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Research Article

AN EFFICIENT MICROWAVE ASSISTED MULTICOMPONENT SYNTHESIS OF SOME 7-AMINO-3-(SUBSTITUTED PHENYL)-5-(SUBSTITUTED PHENYL)-[1,2,4]TRIAZOLO[4,3A]PYRIMIDINE-6-CARBONITRILE DERIVATIVES

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ABSTRACT

A series of 7-amino-3-(substituted phenyl)-5-(substituted phenyl)-[1,2,4]triazolo [4,3a] pyrimidine-6-carbonitrile derivatives were synthesized from 4-amino-2-hydroxy (OR mercapto)-6-(substituted phenyl)-pyrimidine-5-carbonitrile, hydrazine hydrate and aromatic aldehydes. The derivatives were obtained in good yields by the microwave-assisted one-pot protocol in very short reaction time. The synthesized compounds were studied for QSAR by subjecting to a prediction of biological activities applying computer programme PASS. It is found that 7-Amino-3-(4-chloro-phenyl)-5-(2,4-dichloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile is a promising anticonvulsant agent; which can be synthesized by an efficient, promising, and green synthetic method with high yield.

Keywords: Pyrimidine, Triazolo pyrimidine, Eco-friendly organic synthesis, Green Chemistry, Microwave Irradiation.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen-containing heterocycles are an important class of compounds in medicinal chemistry. There has been considerable interest in the development of preparative methods for the production of pyrimidines. Pyrimidine and its derivatives have been studied for over a century due to a variety of important chemical and biological applications. A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities such as antibacterial, antiviral and antitumor agents.[1-6]

The importance of triazolo pyrimidines as biologically active compounds includes their use as antibacterial [7-9], antimicrobial [10], antihypertensive [11], antileishmanial [12], anticonvulsant [13] agents.

However, instead of their common use, most reported methods to prepare these heterocyclic compounds suffer from long reaction times and often require the use of strong acid media. Consequently, new mild and expedient protocols for this valuable and widely utilized reaction are of significant importance.

In the last decade microwave irradiation technique has been utilized as a powerful tool for the various organic transformations.[14] The main benefits of the use of microwave irradiation include significant enhancement of the rate of the reactions, improvement in the yields and selectivity.[15] In recent years, microwave irradiation using scientific domestic ovens has been rapidly increased for optimization and acceleration of organic synthesis under solvent free conditions[16-17]. It has been reported for the variety of reactions such synthesis of heterocyclic and more recently for synthesis of polymers because of advantages such as reduction in reaction time, improved energy utilization, potential for lower processing temperature and improved product uniformity.

METHODS

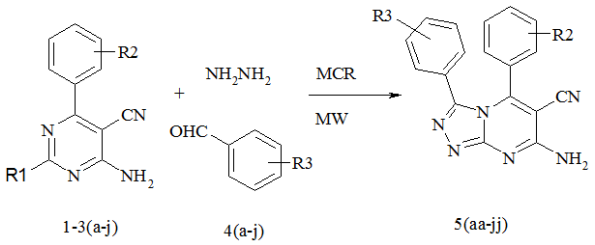
General Procedure

Microwave irradiation was carried out in a scientific microwave oven. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer, using DMSO-*d*6 as solvent and TMS as internal standard. Elemental analysis was done by using a Perkin-Elmer 240c elemental analysis instrument.

The structures of the newly synthesised compounds 3a-3j were deduced by analysis of their ^{1}H and [13]C NMR and mass spectra as well as elemental analysis. The assignments of the ^{1}H NMR spectra were performed on the basis of the chemical shifts, signal intensities and the magnitudes and multiplicities of H–H coupling constants.

General procedure for the preparation of 7-amino-3-(substituted phenyl)-5-(substituted phenyl)-[1,2,4]triazolo[4,3a]pyrimidne-6-carbonitrile under microwave irradiation:

A mixture (1 mmol) each of 4-amino-2-hydroxy (OR mercapto)-6-(substituted phenyl)-pyrimidine-5-carbonitrile, benzaldehyde, hydrazine hydrate and aromatic aldehyde in presence of ethanol was irradiated for 5-7 min. with a 20% power of 200W in microwave oven. After cooling, the reaction mixture was washed with water (15 mL) and then recrystallised from ethanol to get the pure product.



