International Journal of Biological Chemistry

ISSN 1819-155X

Academic Journals Inc.

www.academicjournals.com

International Journal of Biological Chemistry 4 (1): 19-26, 2010
ISSN 1819-155X

Synthesis and Biological Evaluation of N^1-[(3z)-5-Substituted-2-Oxo-1, 2-Dihydro-3H-Indol-3-Ylidene]-5H-Dibenzo [b,f] Azepine-5-Carbohydrazides

[1]K. Ranjit, [1]G.K. Rao and [2]P.N.S. Pai
[1]Department of Pharmaceutical Chemistry,
[2]Department of Quality Assurance, Al-Ameen College of Pharmacy,
Hosur Road, Opp. Lalbagh Main Gate, Bangalore-560027, India

Abstract: A novel synthetic methodology of Schiff bases incorporating dibenzazepine carbohydrazide with isatin is described. The title compounds were prepared by condensation of carbohydrazide and substituted isatins. Structures of all these compounds were confirmed by their spectral studies. These compounds were screened for their *in vitro* antioxidant activity. From the biological studies, it was possible to observe that some of the compounds have shown good antioxidant activity when compared to the standard, ascorbic acid. Compounds with electron withdrawing substitutents (3f) and (3k) have shown better activity at lowest concentration than electron donating substitutents. The ambient conditions, good product yields and easy work up procedures make this methodology a better protocol for the synthesis of newer derivatives which can be explored further for biological activities.

Key words: N^1-[(3z)-5-substituted-2-oxo-1, 2-dihydro-3H-indol-3-ylidene]-5H-dibenzo [b,f] azepine-5-carbohydrazide, Schiff bases, antioxidant activity

INTRODUCTION

In the last years, there is an increasing evidence of the implication of free radicals and reactive oxygen species in a variety of diseases and pathophysiological events including inflammation, cancer, myocardial infarction, arthritis and neurodegenerative disorders (Bast *et al*., 1991). Reactive Oxygen Species (ROS) have been suggested to play an important role in the pathophysiology of myocardial reperfusion injury. They may cause initiation of lipid peroxidation, direct inhibition of mitochondrial respiratory chain enzymes, inactivation of glyceraldehyde- 3-phosphate dehydrogenase, inhibition of membrane sodium/potassium ATPase activity, inactivation of membrane sodium channel and other oxidative modifications of proteins. Additionally, there are a large number of other reactive species that are formed from the reaction of ROS with biological molecules (e.g., polyunsaturated lipids, thiols and nitric oxide (NO)) (Ismaili *et al*., 2008). Dioxygen is a highly important, yet toxic, molecule that reacts *in vivo* to produce reactive oxygen species such as superoxide, peroxides, hydroxyl radicals and other related species (Joan and Edith, 2008).

Corresponding Author: Ranjit Kaur, Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Hosur Road, Opposite Lalbagh Main Gate, Bangalore-560027, India Tel: +9180-22234619 Fax: +9180-22225834

Oxidant-antioxidant imbalance leads to pathophysiological effects associated with asthma such as vascular permeability, mucus hypersecretion, smooth muscle contraction and epithelial shedding. Therefore, the supplementation of antioxidants to boost the endogenous antioxidants or scavenge excessive ROS production could be utilized to dampen/prevent the inflammatory response in asthma by restoring oxidant-antioxidant balance (Nadeem *et al*., 2008). All these toxic effects are likely to play a role in the pathophysiology of shock, inflammation and ischemia-reperfusion injury (Cuzzocrea *et al*., 2001).

Therefore, considerable research interest is focused on the investigation of the antioxidant properties of pharmacologically active compounds and several experimental protocols have been developed for this purpose.

