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Design, Synthesis, Spectral Charecterization of Some New Fully Unsaturated 2-Substituted-4,6 Dichloro Symmetric Triazine-based Chalcone Hybrids

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Received: 16 December 2015 Accepted: 1 January 2016 Published: 15 January 2016

Abstract

Triazines and chalcones are interesting class of heterocyclic compounds with a prominent structural core system present in numerous pharmacologically active compounds. It is proved from the literature that the compounds containing 1,3,5-triazine moiety or chalcone bridge often shows significant biological activity profiles. Based on these observations, it was considered worthwhile to synthesize and characterize some new 1,3,5-triazine-chalcone hybrid molecules in the present investigation. As a part of our research program aimed at search for new hybrid pharmacophores as potential cytotoxic agents, we are interested to have ?,?-unsaturated ketone linker to the 1,3,5-triazine basic nucleus to give a series of 1,3,5-triazine-chalcone hybrid molecules. Therefore, in the present study an attempt has been made to synthesize and characterize various analogs of fully unsaturated 2-substituted-4,6 dichloro-1,3,5 triazine based chalcone hybrids.

Index terms— fully unsaturated, 1, 3, 5-triazine-chalcone hybrids, spectral characterization.

1 I. Introduction

riazines are a class of organic nitrogen-containing six-membered heterocyclic compounds known for a long period of time. They can structurally be existing as three isomers varied with their position of nitrogen atoms on the benzene ring, and are referred to T as 1,2,3-triazine (1), 1,2,4-triazine (2) and 1,3,5-triazine (3). In particular, considerable attention has been devoted to the development of 1,3,5-triazine derivatives in comparison with 1,2,3-triazine and 1,2,4-triazine derivatives, due to their variety of applications in different fields [1,2]. 1,3,5-Triazines can also be called as symmetric or s-triazines. The chemistry of this group of compounds has been studied intensively since past two centuries due to their wide spread applications in the pharmaceutical, textile, plastic and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents. In recent times, several studies have been carried out on the antitumor activity of 1,3,5-triazines. Some of these analogues, hexamethylmelamine (4), almitrine (5) and irsogladine (6) are clinically used as anticancer agents. Baker triazines (4,6-Diamino-2,2-dimethyl-1,2-dihydro-1,3,5triazine based analogs) are becoming increasingly important as pharmaceuticals. Baker triazine antifol (7) had been undergoing clinical trials as a drug candidate in cancer chemotherapy [3][4][5][6][7][8]. Although 1,3,5-triazines are well known in the context of anticancer drugs, this ring is also found in the drug used in the chemotherapy of malaria, as seen in case of cycloguanil (8) [9]. Recently, 2,4,6-trisubstituted -1,3,5-triazine scaffolds were discovered as a potent inhibitors of M. tuberculosis H37Rv [10].N N N NH 2 H 2 N CH 3 CH 3 Cl**(8)**

All 1,3,5-triazine derivatives that have wide practical applications are 2,4,6-mono, di-or trisubstituted, symmetrical and nonsymmetrical compounds bearing different substituents. The most important reagent for obtaining these synthetic molecule transformations is cyanuric chloride (9), due to the reactivity of the chlorine atoms towards nucleophiles [11].N N N Cl Cl Cl**(9)**

2 II. Materials and Methods

A brief description of the solvents, chemicals procured, the instruments and the conditions employed for the characterization of the synthesized compounds are presented here. The organic solvents such as methanol, acetone, chloroform and ethyl acetate were of spectral grade and used as such without further purification. Anhydrous methanol was obtained by fractional distillation and storing over type 4A molecular sieves. The acetone present in methanol was removed by using the following procedure: A mixture of 500 mL of methanol, 25 mL of furfural and 60 ml of 10% sodium hydroxide solution was refluxed for 12 h, then the mixture was distilled and the first few milliliters of the distillate was rejected as it contains trace amount of formaldehyde. Ethanol obtained by distillation of commercial ethyl alcohol was refluxed over ignited calcium oxide for 6 h and distilled at atmospheric pressure and then used. All the major chemicals were purchased from Sigma-Aldrich. The important starting materials were procured from Sigma-Aldrich. Thin layer chromatography (TLC) was performed in the course of the reaction to optimize the reaction for purity and completion of reaction on Merck silica gel precoated GF 254 aluminum plates using mixture of different polar and nonpolar solvents in varying proportions and spots were observed using iodine as visualizing agent. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The column was subjected to gradient elution using n-hexane, mixtures of hexane and ethyl acetate (5%, 10%, 15%, 25%, 50% and 75% hexane in ethyl acetate), ethyl acetate and mixtures of ethyl acetate and methanol (1%, 2%, 5% and 10% ethyl acetate in methanol). Fractions each of 100 mL were collected. The separation of the compounds was checked on TLC under UV lamp and also by spraying the plates with 10% sulphuric acid in methanol.

