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Synthesis of pyrazole-based hybrid molecules: Search for potent multidrug resistance modulators

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Abstract—The hybrid molecules have been designed on the basis of the structural features of pyrazole-based drugs and MDR modulator propafenone. A simple synthetic strategy and solvent-based regioselectivity have been used for the synthesis of newly designed molecules and they are evaluated for their interactions with P-glycoprotein (P-gp). Some of the molecules show considerable interactions with P-gp and compounds **15**, **28** and **40** could be the potential candidates for their use as MDR modulators.

1. Introduction

Pyrazole derivatives have a broad spectrum of biological activities being used as antiinflammatory,[1] antipyretic,[2,3] gastric secretion stimulatory,[4] antidepressant,[5] against rheumatoid arthritis,[6,7] antibacterial,[8] anticonvulsant[9] and antifilarial agents[10] along with their use as herbicides,[11,12] fungicides,[13] pesticides,[14] insecticides[14] and dyestuffs,[15–17] in sunscreen materials[18] and as analytical reagents.[19] Variously substituted pyrazoles like 4-acyl-5-hydroxy-3-methyl-1*H*-pyrazole (or its tautomers) are used as the chelating and extracting reagents for many metal ions[20] and are used as starting materials for the syntheses of biologically active compounds as well as for the construction of condensed heterocyclic systems.

A common problem faced by most of the pyrazole-based drugs is the P-glycoprotein[21] (a transporter protein) mediated efflux from the cells leading to the decrease in their bio-availability and creating a major obstacle in the successful practice of chemotherapy for the treatment of various diseases.[22] This necessitates the use of drugs in combination with another suitable compound (the modulator), which could block P-gp and help in increasing the bio-availability of the drugs.

In continuation with our efforts[23] to develop such compounds, which could be used in combination with drugs for suppressing the activity of P-gp, we explored here the potential of pyrazole derivatives for their interactions with P-gp. Since the drugs as well as the modulators [commonly called multidrug resistance (MDR) modulators] interact with P-gp, it was envisaged that if some of the structural features of pyrazole-based drug[24] (**A**, Fig. 1) and a known MDR modulator (propafenone,[25] **B**, Fig. 1) are combined in one molecule (**C** and **D**,

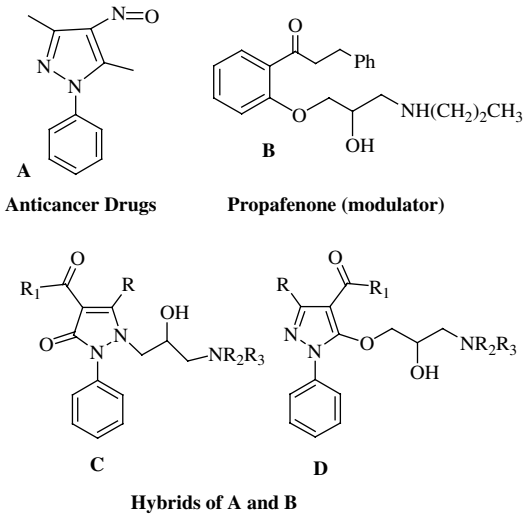

Figure 1.

Keywords: Drugs; Modulators; Hybrid molecules; Synthesis; P-glycoprotein; Interactions.
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Fig. 1), the resulting hybrid molecules will interact more effectively with P-gp. These hybrid molecules when used along with a pyrazole-based drug will block P-gp and help to decrease the P-gp mediated efflux of the drug.

Earlier some analogues of these molecules (**C** and **D**, Fig. 1) were evaluated for their MDR modulating properties.[26] The newly designed compounds (**C** and **D**, Fig. 1) were synthesized and their in vitro interactions with P-gp have been evaluated. The structure–activity relationship studies clearly highlight the role of different fragments of the molecules for interacting with P-gp.

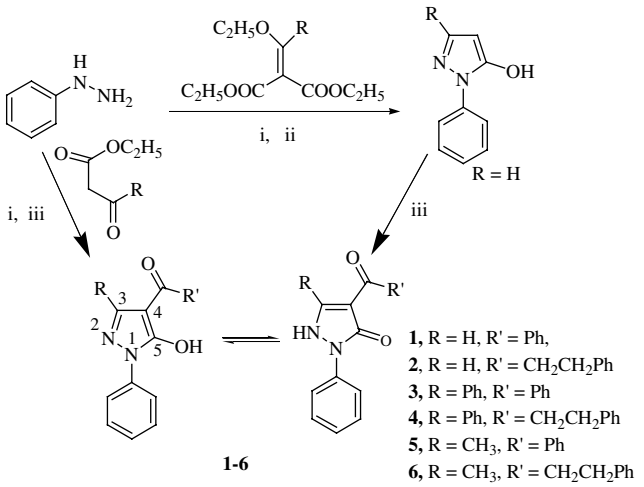
2. Results

2.1. Chemistry

Treatment of phenylhydrazine with diethyl ethoxymethylene malonate in ether followed by the acylation[27] with benzoyl chloride/3-phenylpropionyl chloride in 1,4-dioxane using $Ca(OH)_2$ as base gave compounds **1** and **2**. Similar reactions of phenylhydrazine with ethyl acetoacetate and ethyl benzoylacetate provided compounds **3**–**6** (Scheme 1).

Treatment of pyrazole **1** with NaH in methanol for 5 min followed by the removal of methanol, addition of 1 equivalent of epichlorohydrin in dry DMF and refluxing the reaction mixture gave a yellow oily product (25%) which from its spectral data has been assigned structure **7** (Scheme 2) and 30% of starting pyrazole was recovered. Pyrazoles **4**, **5**, and **6** also reacted with 1 equivalent of epichlorohydrin under the same reaction conditions to give yellow oily products **8** (30%), **9** (20%), and **10** (25%), respectively (Scheme 2).

Compound **7** on stirring with 1.25 equivalent of piperidine in dry methanol at 50 °C, after usual work up and chromatography gave a yellowish oil **11** (30%), [EI mass *m/z* 406, (M^++1)]. Under the same reaction conditions, compounds **8**, **9** and **10** reacted with 1.25 equivalents of piperidine to give yellowish oils **12** (30%), **13** (30%) and **14** (28%), respectively (Scheme 2). Similarly, the reactions of **7**–**10** with morpholine gave respective compounds **15** (33%), **16** (30%), **17** (32%) and **18** (32%) (Scheme 2).



Scheme 1. Reagents and condition: (i) Ether, stirring; (ii) KOH, HCl; (iii) R′COCl, $Ca(OH)_2$, 1,4-dioxane.

Pyrazole **2** on reaction with 1 equivalent of epichlorohydrin gave a white solid (40%), mp 215 °C (decomp.), which from its spectral data has been assigned the structure **20** (Scheme 2) and seems to be formed by the immediate reaction of second molecule of pyrazole **2** on the initially formed intermediate **19**. We could not detect the presence of **19** in this reaction (no appearance of transient spot in TLC or by recording the NMR of the reaction mixture at different intervals of time). However, pyrazole **3** did not react with 1 equivalent of epichlorohydrin even on prolonged heating and only starting pyrazole was recovered.

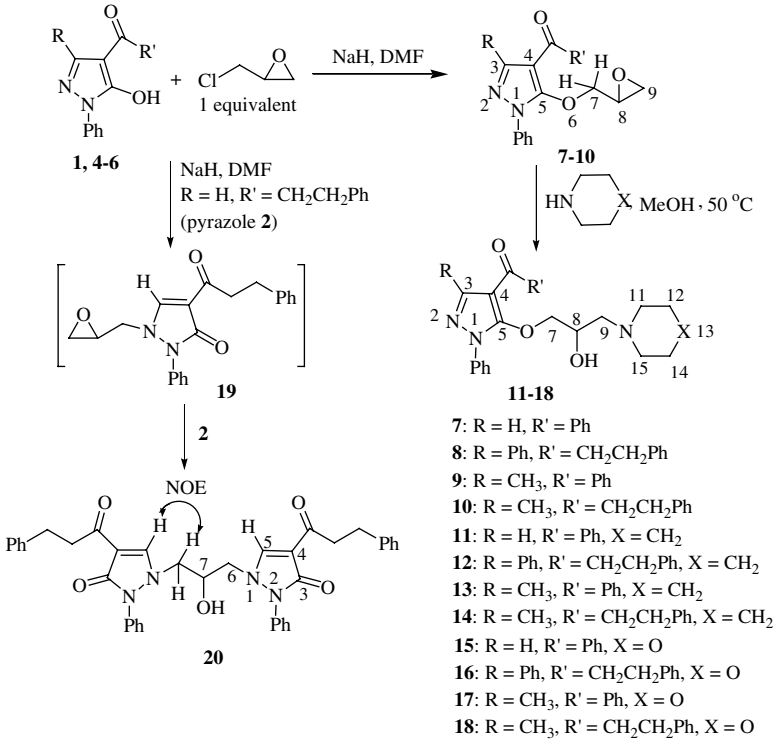
The sodium salt of pyrazole **1** on refluxing with epichlorohydrin (solvent) gave a white crystalline solid (65%), mp 175 °C, that from its spectral data has been assigned structure **21** (Scheme 3). Similarly, pyrazolones **3**, **4**, **5** and **6** on treatment with NaH followed by refluxing in epichlorohydrin gave white solids **22** (65%), **23** (84%), **24** (60%) and **25** (70%), respectively (Scheme 3). In all these reactions, a small amount (<5%)of O-substituted product (**7**, **8**, **9** and **10**) was also formed.

Compound **21** on stirring with 1.25 equivalent of piperidine in dry methanol at 50 °C, after usual work up and recrystallization (ethanol) gave a white crystalline solid **26** (70%), mp 163 °C, [EI mass *m/z* 406, (M^++1)] whose structure has been confirmed on the basis of ^{1}H NMR, decoupling, NOE and ^{13}C normal/DEPT-135 NMR spectra.