1-3(a-j) 4(a-j) 5(aa-jj)

1: R1=OH
2: R1=SH
3: R1=NH_2

R2 and R3
a; 2-Cl
b; 3-Cl
c; 3-Br
d; 3-NO_2
e; 4-Cl
f; 4-OH
g; 4-OMe
h; 2,4-dichloro
i; 3,4-dihydroxy
j; 3,4-dimethoxy

Scheme 1: Synthesis of different triazolo pyrimidine derivatives

From the designed series of compounds 5aa to 5jj, the following compounds were synthesized by above mentioned protocol and studied for their analytical and spectral data.

Comp.	R_2	R_3
5aj	2-Cl	3,4-dimethoxy
5ba	3-Cl	2-Cl
5ca	3-Br	2-Cl
5df	3-NO2	4-OH
5eh	4-Cl	2,4-dichloro
5fc	4-OH	3-Br
5gi	4-OMe	3,4-dihydroxy
5he	2,4-dichloro	4-Cl
5ig	3,4-dihydroxy	4-OMe
5jb	3,4-dimethoxy	3-Cl

Table 1: Analytical Data and Elemental Analysis of synthesized compounds

Entry	Molecular Formula (Mol. Mass)	LC-MS Data	Yield %	Time Mins	Elemental Analysis					
					% C		% H		% N	
					Found	Calcd	Found	Calcd	Found	Calcd
5aj	$C_{20}H_{15}ClN_6O_2$ (406.83)	427	75	5	59.05	59.08	3.72	3.74	20.66	20.71
5ba	$C_{18}H_{10}Cl_2N_6$ (381.23)	402	78	7	56.71	56.78	2.64	2.69	22.04	22.09
5ca	$C_{18}H_{10}BrClN_6$ (425.68)	442	78	6	50.79	50.84	2.37	2.38	19.74	19.77
5df	$C_{18}H_{11}N_7O_3$ (373.33)	404	81	5	57.91	57.62	2.97	3.53	26.12	12.86
5eh	$C_{18}H_9Cl_3N_6$ (415.67)	435	84	6	52.01	52.09	2.18	2.22	20.22	20.23
5fc	$C_{18}H_{11}BrN_6O$ (407.23)	428	86	5	53.09	53.11	2.72	2.73	20.64	20.66
5gi	$C_{19}H_{14}N_6O_3$ (374.36)	402	85	6	60.96	60.99	3.77	3.81	22.45	22.49
5he	$C_{18}H_9Cl_3N_6$ (415.67)	432	82	5	52.01	52.14	2.18	2.11	20.22	20.26
5ig	$C_{19}H_{14}N_6O_3$ (374.36)	402	84	7	60.96	60.97	3.77	3.79	22.45	22.47
5jb	$C_{20}H_{15}Cl\ N_6O_2$ (406.83)	424	79	6	59.05	59.12	3.72	3.76	20.66	20.79

The structures of the synthesized compounds were confirmed and studied for QSAR by subjecting to a computer programme PASS for prediction of biological activities. It is found that 7-Amino-3-(4-chloro-phenyl)-5-(2,4-dichloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile is a promising anticonvulsant agent synthesized b**y** an efficient, promising, and green synthetic method with high yield.

RESULTS AND DISCUSSION

In present work, we report microwave assisted multicomponent synthesis of 7-amino-3-(substituted phenyl)-5-(substituted phenyl)-[1,2,4]triazolo[4,3a]pyrimidine-6-carbonitrile derivatives from 4-amino-2-hydroxy (OR mercapto)-6-(substituted aryl)-pyrimidine-5-carbonitrile, hydrazine hydrate and aromatic aldehyde in presence of EtOH under microwave oven. The reaction is shown in scheme 1. It is found that triazolo pyrimidine derivatives were obtained in good yield under microwave irradiation method as compared to the conventional method. The reaction was completed within 5 - 7 min and the target compounds were obtained in high yields. Herein, we report the details of this simple and efficient method.

QSAR Analysis of Activities with PASS

The relationship between structure and different biological activities was studied using computer programme PASS. The structures of derivatives 5aa-jj were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities such that the Pa>70%. The Following three activities were predicted with top probability for the series of compounds.

Anticonvulsant

Anticonvulsant drugs are medicines used to prevent or treat convulsions (seizures). Anticonvulsant drugs are used to control seizures in people with epilepsy. Epilepsy is not a single disease—it is a set of symptoms that may have different causes in different people. The common thread is an imbalance in the brain's electrical activity. This imbalance causes seizures that may affect part or all of the body and may or may not cause a loss of consciousness. Anticonvulsant drugs act on the brain to reduce the frequency and severity of seizures.

Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers. The heterocyclic compounds mostly used as anticonvulsants are barbexaclone, phenobarbital and rufinamide are carboxamide type anticonvulsant widely used for the control generalized myoclonic seizures.

