INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Research Article

SYNTHESIS AND EVALUATION OF NEW 3- SUBSTITUTED-[3, 4-DIHYDROPYRIMIDINONES]-INDOLIN-2-ONES FOR ANALGESIC ACTIVITY

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Article Received on: 12/05/11 Revised on: 20/06/11 Approved for publication: 02/07/11

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ABSTRACT
45 New 3-substituted [3,4-dihydropyrimidinones]-Indolin-2-ones have been synthesized and tested for Analgesic activity by Eddys Hot plate method on swiss albino mice. Among them compounds AJ_{43}, AJ_{45}, AJ_{41}, AJ_{16} and AJ_{17} exhibited higher Analgesic activity. However, the Analgesic activities are lower than standard pentazosin.
KEY WORDS: Dihydropyrimidinones, Indole-2-ones, Analgesic activity, Pentazosin

INTRODUCTION

Heterocyclic systems possessing an indole moiety exhibit a number of interesting biological activities such as antiviral, antibacterial, anti fungal, anti-inflammatory, analgesic, diuretic and anticonvulsant activities [1-8]. A lot of work has been carried out on indole derivatives and no work has been carried on 3- substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones. It is also evident from the literature that dihydro pyrimidinones are equally important interms of pharmacological activities such as Calcium channel blockers, antifungal, and antihypertensive agents[9-11]. Therefore, it seemed promising to synthesize some new 3- substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones using the multi component one pot condensation of Biginelli's synthesis using Isatin semicarbazone, ethylacetoacetate and aromatic aldehyde[12]. We present here our results on the design of new 3- substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones emphasizing in particular the presence of aromatic nucleus at the 5-postion of 3,4-dihydropyrimidine ring [benzaldehyde,4-chloro Benzaldehyde,4-hydroxybenzaldehyde, 4-methoxy Benzaldehyde and 2-nitrobenzaldehyde] in one skeleton (B_1 to B_9, AJ_1 to AJ_{45}, Scheme-1). All the compounds synthesized were assayed for analgesic activity by Hot plate method using on Swiss albino mice.

MATERIALS AND METHODS

Animals

The experiment was carried out using male, Swiss Albino mice (25-30 g) were obtained from animal house, UCPSc, Kakatiya university, Warangal, India. On arrival the animals were placed at random and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24 ± 2°C and relative humidity of 30 – 70 %. A 12:12 light: day cycle was followed. All animals were allowed to free access to water and fed with standard commercial chaw pallets. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee, Kakatiya University, Warangal, India.

Hot Plate Method

Five groups of six mice weighing between 20-25g were selected for the present study. Group 1 served as control and received the vehicle. The drug concentration of 10 mg/kg was administered orally to groups 2, 3 and 4, respectively and group 5 received the standard drug pentazocine (30 mg/kg, i.p.). The mice were placed on Eddy's hot plate kept at a temperature of 55 ± 0.5 o C for a maximum time of 15 sec (33). Reaction time was recorded when the animals licked their fore-and hind paws and jumped; at before 0 and 15, 30, 45, and 60 min after administration of test drugs. All the results were expressed as Mean ± Standard Error (SEM). Data was analyzed using one-way ANOVA followed by Dunnett's

t-test. P-values < 0.05 were considered as statistically significant.

Synthesis of the compounds

The reaction sequence used in the synthesis of the target compounds AJ $_{1-45}$ was depicted in the scheme-1. Isatin semicarbazone B_{1-9} were obtained from appropriate isatin in alcohol with addition of semicarbazide hydrochloride and sodium acetate in water and refluxed on waterbath for about 1 hour[13]. Compounds AJ $_{1-45}$ were synthesized by refluxing B_{1-9} with ethylacetoacetate and an appropriate aromatic aldehydes (Benzal dehyde, 4-chlorobenzaldehyde,4-hydroxybenzaldehyde, 4-methoxybenzaldehyde and 2-nitro benzaldehyde) by multicomponent one pot condensation using named Bigineli's reaction in presence of catalytic amount of concentrated hydrochloric acid for 10-12 hours. All the newly synthesized compounds were characterized by physical , spectral(IR, Mass, NMR) and Elemental analysis.

