



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

Synthesis Of Schiff Bases Of Indole-3-Carboxaldehyde Derivatives Using Biginelli Reaction And Their Antioxidant Evaluation

Z Shamna*, S Greeshma, A Sumathy, N L Gowrishankar

Department of Pharmaceutical Chemistry, Prime College of Pharmacy, Palakkad, Kerala, 678551, India

ARTICLE INFO

Received: 20 Sep 2024

Accepted: 24 Sep 2024

Published: 05 Oct 2024

Keywords:

Indole-3-carboxaldehyde,
Biginelli reaction, DPPH,
Antioxidant activity.

DOI:

10.5281/zenodo.13893972

ABSTRACT

A series of Schiff bases of indole-3-carboxaldehyde were synthesized using biginelli reaction and examined for their antioxidant potential to probe the most potent analogues using two in vitro models like 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. Through the compounds showed various degree of activity whereas, compound (DP-2 and DP-4) shows superior antioxidant activity relative to other examined derivatives and also exhibit more activity than the standard, Ascorbic acid (AA).

INTRODUCTION

Biginelli reaction, which involves the interaction of ethyl acetoacetate, thiourea, and an aromatic aldehyde. Biginelli products (3,4-dihydropyrimidin-2(1H)-ones) are interesting starting materials due to their significant therapeutic and pharmacological properties[1]. Additionally the dihydropyrimidinones found to exhibit a wide range of biological activities such as antiviral, anticancer, antibacterial, anti-inflammatory, antimalarial, antitubercular, antidiabetic, anti-epileptic, etc[2]. Pyrimidine is one of the most important nucleus in medicinal chemistry. The synthesis of novel derivatives of

pyrimidines remains as main focus in drug discovery. The synthesis of newer generation of pyrimidines would help for further development of better medicinal agents[3]. Indole nucleus also possess a wide range of therapeutic activity. Indole derivatives have found to exhibit potent antifungal, analgesic, anti-inflammatory and antiamoebic activity. Based on preliminary findings indole-3-carboxaldehyde has potent antioxidant activity[4]. The formation of free radical is associated to the normal metabolism of aerobic cell[5]. The inherited oxygen consumption of cell leads to the production of series of oxygen

*Corresponding Author: Z Shamna

Address: Department of Pharmaceutical Chemistry, Prime College of Pharmacy, Palakkad, Kerala, 678551, India

Email ✉: shamnazakir28@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



free radicals and this interact with the lipid molecules generates new radicals such as superoxides, hydroxides and lipid peroxides which interact with biological system in a cytotoxic manner[6]. The uncontrolled production of free radicals is responsible for several pathological processes such as tumours (prostate and colon cancers) and coronary heart disease[7]. Even though lot of study regarding the biological activity of indole-3-carboxaldehyde has been carried out, the antioxidant activity of indole-3-carboxaldehyde linked with dihydropyrimidinones has not been done.

MATERIALS AND METHODS

All the solvents and reagents used were of laboratory grade. Melting points were determined by an open capillary melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was used to determine the purity of compound synthesized respectively. TLC Merck precoated plates were identified by iodine vapour. Solvent system used for developing the chromatogram was ethylacetate : toluene (9:1). The infrared spectrum was taken on SHIMADZU IR Spirit.

EXPERIMENTAL WORK

Synthesis of biginelli compound

The initial steps involve the reaction between thiourea, ethylacetoacetate and various substituted aromatic aldehydes. To a round bottom flask 0.15 mole of thiourea, 0.1 mole of ethylacetoacetate and 0.1 mole of substituted aromatic aldehyde

dissolved in 20ml ethanol and add 2-3 drops of HCl and reflux for 2 hours. The reaction mixture was then poured into 100 ml ice cold water with stirring and left overnight at room temperature. Then this mixture is filtered and dried. Recrystallisation done using ethanol. Recrystallised product is used in the next step. Similar procedure was followed for various substituted aromatic aldehydes. The purity of the compounds was determined by thin layer chromatography.

