, ^{1}H-NMR, Mass spectra and elemental analysis. Its IR spectrum showed strong absorption bands at 3325 and 3125 cm^{-1} due to (O-H) and (N-H) groups respectively. In addition, the appearance of two absorption bands at 1456 and 1232 cm^{-1} corresponding to the C=N and C-O stretching vibrations. In the ^{1}H-NMR spectrum, the characteristic O-H and N-H resonated both as singlets at δ10.28 ppm and δ 4.79 ppm respectively by disappearing two NH_2 groups. Final proof for the structure was obtained by recording its mass spectrum, which exhibited a molecular ion peak at m/z 220 corresponding to its molecular weight.



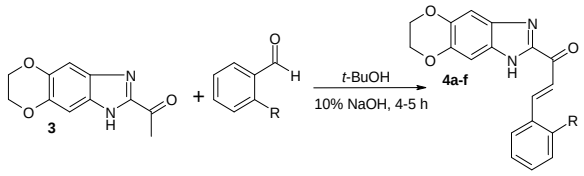
Scheme 1

A solution of compound **2** and manganese dioxide in the presence of concentrated sulphuric acid on constant stirring for 6 hours afforded the next intermediate, 1-(6,7-dihydro-1*H*-5,8-dioxa- 1,3-diaza-cyclopenta [*b*] naphthalene-2-yl)-ethanone (3) in fine yield. The success of the oxidation reaction was confirmed by IR, ^{1}H-NMR and Mass spectral analysis of compound 3. In the IR spectrum, the characteristic C=O group was observed at 1712 cm^{-1}. Its ^{1}H-NMR spectrum not showed O-H signal at its resonance frequency which is present in its precursor 2. The mass spectrum of the prepared compound contains the peak corresponding to its molecular weight at 218.



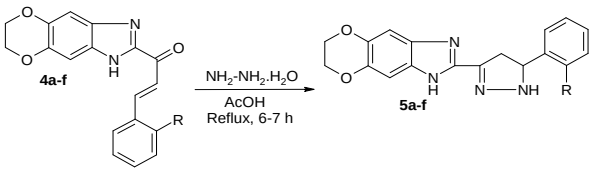
Scheme 2

The condensation between compound **3** with different aromatic aldehydes in presence of sodium hydroxide in refluxing ethanol for 4-5 h on water bath with steady stirring furnished the corresponding and final intermediate, 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-3-phenyl-propenone (4a-f) in healthy yield. The structure of compound 4a was established through by spectroscopic (IR, ^{1}H-NMR, MS) as well as elemental analyses data. The IR spectrum showed common characteristic absorption peak at 3165 cm^{-1} assigned to N-H. From the ^{1}H-NMR spectrum, the disappearance of signal related to the CH_3 group of the corresponding compound 3 and appearance of CH=CH group as doublets at δ 6.71 and 6.52 ppm with same multiplicity was a clear evidence for the formation of condensation product and the MS spectrum of showed M^+ ion peak at m/z 306 consistent with its molecular formula. Remaining all the compounds of this class 4b-f have been characterized with their different spectra.



Scheme 3

Intramolecular ring closure of compound 4 with hydrazine hydrate in refluxing acetic acid for 6-7 h on water bath with stable stirring afforded the affiliated and target compounds, 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene and its derivatives (5a-f) in moderate to good yields. The IR spectrum of compound 5a clearly showed the presence of two characteristic bands at 3274 and 3126 cm^{-1} are assigned to two NH groups. In addition, the disappearance of C=C in open chain of the compound 3 confirmed its involvement in the cyclization. The formation of the pyrazole ring in the proposed structure of compound 5a was also established on the basis of its ^{1}H-NMR spectrum in which the existence of a characteristic singlet at δ 7.85 ppm assigned to the NH group proton confirming the completion of the reaction. The mass spectrum of compound 5a showed M^+ peak at m/z 320 in agreement with its molecular formula. The chemical structures of the rest of compounds of this series 5b-f were identified with their different spectra.