Experimental

All reagents used were purchased from Sd fine chemical company, Mumbai , india. Melting points were determined in an open capilries on a galen camp apparatus (Sanyo gallen camp, lough, borough, UK), and were un corrected. IR spectra (KBR, cm^{-1}) were recorded on perkin elmer spectrophotometer(577 model). H1 NMR spectra were recorded on a brukar WM-400 spectrophotometry (in δppm)

Isatin semicarbazone (B_1 to B_9)

To a stirred solution of an appropriate Isatin(2gm) in 20ml of alcohol at room temperature, semicarbazide hydrochloride, sodium acetate dissolved in water was added to the above solution and refluxed on a water bath for about 1hour, the resultant yellow crystalline solid obtained was filtered, washed repeatedly with small portions of cold water and finally with small portions of cold methanol and recrystllized with methanol to give pure products (B_1 to B_9). The data of the compounds obtained was compared with data available in the literature.

3- Substituted-[3,4-dihydro pyrimidinones]-Indolin-2-ones (AJ $_{1\ to\ 45}$)

Compounds B_1 to B_9 (2.04gm, 0.01mol), ethylacetoacetate and aromatic aldehyde (0.01 mol), in drymethanol and a few drops of concentrated hydrochloric acid as a catalyst was condensed by multicomponent one pot condensation by named Biginelli's reaction for 10 to 12 hours on a water bath. The solvent was evaporated, the precipitated solid was poured on to crushed ice, filtered, dried and recrystallized from methanol to give pure products (AJ_1 to AJ_{45}). The compounds obtained were characterized by physical and spectral data .for eg, the yield of the compound C_2[R_1=H, R_2=H, R_3=benzaldehyde] was 2g[65]M.P246andspectraldata(KBr):159[NH,indole],3330[NH,pyramidine],1720[NHCO],1688[C=O,indole],1621[C=N,1360-1280[C-N,1300-1000[C-O].PMRspectra[inDMSOD6,ppm]12.03[S,1H,N Hindole],11.73 [S,1H,NHpyrimidine] 6.0- .7.0[m,8H,2Ar-H], 0.9[t-CH_3] 4.0[q,2H,O CH_2] 2.20[S,3H,CH_3].compoundsAJ_1-$_{45}$were prepared similarly.

RESULTS

Compounds AJ_1toAJ_{45} consisting of five series,X-3[(4-phenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-ones](A_1toA_9),Y-3[(4-chlorophenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-ones](A_{10}toA_{18}), Z-3[(4-hydroxyphenyl-5carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-ones] (A_{19}toA_{27}), X_1-3[(4-methoxyphenyl-5- carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-onesand, (A_{28}toA_{36}),Y1-3[(2-nitrophenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2 one)indolin-2-ones], ($A_{37}$to$A_{45,}$)showed analgesic activity on mice by Eddys hot plate method. The activity was represented by percent protection. All the results were depicted in table 1

DISCUSSION

The data shows that Among all the compounds, Compounds AJ43(R=R_2=Br,R_1=H) and AJ45(R=R_1=H,R_2=CI) were more potent analgesics which exhibited similar activity with percentage protection of (107.33, 144.44 and 166.66) at 0.5hr,1hr and 2hr time points respectively. Compound AJ41(R=R_1=H,R_2=Br) was next in the order of exhibiting analgesic activity with percentage protection of (103.7,122.6 and 165.0) followed by Compounds AJ16 and AJ14(R=R_2=Br,R_1=H) with percentage protection of (129.5,144.66 and156.88) and (128.8,145.11 and 150.08) at 0.5hr,1hr and 2hr respectively, but only the 2hr results were depicted in the table 1 which was taken as maximum protection.