All the melting points were determined in open capillary tubes in an EZ-MELT automated digital melting point apparatus and are uncorrected. IR spectra were recorded (in KBr) on a Perkin-Elmer FTIR. 1 H NMR and 13 C NMR spectra were recorded on a Bruker spectrometer at 400 MHz using TMS as the internal standard. Mass spectra (ESI) were measured on an LC-MS 6100 QQQ (Agilent Technologies, USA). Elemental analyses were carried out with Carlo Erba 1108 elemental analyzer apparatus. The results of elemental analyses (C, H, N) were within ± 0.4 % of the calculated values.

3 III. Chemistry

The reaction sequence intended for the preparation of title compounds (4a-ii) is shown in Scheme 1, and their physical properties are depicted in Tables 1 and 2. The chief intermediate in the present study 1-(3-(4,6-dichloro-1,3,5-triazin-2-ylamino) phenyl) ethanone (3) was prepared by reaction between cyanuric chloride i.e. 2,4,6-trichloro-1,3,5-triazine (1) and 3-aminoacetophenone (2) [12]. Further, successive base catalyzed Claisen-Schmidt condensation of the compound 3 with appropriate substituted aromatic/ heteroaromatic aldehydes in the presence of 100% potassium hydroxide solution in ethanol afforded a series of 1-(3-(4,6-dichloro-1,3,5-triazin-2-ylamino) phenyl)-3-(substituted)-2-propen-1-ones (4a-ii) in good yield. All the newly synthesized compounds were characterized by CHN elemental analysis and spectroscopic methods such as FT-IR, 1 H NMR, and LC mass spectral analysis. Eventually all the spectra of the new products (4a-ii) are in keeping with the predictable structures. The IR spectrum of all the compounds 4a-ii exhibited the characteristic absorptions at various frequencies correspondingly at 3310-3110 and 1640-1715 cm -1 suggesting the presence of a secondary amine group and ?,?-unsaturated carbonyl group respectively. In the 1 H NMR spectra of 1-(3-(4,6dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(substituted)-2-propen-1-ones (4a-ii), a singlet integrating for one proton characteristic of the secondary amine NH group was observed in between ? 9.2-9.4 ppm as a broad signal. As seen in case of compound 4a, the IR spectrum of 4a exhibited characteristic ?C=C? (aliphatic) and ?C=C? (aromatic) stretching bands at frequencies 1645 and 1513 cm -1 , respectively. The other IR absorptions at various frequencies correspondingly at 3155 and 1688 cm -1 suggesting the presence of a secondary amino group and ?,?-unsaturated ketone group, respectively. The 400 MHz 1 H NMR spectrum of the compound 4a in DMSO-d 6 as solvent with TMS as an internal standard exhibited characteristic peaks of H ? and H ? protons of ?,?-unsaturated ketone bridge appeared as two doublets, one doublet at ? [13][14][15]. mixture was then kept at room temperature for about 48 h with occasional shaking. After 48 h it was poured into ice-cold water, and then neutralized to pH 2 using 5 N hydrochloric acid. The light yellow precipitate obtained was filtered, washed, dried, and recrystallized from dry ethanol. The 1,3,5-triazine-chalcone hybrid molecules 4a-ii were obtained in good yield. All the synthesized compounds as mentioned in Table 1 were characterized by spectroscopic methods such as FTIR, 1 H NMR, 13 C NMR and LC mass spectral analysis and presented separately under each compound. (E)-1- (3-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)-3- (phenyl)-2-propen-1-one

4 IV. Experimental Section

[1] [2]

[1] Design, Synthesis, Spectral Charecterization of Some New Fully Unsaturated 2-Substituted-4,6 Dichloro Symmetric Triazine-based Chalcone Hybrids

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Figure 1: Scheme 1 :