Scheme 4

4/5 R a) = H, b) = CH_3, c) = Cl, d) = Br, e) = OCH_3, f) = NO_2

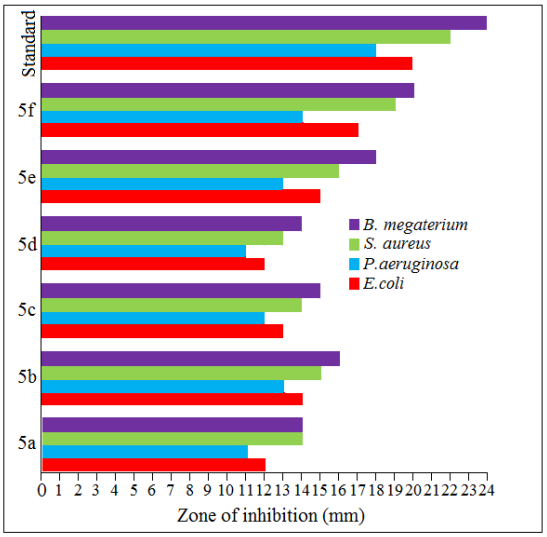


Figure 1: Antibacterial activity of compounds 5a-f.

Antibacterial activity

The antibacterial activity of the newly synthesized compounds, 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8- dioxa-1,3-diaza-cyclopenta[*b*] naphthalene and its derivatives (5a-f) have been tested against two representative Gram-positive bacteria such as *Staphylococcus aureus* & *Bacillus megaterium* and two representative Gram-negative bacteria like *Pseudomonas aeruginosa* & *Escherichia coli* by using DMSO as solvent and a tetracycline as reference standard. The efficiency of activity by the bacterial strains is expressed in terms of zone of inhibition in mm and the results of activity are given in Figure 1. According to the results, it is clear that, both compounds 5a and 5d in the entire study exhibited least activity against examined *P. aeruginosa* with same zone of inhibition 11 mm each. On the other hand all the compounds 5b, 5c, 5d, 5e and 5f were performed highest antibacterial activity towards tested *B. megaterium* with zone of inhibition 16 mm, 15 mm, 14 mm, 18 mm and 20 mm respectively compared to the reference antibiotic. The remaining antibacterial study has been offered the

moderate activity. It is interesting to that, none of the tested compounds is inactive against all the microorganisms employed during the study. The outstanding properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of this series of molecules.

Experimental

Synthesis of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene-2-yl)-ethanol (2)

The uniform solution of 2,3-dihydro-benzo[1,4]dioxine-6,7-diamine (1) (0.01 mol), lactic acid (0.01 mol) and 4N hydrochloric acid (7 ml) was refluxed with uniform stirring on water both for 15 h. The progress of the reaction was monitored by the TLC. Then the mixture was cooled, neutralized with NH_3 solution and generated solid was filtered and recrystallized from ethyl acetate to get 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-ethanol (2) in pure form.

Synthesis of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene-2-yl)-ethanone (3)

To a mixture of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene-2-yl)-ethanol (2) (0.01 mol) and H_2SO_4 (5%, 30 ml) was added a solution of MnO_2 (0.1 mol) and aqueous H_2SO_4 (20%, 60 ml). Thus obtained reaction mixture was stirred constantly at room temperature for 6 h. The development of the reaction was examined by the TLC. Then the solution was neutralized with NH_3 solution (1:1) to get precipitate and it was filtered, washed with water and dried, recrystallized from ethyl acetate to achieve pure 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene -2-yl)-ethanone (3).

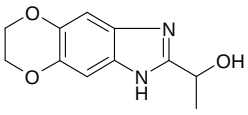
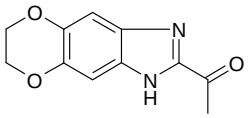
Synthesis of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene-2-yl)-3-phenyl-propenone (4a-f)

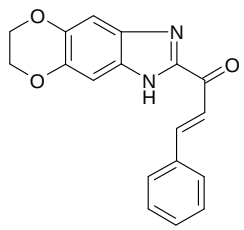
To the homogenous solution of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene -2-yl)-ethanone (3) (0.01 mol), benzaldehyde (0.01 mol) in *t*-BuOH (20 ml) was added 10% aq. NaOH (5 ml). The resulted mixture was maintained at ambient temperature with steady stirring for 4 h. The improvement of the reaction was observed by the TLC, the solution was dropped into cold water (20 ml) and neutralized with dil HCl solution, the precipitate that was formed was filtered off and recrystallized from EtOH to give pure 1-(6,7-dihydro-1*H*-5,8- dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-3-phenyl-propenone (4a). The rest of compounds of this series 4b-f have been synthesized with same procedure.

