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BREDERECK'S REAGENT: A FACILE SYNTHESIS OF 5H-BENZO[E]PYRROLO[1,2-A][1,4]DIAZEPIN-10(11H)-YL)(4-(1-METHYL-1H-PYRAZOL-5-YL)PHENYL)METHANONE AND MOLECULAR DOCKING STUDIES

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ABSTRACT
A simple and efficient method was developed to synthesize 5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(4-(1-methyl-1H-pyrazole-5-yl)phenyl)methanone from Pyrrole-2-carboxaldehyde and 1-(chloromethyl)-2-nitrobenzene as starting materials. A reagent tertbutoxybis(dimethylamino) methane (Bredereck's reagent, TBDMAM) used for selective formation of chalcones. All the compounds obtained were characterized by different spectroscopic techniques such as IR, NMR and mass analysis. Molecular docking study of the synthesized compounds was showed the best fit with the minimum binding energies of -5.78 kcal/mol.
Keywords: Bredereck's Reagent, Chalcones, Chemical Shift, Free Energy of Binding, Molecular Docking
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INTRODUCTION

In organic synthesis, either natural or synthetic chalcones play a vital role as they are known to exhibit various biological activities. Chalcones can be prepared by condensation of acetophenone with aromatic aldehydes in the presence of a suitable condensing agent[1,2]. They undergo a diversity of chemical reactions that direct to numerous heterocyclic compounds[3-6]. Chalcones have been used as transitional for the preparation of compounds having therapeutic value[7,8]. Several reports show that chalcone derivatives exhibit diverse pharmacological activities, such as potential Cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetic, etc.[9,10]. Heterocycles bearing nitrogen are reported to possess various biological activities. The synthesis of pyrazole and its analogs has been a subject of unfailing interest because of the extensive range of applications for such heterocycles in the pharmaceutical and agrochemical industries.[11] Therefore; broad research efforts are continually heading for the discovery of new heterocycles with appropriate pharmacological effects. Among their range of properties, the compounds containing a pyrazole scaffold have been shown to exhibit HIV-1 reverse transcriptase and IL-1 synthesis inhibition, as well as antihyperglycemic, antibacterial, sedative-hypnotic, anti-inflammatory, antipyretic and analgesic activity.[12] In part, the anti-inflammatory, antipyretic and analgesic properties of pyrazole derivatives have been linked with the inhibition of prostaglandin biosynthesis in the cyclooxygenase step.[13] However, their analgesic special effects may rivet other mechanisms, such as the release of endogenous opioids,[14] the modulation of nitric oxide production,[15] and the inhibition of excitatory amino acid receptors.[16]

Several α-carbon-substituted β-(dimethylamino)enones with general formula are ready antecedently by condensation of active methylene compounds like one,3-diketones or β-keto esters, with reactive DMF derivatives DMADMA, DMFDMA, DMFDEA and Bredereck's agent, TBDMAM. they need been most often employed in the synthesis of heterocycles, like pyrazoles, isoxazoles, pyrimidines and others.[17]