In the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting pharmacological profiles. According to literature isatins possess diverse chemotherapeutic activities such as antibacterial (Daisley and Shah, 1984), antifungal, antiviral, anti-HIV (Teitz *et al*., 1994), anti-mycobacterial (Karal *et al*., 2007), anti-cancer (Gursoy and Karali, 2003) anti-inflammatory (Sridhar *et al*., 2001) and anticonvulsant (Smitha *et al*., 2008). On the other hand, tricyclic moiety is associated with diverse pharmacological activities such as antiepileptic activity, antiviral activity (Khunnawutmanotham *et al*., 2007), antibacterial (Székelyhidi *et al*., 2005) antifungal (Panwar *et al*., 2006) anti-inflammatory (Weyler *et al*., 2008) and anticonvulsant activity, while it incorporates a considerable antioxidant potential (Hadjimitova *et al*., 2002).

The combination of these two pharmacophores in the same molecule is an interesting challenge for the development of new pharmacologically active antioxidants.

The study describes the synthesis of novel Schiff's bases of substituted isatins condensed with carbohydrazide. Title compounds were screened for their *in vitro* antioxidant activity using reducing power and DPPH radical scavenging assay.

MATERIALS AND METHODS

Melting points were determined in open capillaries on a Thermonik melting point apparatus and are found uncorrected. Infra red spectra were recorded on Fourier Transform IR spectrophotometer (Shimadzu FT-IR 8700) using KBr (transmittance, ν_{max} in cm^{-1}) disc method. ^{1}H NMR spectra were recorded in DMSO on Bruker-200 NMR spectrophotometer using TMS as internal reference standard (chemical shifts in δ, ppm). Mass spectra were recorded on Shimadju 2010 A LCMS spectrophotometer (mz^{-1} and relative intensity). All the reactions were routinely monitored and purity was determined on thin layer chromatography using Merk silica gel 60 F_{254} coated alumina plates using several solvent systems of different polarity. All the chemicals used were of AR grade (Sigma-Aldrich; Acros; Hi-media). The antioxidant activity was determined using Reducing Power and DPPH Radical Scavenging methods.

This study was carried out from 16th September 2008 to 6th November 2009 at Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Bangalore-560027, India and Sangenomics Research Labs Pvt Ltd, Bangalore 560071, India.

Synthesis of 5H-Dibenzo (b,f) Azepine-5H-Acid Hydrazide (1)

Compound 1 was prepared according to the method described by Bhatt and Patel (2005). A mixture of 5H-dibenzo (b,f) azepine-5-carbonyl chloride (2.5 g, 0.01 mole) and hydrazine hydrate (0.01 mol, 80%) in absolute alcohol was stirred for 2 h and then refluxed

for 30 min. The product obtained was filtered, washed with cold alcohol, dried and purified by recrystallization from methanol to give 5H-dibenzo (b,f) azepine-5-acid hydrazide. Yield 75%, m.p. 178°C. TLC (methanol: toluene, 2:8, R_f 0.20).

- **IR (KBr, v_{max} in cm^{-1}):** 3470, 3352 (-$NHNH_2$, str), 3019 (Ar-C-H str), 1647 (C=O, str), 1601, 1566 and 1452 (Ar-C=C, str)
- **^{1}HNMR ($CDCl_3$, δ ppm):** 7.35 (m, 8H, Ar-H), 6.87 (s, 2H,CH=CH), 5.85(bs, 1H, -NH), 3.47 (bs, 2H, -NH_2)
- **Synthesis of Isatins (2a-l):** Isatins were prepared as per the method described by Marvel and Hiers (1941)

Step-1 (Isonitrosoacetanilide)

In a 5 L round-bottomed flask are placed 90 g (0.54 mole) of chloral hydrate and 1200 mL of water. To this solution are then added, in order: 1300 g crystallized sodium sulphate, a solution of appropriate aromatic amine (0.5 mole) in 300 mL of water to which (0.52 mole) concentrated hydrochloric acid (sp.gr.1.19) is added to dissolve the amine and finally, a solution of hydroxylamine hydrochloride (1.58 moles) in 500 mL water. The contents in the flask are heated over wire gauze so that vigorous boiling begins and the heating is continued till the reaction is completed. The product solidifies, filtered under suction and air dried and this intermediate (isonitrosoacetanilide) was used in step-2.