CONCLUSION

Hence we conclude that among all the series, compounds of Y1series having Nitro and Yseries having 4-chloro substituent at 5-position of pyrimidine ring have greater analgesic activity followed by X, Z and X1 series..The order of activity was found to be as follows AJ_{45}=AJ_{43}>AJ_{41}> AJ_{16}> AJ_{14} and AJ_{15} followed by X, Z and X1 series. Among Isatins, 5,7-disubstituted halogens are more active than mono subsituted halogens against analgesic activity followed by Br,C1,F.

ACKNOWLEDGEMENT

The authors are thankful to U.G.C., New Delhi for the financial assistance. Authors are also grateful to Dr. Reddy's Research Foundation, Hyderabad. for providing I.R and PMR spectral analysis.;

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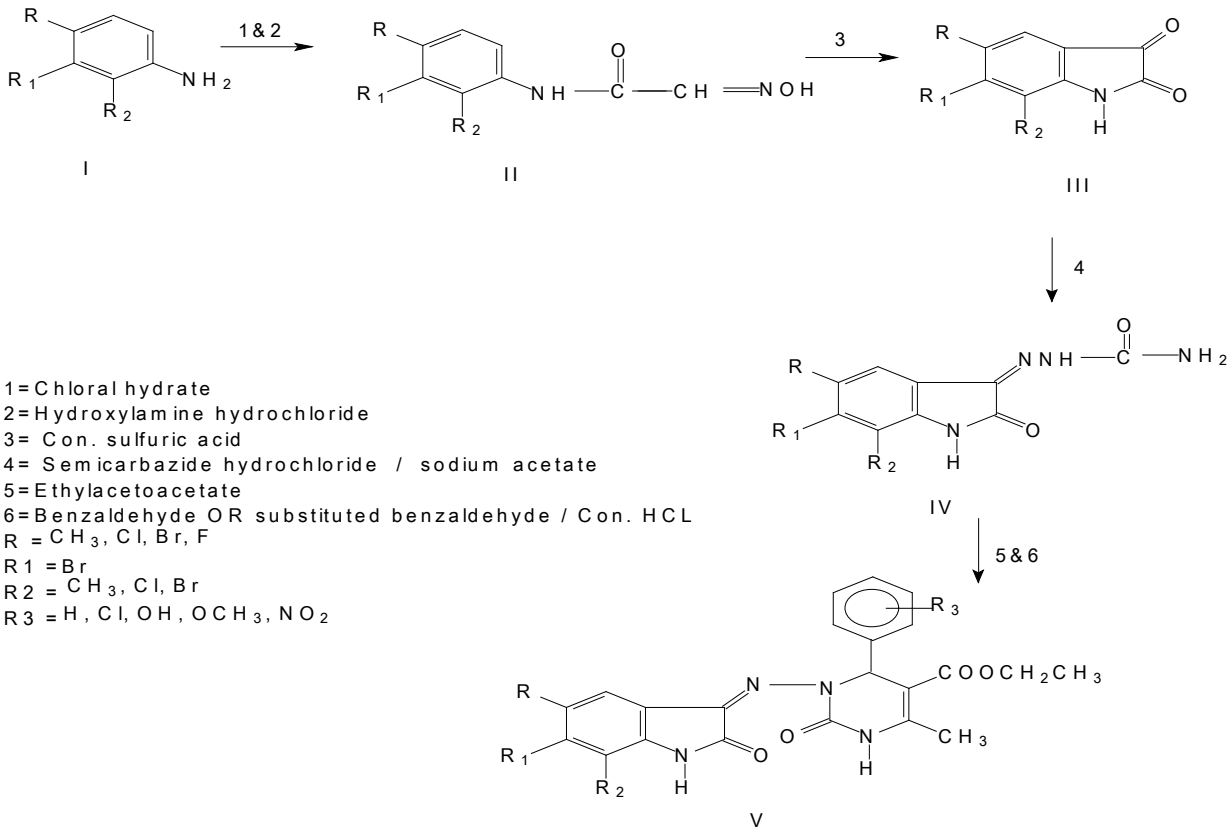
Table 1: Physical and spectral data for 3-substituted [3,4-dihydropyrimidinones]-Indolin-2-ones

