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Synthesis and Insilico Characterization of Some Novel 3,4 -Dihydropyrimidin -2-(1h)-Thione Derivatives

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Abstract

Various novel 3,4-dihydropyrimidin-2-(1H)-thione derivatives were prepared by using substituted benzaldehydes, ethylacetoacetate and thiourea in the presence of ammonium molybdate and acetic acid at a temperature of 80-90°C to give corresponding titled compounds in good yields. The synthesized compounds were characterized by physical properties and spectral studies (IR, 1H-NMR) and for all the titled compounds physical data like LogP values and biological properties were predicted by using molinspiration soft ware.

Keywords: Substituted benzaldehydes, ethylacetoacetate, thiourea, ammonium molybdate and acetic acid.

Introduction

Heterocyclic systems possessing pyrimidine moiety exhibit a number of interesting biological activities such as antiviral, antimicrobial[1,2] anti-fungal,[3] anti-inflammatory, analgesic[4] diuretic and anticonvulsant activities. It is also evident from the literature that dihydropyrimidinones are equally important in terms of pharmacological activities such as calcium channel blockers[5] antifungal and antihypertensive agent.[6] Racemic dihydropyrimidinone is reported to be an allosteric inhibitor of human kinesin and unlike taxanes, it is nontoxic to neuron cells.[7]

Therefore, it seems promising to synthesize some new substituted 3,4-dihydropyrimidin-2-(1H)-thiones using compounds like urea, ethylacetoacetate and aromatic aldehydes like tolualdehyde, benzaldehyde, etc. We present here our results on the design of newly substituted 3,4-dihydropyrimidin-2-(1H)-thiones emphasizing in particular the presence of aromatic nucleus at the 4th position of 3,4-dihydropyrimidine ring with benzaldehyde, 4-methylbenzaldehyde, 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde and 4-flourobenzaldehyde.

Aim and objectives:

- ✓ The heterocyclic derivatives possess a wide range of biological properties and they act as anthelmintic, antitumor, analgesic, anticancer, antiinflammatory, antibacterial and antifungal activity.
- ✓ Our aim is to synthesize the title compounds viz. 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione derivatives, by following the scheme mentioned in the experimental part.
- ✓ To characterize all the synthesized compounds by physical (Molecular weight, Molecular formula, Melting point, Recrystallization, Rf value) and spectral data.

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- ✓ For all the titled compounds physical data like LogP values and biological properties were predicted by using molinspiration soft ware.

Materials and methods

Materials and reagents were obtained from commercial suppliers (Merck grade) and were used without further purification. Melting points were determined by using electrical melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using Silica Gel G (Merck). IR spectra were recorded in KBr discs on a Bruker analyzer. 1H NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in γ, ppm) in DMSO using TMS as internal standard.

Experimental work: [8] Scheme shown in Fig. 1.

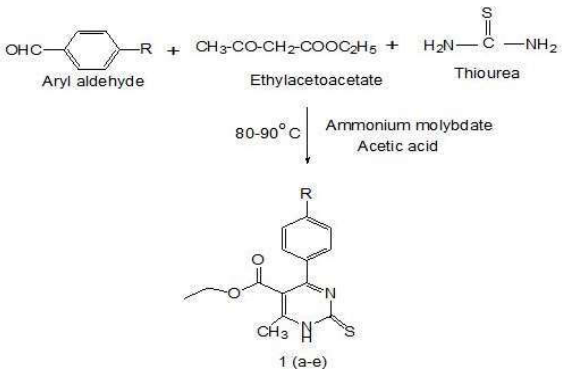

Fig. 1: Schematic representation

General procedure:[9,10]

A mixture of substituted benzaldehyde (0.01M), ethylacetoacetate (0.01M) and thiourea (0.01M) condenses in presence of catalyst ammonium molybdate (0.001M) by using 10 ml of acetic acid for a period of 2 hrs at 80-90 oC. The progress of the reaction was monitored by using TLC. After completion of the reaction the solution poured into crushed ice. Filter the product and washed with cold water and recrystallize by using 95% ethanol.