Step-2 (Isatin)

Sulfuric acid, concentrated, (sp.gr.1.84) 600 g (326 mL) is warmed to 50°C in a 1 L, round-bottomed flask fitted with a mechanical stirrer. To this, isonitrosoacetanilide (0.46 mole) is added at such a rate as to maintain the temperature between 60-70°C to complete the reaction. The reaction mixture is cooled to room temperature and poured on crushed ice. The isatin is filtered with suction, washed several times with cold water to remove the sulphuric acid and then air dried. The isatin so obtained is crystallized using glacial acetic acid. All the isatins synthesized were obtained in good yields (65-75%).

IR (KBr, v_{max} in cm^{-1}) (2a)

3193 (N-H, str), 2813 (Ar C-H, str), 1731.96 (C=O, str), 1332 (C-N, str).

Synthesis of N^1-[(3z)-5-Substituted -2-Oxo-1,2-Dihydro-3H-Indol-3-Ylidene]-5H-Dibenzo [b, f] Azepine-5-Carbohydrazide (3a-l)

- **General Procedure:** An equimolar mixture of 5H-dibenzo (b,f) azepine-5H-acid hydrazide (1) 0.01 M and substituted isatin derivatives (2a-l) (0.01 M) is dissolved in 25 mL of warm alcohol containing 4-5 drops of glacial acetic acid. The reaction mixture was refluxed for 50 h and left overnight. The solid obtained was filtered and washed with cold ethanol, dried and recrystallized from ethanol-chloroform mixture (1:1). Similarly, the other title compounds were synthesized using the above procedure and the results are shown in Table 1.

(3Z)-3-{2-[1-(5H-Dibenzo [b,f] Azepin-5-yl) Ethenyl] Hydrazinylidene}-1,3-Dihydro-2H-Indol-2-one (3a)

- **IR (KBr, v_{max} in cm^{-1}):** 3248.87 (N-H str), 3070.46 (ArC-H str), 1702.06 (C=O str), 1676.03 (C=N str), 1619.13 (C = C str), 1319.22 (C-N str)

Table 1: Physical constants of the synthesized compounds (3a-l)

Compound code	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	R_f value
3a	$C_{23}H_{16}N_4O_2$	380.0	235	80	0.68
3b	$C_{24}H_{18}N_4O_2$	394.0	282	88	0.66
3c	$C_{24}H_{18}N_4O_2$	394.0	296	65	0.61
3d	$C_{24}H_{18}N_4O_2$	394.0	241	89	0.58
3e	$C_{23}H_{15}N_4O_2Br$	427.0	285	75	0.64
3f	$C_{23}H_{15}N_4O_2Br$	427.0	266	73	0.58
3g	$C_{23}H_{15}N_4O_2F$	398.0	282	78	0.45
3h	$C_{23}H_{15}N_4O_2Cl$	415.5	272	80	0.50
3i	$C_{23}H_{15}N_4O_2Cl$	415.5	270	60	0.48
3j	$C_{23}H_{15}N_4O_2Cl$	415.5	248	62	0.50
3k	$C_{23}H_{15}N_5O_4$	425.0	289	70	0.61
3l	$C_{23}H_{15}N_5O_4$	425.0	205	64	0.59

- **LCMS, m/e :** (M + 1) 383. Base peak (196)
- **^{1}H-NMR (DMSO, δ ppm):** 12.48-12.65 (s, 1H, NH), 10.94 (s, 1H, CONH), 7.02-7.66 (m, 12H, ArH), 6.88-6.92 (d, 2H, CH = CH)

(3Z)-3-{2-[1-(5H-Dibenzo [b,f] Azepin-5-yl) Ethenyl] kydrazinylidene}-5-Methyl-1, 3-Dihydro-2H-indol-2-one (3c)

- **IR (KBr, v_{max} in cm^{-1}):** 3427.27 (N-H str), 2924.85 (ArC-H str), 2855.42 (Alph C-H str), 1736.78 (C = O str), 1683.74 (C = N str), 1654.81 (C = C str), 1325.97 (C-N str), 748.33 (Ar-CH_3 str)
- **LCMS, m/e:** (M + 1) 395
- **^{1}H-NMR (DMSO, δ ppm):** 12.68 (s, 1H, NH), 12.52 (s, 1H, CONH), 7.07-7.66 (m, 11H, ArH), 6.64- 6.66 (d, 2H, CH = CH) 2.40 (s, 3H, CH_3)