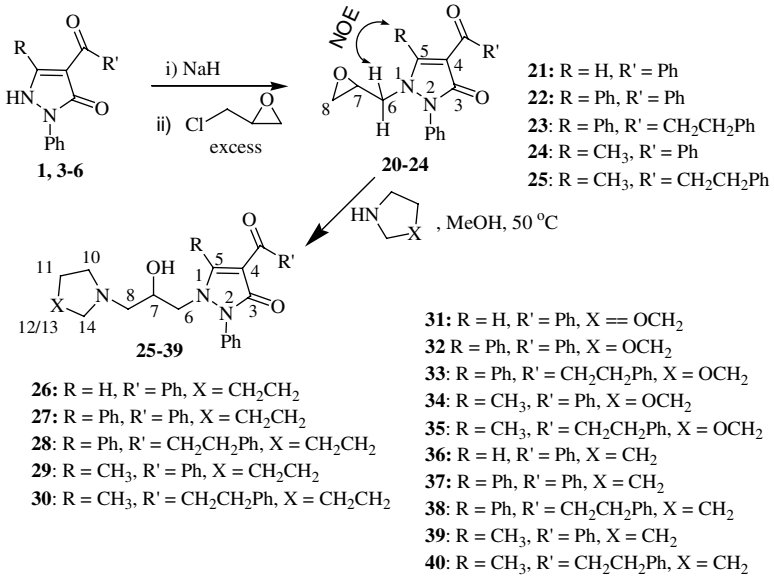
Compounds **22**, **23**, **24** and **25** also reacted with 1.25 equivalent of piperidine in dry methanol to give white solid compounds **27** (65%), **28** (64%), **29** (69%) and **30** (71%), respectively (Scheme 3). Under the same reaction conditions compounds **21**–**25** reacted with morpholine to give compounds **31** (70%), **32** (76%), **33** (71%), **34** (70%) and **35** (75%) and their reactions with pyrrolidine gave compounds **36** (72%), **37** (77%), **38** (73%), **39** (67%) and **40** (69%) (Scheme 3). However, pyrazolone **2** on reaction with excess epichlorohydrin provided compound **20**.

Therefore, the reaction of sodium salt of pyrazole with 1 equivalent of epichlorohydrin in DMF gave O-substituted products **7**–**10** which on reaction with appropriate cyclic nitrogen base gave compounds **11**–**18**, while the reaction of sodium salt of pyrazole with excess epichlorohydrin provided N-substituted products **21**–**25** which on further reaction with piperidine, morpholine and pyrrolidine provided compounds **26**–**40**.

The formation of N- and O-alkylated products has been explained on the basis of the polarity of the reaction solvent. The initially formed Na^+ salt of pyrazole (**41**) gets polarized in presence of polar solvent (DMF) making O^- free (**42**) to react at epoxy ring (route 1, Scheme 4) forming O-alkylated products **7**–**10** while in the presence



Scheme 2.

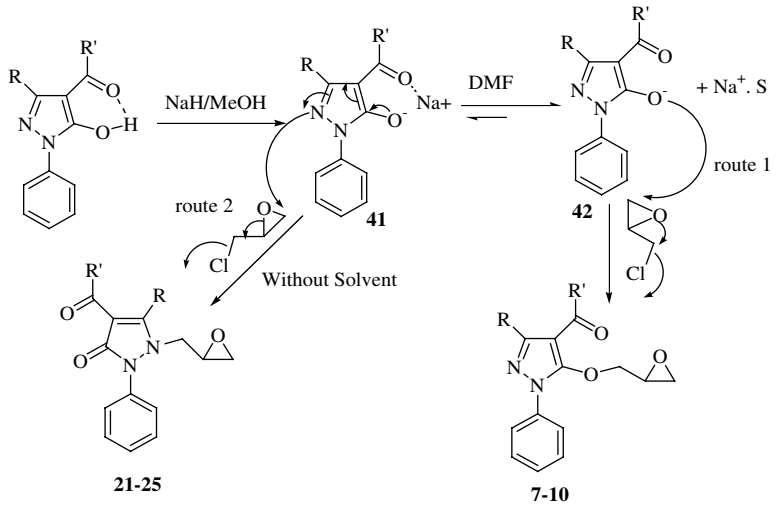


Scheme 3.

of epichlorohydrin, a relatively non-polar solvent, Na^+ salt of pyrazole (**41**), is not polarized and the reaction takes place from nitrogen (route 2, Scheme 4) which leads to the formation of N-alkylated products **21**–**25**. To substantiate the role of solvent in these reactions, **41** (R = CH_3, R′ = Ph) was treated with excess epichlorohydrin in DMF where it provided a mixture of **9** (20%) and **24** (35%), while no reaction takes place when **41** (R = CH_3, R′ = Ph) was made to react with one equivalent of epichlorohydrin in benzene or toluene at refluxing temperatures. Therefore, the solvent-dependent regioselectivity forms the basis for the O-alkylations and N-alkylations of pyrazoles. The formation of **20** from pyrazole **2**, on using DMF or epichlorohydrin as solvents, seems to be due to the easy transfer of the dipole of **41** (R = H, R′ = CH_2CH_2Ph) (Scheme 4) towards N-2 under both types of reaction conditions.

2.2. Biology

In vitro interactions of the compounds with P-gp were studied using 'Drug-P-glycoprotein' assay kit, which



Scheme 4.

contains the P-gp vesicles, prepared from highly resistant MDR cells, the DC-3F/ADX line and permits to assess the interactions of the compounds with P-gp in terms of increase in the basal activity or decrease in the stimulated (verapamil, progesterone induced) activity of P-gp. Here we have studied the modulation of basal ATPase activity of P-gp, which was measured by spectrophotometric method by continuous monitoring of ADP formation in the vesicle suspension medium. The basal ATPase activity of P-gp is its MgATP hydrolysis activity determined in the absence of any added drug. The interactions of the added compound (test compound) with P-gp result in the inhibition of ATPase activity of P-gp, which slows down the conversion of phosphoenolpyruvate to pyruvate and further to lactate and hence less conversion of NADH to NAD^+. Therefore, the wells (of the 96-well plate) containing test compounds showing better interactions with P-gp have higher concentration of NADH in comparison to other wells in which compounds show less interactions with P-gp or wells without test compounds (basal activity of P-gp). As a result, the absorption of NADH at 340 nm, in the wells where compound-P-gp interactions are better, gets increased which is manifested as increase in the basal activity of P-gp. As per the manufacturer's specifications, a 30% increase (modulation) in the basal activity of P-gp, on the addition of a compound implies that the compound is interacting with P-gp.

Table 1. Percentage increase of basal activity of P-gp by pyrazole derivatives at various concentrations

Compound	% increase of basal activity of P-gp[a]			
	50 μM	5 μM	0.5 μM	0.05 μM
15	5	18	**31**	nd
16	16	6	8	−0.06
17	8	18	16	0.00
18	−0.12	10	5	10
27	**33**	−0.05	13	6
28	**35**	**35**	**30**	15
29	−0.56	10	2	nd
30	16	9	15	nd
31	14	−0.10	−0.06	nd
32	14	21	4	−0.50
33	**30**	16	16	14
34	−0.23	13	−0.10	nd
35	3	−0.05	−0.07	nd
37	**29**	8	15	nd
38	20	−0.10	19	nd
40	7	9	**37**	nd
Propafenone	31% (10^{-5} M)			
Verapamil	33% (6×10^{-5} M)			
Vinblastine	31% (10^{-5} M)			
Progesterone	34% (1.2×10^{-4} M)			

nd, not done.

[a] A 30% increase in basal activity of P-gp signifies the interaction of the compound with P-gp.

3. Discussion

The results of the interactions of various compounds with P-gp at different concentrations are given in Table 1. The anticancer drugs like progesterone, vinblastine and MDR modulators propafenone and verapamil are also included for comparison.

It has been found that the compounds **15**, **27**, **28**, **33** and **40** exhibit significant interaction with P-gp. Amongst the O-alkylated pyrazoles **15**–**18**, compound **15** with H at C-3 shows better interaction with P-gp than the compounds **16**–**18** which have CH_3 and Ph groups at C-3. From the N-alkylated pyrazoles **27**–**40**, compounds **27** and **28** with piperidine moiety at the end of C-3 chain and Ph group at C-5 exhibit significant interactions with P-gp. However, compound **28** with 3-phenylpropionyl group at C-4 is better interacting with P-gp than **27** with benzoyl group at C-4. The replacement of piperidine moiety in compound **28** with morpholine in compound **33** and with pyrrolidine in compound **38** decreases the interactions with P-gp. The significant modulation of P-gp basal activity has been observed when Ph group of compound **38** was replaced with CH_3 group in compound **40**. Therefore, a change of substituent at one position requires a change at another position for

showing significant interactions with P-gp and a further tuning of the molecules could improve their interactions with P-gp.

The whole set of compounds could be divided into two categories: one with compounds **15**, **28** and **40** showing best interactions with P-gp at 0.5 μM concentration and no dose responses are observed which reflects the saturation of P-gp and necessitates the evaluation of these compounds at further low concentrations and the second category of compounds showing interactions at 50 μM (**27** and **33**) concentration or no interactions (all other compounds) with P-gp and hence no dose dependency.

Since the structural features of a molecule affect its biological activities, the properties of the hybrid molecules (**C** and **D**, Fig. 1), obtained by the mixing of two molecules (**A** and **B**, Fig. 1), both of which interact with P-gp, are clearly expressed in the form of better interactions with P-gp than the parent MDR modulator, propafenone (**B**, Fig. 1) and some of the anticancer drugs (progesterone and vinblastine) studied here. Due to the interactions of the anticancer drugs and MDR modulators with the same protein (P-gp), the idea of synthesizing and evaluating the hybrid molecules will provide a new platform for the development of better MDR modulators. However, for a hybrid molecule to be more active than the parent molecules, a suitable combination of substituents placed at the appropriate positions of hybrid molecules is very important. The interactions of 3 of the 16 compounds studied here, viz. **15**, **28** and **40**, with P-gp are better than those exhibited by anticancer drugs (progesterone and vinblastine) and MDR modulators propafenone and verapamil, these three compounds could be further explored for their in vivo MDR modulating properties.