Various synthesized 3, 4-dihydro pyrimidin-2(1H)-thione derivatives are:

- 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2 (1H)-thione (Ia)
- 5-ethoxycarbonyl-6-methyl-4-(4-hydroxy phenyl)-3, 4-dihydro pyrimidine-2(1H)–thione (Ib)
- 5-ethoxycarbonyl-6-methyl-4-(4-methoxy phenyl)-3,4-dihydro pyrimidin-2 (1H)-thione (Ic)
- 5-ethoxycarbonyl-6-methyl-4-(4-methyl phenyl)-3,4-dihydro pyrimidin-2 (1H)-thione (Id)
- 5-ethoxycarbonyl-6-methyl-4-(4-fluoro phenyl)-3,4-dihydro pyrimidin-2 (1H)-thione (Ie)

Physical characterization of the synthesized compounds

Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was identified by the TLC by using silica gel-G as stationary phase. Physical results shown in Table I.

Spectral data (IR and 1H NMR):

(I a) 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2 (1H)-thione :

IR [Cm-1, KBr]:

3221.33(-NH), 3132.33 (-NH), 2873.76 (-CH3), 1680.32(C=S), 1701.13(C=O of ester group).

1H NMR (400 MHz, DMSO-d6) d: 1.088-1.123 (t, J =14 Hz, 3H,-O-CH2-CH3), 2.235 (s, 3H, -CH3), 3.957-4.010 (q, J = 21 Hz 2H, O-CH2 CH3), 5.040-5.048 (d, J = 3.2 Hz, 1H, –CH), 7.019-7.040 (d, J = 8.4 Hz, 2H, H-2'and 6' Ph), 6.678-6.701 (d, J=9.2 Hz, 2H,H-3'and 5'Ph), 7.601 (s,1H, NH), 9.091 (s,1H, NH).

(I b) 5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydro pyrimidin-2(1H)-thione:

IR [Cm-1, KBr]:

3492.37(OH), 3221.33(-NH), 3132.33 (-NH), 2873.76 (-CH3), 1680.32(C=S), 1701.13(C=O of ester group).

1H NMR (400 MHz, DMSO-d6) d: 1.088-1.123 (t, J =14 Hz, 3H,-O-CH2-CH3), 2.235(s, 3H, -CH3), 3.957-4.010 (q, J = 21 Hz 2H, O-CH2 CH3), 5.040-5.048 (d, J = 3.2 Hz, 1H, –CH), 7.019-7.040 (d, J = 8.4 Hz, 2H, H-2'and 6' Ph), 6.678-6.701 (d, J=9.2 Hz, 2H,H-3'and 5'Ph), 7.601 (s,1H, NH), 9.091 (s,1H, NH), 9.314 (s,1H, OH).

(I c) 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydro pyrimidin-2(1H)-thione:

IR [Cm-1, KBr]:

3221.33(-NH), 3132.33 (-NH), 2873.76 (-CH3), 1680.32(C=S), 1701.13(C=O of ester group).

1H NMR (400 MHz, DMSO-d6) d: 1.088-1.123 (t, J =14 Hz, 3H,-O-CH2-CH3), 2.235(s, 3H, -CH3),

3.957-4.010 (q, J = 21 Hz 2H, O-CH2 CH3), 5.040-5.048 (d, J = 3.2 Hz, 1H, –CH), 7.019-7.040 (d, J = 8.4 Hz, 2H, H-2'and 6' Ph), 6.678-6.701 (d, J=9.2 Hz, 2H,H-3'and 5'Ph), 7.601 (s,1H, NH), 9.091 (s,1H, NH).

(I d) 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydro pyrimidin-2(1H)-thione

IR [Cm-1, KBr]:

3410.57(-NH), 3234.13 (-NH), 2923.91 (-CH3), 1701.13(C=O of ester group), 1640.69 (C=S).

1H NMR (400 MHz, DMSO-d6) d: 1.091-1.127 (t, J = 14 Hz, 3H,-O-CH2-CH3), 2.242-2.267(d, 6H, -2CH3), 3.963-4.012 (q, J = 19 Hz, 2H, O-CH2 CH3), 5.104-5.112 (d, J = 3.2 Hz, 1H, –CH), 7.122 (d, 4H, H-2', 3', 5'and 6' Ph), 7.672 (s,1H, NH), 9.138 (s,1H, NH).