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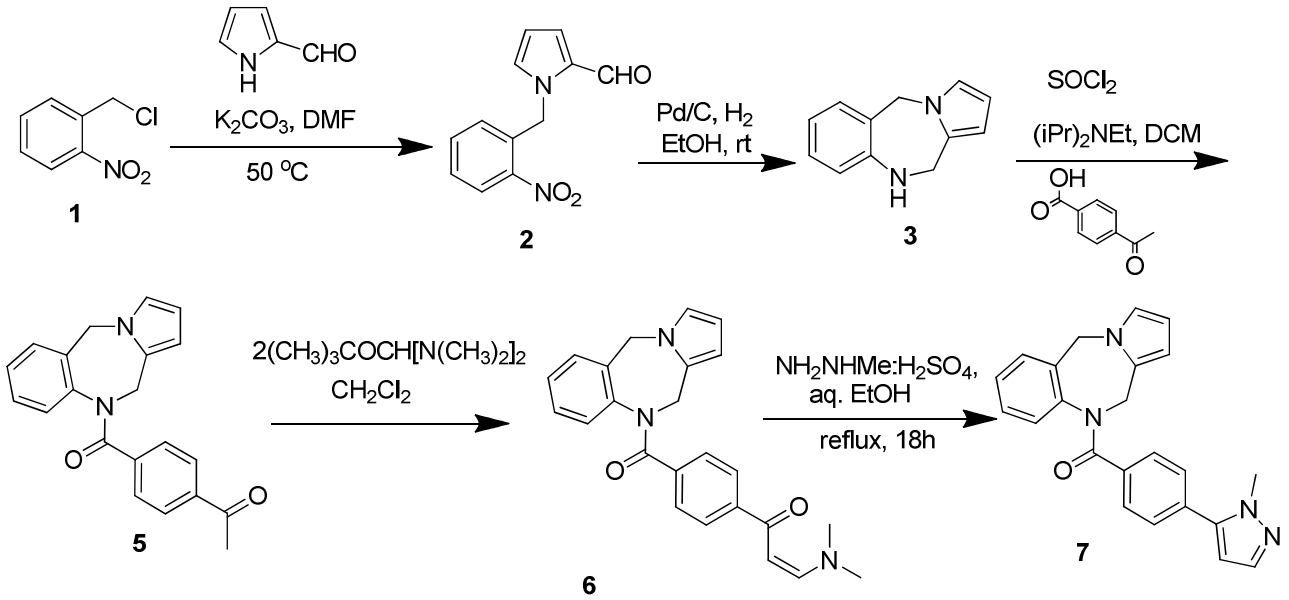
In the view of the varied biological and pharmacological application of pyrazole derivatives we herein report the synthesis of title compounds.

EXPERIMENTAL

All chemicals are commercially available. TLC was run on silica gel – G and visualization were done using iodine or UV light. IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. NMR spectra were recorded on Varian Gemini 300 MHz instrument using tetramethylsilane as an internal standard in DMSO-d_6. Chemical shifts are expressed in ppm. Mass spectra were recorded on a Agilent-LCMS instrument.



Scheme-1

10,11-Dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine

10% Pd-C was added to the ethanolic solution of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde **2** and hydrogenated at 60 psi for 24 h at rt. Filtered the reaction mixture and concentrated to afford crude product. IR: 3650 cm^{-1} (NH), 3084 cm^{-1} (C-H aromatic), 1491 cm^{-1}(C=N); ^{1}H NMR (DMSO-d_6) : δ=4.19 (brs, 2H), 4.45 (s, 2H) 5.21 (s, 2H), 6.03 (d, 2H), 6.45 (d, 1H), 6.61 (m, 1H), 6.65 (d, 1H), 6.96 (m, 2H).

1-(4-(10,11-Dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10 carbonyl)phenyl)ethanone

4-Acetylbenzoic acid was dissolved in dry thionyl chloride and heated to reflux for 1h. The excess thionyl chloride was distilled out and the residue was azeotroped with toluene. The residue was used for next step as such. **(ii)** DIPEA, acid chloride was added to 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine **3** in dry DCM at 0 °C and stirred the reaction mixture at rt for 16 h. Evaporated the solvent to afford crude product. IR: 2923 cm^{-1} (C-H aromatic), 1684 cm^{-1}(C=O), 1403 cm^{-1}(C=N); ^{1}H NMR (400 MHz, CDCl3): 7.76 (d, 2H), 7.38 (d, 3H), 7.2-7.0 (m, 6H), 6.7 (d, 2H), 6.1 (d, 2H), 5.2 (brs, 4H), 2.7 (s, 3H); Mass: m/z 331 (M+1).

1-(4-(10,11-Dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10-carbonyl)phenyl)-3-(dimethylamino)prop-2-en-1-one

Bredereck's reagent was added to the solution of 1-(4-(10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10-carbonyl)phenyl)ethanone **5** in dry DCM and stirred for 18 h at rt. The mixture was concentrated under vacuum to afford crude product. IR: 2923cm^{-1} (C-H aromatic), 1702 cm^{-1}(C=O), 1490 cm^{-1}(C=N); ^{1}H NMR (400 MHz, CDCl3):7.8 (d, 1H), 7.58 (d, 2H), 7.38 (t, 3H), 7.15 (t, 1H), 7.1 (s,1H),

6.78 (brs,1H), 6.61 (s, 1H), 6.2 (d,1H), 6.1 (s, 1H), 5.6 (d, 1H), 5.2 (brs, 2H), 3.18 (s, 3H), 2.9 (s, 3H); Mass: m/z 386 (M+1).