4. Conclusions

The hybrid molecules (**C** and **D**, Fig. 1) carrying the structural features of the pyrazole-based drugs as well as the MDR modulators (propafenone) were synthesized by following the simple synthetic strategies and exploiting the solvent-based tautomerism of pyrazoles. The compounds **15**, **28** and **40** showing significant interactions with P-gp at sub-micromolar concentrations could be the potential MDR modulators and provide a new facet for the synthesis of hybrid molecules as MDR modulators.

5. Experimental

Melting points were determined in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz and JEOL JNM 300 MHz NMR spectrometers using $CDCl_3$ solution containing tetramethylsilane as an internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (J) are expressed in Hz. In ^{13}C NMR spectral data, +ve signals correspond to CH_3 and CH carbons and −ve signals correspond to CH_2 carbons in the DEPT-135 NMR spectrum. UV spectra were recorded on a UV-1601 PC-Shimadzu UV–Visible Spectrophotometer by using CH_3CN as a solvent. Infrared spectra were recorded on an FTIR Shimadzu 8400 spectrometer on a thin dispersed film (chloroform) or on the solid surface using KBr as medium. The EI mass spectra were recorded on ''Electrospray Ionization Interface in the +ve mode'' and the FAB mass was recorded on a JEOL SX 102/DA-6000 Mass Spectrometer/Data System using argon/xenon (6 kV, 10 mA) as the FAB gas. Column chromatography separations were performed on Merck Kiesel gel 60–120 meshes. Yields given below are not optimized and refer to analytically pure material. The drug–P-glycoprotein interaction assay kit was purchased from Cayman Chemical.

5.1. General procedure of compounds 1–6

With stirring, to a mixture of pyrazolone[27] (10 mmol) and $Ca(OH)_2$ (20 mmol) in dry 1,4-dioxane was added the appropriate acid chloride (10 mmol) and the reaction mixture was refluxed at 100 °C for 3 h. After cooling to room temperature, 2 N HCl was added and stirring was continued for 1 h. Then water was added and the mixture was further stirred for 10 min. The precipitates were filtered off, washed several times with water and dried to get a solid product.

5.1.1. 4-Benzoyl-1-phenyl-1,2-dihydropyrazol-5-one (1). Mp 115 °C (ethanol); yield 71%; ^{1}H NMR (300 MHz) δ 7.39–7.74 (m, 10H, 2× Ph), 7.82 (s, 1H, H-3); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 106 (C-4), 123.3 (+ve, ArCH), 127.7 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 129.3 (+ve, ArCH), 132.0 (+ve, ArCH), 137.7 (N-ArC), 139.0 (ArC), 143.0 (+ve, C-3), 154.7 (C-5), 190.0 (C═O); UV (CH_3CN) λ_{max} (nm): 280, 230.

5.1.2. 1-Phenyl-4-(3-phenylpropionyl)-1,2-dihydropyrazol-5-one (2). Mp 128 °C (ethanol); yield 71%; ^{1}H NMR (300 MHz) δ 3.08 (s, 4H, CH_2CH_2), 7.23–7.84 (m, 10H, 2× Ph), 7.74 (1H, s, H-3); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 30.3 (−ve, CH_2), 40.4 (−ve, CH_2), 104.5 (C-4), 120.9 (+ve, ArCH), 126.4 (+ve, ArCH), 127.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.6 (+ve, ArCH), 129.1 (+ve, ArCH), 137.3 (N-ArC), 138.3 (+ve, C-3), 140.4 (ArC), 158.2 (C-5), 197.0 (C═O); UV (CH_3CN) λ_{max} (nm): 262, 234.

5.1.3. 4-Benzoyl-1,3-diphenyl-1,2-dihydropyrazol-5-one (3). Mp 122 °C (ethanol); yield 68%; ^{1}H NMR (300 MHz) δ 7.18–8.00 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 109.7 (C-4), 123.3 (+ve, ArCH), 127.1 (+ve, ArCH), 127.9 (+ve, ArCH), 128.1 (+ve, ArCH), 128.3 (+ve, ArCH), 128.6 (+ve, ArCH), 129.4 (+ve, ArCH), 130.5 (+ve, ArCH), 132.2 (+ve, ArCH), 134.3 (ArC), 137.9 (N-ArC), 145.6 (ArC), 151.8 (C-3), 162.2 (C-5), 189.6 (C═O); UV (CH_3CN) λ_{max} (nm): 244.

5.1.4. 1,3-Diphenyl-4-(3-phenylpropionyl)-1,2-dihydropyrazol-5- one (4). Mp 130 °C (ethanol); yield 65%; ^{1}H NMR (300 MHz) δ 2.76 (t, J = 5.0 Hz, 2H, CH_2), 2.88

(t, J = 5.0 Hz, 2H, CH_2), 6.94–7.93 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 30.9 (−ve, CH_2), 40.2 (−ve, CH_2), 103.6 (C-4), 121.0 (+ve, ArCH), 126.2 (+ve, ArCH), 126.8 (+ve, ArCH), 128.2 (+ve, ArCH), 128.4 (+ve, ArCH), 128.6 (+ve, ArCH), 129.1 (+ve, ArCH), 129.3 (+ve, ArCH), 133.1 (ArC), 137.3 (N-ArC), 140.2 (ArC), 151.1 (C-3), 160.5 (C-5), 197.4 (C═O); UV (CH_3CN) λ_{max} (nm): 257.

5.1.5. 3-Methyl-1-phenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-5-one (6). Mp 118 °C (ethanol); yield 65%; ^1H NMR (300 MHz) δ 2.41 (s, 3H, CH_3), 3.04 (s, 4H, CH_2CH_2), 7.19–7.85 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 15.7 (+ve, CH_3), 30.1 (−ve, CH_2), 40.7 (−ve, CH_2), 106.0 (C-4), 120.4 (+ve, ArCH), 126.3 (+ve, ArCH), 128.2 (+ve, ArCH), 128.6 (+ve, ArCH), 128.9 (+ve, ArCH), 130.2 (+ve, ArCH), 137.3 (N-ArC), 140.5 (ArC), 147.0 (C-3), 160.4 (C-5), 196.0 (C=O); UV (CH_3CN) λ_{max} (nm): 264, 235.

5.2. General procedure for the preparation of (5-oxiranylmethoxy-1-phenyl-4-acyl-1*H*-pyrazol) derivatives 7–10

Twenty-four milligram (1 mmol) of NaH after washing with dry hexane was dissolved in dry methanol (5 ml). Appropriate pyrazoles **1**–**6** (1 mmol) were added to the above solution and stirred for 5 min. Methanol was removed under vacuum and the residue was dissolved in 10 ml of dry DMF. To this solution, 0.064 ml (1 mmol) of epichlorohydrin was added and the reaction mixture was stirred at 105 °C for 18 h. After filtration, DMF was removed under vacuum. The remaining gummy material was purified by column chromatography on silica gel using ethyl acetate and hexane (2:8) as eluent.

5.2.1. (5-Oxiranylmethoxy-1-phenyl-1*H*-pyrazol-4-yl)-phenylmethanone (7). Column chromatography (eluent: hexane–ethyl acetate, 8:2) afforded a yellowish oil; yield 25%; ^1H NMR (300 MHz) δ 2.56 (dd, ^2J = 5.2 Hz, ^3J = 3.0 Hz, 1H, H-9), 2.77 (dd, ^2J = 4.8 Hz, ^3J = 2.8 Hz, 1H, H-9), 3.24 (m, 1H, H-8), 4.24 (dd, ^2J = 12.2 Hz, ^3J = 5.8 Hz, 1H, H-7), 4.74 (dd, ^2J = 13.8 Hz, ^3J = 6.0 Hz, 1H, H-7), 7.39–7.87 (m, 10H, 2× Ph), 7.79 (s, 1H, H-3); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 44.1 (−ve, C-9), 49.8 (+ve, C-8), 76.1 (−ve, C-7), 107.8 (C-4), 123.5 (+ve, ArCH), 127.9 (+ve, ArCH), 128.5 (+ve, ArCH), 129.1 (+ve, ArCH), 132.4 (+ve, ArCH), 137.5 (N-ArC), 139.1 (ArC), 142.9 (+ve, C-3), 154.8 (C-5), 188.7 (C═O); UV(CH_3CN) λ_{max} (nm): 272, 239.

5.2.2. 1-(5-Oxiranylmethoxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-3-phenylpropan-1-one (8). Column chromatography (eluent: hexane–ethyl acetate, 8:2) afforded a yellowish oil; yield 30%; ^1H NMR (300 MHz) δ 2.50 (dd, ^2J = 4.8 Hz, ^3J = 2.7 Hz, 1H, H-9), 2.74 (t, J = 4.5 Hz, 1H, H-9), 2.87 (m, 4H, 2× CH_2), 3.16 (m, 1H, H-8), 3.92 (dd, ^2J = 11.1 Hz, ^3J = 6.6 Hz, 1H, H-7), 4.36 (dd, ^2J = 11.1 Hz, ^3J = 3.0 Hz, 1H, H-7), 7.01–7.75 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 30.2 (−ve, CH_2), 43.5 (−ve, CH_2), 44.2 (−ve, C-9), 49.6 (+ve, C-8), 76.8 (−ve, C-7), 109.0 (C-4), 123.4 (+ve, ArCH), 125.8 (+ve, ArCH), 127.9 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 128.8 (+ve, ArCH), 129.1 (+ve, ArCH), 132.4 (+ve, ArCH), 133.4 (ArC), 137.2 (N-ArC), 140.9 (ArC), 151.9 (C-3), 153.7 (C-5), 195.7 (C═O).