Synthesis of 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthaene (5a)

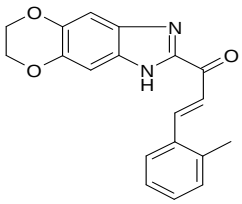
A mixture of 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*]naphthalene-2-yl)-3-phenyl-propenone (4a) (0.01 mol) and hydrazine hydrate (0.02 mol) in glacial acetic acid (15 ml) was refluxed on water bath with stable stirring till the completion of the reaction (TLC) and then cooled. The cold reaction mixture was neutralized with ammonia solution, thus the formed precipitated was collected, washed with water several times, dried and recrystallized from ethanol to give pure 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene (5a). The remaining of the products of this class 5b-f was prepared by following similar method.

Table 1: Physical and spectral characterization data.

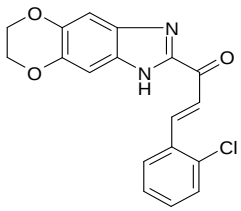
Entry	Physical and spectral characterization data
	*1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b]naphthalene-2-yl)-ethanol* (2): Yield: 68 %, M.P: 130.-132 °C, IR (KBr): 3325 (O-H), 3125 (N-H), 3042 (C-H, Ar), 2971 (C-H, CH_3), 1632 (C=C, Ar), 1456 (C=N), 1232 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 10.28 (s, 1H, OH), 7.62 (s, 1H, CH, Ar), 7.51 (s, 1H, CH, Ar), 4.79 (s, 1H, NH), 4.02 (t, 2H, CH_2, J = 5.2 Hz), 3.96 (t, 2H, CH_2, J = 5.2 Hz), 3.46 (q, 1H, CH, J = 5.7 Hz), 1.75 (d, 3H, CH_3, J = 5.7 Hz). MS: *m/z* 220 (M^+). Elemental Analysis: Calculated for $C_{11}H_{12}N_2O_3$: C-59.99, H-5.49, N-12.72, O-21.80. Found: C-58.85, H-5.48, N-12.70, O-21.59.
	*1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b]naphthalene-2-yl)-ethanone* (3): Yield: 66 %, M.P: 120-122 °C, IR (KBr): 3135 (N-H), 3056 (C-H, Ar), 2968 (C-H, CH_3), 1712 (C=O), 1640 (C=C, Ar), 1448 (C=N), 1240 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.56 (s, 1H, CH, Ar), 7.52 (s, 1H, CH, Ar), 4.73 (s, 1H, NH), 3.97 (t, 2H, CH_2, J = 5.0 Hz), 3.89 (t, 2H, CH_2, J = 5.0 Hz), 2.85 (s, 3H, CH_3). MS: *m/z* 218 (M^+). Elemental Analysis: Calculated for $C_{11}H_{10}N_2O_3$: C-60.55, H-4.62, N-12.84, O-22.00. Found: C-59.86, H-4.61, N-12.79, O-21.68.



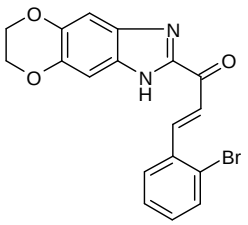
1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b]naphthalene-2-yl)-3-phenyl-propenone (4a): Yield: 69 %, M.P: 115-117 °C, IR (KBr): 3165 (N-H), 3071 (C-H, Ar), 2935 (C-H, CH_2), 1715 (C=O), 1644 (C=C, Ar), 1450 (C=N), 1236 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.60 (s, 1H, CH, Ar), 7.55 (s, 1H, CH, Ar), 7.48-7.32 (m, 5H, Ar), 6.71 (d, 1H, CH, J = 8.2 Hz), 6.52 (d, 1H, CH, J = 8.2 Hz), 4.81 (s, 1H, NH), 3.99 (t, 2H, CH_2, J = 5.4 Hz), 3.87 (t, 2H, CH_2, J = 5.4 Hz). MS: *m/z* 306 (M^+). Elemental Analysis: Calculated for $C_{18}H_{14}N_2O_3$: C-70.58, H-4.61, N-9.15, O-16.67. Found: C-69.12, H-4.60, N-9.14, O-16.65.