(5H-Benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(4-(1-methyl-1H-pyrazol-5-yl)phenyl)methanone

1-(4-(10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10-carbonyl)phenyl)-3-(dimethylamino)prop-2-en-1-one **6** and methylhydrazine sulfate were refluxed in aqueous ethanol for 18h. Concentrated the reaction mixture. The crude residue was dissolved in DCM, dried over anhydrous Na_2SO_4 and concentrated to afford crude product. IR: 3134 cm^{-1} (C-H aromatic), 1643 cm^{-1}(C=O), 1494 cm^{-1}(C=N); ^{1}H NMR (400 MHz, CDCl3): 7.5 (s, 1H), 7.4 (m, 3H), 7.23(d, 1H), 7.2(t, 1H), 7.1 (brs, 1H), 6.82(brs, 1H), 6.7 (s, 1H),6.3 (s, 1H), 6.2-6.1(d,2H), 5.2 (brs, 2H), 3.8 (s, 3H), Mass: m/z 369 (M+1).

Molecular Docking

Docking studies were done using the docking server[18]. The enzyme cyclooxygenase was downloaded and was docked with the synthesized compound. Docking pose between the compound and the ligand is shown in Fig.-1. The various amino acids involved in the docking are clearly seen. The estimated free energy of binding was found to be -5.44kcal/mol which indicates the interaction between the compound and the enzyme is feasible (Table-1). Asparagine, tyrosine, glutamic acid and threonine were found to be involved in the hydrogen and polar bonding (Table-2). Interaction showing various bonds and interactions of amino acids with the ligand carbon and nitrogen atoms is shown in Table-3. Figure-2 shows the ligand and non ligand bonds involved in the binding of the ligand to the enzyme.

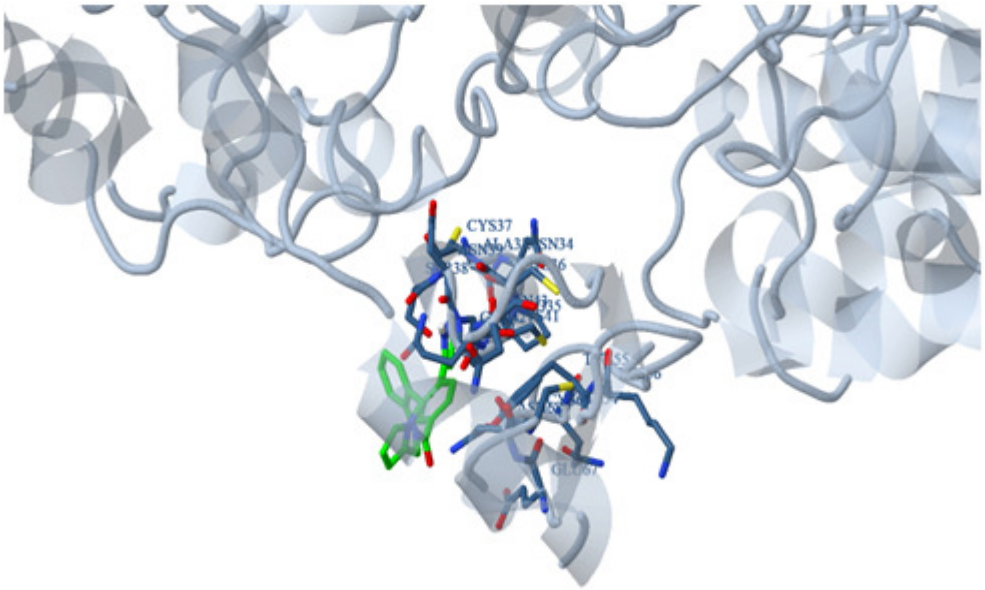


Fig.-1: Docking Pose between the Compound and the Enzyme Cycloxygenase

Table-1: Estimated Free Energy of Binding Between the Ligand and the Enzyme

Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW + H-bond + dissolve Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact. Surface
-5.44 kcal/mol	103.33 uM	-5.79 kcal/mol	+0.01 kcal/mol	-5.78 kcal/mol	50%	543.892