5.2.3. (3-Methyl-5-oxiranylmethoxy-1-phenyl-1*H*-pyrazol-4-yl)-phenylmethanone (9). Column chromatography (eluent: hexane–ethyl acetate, 8:2) afforded a yellowish oil; yield 20%; ^1H NMR (300 MHz) δ 2.27 (s, 3H, CH_3), 2.29 (dd, ^2J = 4.9 Hz, ^3J = 2.6 Hz, 1H, H-9), 2.59 (dd, ^2J = 6.6 Hz, ^3J = 4.9 Hz, 1H, H-9), 2.84 (m, 1H, H-8), 3.71 (dd, ^2J = 8.0 Hz, ^3J = 3.2 Hz, 1H, H-7), 4.02 (dd, ^2J = 8.0 Hz, ^3J = 6.1 Hz, 1H, H-7), 7.34-7.84 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 15.4 (+ve, CH_3), 30.1 (−ve, C-9), 44.5 (−ve, C-7), 49.5 (+ve, C-8), 107.5 (C-4), 123.6 (+ve, ArCH), 127.9 (+ve, ArCH), 128.9 (+ve, ArCH), 129.8 (+ve, ArCH), 132.9 (+ve, ArCH), 137.8 (N-ArC), 139.5 (ArC), 150.7 (C-3), 154.1 (C-5), 190.8 (C═O).

5.2.4. 1-(3-Methyl-5-oxiranylmethoxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylpropan-1-one (10). Column chromatography (eluent: hexane–ethyl acetate, 8:2) afforded a yellowish oil; yield 25%; ^1H NMR (300 MHz) δ 2.69 (s, 3H, CH_3), 2.88 (dd, ^2J = 7.6 Hz, ^3J = 4.6 Hz, 1H, H-9), 2.92 (t, J = 8.0 Hz, 2H, CH_2), 3.00 (dd, ^2J = 7.6 Hz, ^3J = 4.0 Hz, 1H, H-9), 3.11 (t, J = 8.0 Hz, 2H, CH_2), 3.17 (m, 1H, H-8), 3.70 (dd, ^2J = 12.3 Hz, ^3J = 7.2 Hz, 1H, H-7), 4.09 (dd, ^2J = 12.3 Hz, ^3J = 7.0 Hz, 1H, H-7), 7.13–7.49 (m, 10H, 2× Ph).

5.3. General procedure for the reaction of epoxy compounds 7–10 with piperidine and morpholine

One millimole of appropriate epoxy compounds **7**–**10** and 0.06 ml (1.25 mmol) piperidine/morpholine were taken in dry methanol and stirred at 50 °C. After the completion of the reaction (TLC), methanol was removed under vacuum to get a gummy residue. Compounds **11**–**18** were purified by column chromatography by silica gel using hexane–ethyl acetate (7:3) as eluent.

5.3.1. [5-(2-Hydroxy-3-piperidin-1-yl-propoxy)-1-phenyl-1*H*-pyrazol-4-yl]-phenylmethanone (11). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 30%; ^1H NMR (300 MHz) δ 1.42 (m, 2H, H-13), 1.54 (m, 4H, H-12, H-14), 2.34 (m, 4H, H-11/H-15, H-9), 2.52 (m, 2H, H-11/H-15), 3.10 (br s, 1H, OH, exchangeable with D_2O), 3.98 (m, 1H, H-8), 4.24 (dd, ^2J = 10.4 Hz, ^3J = 5 Hz, 1H, H-7), 4.32 (dd, ^2J = 10.4 Hz, ^3J = 3.4 Hz, 1H, H-7), 7.37–7.87 (m, 10H, 2× Ph), 7.78 (s, 1H, H-3); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.9 (−ve, C-13), 25.7 (−ve, C-12,C-14), 54.6 (−ve, C-11,C-15), 60.2 (−ve, C-9), 65.5 (+ve, C-8), 77.1 (−ve, C-7), 107.7 (C-4), 123.4 (+ve, ArCH), 127.9 (+ve, ArCH), 128.2 (+ve, ArCH), 128.5 (+ve, ArCH), 128.7 (+ve, ArCH), 132.4 (+ve, ArCH), 137.4 (N-ArC), 138.9 (ArC), 142.8 (+ve, C-3), 155.4 (C-5), 188.9 (C═O); EI MS m/z 406 (M^++1). Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.35; H, 6.87; N, 10.01.

5.3.2. 1-[5-(2-Hydroxy-3-piperidin-1-yl-propoxy)-1,3-diphenyl-1*H*-pyrazol-4-yl]-3-phenyl-propan-1-one (12). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 30%; ^{1}H NMR (300 MHz) δ 1.26 (m, 2H, H-13), 1.60 (m, 4H, H-12, H-14), 2.05 (m, 2H, H-11/H-15), 2.10 (dd, ^2J = 8.8 Hz, ^3J = 3.0 Hz, 2H, H-9), 2.20 (m, 2H, H-11/H-15), 2.75 (t, J = 8.0 Hz, 2H, CH_2), 2.95 (t, J = 8.0 Hz, 2H, CH_2), 3.42 (m, 1H, H-8), 3.49 (dd, ^2J = 8.4 Hz, ^3J = 4.4 Hz, 1H, H-7), 3.56 (dd, ^2J = 8.4 Hz, ^3J = 6.2 Hz, 1H, H-7), 6.73–8.03 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 20.2 (−ve, C-13), 29.8 (−ve, CH_2), 29.9 (−ve, C-12, C-14), 43.5 (−ve, CH_2), 49.0 (−ve, C-11, C-15), 60.3 (−ve, C-9), 65.7 (+ve, C-8), 78.3 (−ve, C-7), 107.9 (C-4), 123.3 (+ve, ArCH), 125.8 (+ve, ArCH), 128.1 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 128.4 (+ve, ArCH), 128.6 (+ve, ArCH), 129.3 (+ve, ArCH), 133.2 (ArC), 137.4 (N-ArC), 140.7 (ArC), 152.1 (C-3), 154.4 (C-5), 196.8 (C═O); UV λ_{max} (nm): 291, 253; EI MS m/z 510 (M^++1). Anal. Calcd for $C_{32}H_{35}N_3O_3$: C, 75.41; H, 6.92; N, 8.25. Found: C, 75.30; H, 6.85; N, 8.01.

5.3.3. [5-(2-Hydroxy-3-piperidin-1-yl-propoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-phenylmethanone (13). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 30%; ^{1}H NMR (300 MHz) δ 1.40 (m, 2H, H-13), 1.50 (m, 4H, H-12, H-14), 2.06 (dd, ^2J = 7.4 Hz, ^3J = 4.8 Hz, 2H, H-9), 2.18 (m, 2H, H-11/H-15), 2.28 (s, 3H, CH_3), 2.39 (m, 2H, H-11/H-15), 3.61 (m, 1H, H-8), 3.75 (dd, ^2J = 8.8 Hz, ^3J = 6.0 Hz, 2H, H-7), 7.32–7.97 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 14.9 (+ve, CH_3), 23.9 (−ve, C-13), 25.7 (−ve, C-12, C-14), 54.5 (−ve, C-11, C-15), 60.1 (−ve, C-9), 65.0 (+ve, C-8), 78.0 (−ve, C-7) 107.0 (C-4), 123.3 (+ve, ArCH), 127.5 (+ve, ArCH), 128.4 (+ve, ArCH), 129.0 (+ve, ArCH), 129.2 (+ve, ArCH), 132.5 (+ve, ArCH), 137.7 (N-ArC), 139.3 (ArC), 150.4 (C-3), 154.3 (C-5), 190.5 (C═O); UV λ_{max} (nm): 291, 246; EI MS m/z 420 (M^++1). Anal. Calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.97; N, 10.02. Found: C, 71.55; H, 6.82; N, 10.09.

5.3.4. 1-[5-(2-Hydroxy-3-piperidin-1-yl-propoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-3-phenyl-propan-1-one (14). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 28%; ^{1}H NMR (300 MHz) δ 1.30 (m, 2H, H-13), 1.42 (m, 4H, H-12, H-14), 1.70 (dd, ^2J = 5.8 Hz, ^3J = 4.0, 2H, H-9), 2.15 (m, 2H, H-11/H-15), 2.45 (m, 2H, H-11/H-15), 2.73 (s, 3H, CH_3), 2.98 (t, J = 8.0 Hz, 2H, CH_2), 3.09 (t, J = 8.0 Hz, 2H, CH_2), 3.38 (m, 1H, H-8), 3.81 (dd, ^2J = 7.2 Hz, ^3J = 5.8 Hz, 2H, H-7), 7.24–7.80 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.1 (+ve, CH_3), 19.1 (−ve, C-13), 29.8 (−ve, C-12, C-14), 30.1 (−ve, CH_2), 43.1 (−ve, CH_2), 48.2 (−ve, C-11, C-15), 59.0 (−ve, C-7), 61.0 (−ve, C-9), 70.3 (+ve, C-8), 105.0 (C-4), 125.6 (+ve, ArCH), 128.0 (+ve, ArCH), 128.5 (+ve, ArCH), 129.0 (+ve, ArCH), 129.5 (+ve, ArCH), 130.0 (+ve, ArCH), 132.1 (+ve, ArCH), 134.0 (N-ArC), 141.8 (ArC), 158.0 (C-3), 165.0 (C-5), 196.0 (C═O); UV λ_{max} (nm): 291, 246; EI MS m/z 448 (M^++1). Anal. Calcd for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.35; H, 7.87; N, 9.20.