Synthesis of carbohydrazido derivative

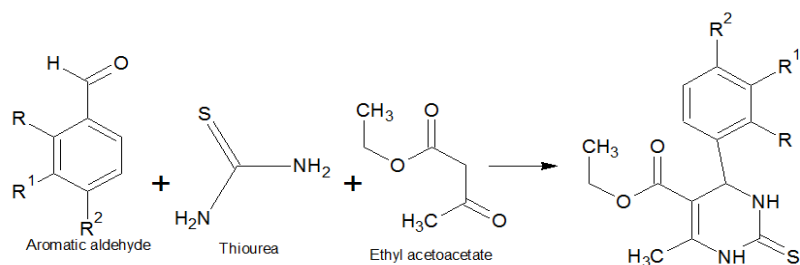
A mixture of 0.1 mole of biginelli compound (1st step product) and 0.1 mole of hydrazine hydrate were dissolved in 20 ml of ethanol. To this add 4 drops of conc. sulphuric acid and refluxed for 3-4 hours. The reaction mixture was evaporated to obtain a residue. The residue is then recrystallised from ethanol. The purity of the compounds was determined by thin layer chromatography.

Synthesis of schiff bases of Indole-3-carboxaldehyde derivatives

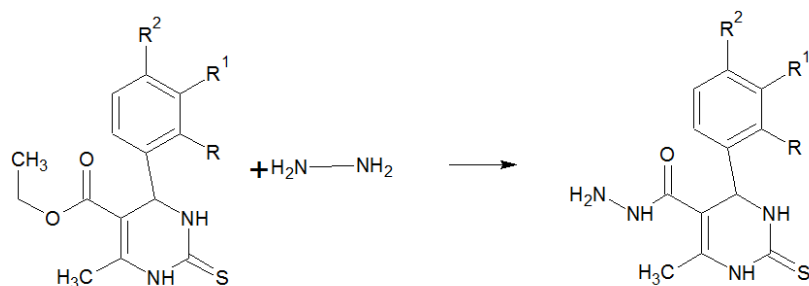
A mixture of 0.01 mole of hydrazido product (2nd step product) and 0.01 mole of indole-3-carboxaldehyde dissolved in ethanol along with 5 ml of glacial acetic acid were refluxed for 4-5 hours. The reaction mixture was then poured into ice cold water in a beaker, filtered and dried. The precipitate was then recrystallised from ethanol. The purity of the compounds was determined using thin layer chromatography.

SCHEME OF THE WORK

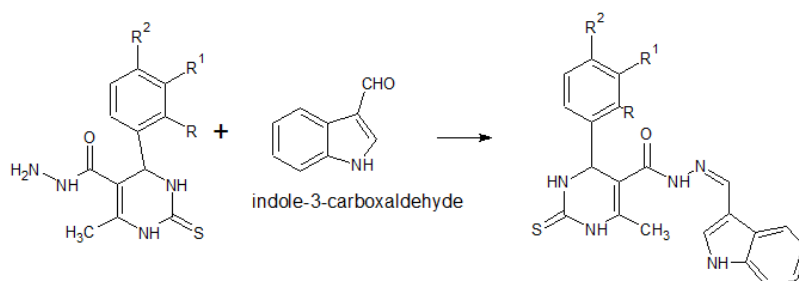
STEP1



STEP2



STEP3



S.NO	Compound code	R	R ¹	R ²
1	DP1	NO ₂	H	H
2	DP2	H	H	F
3	DP3	H	H	Cl
4	DP4	H	H	CH ₃
5	DP5	H	H	NO ₂
6	DP6	Cl	H	H

Physiochemical properties of the synthesized compounds

S.NO	Compound code	Molecular formula	Percentage yield (%)	Melting point (C)	Rf value
1	DP1	C ₂₁ H ₂₀ N ₆ O ₃ S	80%	210-215	0.63
2	DP2	C ₂₁ H ₂₀ FN ₅ OS	76%	215-220	0.71
3	DP3	C ₂₁ H ₂₀ ClN ₅ OS	75%	205-210	0.62
4	DP4	C ₂₂ H ₂₃ N ₅ OS	85%	210-215	0.71
5	DP5	C ₂₁ H ₂₀ N ₆ O ₃ S	54%	210-215	0.54
6	DP6	C ₂₁ H ₂₀ ClN ₅ OS	62%	205-210	0.53