Table-2: Decomposed Interaction Energies in Kcal/mol

Hydrogen Bonds	Polar
ASN295 ()	GLU332 ()
TYR330 ()	THR297 ()

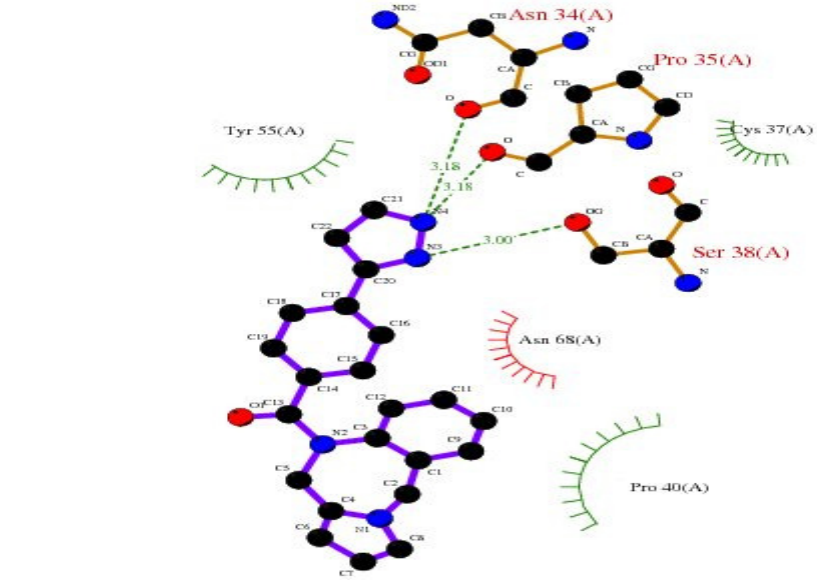


Fig.-2: Bonds involved in the Binding of the Ligand to the Enzyme

Table-3: Interaction Table Showing Various Bonds and Interactions of Amino Acids with the Ligand Carbon and Nitrogen Atoms

Hydrogen Bonds	Polar	Hydrophobic	pi-pi	Other
N4 () [*3.18*] – ASN34 (*O*)	H16 () [*2.15*] – SER38 (*OG*)	C1 () [*3.87*] – PRO40 (*CB*)	C15 () [*3.11*] – TYR55 (*CD1, CE1, CZ*)	N4 () [*3.70*] – CYS37 (*CB*)
N4 () [*3.18*] – PRO35 (*O*)	N1 () [*2.78*] – ASN68 (*ND2*)	C2 () [*3.78*] – PRO40 (*CB*)	C16 () [*3.49*] – TYR55 (*CD1, CE1*)	C10 () [*3.60*] – SER38 (*CB, OG*)
N3 () [*2.72*] – PRO35 (*O*)		C15 () [*3.47*] – PRO40 (*CB, CG*)		C11 () [*3.40*] – SER38 (*CB, OG*)
N3 () [*3.00*] – SER38 (*CB, OG*)		C16 () [*3.50*] – PRO40 (*CG*)		H16 () [*2.74*] – SER38 (*CB*)
				C15 () [*3.55*] – SER38 (*OG*)
				C16 () [*2.93*] – SER38 (*OG*)

				C17 () – SER38 [*3.27*] (*OG*)
				C20 () – SER38 [*3.53*] (*OG*)
				C15 () – TYR55 [*3.86*] (*OH*)
				C2 () – ASN68 [*3.07*] (*CG, ND2, OD1*)
				N1 () – ASN68 [*3.68*] (*CG*)
				C4 () – ASN68 [*3.04*] (*ND2*)
				C5 () – ASN68 [*3.40*] (*ND2*)
				C6 () – ASN68 [*3.70*] (*ND2*)
				C7 () – ASN68 [*3.87*] (*ND2*)
				C8 () – ASN68 [*3.36*] (*ND2*)

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