5.3.5. [5-(2-Hydroxy-3-morpholin-4-yl-propoxy)-1-phenyl-1*H*-pyrazol-4-yl]-phenylmethanone (15). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil: yield 33%; ^{1}H NMR (300 MHz) δ 2.46 (m, 6H, H-11, H-15, H-9), 3.68 (t, J = 4.8 Hz, 4H, H-12, H-14), 3.97 (m, 1H, H-8), 4.24 (dd, ^2J = 10.5 Hz, ^3J = 5.4 Hz, 1H, H-7), 4.37 (dd, ^2J = 10.5 Hz, ^3J = 3.3 Hz, 1H, H-7), 7.27–7.85 (m, 10H, 2× Ph), 7.79 (s, 1H, H-3); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 53.6 (−ve, C-11, C-15), 60.0 (−ve, C-9), 65.6 (+ve, C-8), 66.7 (−ve, C-12, C-14), 77.5 (−ve, C-7), 106.8 (C-4), 123.1 (+ve, ArCH), 127.5 (+ve, ArCH), 128.3 (+ve, ArCH), 129.0 (+ve, ArCH), 129.1 (+ve, ArCH), 132.5 (+ve, ArCH), 137.3 (N-ArC), 139.0 (ArC), 150.2 (+ve, C-3), 154.1 (C-5), 190.4 (C═O); FAB MS m/z 408 (M^++1). Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.72; H, 6.25; N, 10.12.

5.3.6. 1-[5-(2-Hydroxy-3-morpholin-4-yl-propoxy)-1,3-diphenyl-1*H*-pyrazol-4-yl]-3-phenyl-propan-1-one (16). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 30%; ^{1}H NMR (300 MHz) δ 2.38 (m, 4H, H-11/H-15, H-9), 2.49 (m, 2H, H-11/H-15), 2.86 (m, 4H, 2× CH_2, two triplets merged), 3.66 (t, J = 4.5 Hz, 4H, H-12, H-14), 3.90 (m, 1H, H-8), 4.02 (dd, ^2J = 9.9 Hz, ^3J = 5.4 Hz, 1H, H-7), 4.12 (dd, ^2J = 9.9 Hz, ^3J = 3.3 Hz, 1H, H-7), 6.97–7.74 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 30.2 (−ve, CH_2), 43.6 (−ve, CH_2), 53.6 (−ve, C-11, C-15), 60.1 (−ve, C-9), 65.6 (+ve, C-8), 66.7 (−ve, C-12, C-14), 78.0 (−ve, C-7), 108.9 (C-4), 123.5 (+ve, ArCH), 125.8 (+ve, ArCH), 128.0 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 128.4 (+ve, ArCH), 128.8 (+ve, ArCH), 129.1 (+ve, ArCH), 133.4 (ArC), 137.3 (N-ArC), 140.8 (ArC), 152.0 (C-3), 154.2 (C-5), 196.1 (C═O); FAB MS m/z 512 (M^++1). Anal. Calcd for $C_{31}H_{33}N_3O_4$: C, 72.78; H, 6.50; N, 8.21. Found: C, 72.70; H, 6.55; N, 8.05.

5.3.7. [5-(2-Hydroxy-3-morpholin-4-yl-propoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-phenylmethanone (17). Column chromatography (eluent: hexane–ethyl acetate, 7:3) afforded a yellowish oil; yield 32%; ^{1}H NMR (300 MHz) δ 2.03 (m, 4H, H-11/H-15, H-9), 2.39 (m, 2H, H-11/H-15), 2.84 (s, 3H, CH_3), 3.38 (t, J = 6.9 Hz, 2H, H-7), 3.64 (t, J = 4.8 Hz, 4H, H-12, H-14), 3.77 (m, 1H, H-8), 7.27–7.85 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 14.8 (+ve, CH_3), 53.3 (−ve, C-11, C-15), 59.8 (−ve, C-9), 65.0 (+ve, C-8), 66.4 (−ve, C-12, C-14), 77.7 (−ve, C-7), 106.8 (C-4), 123.1 (+ve, ArCH), 127.5 (+ve, ArCH), 128.3 (+ve, ArCH), 129.0 (+ve, ArCH), 129.1 (+ve, ArCH), 132.5 (+ve, ArCH), 137.3 (N-ArC), 139.0 (ArC), 150.2 (C-3), 154.1 (C-5), 190.4 (C═O); FAB MS m/z 422 (M^++1). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.35; H, 6.67; N, 9.90.

5.3.8. 1-[5-(2-Hydroxy-3-morpholin-4-yl-propoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-3-phenyl-propan-1-one (18). Column chromatography (eluent: hexane–ethyl

acetate, 7:3) afforded a yellowish oil; yield 32%; ^{1}H NMR (300 MHz) δ 2.12 (m, 4H, H-11/H-15, H-9), 2.42 (m, 2H, H-11/H-15), 2.74 (s, 3H, CH_3), 2.97 (t, J = 7.8 Hz, 2H, CH_2), 3.24 (t, J = 7.8 Hz, 2H, CH_2), 3.56 (t, J = 4.2 Hz, 4H, H-12, H-14), 3.74 (m, 1H, H-8), 3.78 (m, 2H, H-7 merged with H-8), 7.11–7.51 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 16.0 (+ve, CH_3), 29.8 (−ve, CH_2), 43.2 (−ve, CH_2), 53.4 (−ve, C-11, C-15), 60.0 (−ve, C-9), 65.2 (+ve, C-8), 66.7 (−ve, C-12, C-14), 77.4 (−ve, C-7), 108.6 (C-4), 123.4 (+ve, ArCH), 125.9 (+ve, ArCH), 127.9 (+ve, ArCH), 128.3 (+ve, ArCH), 129.2 (+ve, ArCH), 137.3 (N-ArC), 141.4 (ArC), 150.1 (C-3), 154.5 (C-5), 194.3 (C═O); FAB MS m/z 450 (M^++1). Anal. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.47; H, 6.95; N, 9.35. Found: C, 69.30; H, 6.86; N, 9.22.

5.3.9. Compound 20. Mp 215 °C [decomp.] (ethanol); yield 40%; ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz) δ 2.83 (t, J = 5.2 Hz, 4H, CH_2), 3.03 (t, J = 5.2 Hz, 4H, CH_2), 3.38 (m, 1H, H-7) 3.55 (dd, ^2J = 10.0 Hz, ^3J = 2.4 Hz, 2H, H-6), 3.65 (dd, ^2J = 10.0 Hz, ^3J = 5.8 Hz, 2H, H-6), 7.13–7.49 (m, 20H, 4× Ph), 8.45 (s, 2H, H-5); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 29.3 (−ve, CH_2), 41.6 (−ve, CH_2), 52.6 (−ve, C-6), 64.2 (+ve, C-7), 106.7 (C-4), 125.7 (+ve, ArCH), 126.4 (+ve, ArCH), 128.1 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 129.3 (+ve, ArCH), 133.1 (N-ArC), 141.6 (ArC), 145.4 (+ve, C-5), 162.9 (C-3), 192.4 (C═O); UV λ_{max} (nm): 303, 240; IR (cm^{-1}): 1630 (C═O), 3310 (OH).

5.4. Synthesis of (4-acyl-1-oxiranylmethyl-2-phenyl-1*H*-pyrazole) derivatives 21–25

Twenty-four milligram (1 mmol) of NaH was dissolved in 5 ml of dry methanol followed by the addition of 1 mmol of appropriate pyrazoles **1**–**6**. After stirring for 5 min, methanol was removed under vacuum and to the residue 0.83 ml (13 mmol) of epichlorohydrin was added and the reaction mixture was refluxed at 110 °C for 20 h. After the completion of the reaction (TLC), excess epichlorohydrin was removed under vacuum and the washings with ether–ethanol mixture gave a solid product, which was recrystallized from ethanol.

5.4.1. 4-Benzoyl-1-oxiranylmethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (21). Mp 175 °C (ethanol); yield 65%; ^{1}H NMR (300 MHz) δ 2.43 (dd, ^2J = 4.5 Hz, ^3J = 2.5 Hz, 1H, H-8), 2.79 (dd, ^2J = 4.5 Hz, ^3J = 4.0 Hz, 1 H, H-8), 3.07 (m, 1H, H-7), 3.64 (dd, ^2J = 15.1 Hz, ^3J = 6.5 Hz, 1H, H-6), 4.08 (dd, ^2J = 15.1 Hz, ^3J = 3.1 Hz, 1H, H-6), 7.32–7.99 (m, 10H, 2× Ph), 8.25 (s, 1H, H-5); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 45.4 (−ve, C-8), 48.8 (+ve, C-7), 52.1 (−ve, C-6), 109.9 (C-4), 126.4 (+ve, ArCH), 128.0 (+ve, ArCH), 128.8 (+ve, ArCH), 129.4 (+ve, ArCH), 129.7 (+ve, ArCH), 133.3 (N-ArC), 137.8 (ArC), 146.9 (+ve, C-5), 162.6 (C-3), 188.1 (C═O); UV λ_{max} (nm): 238, 312.

5.4.2. 4-Benzoyl-1-oxiranylmethyl-2,5-diphenyl-1,2-dihydro-pyrazol-3-one (22). Mp 178 °C (ethanol); yield 65%; ^{1}H NMR (300 MHz) δ 2.25 (dd, ^2J = 4.8 Hz, ^3J = 2.5 Hz, 1H, H-8), 2.51 (dd, ^2J = 4.8 Hz, ^3J = 4.5 Hz, 1H, H-8), 2.86 (m, 1H, H-7), 3.49 (dd, ^2J = 15.8 Hz, ^3J = 6.6 Hz, 1H, H-6), 3.88 (dd, ^2J = 15.8 Hz, ^3J = 3.4 Hz, 1H, H-6), 7.28–7.80 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 44.3 (−ve, C-8), 47.9 (+ve, C-7), 51.1 (−ve, C-6), 110.1 (C-4), 125.0 (+ve, ArCH), 127.4 (+ve, ArCH), 127.6 (+ve, ArCH), 128.1 (+ve, ArCH), 128.7 (+ve, ArCH), 129.2 (+ve, ArCH), 129.5 (+ve, ArCH), 130.6 (+ve, ArCH), 132.7 (+ve, ArCH), 134.0 (ArC), 134.4 (N-ArC), 137.6 (ArC), 159.7 (C-5), 162.2 (C-3), 188.5 (C═O); UV λ_{max} (nm): 249, 319.