Com	R	R_1	R_2	R_3	Mol. Formula	M.P (^oC)	Mass spectra/H^1NMR	% protection Max.*
AJ1	H	H	H	H	$C_{22}H_{20}N_4O_4$	243	405,11.70[S,1H,NH indole]11.25[S,1H,NH pyrimidine] 6.6-7.6[m,9H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	184.44*
AJ2	CH_3	H	H	H	$C_{23}H_{22}N_4O_4$	246	12.03[S,1H,NH indole]11.73[S,1H,NH pyrimidine] 6.0-7.0[m,8H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	70.44*
AJ_3	F	H	H	H	$C_{22}H_{19}N_4O_4F$	248	11.75[S,1H,NH indole]11.50[S,1H,NH pyrimidine] 6.1-7.2[m,8H,2Ar-H] 0.9[t,CH_3], 2.20[S,3H,CH_3], 4[q,2H,0CH_2]	88.88*
AJ4	Cl	H	H	H	$C_{22}H_{19}N_4O_4C1$	251	11.75[S,1H,NH indole]11.50[S,1H,NH pyrimidine] 6.1-7.2[m,8H,2Ar-H] 0.9[t,CH_3], 2.20[S,3H,CH_3], 4[q,2H,0CH_2]	111.11*
AJ5	Br	H	H	H	$C_{22}H_{19}N_4O_4Br$	252	11.75[S,1H,NH indole]11.50[S,1H,NH pyrimidine] 6.1-7.2[m,8H,2Ar-H] 0.9[t,CH_3], 2.20[S,3H,CH_3], 4[q,2H,0CH2]	124.44*
AJ6	H	Br	H	H	$C_{22}H_{19}N_4O_4Br$	253	11.75[S,1H,NH indole]11.50[S,1H,NH pyrimidine] 6.0-7.2[m,8H,2Ar-H] 0.9[t,CH_3], 2.20[S,3H,CH_3], 4[q,2H,0CH_2]	137.77*
AJ7	Br	H	Br	H	$C_{22}H_{18}N_4O_4Br_2$	255	11.50[S,1H,NH indole]11.25[S,1H,NH pyrimidine] 6.0-7.2[m,6H,2Ar-H] 0.9[t,CH_3], 2.20[S,3H,CH_3], 4[q,2H,0CH_2]	78.0*
AJ8	H	H	CH_3	H	$C_{23}H_{22}N_4O_4$	244	12.0[S,1H,NH indole]11.70[S,1H,NH pyrimidine] 6.0-7.0[m,8H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH3], 3.9[q,2H,0CH_2]	166.88*
AJ9	H	H	C1	H	$C_{22}H_{19}N_4O_4C1$	245	439.5, 11.70[S,1H,NH indole]11.55[S,1H,NH pyrimidine] 6.6-7.6[m,8H,2Ar-H] 0.9[t,CH_3], 2.19[S,3H,CH3], 4.2[q,2H,0CH_2]	80.44*
AJ10	H	H	H	C1	$C_{22}H_{19}N_4O_4C1$	244	439.5, 11.20[S,1H,NH indole]10.80[S,1H,NH pyrimidine] 6.3-7.2[m,7H,2Ar-H] 0.9[t,CH_3], 2.50[S,3H,CH_3], 3.9[q,2H,0CH_2]	48.88
AJ11	CH_3	H	H	C1	$C_{23}H_{20}N_4O_4C1$	246	11.18[S,1H,NH indole]10.88[S,1H,NH pyrimidine] 6.8-7.8[m,6H,2Ar-H] 1.9[t,CH_3], 2.6[S,3H,CH_3], 3.8[q,2H,0CH2]	66.66*
AJ12	F	H	H	C1	$C_{22}H_{18}N_4O_4C1F$	248	10.99 [S,1H,NH indole]10.80[S,1H,NH pyrimidine] 6.6-7.6[m,6H,2Ar-H] 0.8[t,CH_3], 2.53[S,3H,CH_3], 3.8[q,2H,0CH_2]	88.88*