(3Z)-4-Bromo-3-{2-[1-(5H-Dibenzo [b,f] Azepin-5-yl) Ethenyl] hydrazinylidene}-1,3-Dihydro-2H-Indol-2-one (3f)

- **IR (KBr, v_{max} in cm^{-1}):** 3210.29 (N-H str), 2925.81 (ArC-H str), 1675.06 (C = O str), 1595.99 (C = N str), 1336.58 (C-N str), 749.29 (ArC-Br str)
- **^{1}H-NMR (DMSO,δ ppm):** 12.46-12.62 (s, 1H, NH), 11.07 (s, 1H, CONH), 7.08-7.62 (m, 11H, ArH), 6.85-6.89 (d, 2H, CH=CH)

(3Z)-3-{2-[1-(5H-Dibenzo [b,f] Azepin-5-yl) Ethenyl] Hydrazinylidene}-6-fluoro-1, 3-Dihydro-2H-indol-2-one (3g)

- **IR (KBr, v_{max} in cm^{-1}):** 3270.08 (N-H str), 3185.22 (ArC-H str), 1697.24 (C = O str), 1686.83 (C = N str), 1389.62 (ArC-F), 1322.11 (C-N str)
- **^{1}H-NMR (DMSO, δ ppm):** 12.51-12.68 (s, 1H, NH), 10.96 (s, 1H, CONH), 7.15-7.62 (m, 11H, ArH), 6.90- 6.92 (d, 2H, CH = CH)

(3Z)-6-Chloro-3-{2-[1-(5H-Dibenzo [b,f] Azepin-5-yl) Ethenyl] Hydrazinylidene}-1, 3-ihydro-2H-indol-2-one (3 h)

- **IR (KBr, v_{max} in cm^{-1}):** 3163.04 (N-H str), 3067.57 (ArC-H str), 1696.28 (C = O str), 1621.06 (C = N str), 1319.22 (C-N str), 1034.74 (ArC-Cl)
- **^{1}H-NMR (DMSO, δ ppm):** 12.47 (s, 1H, NH), 11.06 (s, 1H, CONH), 7.08-7.62 (m, 11H, ArH), 6.89-6.93 (d, 2H, CH = CH)

(3Z)-5-Chloro-3-{2-[1-(5H-Dibenzo [b,f]Azepin-5-yl) Ethenyl] Hydrazinylidene}-1, 3-Dihydro-2H-indol-2-one (3i)

- **IR (KBr, v_{max} in cm^{-1}):** 3166.90 (N-H str), 3110.97 (ArC-H str), 1695.31 (C = O str), 1620.09 (C = N str), 1319.22 (C-N str), 1062.70 (ArC-Cl)
- **LCMS m/e:** (M +) 415
- **^{1}H-NMR (DMSO, δ ppm):** 12.41-12.58 (s, 1H, NH), 11.08 (s, 1H, CONH), 7.08-7.66 (m, 11H, ArH), 6.88- 6.93 (d, 2H, CH = CH)

Antioxidant Activity

The antioxidant activity of all the synthesized compounds was determined using Reducing Power (Jayashree *et al.*, 2009) and DPPH Radical Scavenging (Mathew and Sasikumar, 2007) methods.

Reducing Power

Reaction mixture containing test samples at different concentrations in phosphate buffer (0.2 M, ph 6.6), was incubated with potassium ferricyanide (1% w/v) at 50°C for 20 min. The reaction was terminated by the addition of trichloro acetic acid solution (10%, w/v) and the mixture was centrifuged at 3000 rpm for 20 min. The supernatant was mixed with distilled water and ferric chloride (0.1% w/v) solution and the absorbance was measured at 700 nm. Increased absorbance of the reaction mixture indicated increased reducing power as shown in Table 2.