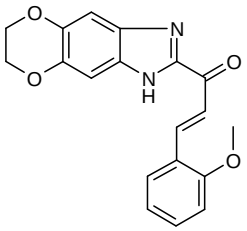
1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b]naphthalene-2-yl)-3-o-tolyl-propenone (4b): Yield: 70 %, M.P: 108-110 °C, IR (KBr): 3180 (N-H), 3066 (C-H, Ar), 2942 (C-H, CH_2), 1718 (C=O), 1638 (C=C, Ar), 1447 (C=N), 1239 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.62 (s, 1H, CH, Ar), 7.58 (s, 1H, CH, Ar), 7.50-7.35 (m, 4H, Ar), 6.74 (d, 1H, CH, J = 8.0 Hz), 6.55 (d, 1H, CH, J = 8.0 Hz), 4.86 (s, 1H, NH), 3.94 (t, 2H, CH_2, J = 5.3 Hz), 3.89 (t, 2H, CH_2, J = 5.3 Hz), 2.56 (s, 3H, CH_3). MS: *m/z* 320 (M^+). Elemental Analysis: Calculated for $C_{19}H_{16}N_2O_3$: C-71.24, H-5.03, N-8.74, O-14.98. Found: C-70.36, H-5.02, N-8.73, O-14.94.



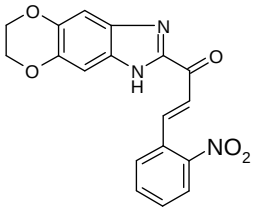
3-(2-Chloro-phenyl)-1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene-2-yl)-propenone (4c): Yield: 71 %, M.P: 122-124 °C, IR (KBr): 3172 (N-H), 3056 (C-H, Ar), 2938 (C-H, CH_2), 1716 (C=O), 1644 (C=C, Ar), 1452 (C=N), 1247 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.59 (s, 1H, CH, Ar), 7.55 (s, 1H, CH, Ar), 7.53-7.32 (m, 4H, Ar), 6.78 (d, 1H, CH, J = 7.9 Hz), 6.59 (d, 1H, CH, J = 7.9 Hz), 4.84 (s, 1H, NH), 3.97 (t, 2H, CH_2, J = 5.5 Hz), 3.91 (t, 2H, CH_2, J = 5.5 Hz). MS: *m/z* 340 (M^+). Elemental Analysis: Calculated for $C_{18}H_{13}ClN_2O_3$: C-63.44, H-3.85, Cl-10.40, N-8.22, O-14.09. Found: C-62.89, H-3.84, Cl-10.38, N-8.21, O-14.02.



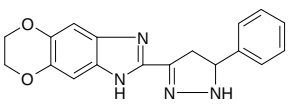
3-(2-Bromo-phenyl)-1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene-2-yl)-propenone (4d): Yield: 69 %, M.P: 129-131 °C, IR (KBr): 3170 (N-H), 3050 (C-H, Ar), 2940 (C-H, CH_2), 1719 (C=O), 1636 (C=C, Ar), 1456 (C=N), 1252 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.57 (s, 1H, CH, Ar), 7.52 (s, 1H, CH, Ar), 7.50-7.34 (m, 4H, Ar), 6.80 (d, 1H, CH, J = 7.8 Hz), 6.62 (d, 1H, CH, J = 7.8 Hz), 4.86 (s, 1H, NH), 4.02 (t, 2H, CH_2, J = 5.4 Hz), 3.87 (t, 2H, CH_2, J = 5.4 Hz). MS: *m/z* 384 (M^+). Elemental Analysis: Calculated for $C_{18}H_{13}BrN_2O_3$: C-56.12, H-3.40, Br-20.74, N-7.27, O-12.46. Found: C-55.68, H-3.39, Br-20.62, N-7.26, O-12.44.



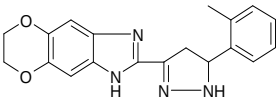
3-(2-Methoxy-phenyl)-1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta [b]naphthalene-2-yl)-propenone (4e): Yield: 73 %, M.P: 131-133 °C, IR (KBr): 3177 (N-H), 3055 (C-H, Ar), 2943 (C-H, CH_2), 1717 (C=O), 1639 (C=C, Ar), 1457 (C=N), 1255 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.61 (s, 1H, CH, Ar), 7.55 (s, 1H, CH, Ar), 7.53-7.38 (m, 4H, Ar), 6.84 (d, 1H, CH, J = 7.7 Hz), 6.65 (d, 1H, CH, J = 7.7 Hz), 4.89 (s, 1H, NH), 4.06 (t, 2H, CH_2, J = 5.6 Hz), 3.91 (t, 2H, CH_2, J = 5.6 Hz), 3.06 (s, 3H, OCH_3). MS: *m/z* 336 (M^+). Elemental Analysis: Calculated for $C_{19}H_{16}N_2O_3$: C-67.85, H-4.79, N-8.33, O-19.03. Found: C-66.92, H-4.78, N-8.32, O-18.98.