(I e) 5-ethoxycarbonyl-6-methyl-4-(4-fluorolphenyl)-3,4-dihydro pyrimidin-2(1H)-thione

IR [Cm-1, KBr]:

3410.57(-NH), 3234.13 (-NH), 2923.91 (-CH3), 1701.13(C=O of ester group), 1640.69 (C=S).

1H NMR (400 MHz, DMSO-d6) d: 1.091-1.127 (t, J = 14 Hz, 3H,-O-CH2-CH3), 2.242-2.267(d, 6H, -2CH3), 3.963-4.012 (q, J = 19 Hz, 2H, O-CH2 CH3), 5.104-5.112 (d, J = 3.2 Hz, 1H, –CH), 7.122 (d, 4H, H-2', 3', 5'and 6' Ph), 7.672 (s,1H, NH), 9.138 (s,1H, NH).

Prediction of bioactivity:[11,12]

1) Molecular property: Molecular properties of the five synthesized compounds were calculated using molinspiration and the values were given in Table 2.
2) Bioactivity scores: The bioactivity scores of the five synthesized compounds towards GPCR ligand, and as ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitors were given in Table 3.

Results and discussion

3,4-dihydropyrimidin-2-(1H)-thione derivatives were prepared by one-pot synthesis using ammonium molybdate as catalyst. 3,4-dihydropyrimidin-2(1H)-thione derivatives were synthesized using the appropriate synthetic procedure i.e. reaction of aromatic aldehyde, dicarbonyl compound (ethylacetoacetate) and thiourea in presence of ammonium molybdate as catalyst.

Melting points were determined in open capillaries and are uncorrected.

IR spectra were recorded in KBr discs on an Bruker (300 FT-IR)

Thin layer chromatography was performed on silica gel G (Merck).

1H NMR spectra were recorded on a Bruker 400 spectrometer operating at 400.13 MHz for 1H in DMSO.

The five synthesized compounds obeyed the Lipinski's rule of five and showed good drug likeness scores. MiLogP values of these compounds were found to be < 5 indicate their good permeability across the cell membrane, TPSA value between 54.99–75.22, molecular weight < 300, Number of hydrogen bond donors < 5, hydrogen bond acceptors < 8, number of rotatable flexible bonds < 5 and n-violations 0.