DPPH Radical Scavenging Activity

Radical Scavenging Activity Was Determined by the Following Method

To 2.5 mL of the sample solution at different concentrations (125, 250 and 500 μgm mL^{-1}) 1 mL of 0.3 mM alcoholic solution of DPPH (2, 2-diphenyl-1-picrylhydrazyl) was added and the samples were kept in dark for 30 min and the optical density was measured at 518 nm. Similarly blank was prepared under same conditions without the sample. Control was prepared by the addition of 1 mL of 0.3 mM DPPH to 2.5 mL of methanol. The optical density of the samples and the standard were measured against methanol as blank and percentage inhibition was calculated as shown in the Table 3.

Table 2: Reducing power of (3a-l) at 700 nm

	Concentrations in (μg mL^{-1})			
Compound code	125	250	500	1000
3a	2.723	2.883	2.959	3.141
3b	2.260	2.669	2.851	3.125
3c	1.965	2.435	2.971	3.550
3d	2.025	2.136	2.283	2.295
3e	1.883	2.032	2.096	2.283
3f	1.434	2.009	2.604	2.619
3g	2.446	2.551	2.609	2.627
3h	1.430	1.937	2.480	2.642
3i	1.417	2.500	2.621	2.904
3j	1.880	2.037	2.365	2.469
3k	2.187	2.284	2.337	2.412
3l	1.707	2.008	3.000	3.125
Standard (ascorbic acid)	1.996	2.144	2.162	2.233

Table 3: DPPH radical scavenging activity expressed as percentage inhibition of 3a-l

	Concentrations in (μg mL^{-1})		
Compound code	125	250	500
3a	4	5	8
3b	4	10	31
3c	32	33	49
3d	48	54	76
3e	15	21	36
3f	77	90	93
3g	11	14	18
3h	36	60	64
3i	28	35	59
3j	09	15	21
3k	74	90	93
3l	27	77	78
Standard (ascorbic acid)	77	83	87

RESULTS AND DISCUSSION

In this study, we have synthesized a new series of Schiff's bases of carbohydrazide coupled with isatins. Yields of all synthesized compounds were obtained in the range of 60-90%. All the derivatives were subjected to antioxidant activity using DPPH Free Radical Scavenging and Reducing power.

From the Table 2 of reducing power it was seen that as the concentration increased absorbance also increased. The activity was carried for different concentrations 1000, 500, 250 and 125 μg mL^{-1}. Among these compounds, (3a, 3b, 3c, 3g and 3k) have shown good antioxidant activity at 125 μg mL^{-1} when compared to the standard with the same concentrations. Compounds (3c, 3e 3j and 3l) have shown moderate activity at the same concentrations.

From the DPPH free radical scavenging activity, it was seen that some of the compounds have shown promising antioxidant activity as shown by percent inhibition (Table 3). Compounds 3f, 3k with p-bromo and p-nitro substitutents have shown very good antioxidant activity with percentage inhibition of 77 and 74, respectively at 125 μg mL^{-1}. Rest of the compounds have shown mild to moderate activity. But none of the compounds have shown activity greater than the standard.

The structure of isatin has been the subject of numerous investigations. The presence of carbonyl group at position 3 in 2, 3-indolindione and free amino group of the hydrazide furnishes reaction site at position 3 for condensation reaction.

Although, rarely described in nature, synthetic isatin hydrazone clubbed with dibenzazepine moiety could be taken for evaluation of antioxidant activity. The objective of the project was to synthesize and evaluate the new derivatives bearing isatin with dibenzazepine for antioxidant potential. Initial starting compound, (1) 5H-dibenzo (b,f) azepine-5H-acid hydrazide was prepared by condensation of 5H-dibenzo (b,f) azepine-5-carbonyl chloride and hydrazine hydrate in absolute alcohol. Various substituted isatins (2a-l) were synthesized using chloral hydrate and substituted aromatic amines. Finally, the title compounds were synthesized by condensation reactions of (1) and (2a-l) to give N^1-[(3z)-5-substituted-2-oxo-1, 2-dihydro-3H-indol-3-ylidene]-5H-dibenzo [b,f] azepine-5-carbohydrazide (3a-l). The compounds were confirmed by spectral studies such as IR, ^{1}HNMR and LCMS. All the above reactions are briefly summarized in scheme Fig. 1a-c. The infrared spectrum of intermediate (1) shows NH_2doublet at 3470, 3352 $cm^{-1}$and C = O 1647 cm^{-1}. Further isatins were confirmed by the appearance of a sharp peak at 1731 cm^{-1} for