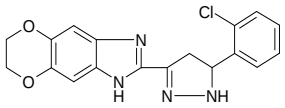
3-(2-Nitro-phenyl)-1-(6,7-Dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene-2-yl)-propenone (4f): Yield: 67 %, M.P: 126-128 °C, IR (KBr): 3172 (N-H), 3062 (C-H, Ar), 2940 (C-H, CH_2), 1720 (C=O), 1642 (C=C, Ar), 1461 (C=N), 1258 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.65 (s, 1H, CH, Ar), 7.60 (s, 1H, CH, Ar), 7.58-7.35 (m, 4H, Ar), 6.87 (d, 1H, CH, J = 7.9 Hz), 6.69 (d, 1H, CH, J = 7.9 Hz), 4.91 (s, 1H, NH), 4.10 (t, 2H, CH_2, J = 5.8 Hz), 3.96 (t, 2H, CH_2, J = 5.8 Hz). MS: *m/z* 351 (M^+). Elemental Analysis: Calculated for $C_{18}H_{13}N_3O_5$: C-61.54, H-3.73, N-11.96, O-22.77. Found: C-60.36, H-3.72, N-11.92, O-22.59.



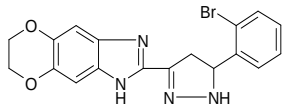
2-(5-Phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diazacyclo-penta[b] naphthalene (5a): Yield: 65 %, M.P: 130-132 °C, IR (KBr): 3274 (N-H), 3126 (N-H), 3055 (C-H, Ar), 2956 (C-H, CH_2), 1625 (C=C, Ar), 1456 (C=N), 1252 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.85 (s, 1H, NH), 7.69 (s, 1H, CH, Ar), 7.62 (s, 1H, CH, Ar), 7.53-7.38 (m, 5H, Ar-H), 4.98 (s, 1H, NH), 4.15 (t, 2H, CH_2, J = 5.4 Hz), 4.38 (t, 2H, CH_2, J = 5.4 Hz), 2.85 (t, 1H, CH, J = 4.8 Hz), 2.12 (d, 2H, CH_2, J = 4.8 Hz). MS: *m/z* 320 (M^+). Elemental Analysis: Calculated for $C_{18}H_{16}N_4O_2$: C-67.49, H-5.03, N-17.49, O-9.99. Found: C-66.85, H-5.02, N-17.25, O-9.98.



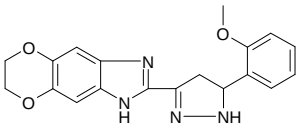
2-(5-o-Tolyl-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diaza-cyclo-penta[b] naphthalene (5b): Yield: 68 %, M.P: 125-127 °C, IR (KBr): 3285 (N-H), 3136 (N-H), 3048 (C-H, Ar), 2950 (C-H, CH_3), 1635 (C=C, Ar), 1451 (C=N), 1258 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.88 (s, 1H, NH), 7.72 (s, 1H, CH, Ar), 7.68 (s, 1H, CH, Ar), 7.59-7.42 (m, 4H, Ar-H), 4.92 (s, 1H, NH), 4.41 (t, 2H, CH_2, J = 5.6 Hz), 4.21 (t, 2H, CH_2, J = 5.6 Hz), 2.89 (t, 1H, CH, J = 5.0 Hz), 2.62 (s, 3H, CH_3), 2.18 (d, 2H, CH_2, J = 5.0 Hz). MS: *m/z* 334 (M^+). Elemental Analysis: Calculated for $C_{19}H_{18}N_4O_2$: C-68.25, H-5.43, N-16.76, O-9.57. Found: C-67.58, H-5.42, N-16.62, O-9.56.