1

Cl
N
N
N
Cl
N
H

Year	Compound	R	4a-ii formula	Molecular
2016				
Volume XVI Issue I Version I	4a 4b 4c 4d 4e 4f 4g 4h 4i 4j 4k 4l 4m 4n	Phenyl 2-MeC 6 H 4 3-MeC 6 H 4 4-MeC 6 H 4 2-OMeC 6 H 4 3-OMeC 6 H 4 4-OMeC 6 H 4 3-OHC 6 H 4 4-OHC 6 H 4 3,5-diOHC 6 H 3 4,5-diOHC 6 H 3 2-Me,5-OHC 6 H 3 2-NH 2 C 6 H 4 3-NH 2 C 6 H 4	C 18 H 12 Cl 2 N 4 O C 19 H 14 Cl 2 N 4 O C 19 H 14 Cl 2 N 4 O C 1
D D D D) (B	4o 4p	4-NH 2 C 6 H 4 2-NO 2 C 6 H 4	C 18 H 13 Cl 2 N 5 O C 18 H 11 Cl 2 N 5 O 3
	4q	3-NO 2 C 6 H 4	C 18 H 11 Cl 2 N 5 O 3
	4r	4-NO 2 C 6 H 4	C 18 H 11 Cl 2 N 5 O 3
	4s	2-ClC 6 H 4	C 18 H 11 Cl 3 N 4 O
	4t	3-ClC 6 H 4	C 18 H 11 Cl 3 N 4 O
	4u	4-ClC 6 H 4	C 18 H 11 Cl 3 N 4 O
	4v	2,4-diClC 6 H 3	C 18 H 10 Cl 4 N 4 O
	4w	2-FC 6 H 4	C 18 H 11 Cl 2 FN 4 O
	4x	3-FC 6 H 4	C 18 H 11 Cl 2 FN 4 O
	4y	4-FC 6 H 4	C 18 H 11 Cl 2 FN 4 O
	4z	2,4-diFC 6 H 3	C 18 H 10 Cl 2 F 2 N 4 O
	4aa	Furan-2yl	C 16 H 10 Cl 2 N 4 O 2
	4bb	Thiophen-3-yl	C 16 H 10 Cl 2 N 4 OS
	4cc	Pyrrol-2yl	C 16 H 11 Cl 2 N 5 O
	4dd	Pyridin-2-yl	C 17 H 11 Cl 2 N 5 O
	4ee	Pyridin-3-yl	C 17 H 11 Cl 2 N 5 O
	4ff	Pyridin-4-yl	C 17 H 11 Cl 2 N 5 O
	4gg	Naphthalen-2-yl	C 22 H 14 Cl 2 N 4 O
	4hh	Naphthalen-3-yl	C 22 H 14 Cl 2 N 4 O
	4ii	Anthracen-9-yl	C 26 H 16 Cl 2 N 4 O

Figure 2: Table 1 :

2

Cl
N N
Cl N N H O R
4a-ii

% Elemental analysis of C, H, N b

Compound	Calculated			Found		
	C	H	N	C	H	N
4a	58.24	3.26	15.09	58.21	3.21	15.05
4b	59.24	3.66	14.54	59.22	3.62	14.52
4c	59.24	3.66	14.54	59.25	3.61	14.53
4d	59.24	3.66	14.54	59.22	3.64	14.51
4e	56.87	3.52	13.96	56.82	3.51	13.95
4f	56.87	3.52	13.96	56.83	3.51	13.91
4g	56.87	3.52	13.96	56.84	3.56	13.96
4h	55.83	3.12	14.47	55.85	3.11	14.42
4i	55.83	3.12	14.47	55.83	3.11	14.45
4j	53.62	3.00	13.89	53.61	3.02	13.81
4k	53.62	3.00	13.89	53.61	3.04	13.82
4l	56.87	3.52	13.96	56.86	3.51	13.93
4m	55.97	3.39	18.13	55.95	3.31	18.11
4n	55.97	3.39	18.13	55.94	3.32	18.12
4o	55.97	3.39	18.13	55.93	3.35	18.14
4p	51.94	2.66	16.83	51.95	2.62	16.82
4q	51.94	2.66	16.83	51.92	2.65	16.85
4r	51.94	2.66	16.83	51.93	2.62	16.81
4s	53.29	2.73	13.81	53.21	2.71	13.82
4t	53.29	2.73	13.81	53.22	2.74	13.81
4u	53.29	2.73	13.81	53.23	2.71	13.84
4v	49.12	2.29	12.73	49.11	2.25	12.71
4w	55.55	2.85	14.39	55.53	2.82	14.35
4x	55.55	2.85	14.39	55.52	2.84	14.35
4y	55.55	2.85	14.39	55.51	2.81	14.32
4z	53.09	2.48	13.76	53.01	2.42	13.72
4aa	53.21	2.79	15.51	53.22	2.75	15.50
4bb	50.94	2.67	14.85	50.97	2.65	14.82
4cc	66.25	3.42	11.89	66.22	3.41	11.86
4dd	54.86	2.98	18.82	54.82	2.96	18.88
4ee	54.86	2.98	18.82	54.81	2.95	18.89
4ff	54.86	2.98	18.82	54.85	2.92	18.81
4gg	62.72	3.35	13.30	62.71	3.32	13.32
4hh	62.72	3.35	13.30	62.72	3.31	13.33
4ii	66.25	3.42	11.89	66.22	3.40	11.85

Figure 3: Table 2 :

.1 V. Acknowledgements

The author is thankful to KC Reddy Institute of Pharmaceutical Sciences, Jangamguntapalem, Medikonduru, Guntur District for availing the facilities of Research laboratory, text-and e-journal access in their library sections.

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