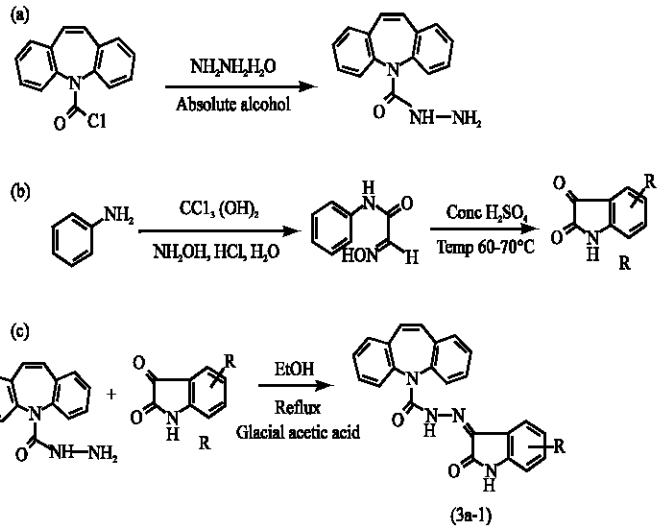

Fig. 1: Scheme of reactions. (a) Step-1: 5H-dibenzo (b,f) azepine-5H-acid hydrazide (1), (b) Step-2: Isatins (2a-l) and (c) Step-3: N^1-[(3z)-5-substituted -2-oxo-1, 2-dihydro-3H-indol-3-ylidene]-5H-dibenzo [b,f] azepine-5-carbohydrazide (3a-l)

the presence of C = O group. The peaks at 1660 and 1600 nm confirmed the presence of C = N in schiff bases and absence of NH_2 doublet peak. Similarly the signals of ^{1}HNMR spectra at δ ppm 3.47 and 5.85 confirm the NH_2 protons of hydrazide and NH of -CONH, respectively. The formation of Schiff base was evidenced by the appearance of singlet peak of NH at 12.46 and 11.07 of CONH. The multiplet signals at δ ppm 7.08-7.62 are characteristic aromatic ring protons. Further compounds were confirmed by the LCMS and are in accordance with the proposed structures.

In conclusion, the results of the antioxidant activity revealed the compounds to possess good spectrum of antioxidant activity by incorporation of electron withdrawing substitutents. Therefore, this study would be fruitful matrix for the development of novel class of antioxidant agents. This study can be further confirmed by carrying out *in-vivo* activity to know the mechanism of action of schiff's bases of dibenzazepines carbohydrazide with isatins.

ACKNOWLEDGMENTS

Authors are thankful to Prof. B.G. Shivananda, Principal Al-Ameen College of Pharmacy, Bangalore for providing necessary facilities and the director, Astra-Zeneca India Pvt. Limited for spectral analysis. Authors are also thankful to Sangenomics Research Labs Pvt. Ltd., Bangalore for providing facilities for biological studies.

REFERENCES

Bast, A., G. Haenen and C. Doelman, 1991. Antioxidant activity of some ascorbic and cinnamic acids derivatives. Am. J. Med., 92: 85-88.

Bhatt, P.V. and P. Patel, 2005. Synthesis of 5H-dibenzo (b, f) azepine-5-carboxylic acid [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amide from 5H-dibenzo (b,f)azepine carbonyl chloride. Indian J. Chem., 44: 2082-2086.

Cuzzocrea, S., D.P. Riley, A.P.Caputi and D. Salvemini, 2001. A nonpeptidyl mimic of superoxide dismutase with therapeutic activity in rats. Pharmacol. Rev., 53: 135-159.

Daisley, R.W. and V.K. Shah, 1984. Synthesis and antimicrobial activity of Mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl)amino] phenylacetic acid. J. Pharm. Sci., 73: 51-57.