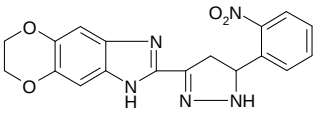
2-[5-(2-Chloro-phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene (5c): Yield: 71 %, M.P: 110-112 °C, IR (KBr): 3278 (N-H), 3128 (N-H), 3051 (C-H, Ar), 2953 (C-H, CH_2), 1639 (C=C, Ar), 1447 (C=N), 1261 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.85 (s, 1H, NH), 7.76 (s, 1H, CH, Ar), 7.65 (s, 1H, CH, Ar), 7.62-7.36 (m, 4H, Ar-H), 4.95 (s, 1H, NH), 4.43 (t, 2H, CH_2, J = 5.5 Hz), 4.19 (t, 2H, CH_2, J = 5.5 Hz), 2.85 (t, 1H, CH, J = 5.3 Hz), 2.23 (d, 2H, CH_2, J = 5.3 Hz). MS: *m/z* 354 (M^+). Elemental Analysis: Calculated for $C_{18}H_{15}ClN_4O_2$: C-60.94, H-4.26, Cl-9.99, N-15.79, O-9.02. Found: C-59.68, H-4.25, Cl-9.98, N-15.65, O-9.01.



2-[5-(2-Bromo-phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diazacy-clopenta[b] naphthalene (5d): Yield: 73 %, M.P: 130-132 °C, IR (KBr): 3266 (N-H), 3130 (N-H), 3057 (C-H, Ar), 2949 (C-H, CH_2), 1643 (C=C, Ar), 1451 (C=N), 1267 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.88 (s, 1H, NH), 7.79 (s, 1H, CH, Ar), 7.68 (s, 1H, CH, Ar), 7.60-7.34 (m, 4H, Ar-H), 4.89 (s, 1H, NH), 4.47 (t, 2H, CH_2, J = 5.3 Hz), 4.23 (t, 2H, CH_2, J = 5.3 Hz), 2.88 (t, 1H, CH, J = 5.1 Hz), 2.20 (d, 2H, CH_2, J = 5.1 Hz). MS: *m/z* 398 (M^+). Elemental Analysis: Calculated for $C_{18}H_{15}BrN_4O_2$: C-54.15, H-3.79, Br-20.01, N-14.03, O-8.01. Found: C-53.58, H-3.78, Br-19.95, N-13.95, O-7.98.



2-[5-(2-Methoxy-phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene (5e): Yield: 75 %, M.P: 117-119 °C, IR (KBr): 3270 (N-H), 3122 (N-H), 3063 (C-H, Ar), 2941 (C-H, CH_2), 1647 (C=C, Ar), 1456 (C=N), 1270 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.83 (s, 1H, NH), 7.76 (s, 1H, CH, Ar), 7.63 (s, 1H, CH, Ar), 7.59-7.38 (m, 4H, Ar-H), 4.85 (s, 1H, NH), 4.51 (t, 2H, CH_2, J = 5.2 Hz), 4.27 (t, 2H, CH_2, J = 5.2 Hz), 3.05 (s, 3H, OCH_3), 2.91 (t, 1H, CH, J = 5.3 Hz), 2.25 (d, 2H, CH_2, J = 5.3 Hz). MS: *m/z* 398 (M^+). Elemental Analysis: Calculated for $C_{19}H_{18}N_4O_3$: C-65.13, H-5.18, N-15.99, O-13.70. Found: C-64.39, H-5.17, N-15.87, O-13.61.



2-[5-(2-Nitro-phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6,7-dihydro-1H-5,8-dioxa-1,3-diaza-cyclopenta[b] naphthalene (5f): Yield: 72 %, M.P: 109-111 °C, IR (KBr): 3262 (N-H), 3135 (N-H), 3070 (C-H, Ar), 2952 (C-H, CH_2), 1649 (C=C, Ar), 1462 (C=N), 1263 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.87 (s, 1H, NH), 7.79 (s, 1H, CH, Ar), 7.67 (s, 1H, CH, Ar), 7.55-7.35 (m, 4H, Ar-H), 4.81 (s, 1H, NH), 4.46 (t, 2H, CH_2, J = 5.5 Hz), 4.21 (t, 2H, CH_2, J = 5.5 Hz), 2.95 (t, 1H, CH, J = 5.2 Hz), 2.26 (d, 2H, CH_2, J = 5.2 Hz). MS: *m/z* 365 (M^+). Elemental Analysis: Calculated for $C_{18}H_{15}N_5O_4$: C-59.18, H-4.14, N-19.17, O-17.52. Found: C-58.35, H-4.13, N-19.08, O-17.46.

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