AJ13	Cl	H	H	C1	$C_{22}H_{18}N_{4254}O_4C1_2$	254	10.99[S,1H,NH indole]10.80[S,1H,NH pyrimidine] 6.6-7.6[m,9H,2Ar-H],2.53[S,3H,CH_3], 0.9[t,CH3],3.9[q ,2H,OCH_2]	148.11*
AJ14	Br	H	H	C1	$C_{22}H_{18}N_4O_4C1Br$	256	10.99[S,1H,NH indole]10.88[S,1H,NH pyrimidine] 6.6-7.6[m,9H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,$CH3_1$, 3.8[q,2H,$0CH_2$]	150.77*
AJ15	H	Br	H	Cl	$C_{22}H_{18}N_4O_4C1Br$	257	10.99[S,1H,NH indole]10.88[S,1H,NH pyrimidine] 6.6-7.6[m,9H,2Ar-H] 0.9[t,CH3], 2.25[S,3H,CH_3], 3.8[q,2H,$0CH_2$]	58.66
AJ16	Br	H	Br	Cl	$C_{21}H_{17}N_4O_4C1Br_2$	259	11.00[S,1H,NH indole]10.92[S,1H,NH pyrimidine] 6.4-7.1[m,5H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	155.88*
AJ17	H	H	CH_3	C1	$C_{23}H_{20}N_4O_4C1$	246	11.00[S,1H,NH indole]10.92[S,1H,NH pyrimidine] 6.4-7.1[m,5H,2Ar-H] 0.9[t,CH3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	60.0*
AJ18	H	H	Cl	Cl	$C_{22}H_{18}N_4O_4C1_2$	255	11.00[S,1H,NH indole]10.92[S,1H,NH pyrimidine] 6.6-7.6[m,5H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	128.88*
AJ19	H	H	H	OH	$C_{22}H_{19}N_4O_5$	258	420, 11.90[S,1H,NH indole]11.85[S,1H,NH pyrimidine] 6.4-7.4[m,7H,2Ar-H] 0.9[t,CH_3], 2.3[S,3H,CH_3], 4[q,2H,$0CH_2$]	26.66
AJ20	CH_3	H	H	OH	$C_{23}H_{21}N_4O_5$	259	11.88[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.2-7.4[m,6H,2Ar-H] 1.1[t,,CH_3], 2.6[S,3H,CH_3], 3.8[q,2H,$0CH_2$]	40.0
AJ21	F	H	H	OH	$C_{22}H_{18}N_4O_5F$	261	11.92[S,1H,NH indole]11.80[S,1H,NH pyrimidine] 6.6-7.6[m,6H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	66.66*
AJ22	Cl	H	H	OH	$C_{22}H_{18}N_4O_5C1$	263	11.92[S,1H,NH indole]11.80[S,1H,NH pyrimidine] 6.6-7.6[m,6H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	82.22*
AJ23	Br	H	H	OH	$C_{22}H_{18}N_4O_5Br$	266	11.92[S,1H,NH indole]11.80[S,1H,NH pyrimidine] 6.6-7.6[m,6H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	104.44*
AJ24	H	Br	H	OH	$C_{22}H_{18}N_4O_5Br$	267	11.92[S,1H,NH indole]11.80[S,1H,NH pyrimidine] 6.6-7.6[m,6H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	34.66
AJ25	Br	H	Br	OH	$C_{22}H_{17}N_4O_5Br_2$	270	11.80[S,1H,NH indole]11.00[S,1H,NH pyrimidine] 6.6-7.6[m,5H,2Ar-H] 1.0[t,CH_3], 2.20[S,3H,CH_3], 3.9[q,2H,$0CH_2$]	91.66*
AJ26	H	H	CH_3	OH	$C_{23}H_{21}N_4O_5$	258	11.88[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.2-7.4[m,6H,2Ar-H] 0.9[t,CH_3], 2.6[S,3H,CH_3],3.8[q,2H,$0CH_2$],3.8[S,3H,$0CH_3$]	33.55
AJ27	H	H	Cl	OH	$C_{23}H_{22}N_4O_5$	263	11.88[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.2-7.4[m,6H,2Ar-H] 0.9[t,CH3], 2.6[HS,3H,CH3], 3.8[q,2H,$0CH_2$]	115.55*