Gursoy, A. and N. Karali, 2003. Synthesis and primary cytotoxicity evaluation of 3-[[(3-phenyl-4(3H)-quinazolinone-2-yl)mercaptoacetyl]hydrazono]-1H-2-indolinones. Eur. J. Med. Chem., 38: 633-643.

Hadjimitova, V., T. Traykov, M. Mileva, S. Ribarov, 2002. Effect of some psychotropic drugs on luminol-dependant chemiluminescence induced by O_2-, $^{\bullet}OH$, HOCl. Z. Naturforsch C., 57: 1066-1071.

Ismaili, L., A. Nadaradjane, L. Nicod, C. Guyon, A. Xicluna, J.F. Robert and B. Refouvelet, 2008. Synthesis and antioxidant activity evaluation of new hexahydropyrimido [5,4-c]quinoline-2,5-diones and 2 thioxohexahydropyrimido[5,4-c]quinoline-5-ones obtained by Biginelli reaction in two steps. Eur. J. Med. Chem., 43: 1270-1275.

Jayashree, M.A., L. Mathew and A. Radha, 2009. A report on the antioxidant activity of leaves and rhizomes of *Costus pictus* D. Don. Int. J. Integrative Biol., 5: 20-26.

Joan, S. and B.G. Edith, 2008. Introduction: Reactive oxygen species special feature. PNAS, 105: 8163-8482.

Karal, N., A. G u rsoy, F. Kandemirli, N. Shvets and F.B. Kaynak *et al*., 2007. (Z)-4-Hexyl-1-(5-nitro-2-oxo-2,3-dihydro1H-indol-3- ylidene) thiosemicarbazide. Bioorganic Med. Chem., 15: 5888-5904.

Khunnawutmanotham, N., N. Chimnoi, P. Saparpakorn, P. Pungpo, S. Louisirirotchanakul, S. Hannongbua, S. Techasakul, 2007. Novel 2-chloro-8 arylthiomethyldipyridodiazepinone derivatives with activity against HIV-1 reverse transcriptase. Molecules, 12: 218-230.

Marvel, C.S. and G.S. Hiers, 1941. The synthesis of nitrogen ring compounds. Organic Synthesis, 1: 327-327.

Mathew, G.M. and J.M. Sasikumar, 2007. Antioxidant activity of *Pseudarthria viscida*. Indian J. Pharm. Sci., 69: 581-582.

Nadeem, A., A. Masood and N. Siddiqui, 2008. Review: Oxidant-antioxidant imbalance in asthma: Scientific evidence, epidemiological data and possible therapeutic options. Ther. Adv. Respiratory Dis., 2: 215-235.

Panwar, H., R.S. Verma, V.K. Srivastava and A. Kumar, 2006. Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b] indoles as prospective antimicrobial agents. Chemlnform,

Smitha, S.S., N. Pandeya, J.P. Stables and S. Ganapathy, 2008. Anticovulsant and sedative-hypnotic activities of N-acetyl/Methyl isatin derivatives. Sci. Pharm., 76: 621-636.

Sridhar, S.K., M. Saravanan and A. Ramesh, 2001. Synthesis and antibacterial screening of hydrazones, schiff and mannich bases of isatin derivatives. Eur. J. Med. Chem., 24: 615-625.

Székelyhidi, Z., J. Pató, F. Wáczek, P. Bánhegyi and B. Hegymegi-Barakonyi, 2005. Synthesis of selective SRPK-1 inhibitor: Novel tricyclic quinoxaline derivatives. Bioorganic Med. Chem. Lett., 15: 3241-3246.

Teitz, Y., D. Ronen, A. Vansover, T. Stematsky and J.L. Rigg, 1994. Synthesis of 1,4 benzothiazine containing isatin hydrazone moiety as antimicrobial agent. Antiviral. Res., 24: 215-215.

Weyler, S., Y. Baqi, P. Hillmann, M. Kaulich, A.M. Hunder, I.A. Müller and C.E. Müller, 2008. Combinatorial synthesis of anilinoanthraquinone derivatives and evaluation as non-nucleotide-derived P_2Y_2 receptor antagonists. Bioorganic Med. Chem. Lett., 18: 223-227.