5.4.3. 1-Oxiranylmethyl-2,5-diphenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (23). Mp 170 °C (ethanol); yield 84%; ^{1}H NMR (300 MHz) δ 2.89 (dd, ^2J = 4.8 Hz, ^3J = 2.4 Hz, 1H, H-8), 2.93 (t, J = 6.0 Hz, 2H, CH_2), 3.03 (t, J = 6.0 Hz, 2H, CH_2), 3.11 (dd, ^2J = 4.8 Hz, ^3J = 4.4 Hz, 1H, H-8), 3.35 (m, 1H, H-7), 3.67 (dd, ^2J = 15.6 Hz, ^3J = 6.4 Hz, 1H, H-6), 3.70 (dd, ^2J = 15.6 Hz, ^3J = 3.8 Hz, 1H, H-6), 7.12–7.57 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 29.7 (−ve, CH_2), 43.2 (−ve, CH_2), 50.5 (−ve, C-8), 58.8 (+ve, C-7), 66.9 (−ve, C-6), 107.4 (C-4), 125.4 (+ve, ArCH), 125.6 (+ve, ArCH), 128.1 (+ve, ArCH), 128.2 (+ve, ArCH), 128.4 (+ve, ArCH), 128.6 (+ve, ArCH), 129.5 (+ve, ArCH), 130.0 (+ve, ArCH), 130.4 (ArC), 134.0 (N-ArC), 141.6 (ArC), 160.2 (C-5), 164.1 (C-3), 194.2 (C═O).

5.4.4. 4-Benzoyl-5-methyl-1-oxiranylmethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (24). Mp 138 °C (ethanol); yield 60%; ^{1}H NMR (300 MHz) δ 2.43 (dd, ^2J = 4.5 Hz, ^3J = 2.5 Hz, 1H, H-8), 2.65 (s, 3H, CH_3), 2.74 (dd, ^2J = 4.5 Hz, ^3J = 4.0 Hz, 1H, H-8), 3.01 (m, 1H, H-7), 3.78 (dd, ^2J = 15.9 Hz, ^3J = 6.1 Hz, 1H, H-6), 4.04 (dd, ^2J = 15.9 Hz, ^3J = 3.2 Hz, 1H, H-6), 7.30–7.95 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 12.5 (+ve, CH_3), 45.2 (−ve, C-8), 48.2 (−ve, C-6), 48.9 (+ve, C-7), 108.2 (C-4), 126.2 (+ve, ArCH), 127.7 (+ve, ArCH), 128.3 (+ve, ArCH), 129.4 (+ve, ArCH), 129.5 (+ve, ArCH), 132.2 (+ve, ArCH), 134.3 (N-ArC), 138.4 (ArC), 159.1 (C-5), 163.8 (C-3), 190.4 (C═O); UV λ_{max} (nm): 239, 315.

5.4.5. 5-Methyl-1-oxiranylmethyl-2-phenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (25). Mp 175 °C (ethanol); yield 70%; ^{1}H NMR (300 MHz) δ 2.73 (s, 3H, CH_3), 2.85 (t, J = 6.0 Hz, 2H, CH_2), 2.90 (dd, ^2J = 7.0 Hz, ^3J = 5.6 Hz, 1H, H-8), 2.96 (dd, ^2J = 7.0 Hz, ^3J = 6.0 Hz, 1H, H-8), 3.07 (t, J = 6.0 Hz, 2H, CH_2), 3.30 (m, 1H, H-7), 3.79 (dd, ^2J = 13.6 Hz, ^3J = 4.6 Hz, 1H, H-6), 3.94 (dd, ^2J = 13.6 Hz, ^3J = 5.6 Hz, 1H, H-6), 7.13–7.45 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.1 (+ve, CH_3), 29.7 (−ve, CH_2), 43.3 (−ve, CH_2), 45.5 (−ve, C-8), 48.6 (−ve, C-6), 67.9 (+ve, C-7), 105.5 (C-4), 125.7 (+ve, ArCH), 126.7 (+ve, ArCH), 128.1 (+ve, ArCH), 128.3 (+ve, ArCH), 129.1 (+ve, ArCH), 129.6 (+ve, ArCH), 133.3 (N-ArC), 141.6 (ArC), 158.3 (C-5), 164.6 (C-3), 195.6 (C═O).

5.5. General procedure for the reaction of epoxy compounds 21–25 with piperidine/morpholine/pyrrolidine

One millimole of appropriate epoxy compounds **21**–**25** and 0.06 ml (1.25 mmol) piperidine/morpholine/pyrrolidine were taken in dry methanol and stirred at 50 °C. After the completion of the reaction (TLC), methanol was removed under vacuum to get a gummy residue. Compounds **26**–**40** were obtained as white solids after washing the residue with ether–ethanol and then recrystallized from ethanol.

5.5.1. 4-Benzoyl-1-(2-hydroxy-3-piperidin-1-yl-propyl)-2-phenyl-1,2-dihydro-pyrazol-3-one (26). Mp 163 °C (ethanol); yield 70%; ^{1}H NMR (300 MHz) δ 1.38 (m, 2H, H-12), 1.47 (m, 4H, H-11, H-13), 2.22–2.36 (m, 4H, H-10/H-14, H-8), 2.45 (m, 2H, H-10/H-14), 3.64 (dd, ^2J = 9.8 Hz, ^3J = 5.6 Hz, 1H, H-6), 3.91 (m, 1H, H-7), 3.93 (dd, ^2J = 9.8 Hz, ^3J = 6.6 Hz, 1H, H-6), 7.35–7.44 (m, 10H, 2× Ph), 8.31 (s, 1H, H-5); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.6 (−ve, C-12), 25.4 (−ve, C-11, C-13), 54.4 (−ve, C-6), 54.5 (−ve, C-10, C-14), 61.0 (−ve, C-8), 64.1 (+ve, C-7), 107.6 (C-4), 126.9 (+ve, ArCH), 128.0 (+ve, ArCH), 128.8 (+ve, ArCH), 129.2 (+ve, ArCH), 129.6 (+ve, ArCH), 132.0 (+ve, ArCH), 133.3 (N-ArC), 138.4 (ArC), 147.1 (+ve, C-5), 163.1 (C-3), 188.3 (C═O); UV λ_{max} (nm): 312, 237; IR (cm^{-1}): 1630 (C═O), 3310 (OH); EI MS *m*/*z* 406 (M$^+$+1). Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.14; H, 7.01; N, 10.04.

5.5.2. 4-Benzoyl-1-(2-hydroxy-3-piperidin-1-yl-propyl)-2,5-diphenyl-1,2-dihydro-pyrazol-3-one (27). Mp 135 °C (ethanol); yield 65%; ^{1}H NMR: δ 1.37 (m, 2H, H-12), 1.51 (m, 4H, H-11, H-13), 2.14 (dd, ^2J = 11.8 Hz, ^3J = 6.3 Hz, 2H, H-8), 2.33 (m, 2H, H-10/H-14), 2.49 (m, 2H, H-10/H-14), 3.70 (dd, ^2J = 10.2 Hz, ^3J = 6.0 Hz, 1H, H-6), 3.80 (dd, ^2J = 10.2 Hz, ^3J = 5.6 Hz, 1H, H-6), 3.92 (m, 1H, H-7), 7.17–7.78 (m, 15H, 3xPh); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.2 (−ve, C-12), 24.9 (−ve, C-11, C-13), 52.7 (−ve, C-6), 54.0 (−ve, C-10, C-14), 61.0 (−ve, C-8), 63.6 (+ve, C-7), 109.7 (C-4), 125.0 (+ve, ArCH), 127.7 (+ve, ArCH), 128.5 (+ve, ArCH), 129.3 (+ve, ArCH), 129.5 (+ve, ArCH), 130.0 (+ve, ArCH), 130.3 (+ve, ArCH), 132.0 (ArC), 134.0 (N-ArC), 137.9 (ArC), 161.0 (C-5), 163.0 (C-3), 189.3 (C═O); UV λ_{max} (nm): 310, 232; IR (cm^{-1}): 1585 (C═O), 3200 (OH); EI MS *m*/*z* 482 (M$^+$+1). Anal. Calcd for $C_{30}H_{31}N_3O_3$: C, 74.82; H, 6.49; N, 8.73. Found: C, 74.99; H, 6.36; N, 8.53.

5.5.3. 1-(2-Hydroxy-3-piperidin-1-yl-propyl)-2,5-diphenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (28). Mp 158 °C (ethanol); yield 64%; ^{1}H NMR (300 MHz) δ 1.30 (m, 2H, H-12), 1.62 (m, 4H, H-11, H-13), 2.07 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 2H, H-8), 2.17 (m, 2H, H-10/H-14), 2.34 (m, 2H, H-10/H-14), 2.94 (t, J = 8.0 Hz, 2H, CH$_2$), 3.08 (t, J = 8.0 Hz, 2H, CH$_2$), 3.36 (m, 1H, H-7), 3.56 (dd, ^2J = 10.0 Hz, ^3J = 6.0 Hz, 1H, H-6), 3.60 (dd, ^2J = 10.0 Hz, ^3J = 6.6 Hz, 1H, H-6), 7.14-7.51 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 22.4 (−ve, C-12), 24.7 (−ve, C-11, C-13), 29.9 (−ve, CH$_2$), 43.0 (−ve, CH$_2$), 44.4 (−ve, C-10, C-14), 52.0 (−ve, C-6), 54.0 (−ve, C-8), 63.5 (+ve, C-7), 109.2 (C-4), 125.6 (+ve, ArCH), 128.1 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 129.5 (+ve, ArCH), 130.0 (+ve, ArCH), 135.5 (+ve, ArCH), 133.9 (ArC), 134.5 (N-ArC), 142.0 (ArC), 160.1 (C-5), 164.5 (C-3), 195.4 (C═O); UV λ_{max} (nm): 306, 240; IR (cm^{-1}): 1610 (CO), 3300 (OH); EI MS *m*/*z* 510 (M$^+$+1). Anal. Calcd for $C_{32}H_{35}N_3O_3$: C, 75.41; H, 6.92; N, 8.25. Found: C, 75.60; H, 6.92; N, 7.95.