AJ28	H	H	H	OCH_3	$C_{23}H_{22}N_4O_5$	245	43, 11.99[S,1H,NH indole]12.0[S,1H,NH pyrimidine] 6.5-7.6[m,7H,2Ar-H] 0.8[t,CH_3], 2.6[S,3H,CH_3], 3.8[q,2H,$0CH_2$],3.8[S,3H,CH_3]	15.55
AJ29	CH_3	H	H	OCH_3	$C_{24}H_{23}N_4O_5$	246	11.90[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3, 2.5[S,3H,CH_3], 4[q,2H,$0CH_2$],6.4[S,3H,CH_3],3.8[S,3H,$0CH_3$]	33.55
AJ30	F	H	H	OCH_3	$C_{23}H_{21}N_4O_5F$	248	12.70[S,1H,NH indole]12.0[S,1H,NH pyrimidine] 6.2-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.5[S,3H,CH_3], 4[q,2H,$0CH_2$],3.8[S,3H,OCH_3-Ar]	51.11
AJ31	Cl	H	H	OCH_3	$C_{23}H_{21}N_4O_5C1$	250	12.70[S,1H,NH indole]12.5[S,1H,NH pyrimidine] 6.6-7.6[m,7,2Ar-H] 0.9[t,CH_3], 2.5[S,3H,CH_3], 4[q,2H,$0CH_2$],3.8[S,3H,$0CH_3$]	60.0*
AJ32	Br	H	H	OCH_3	$C_{23}H_{21}N_4O_5Br$	252	12.70[S,1H,NH indole]12.20[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.5[S,3H,CH_3], 4[q,2H,	117.77*
AJ33	H	Br	H	OCH_3	$C_{23}H_{21}N_4O_5Br$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	28.88
AJ34	Br	H	Br	OCH_3	$C_{23}H_{20}N_4O_5Br_2$	254	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	124.44*
AJ35	H	H	CH_3	OCH_3	$C_{24}H_{23}N_4O_5$	246	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	44.44
AJ36	H	H	Cl	OCH_3	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	118.44*
AJ37	H	H	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,$0CH_2$]	44.44

AJ38	CH3	H	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	60.0*
AJ39	F	H	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	77.77*
AJ40	CI	H	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	104.44*
AJ41	Br	H	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	165.88*
AJ42	H	Br	H	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	48.88
AJ43	Br	H	Br	NO_2	$C_{23}H_{21}N_4O_5C1$	251	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	166.66*
AJ44	H	H	CH3	NO_2	$C_{23}H_{22}N_5O_6$	271	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	60.0*
AJ45	H	H	CI	NO_2	$C_{22}H_{18}N_4O_6C1$	277	12.70[S,1H,NH indole]11.75[S,1H,NH pyrimidine] 6.6-7.6[m,7H,2Ar-H] 0.9[t,CH_3], 2.25[S,3H,CH_3], 4[q,2H,0CH_2]	166.66*

Scheme: 1: Schematic diagram of 3- substituted-[3,4-dihydro pyrimidinones]-Indolin-2-ones



R=H, CH_3, F, Cl, Br
R_1= Br
R_2 = Br, CI, CH_3
R_3 = Benzaldehyde, 4-Cl benzaldehyde, 4-OH benzaldehyde, 4-OCH_3 benzaldehyde, 2-nitro benzaldehyde.

Source of support: Nil, Conflict of interest: None Declared