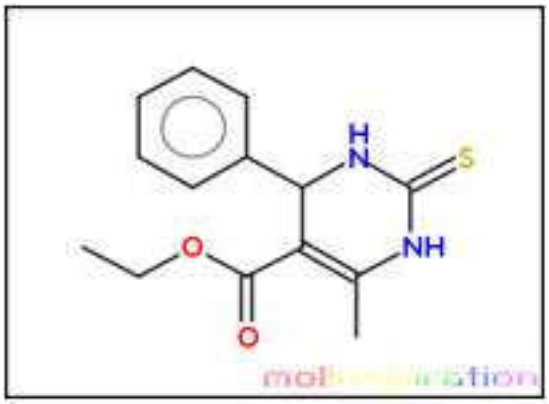

Fig. 2: Compound-Ia

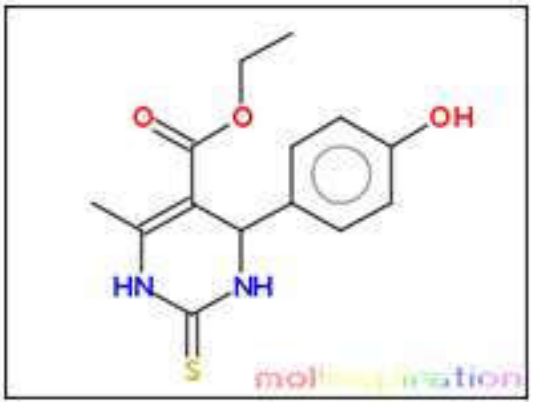

Fig. 3: Compound-Ib

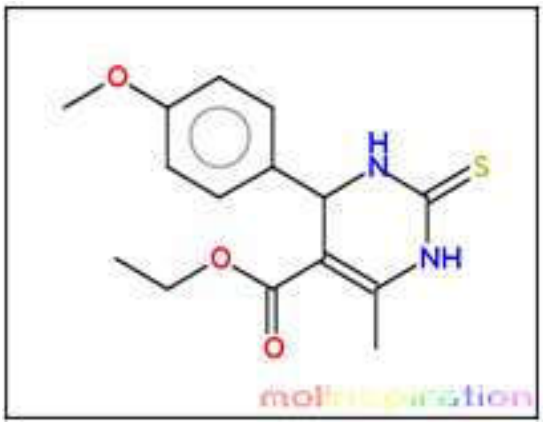

Fig.4: Compound-Ic

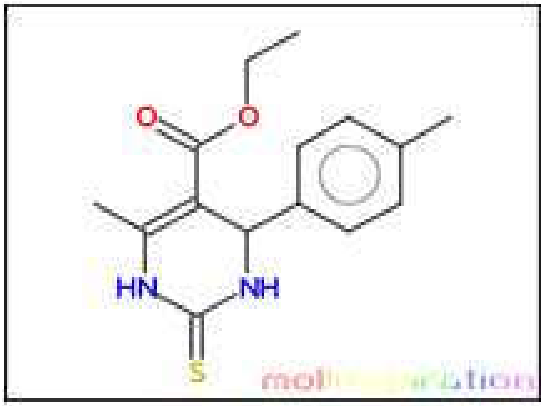

Fig.5: Compound-Id

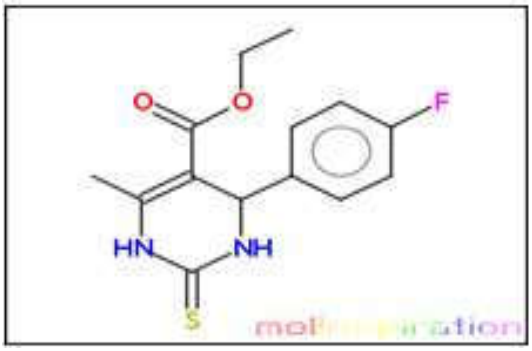

Fig.6 : Compound-Ie

Table 1: Physical data of the synthesized compounds

Compound	Molecular formula	Molecular weight (gm)	Melting point (˚C)	% yield	Rf value
Ia	C14H16O2N2S	276	200	61.59	0.90
Ib	C14H16O3N2S	292	180	70.2	0.65
Ic	C15H18O2N2S	306	110	52.61	0.85
Id	C14H16O2N2SF	290	100	46.8	0.77
Ie	C14H14O2N2SF	293	160	72.2	0.66

Table 2: Molecular property of the five synthesized compounds

S. No.	Compounds	miLogP	TPSA	natoms	nON	Nohnh	nviolations	nrotb	volume	MW
1	Ia	2.91	50.36	19	4	2	0	4	248.00	276.36
2	Ib	2.43	70.59	20	5	3	0	4	256.02	292.36
3	Ic	2.97	59.99	21	5	2	0	5	273.55	306.39
4	Id	3.36	50.36	20	4	2	0	4	264.57	290.39
5	Ie	3.08	50.36	20	4	2	0	4	252.94	294.35

Table 3: Bioactivity scores of the five synthesized compounds

S.No.	Compounds	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1	Ia	-1.05	-0.53	-1.54	-1.01	-1.48	-0.87
2	Ib	-0.91	-0.45	-1.37	-0.74	-1.34	-0.75
3	Ic	-0.94	-0.56	-1.36	-0.84	-1.32	-0.82
4	Id	-1.01	-0.59	-1.47	-0.95	-1.43	-0.88
5	Ie	-0.95	-0.52	-1.38	-0.89	-1.39	-0.83

Conclusion

In the present work different aromatic aldehydes were used to prepare 3,4-dihydropyrimidin-2(1H)-thione derivatives by cyclization with ethylacetoacetate and thiourea in presence of ammonium molybdate as catalyst gives good yields. A facile method under mild conditions has been developed for the synthesis of the title compounds.

All the compounds synthesized were characterized by physically (Rf values, Melting point, Molecular weight, Molecular formula) and few compounds were characterized by spectral data (1H NMR, IR spectra). Among the synthesized compounds-5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (Ib) gives high % yield.

The five synthesized compounds evaluation for the molecular properties and bioactivity scores, they found to obey the Lipinski's rule and shows bioactivity scores against various receptors. All the compounds shows good bioactivity score against ion channel receptors.

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