5.5.4. 4-Benzoyl-1-(2-hydroxy-3-piperidin-1-yl-propyl)-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one (29). Mp 165 °C (ethanol); yield 69%; ^{1}H NMR (300 MHz) δ 1.38 (m, 2H, H-12), 1.47 (m, 4H, H-11, H-13), 2.06 (dd, ^2J = 10.8 Hz, ^3J = 6.8 Hz, 2H, H-8), 2.15 (m, 2H, H-10/H-14), 2.39 (m, 2H, H-10/H-14), 2.67 (s, 3H, CH$_3$), 3.86 (m, 1H, H-7), 3.80 (dd, ^2J = 14.4 Hz, ^3J = 8.0 Hz, 2H, H-6), 7.27-7.69 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.1 (+ve, CH$_3$), 23.9 (−ve, C-12), 25.8 (−ve, C-11, C-13), 50.4 (−ve, C-6), 54.5 (−ve, C-10, C-14), 61.6 (−ve, C-8), 64.8 (+ve, C-7), 106.8 (C-4), 126.2 (+ve, ArCH), 127.7 (+ve, ArCH), 128.1 (+ve, ArCH), 129.4 (+ve, ArCH), 131.9 (+ve, ArCH), 134.5 (N-ArC), 138.8 (ArC), 159.7 (C-5), 164.1 (C-3), 190.6 (C═O); UV λ_{max} (nm): 317, 236; IR (cm^{-1}): 1635 (CO), 3340 (OH); EI MS *m*/*z* 420 (M$^+$+1). Anal. Calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.97; N, 10.02. Found: C, 71.37; H, 7.26; N, 9.81.

5.5.5. 1-(2-Hydroxy-3-piperidin-1-yl-propyl)-5-methyl-2-phenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (30). Mp 162 °C (ethanol); yield 71%; ^{1}H NMR (300 MHz) δ 1.44 (m, 2H, H-12), 1.56 (m, 4H, H-11, H-13), 2.07 (dd, ^2J = 8.0 Hz, ^3J = 5.6 Hz, 2H, H-8), 2.19 (m, 2H, H-10/H-14), 2.29 (m, 2H, H-10/H-14), 2.50 (t, J = 7.6 Hz, 2H, CH$_2$), 2.75 (s, 3H, CH$_3$), 2.97 (t, J = 7.6 Hz, 2H, CH$_2$), 3.31 (dd, ^2J = 8.8 Hz, ^3J = 4.0 Hz, 1H, H-6), 3.70 (m, 1H, H-7), 3.79 (dd, ^2J = 8.8 Hz, ^3J = 6.0 Hz, 1H, H-6), 7.15–7.50 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.3 (+ve, CH$_3$), 23.5 (−ve, C-12), 25.3 (−ve, C-11, C-13), 30.0 (−ve, CH$_2$), 43.1 (−ve, CH$_2$), 49.8 (−ve, C-10, C-14), 54.5 (−ve, C-6), 61.5 (−ve, C-8), 64.5 (+ve, C-7), 107.0 (C-4), 125.5 (+ve, ArCH), 125.9 (+ve, ArCH), 128.1 (+ve, ArCH), 128.5 (+ve, ArCH), 129.4 (+ve, ArCH), 134.5 (N-ArC), 141.8 (ArC), 160.5 (C-5), 164.3 (C-3), 195.9 (C═O); UV λ_{max} (nm): 301, 242; IR (cm^{-1}): 1650 (CO), 3280 (OH); EI MS *m*/*z* 448 (M$^+$+1). Anal. Calcd for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.59; H, 7.38; N, 9.67.

5.5.6. 4-Benzoyl-1-(2-hydroxy-3-morpholin-4-yl-propyl)-2-phenyl-1,2-dihydro-pyrazol-3-one (31). Mp 162 °C (ethanol); yield 70%; ^{1}H NMR (300 MHz) δ 2.21 (m, 4H, H-10/H-14, H-8), 2.44 (dd, ^2J = 6.6 Hz, ^3J = 4.2 Hz, 2H, H-10/H-14), 3.57 (t, J = 4.5 Hz, 4H, H-11, H-13), 3.67 (m, 1H, H-7, merged with H-11, H-13), 3.93 (dd, ^2J = 14.7 Hz, ^3J = 2.4 Hz, 2H, H-6), 7.34–7.94 (m, 10H, 2× Ph), 8.31 (s, 1H, H-5); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 53.4 (−ve, C-6), 54.6 (−ve, C-10,

C-14), 61.1 (−ve, C-8), 64.0 (+ve, C-7), 66.7 (−ve, C-11, C-13), 107.4 (C-4), 127.1 (+ve, ArCH), 128.0 (+ve, ArCH), 128.8 (+ve, ArCH), 129.1 (+ve, ArCH), 129.5 (+ve, ArCH), 132.0 (+ve, ArCH), 133.2 (N-ArC), 138.3 (ArC), 146.9 (+ve, C-5), 163.0 (C-3), 189.5 (C═O); FAB MS *m/z* 408 (M^++1). Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.70; H, 6.15; N, 10.05.

5.5.7. 4-Benzoyl-1-(2-hydroxy-3-morpholin-4-yl-propyl)-2,5-diphenyl-1,2-dihydro-pyrazol-3-one (32). Mp 170 °C; yield 76%; ^{1}H NMR (300 MHz) δ 2.00 (m, 4H, H-10/H-14, H-8), 2.27 (dd, ^2J = 11.4 Hz, ^3J = 3.9 Hz, 2H, H-10/H-14), 3.47 (t, J = 4.8 Hz, 4H, H-11, H-13), 3.77 (m, 1H, H-7), 3.82 (dd, ^2J = 12.6 Hz, ^3J = 5.7 Hz, 2H, H-6), 7.15-7.80 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 53.0 (−ve, C-6), 53.4 (−ve, C-10, C-14), 61.4 (−ve, C-8), 64.3 (+ve, C-7), 66.6 (−ve, C-11, C-13), 109.7 (C-4), 125.1 (+ve, ArCH), 125.4 (+ve, ArCH), 127.7 (+ve, ArCH), 127.8 (+ve, ArCH), 128.6 (+ve, ArCH), 129.4 (+ve, ArCH), 129.5 (+ve, ArCH), 129.9 (+ve, ArCH), 130.4 (ArC), 132.3 (+ve, ArCH), 134.3 (N-ArC), 137.9 (ArC), 160.8 (C-5), 163.3 (C-3), 189.7 (C═O); FAB MS *m/z* 484 (M^++1). Anal. Calcd for $C_{29}H_{29}N_3O_4$: C, 72.03; H, 6.04; N, 8.69. Found: C, 72.31; H, 6.30; N, 8.60.

5.5.8. 1-(2-Hydroxy-3-morpholin-4-yl-propyl)-2,5-diphenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (33). Mp 165 °C (ethanol); yield 71%; ^{1}H NMR (300 MHz) δ 1.94 (d, J = 6.3 Hz, 2H, H-8), 2.07 (dd, ^2J = 9.9 Hz, ^3J = 4.2 Hz, 2H, H-10/H-14), 2.33 (dd, ^2J = 11.1 Hz, ^3J = 4.8 Hz, 2H, H-10/H-14), 2.93 (t, J = 7.8 Hz, 2H, CH_2), 3.34 (t, J = 7.8 Hz, 2H, CH_2), 3.50 (t, J = 4.8, 4H, H-11/H-13), 3.65 (m, 2H, H-6), 3.72 (m, 1H, H-7, merged with H-6), 7.11–7.55 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 29.6 (−ve, CH_2), 43.1 (−ve, CH_2), 51.8 (−ve, C-6), 53.3 (−ve, C-10, C-14), 61.2 (−ve, C-8), 64.4 (+ve, C-7), 66.5 (−ve, C-11, C-13), 107.6 (C-4), 125.4 (+ve, ArCH), 125.6 (+ve, ArCH), 128.1 (+ve, ArCH), 128.3 (+ve, ArCH), 128.4 (+ve, ArCH), 129.5 (+ve, ArCH), 129.9 (ArC), 130.3 (+ve, ArCH), 134.1 (N-ArC), 141.6 (ArC), 160.0 (C-5), 164.0 (C-3), 194.4 (C═O); FAB MS *m/z* 512 (M^++1). Anal. Calcd for $C_{31}H_{33}N_3O_4$: C, 72.78; H, 6.50; N, 8.21. Found: C, 72.70; H, 6.51; N, 8.31.

5.5.9. 4-Benzoyl-1-(2-hydroxy-3-morpholin-4-yl-propyl)-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one (34). Mp 175 °C (ethanol); yield 70%; ^{1}H NMR (300 MHz) δ 2.12 (m, 4H, H-10/H-14, H-8), 2.40 (m, 2H, H-10/H-14), 2.67 (s, 3H, CH_3), 3.56 (t, J = 4.5 Hz, 4H, H-11, H-13), 3.80 (m, 1H, H-7), 3.80 (m, 2H, H-6, merged with H-7), 7.26–7.88 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.1 (+ve, CH_3), 50.3 (−ve, C-6), 53.4 (−ve, C-10, C-14), 61.5 (−ve, C-8), 64.7 (+ve, C-7), 66.7 (−ve, C-11, C-13), 106.4 (C-4), 126.4 (+ve, ArCH), 127.7 (+ve, ArCH), 128.3 (+ve, ArCH), 129.3 (+ve, ArCH), 129.4 (+ve, ArCH), 132.0 (+ve, ArCH), 134.0 (N-ArC), 138.5 (ArC), 159.1 (C-5), 163.8 (C-3), 190.5 (C═O); FAB MS *m/z* 422 (M^++1). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.45; H, 6.52; N, 9.80.