DP1 :-

6-methyl-4-(2-nitrophenyl)-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 1516.91(NO₂ stretching), 2922.92(Ar-H stretching), 3221.87(NH stretching), 1696.28(C=O stretching), 2937.06(CH stretching)

DP2 :-

4-(4-fluorophenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 3119.78 (Ar-H stretching), 3414.35 (NH stretching), 2973.7(CH stretching), 1648.36(C=O stretching)

DP3 :-

4-(4-chlorophenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 799.44(C-Cl stretching), 3234.40(Ar-H stretching), 2923.88(NH stretching), 1703.03 (C=O stretching), 2973.3(CH stretching)

DP4 :-

6-methyl-4-(4-methylphenyl)-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 3115.44 (Ar-H stretching), 3536.33 (NH stretching), 1518.75(NO₂ stretching), 1648.36(C=O stretching), 2931.75(CH stretching), 2926.93(CH stretching)

DP5 :-

6-methyl-4-(4-nitrophenyl)-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 2925.35 (Ar-H stretching), 3223.52 (NH stretching), 1518.75(NO₂ stretching), 1698.55(C=O stretching), 2937.06(CH stretching)

DP6 :-

4-(2-chlorophenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide-1H-indole

IRspectra KBr(cm-1): 3235.50(Ar-H stretching), 2925.75(NH stretching), 1705.55 (C=O stretching), 797.30(C-Cl stretching), 2916.32(CH stretching)

ANTIOXIDANT ACTIVITY

DPPH Radical scavenging activity

The newly synthesized compounds were screened for their antioxidant activity by DPPH free radical scavenging activity. The compounds under study were dissolved in distilled ethanol (50 ml) to prepare 1000 µM stock solution. Solutions of different concentrations (10 µM, 50µM,100 µM, 200 µM and 500 µM) were prepared by serial dilutions and the antioxidant activity was studied. Compound of different concentrations were prepared in distilled ethanol, 1ml of each compound solutions having different concentrations (10 µM, 50 µM, 100 µM, 200 µM and 500 µM) were taken in different test tubes; 4ml of a 0.1Mm ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at RT for 20 min. A DPPH blank was prepared without compound, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration, and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The percentage of inhibition was calculated using the formula:

$$\text{Percentage Inhibition (\%)} = [(A_0 - A_1) / A_0 \times 100]$$

Where A₀ is the absorbance of the control (blank, without compound) and A₁ is the absorbance of the compound. The percentage inhibition of internal standard ascorbic acid was also measured



and IC₅₀ values was calculated and compared with that of the newly synthesized compounds.

Antioxidant activity of synthesized compounds

Compound code	Concentration($\mu\text{g/ml}$)					IC ₅₀ (μM)
	20	40	60	80	100	
DP1	24.99	43.78	66.37	84.37	108.45	40.16
DP2	31.93	54.67	67.49	88.37	112.48	33.18
DP3	21.45	38.49	57.44	71.93	93.05	47.11
DP4	33.81	52.73	66.81	75.37	97.34	34.22
DP5	20.93	32.83	51.74	63.04	89.96	53.28
DP6	24.95	31.48	53.67	79.37	96.28	49.28
Standard	24.16	43.93	56.16	94.16	112.86	41.9

DISCUSSION

The titled compounds were synthesised via biginelli method consist of 3 steps. The first step was synthesis of substituted dihydropyrimidinones by refluxing of thiourea , ethylacetoacetate and substituted aromatic aldehyde in presence of HCl and ethanol . The intermediate obtained in this step is of medicinally important heterocyclic compounds and possess a wide range of biological activity. These substituted dihydropyrimidinones were further made to react with hydrazine hydrate by dissolving it in ethanol in presence of H₂SO₄ yields carbohydrazido derivatives. These carbohydrazidoderivatives were further made to react with indole-3-carboxaldehyde to generate the novel Schiff base derivatives of indole-3-carboxaldehyde that is the titled compounds. The melting point of all the titled compounds were mentioned. The IR spectra of all compounds were elucidated and expressed as wave number in cm⁻¹. The presence of N=CH stretch confirmed the formation of titled compound. The synthesized compound were tested for its antioxidant activity and shows significant result. The compound DP2 and DP4 shows greater activity than the standard Ascorbic acid. The compound DP1 shows similar activity as that of the standard