5.5.10. 1-(2-Hydroxy-3-morpholin-4-yl-propyl)-5-methyl-2-phenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (35). Mp 160 °C (ethanol); yield 75%; ^{1}H NMR (300 MHz) δ 2.24 (m, 4H, H-10/H-14, H-8), 2.42 (m, 2H, H-10/H-14), 2.50 (s, 3H, CH_3), 3.04 (t, J = 7.5 Hz, 2H, CH_2), 3.18 (t, J = 7.5 Hz, 2H, CH_2), 3.62 (t, J = 4.5 Hz, 4H, H-11, H-13), 3.84 (m, 1H, H-7), 3.88 (m, 2H, H-6, merged with H-7), 7.18–7.64 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.3 (+ve, CH_3), 29.8 (−ve, CH_2), 43.0 (−ve, CH_2), 49.7 (−ve, C-6), 53.4 (−ve, C-10, C-14), 61.3 (−ve, C-8), 64.6 (+ve, C-7), 66.7 (−ve, C-11, C-13), 106.0 (C-4), 125.5 (+ve, ArCH), 126.1 (+ve, ArCH), 128.1 (+ve, ArCH), 128.5 (+ve, ArCH), 129.5 (+ve, ArCH), 134.1 (N-ArC), 141.7 (ArC), 158.7 (C-5), 164.9 (C-3), 196.3 (C═O); FAB MS *m/z* 450 (M^++1). Anal. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.47; H, 6.95; N, 9.35. Found: C, 69.70; H, 6.90; N, 9.05.

5.5.11. 4-Benzoyl-1-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-2-phenyl-1,2-dihydro-pyrazol-3-one (36). Mp 160 °C (ethanol); yield 72%; ^{1}H NMR (300 MHz) δ 1.88 (t, J = 6.4 Hz, 4H, H-11, H-12), 2.07 (dd, ^2J = 12.0 Hz, ^3J = 3.8 Hz, 2H, H-8), 2.32 (dd, ^2J = 8.9 Hz, ^3J = 4.2 Hz, 2H, H-10/H-13), 3.02 (dd, ^2J = 8.9 Hz, ^3J = 5.4 Hz, 2H, H-10/H-13), 3.58 (m, 1H, H-7), 4.14 (m, 2H, H-6, merged with H-7), 7.44–7.81 (m, 10H, 2× Ph), 8.46 (s, 1H, H-5); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.4 (−ve, C-11, C-12), 52.9 (−ve, C-6), 54.0 (−ve, C-10, C-13), 58.5 (−ve, C-8), 65.8 (+ve, C-7), 108.6 (C-4), 125.3 (+ve, ArCH), 127.3 (+ve, ArCH), 127.8 (+ve, ArCH), 128.5 (+ve, ArCH), 129.4 (+ve, ArCH), 132.0 (+ve, ArCH), 132.3 (N-ArC), 137.9 (ArC), 149.9 (+ve, C-5), 163.1 (C-3), 190.5 (C═O); FAB MS *m/z* 392 (M^++1). Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.51; H, 6.34; N, 10.60.

5.5.12. 4-Benzoyl-1-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-2,5-diphenyl-1,2-dihydro-pyrazol-3-one (37). Mp 165 °C (ethanol); yield 77%; ^{1}H NMR (300 MHz) δ 1.67 (t, J = 5.2 Hz, 4H, H-11, H-12), 2.07 (dd, ^2J = 12.0 Hz, ^3J = 3.9 Hz, 2H, H-8), 2.30 (dd, ^2J = 8.4 Hz, ^3J = 3.0 Hz, 2H, H-10/H-13), 2.50 (dd, ^2J = 8.4 Hz, ^3J = 5.4 Hz, 2H, H-10/H-13), 3.67 (m, 1H, H-7), 3.73 (m, 2H, H-6, merged with H-7), 7.06–8.04 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.2 (−ve, C-11, C-12), 52.6 (−ve, C-6), 53.9 (−ve, C-10, C-13), 58.8 (−ve, C-8), 65.6 (+ve, C-7), 109.6 (C-4), 125.0 (+ve, ArCH), 125.3 (+ve, ArCH), 127.3 (+ve, ArCH), 127.8 (+ve, ArCH), 128.5 (+ve, ArCH), 129.4 (+ve, ArCH), 129.5 (+ve, ArCH), 129.8 (+ve, ArCH), 130.3 (ArC), 132.0 (+ve, ArCH), 132.3 (N-ArC), 137.9 (ArC), 160.9 (C-5), 163.3 (C-3), 189.5 (C═O); FAB MS *m/z* 468 (M^++1). Anal. Calcd for $C_{29}H_{29}N_3O_3$: C, 74.50; H, 6.25; N, 8.99. Found: C, 74.70; H, 6.45; N, 9.05.

5.5.13. 1-(2-Hydroxy-3-pyrrolidin-1-yl-propyl)-2,5-diphenyl-4-(3-phenylpropionyl)-1,2-dihydro-pyrazol-3-one (38). Mp 180 °C; yield 73%; ^{1}H NMR (300 MHz) δ 1.62 (t, J = 6.6 Hz, 4H, H-11, H-12), 1.95 (dd, ^2J = 12.0 Hz, ^3J = 4.2 Hz, 1H, H-8), 2.15 (m, 3H, H-10/H-13, and 1H of H-8), 2.37 (dd, ^2J = 6.6 Hz, ^3J = 2.1 Hz, 2H,

H-10/H-13), 2.93 (t, $J = 7.8$ Hz, 2H, CH_2), 3.35 (t, $J = 7.5$ Hz, 2H, CH_2), 3.60 (m, 1H, H-7), 3.65 (m, 2H, H-6, merged with H-7), 7.11–7.54 (m, 15H, 3× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 23.2 (−ve, CH_2), 29.6 (−ve, C-11, C-12), 43.1 (−ve, CH_2), 51.9 (−ve, C-6), 53.7 (−ve, C-10, C-13), 58.8 (−ve, C-8), 65.8 (+ve, C-7), 107.5 (C-4), 125.4 (+ve, ArCH), 125.5 (+ve, ArCH), 128.1 (+ve, ArCH), 128.3 (+ve, ArCH), 128.4 (+ve, ArCH), 129.4 (+ve, ArCH), 129.8 (ArC), 130.3 (+ve, ArCH), 134.1 (N-ArC), 141.7 (ArC), 159.9 (C-5), 164.1 (C-3), 194.5 (C═O); FAB MS *m/z* 496 ($M^+ + 1$). Anal. Calcd for $C_{31}H_{33}N_3O_3$: C, 75.13; H, 6.71; N, 8.48. Found: C, 75.30; H, 6.60; N, 8.35.

5.5.14. 4-Benzoyl-1-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one (39). Mp 154 °C (ethanol); yield 67%; ^{1}H NMR (300 MHz) δ 1.81 (t, $J = 6.3$ Hz, 4H, H-11, H-12), 2.45 (dd, $^2J = 11.7$ Hz, $^3J = 1.8$ Hz, 1H, H-8), 2.60 (s, 3H, CH_3), 2.74 (m, 3H, H-10/H-13, 1H of H-8), 2.87 (dd, $^2J = 9.6$ Hz, $^3J = 2.4$ Hz, 2H, H-10/H-13), 3.80 (m, 1H, H-7), 3.95 (m, 2H, H-6, merged with H-7), 7.28–7.83 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.3 (+ve, CH_3), 23.1 (−ve, C-11, C-12), 49.9 (−ve, C-6), 54.4 (−ve, C-10, C-13), 58.5 (−ve, C-8), 65.5 (+ve, C-7), 106.7 (C-4), 126.2 (+ve, ArCH), 127.8 (+ve, ArCH), 128.4 (+ve, ArCH), 129.3 (+ve, ArCH), 129.6 (+ve, ArCH), 132.1 (+ve, ArCH), 134.1 (N-ArC), 138.7 (ArC), 159.6 (C-5), 164.2 (C-3), 190.5 (C═O); FAB MS *m/z* 406 (M^++1). Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.20; H, 6.85; N, 10.52.

5.5.15. 1-(2-Hydroxy-3-pyrrolidin-1-yl-propyl)-5-methyl-2-phenyl-4-(3-phenyl-propionyl)-1,2-dihydro-pyrazol-3-one (40). Mp 148 °C (ethanol); yield 69%; ^{1}H NMR (300 MHz) δ 1.70 (t, $J = 6.6$ Hz, 4H, H-11, H-12), 2.07 (dd, $^2J = 12.0$ Hz, $^3J = 3.9$ Hz, 1H, H-8), 2.11 (dd, $^2J = 8.7$ Hz, $^3J = 2.1$ Hz, 2H, H-10/H-13), 2.45 (dd, $^2J = 12.0$ Hz, $^3J = 5.4$ Hz, 1H, H-8), 2.52 (dd, $^2J = 8.7$ Hz, $^3J = 2.4$ Hz, 2H, H-10/H-13), 2.74 (s, 3H, CH_3), 2.97 (t, $J = 7.8$ Hz, 2H, CH_2), 3.33 (t, $J = 7.8$ Hz, 2H, CH_2), 3.72 (m, 1H, H-7), 3.80 (m, 2H, H-6, merged with H-7), 7.13–7.51 (m, 10H, 2× Ph); ^{13}C normal/DEPT-135 NMR (75 MHz) δ 13.3 (+ve, CH_3), 23.4 (−ve, C-11, C-12), 29.9 (−ve, CH_2), 43.0 (−ve, CH_2), 49.8 (−ve, C-6), 53.8 (−ve, C-10, C-13), 59.0 (−ve, C-8), 66.4 (+ve, C-7), 105.8 (C-4), 125.5 (+ve, ArCH), 126.3 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 129.5 (+ve, ArCH), 134.1 (N-ArC), 141.7 (ArC), 158.5 (C-5), 165.0 (C-3), 196.2 (C═O); FAB MS *m/z* 434 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{31}N_3O_3$: C, 72.03; H, 7.21; N, 9.69. Found: C, 72.22; H, 6.95; N, 9.55.

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