CONCLUSION

In conclusion, a series of Schiff bases of indole-3-carboxaldehyde were synthesized using biginelli

reaction. The entitled work describe the synthesis of dihydropyrimidinones linked with indole-3-carboxaldehyde via biginelli reaction. Purity determination was done by TLC. The structure of the compound were determined by IR , NMR and MASS spectral analysis. The synthesized compounds were screened for its antioxidant activity and found to have significant results. The compounds DP2 and DP4 exhibits greater activity than standard whereas DP1 exhibit activity similar to that of standard. These compound may possess wide range of therapeutic activity as it is worthwhile to investigate other biological activities such as anti-proliferative, antifungal ,anti-inflammatory etc...

REFERENCE

1. Heravi MM, Asadi S, Lashkariani BM. Recent progress in asymmetric Biginelli reaction. *Molecular diversity*. 2013 May;17(2):389-407.
2. Nagarajaiah H, Mukhopadhyay A, Moorthy JN. Biginelli reaction: an overview. *Tetrahedron Letters*. 2016 Nov 23;57(47):5135-49.
3. Beena KP, Rajasekaran A, Manna PK, Suresh R. Design, Synthesis, Characterisation and Antimicrobial Evaluation of Some Substituted Dihydropyrimidinone Derivatives. *Journal of Chemical and Pharmaceutical Research*. 2017;9(4):277-84.



4. Naik N, Kumar HV, Roopashree N. Novel indole-3-carboxaldehyde analogues: synthesis and their antioxidant evaluation. *Der Pharma Chemica*. 2012 Aug 15;4(2):783-90.
5. Aust, S. D.; Sringen, B. A.. In *Free Radicals in Biology*; Academic Press: New York, 1952; vol. 5.
6. Kanazawa, K., Kanazawa, E. & Natake, M. Uptake of secondary autoxidation products of linoleic acid by the rat. *Lipids* 20, 412–419 (1985).
7. Halliwell B. Antioxidants in human health and disease. *Annual review of nutrition*. 1996 Jul;16(1):33-50.
8. Beena KP, Rajasekaran A, Manna PK, Suresh R. Design, synthesis, characterisation and invitro antioxidant evaluation of some substituted dihydropyrimidinone derivatives.
9. Sirivibulkovit K, Nouanthavong S, Sameenoi Y. based DPPH assay for antioxidant activity analysis. *Analytical sciences*. 2018 Jul;34(7):795-800.
10. Aydin A, Arsova-Sarafinovska Z, Sayal A, Eken A, Erdem O, Erten K, Özgök Y, Dimovski A. Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. *Clinical biochemistry*. 2006 Feb 1;39(2):176-9.
11. Molyneux P. The use of the stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. *Songklanakarin J. sci. technol.* 2004 Dec;26(2):211-9.
12. V.R.Shah, J.N.Godhasra, M.C.Patel, N.N.Kansagara, Microwave assisted direct rapid and efficient synthesis of some novel dihydropyrimidines and evaluation of their antimicrobial activities, *International Journal of Chemical Sciences*, 2009; 7(3): 1575-1582.
13. C. Oliver Kappe, 4-aryldihydropyrimidines via the Biginelli condensation: Aza Analogs of Nifedipine-type Calcium Channel Modulators, *Acc. Chem. Res.*, 2000; 33: 879-888.
14. Deng J, Cheng W, Yang G. A novel antioxidant activity index (AAU) for natural products using the DPPH assay. *Food Chemistry*. 2011 Apr 15;125(4):1430-5.
15. Sinha D, Tiwari AK, Singh S, Shukla G, Mishra P, Chandra H, Mishra AK. Synthesis, characterization and biological activity of Schiff base analogues of indole-3-carboxaldehyde. *European journal of medicinal chemistry*. 2008 Jan 1;43(1):160-5.

HOW TO CITE: Z. Shamna , S. Greeshma, A. Sumathy, N. L. Gowrishankar, Synthesis Of Schiff Bases Of Indole-3-Carboxaldehyde Derivatives Using Biginelli Reaction And Their Antioxidant Evaluation, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 10, 218-223. <https://doi.org/10.5281/zenodo.13893972>