Alopecia agent

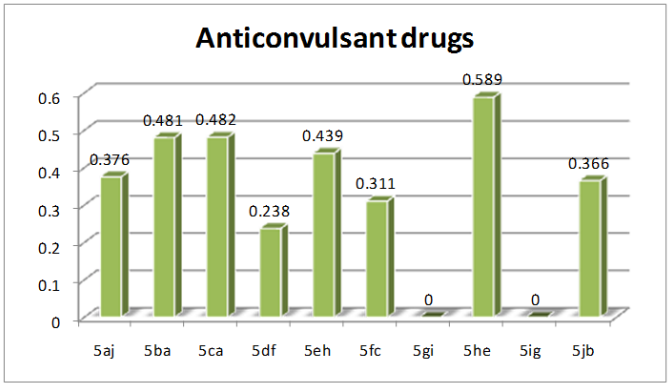
Alopecia is the medical term for hair loss. The agent for the treatment of alopecia containing a natriuretic peptide (NP) as an active ingredient promotes hair regeneration, hair growth, and hair thickening on a hair loss site of an alopecia areata patient, an androgenetic alopecia patient, a female pattern alopecia patient, a postpartum alopecia patient, a seborrheic alopecia patient, an alopecia pityroides patient, a senile alopecia patient, a cancer chemotherapy drug-induced alopecia patient, and a patient with alopecia due to radiation exposure, can improve the alopecia outstandingly.

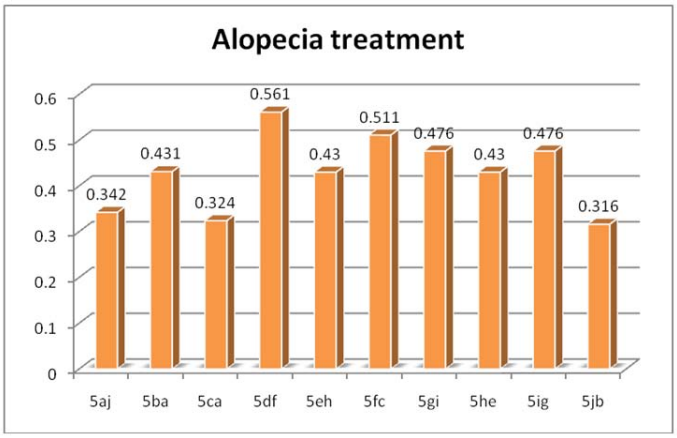
Antineoplastic

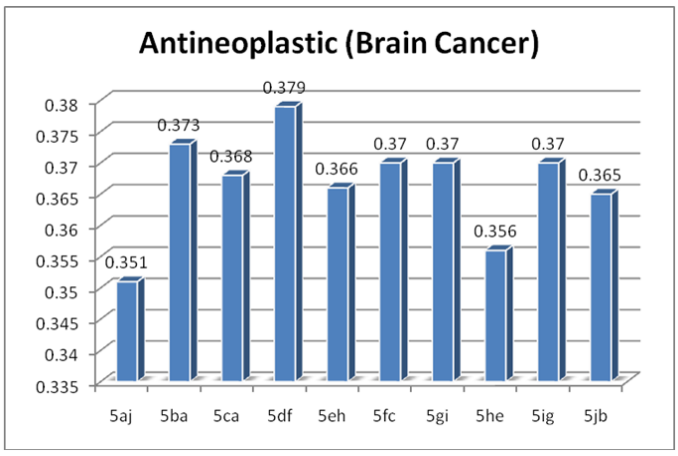
Antineoplastics or Anticancer drugs are the drugs that prevent or inhibit the maturation and proliferation of neoplasms. Antineoplastic agents travel the body and destroy cancer cells. Antineoplastic drugs / Anticancer Drugs are not only used prominently in different types of cancers but also in conjunction with surgery, radiotherapy and immunotherapy in the combined modality approach for many solid tumors, especially metastatic.

Table 2: Predictions of biological activities by PASS

Activity	Anticonvulsant	Alopecia treatment	Antineoplastic (Brain Cancer)
Comp.	Pa	Pa	Pa
5aj	0.376	0.342	0.351
5ba	0.481	0.431	0.373
5ca	0.482	0.324	0.368
5df	0.238	**0.561**	**0.379**
5eh	0.439	0.430	0.366
5fc	0.311	0.511	0.370
5gi	0.000	0.476	0.370
5he	**0.589**	0.430	0.356
5ig	0.000	0.476	0.370
5jb	0.366	0.316	0.365







CONCLUSIONS

It is observed that the compounds in the proposed series are moderately active as far as the three predicted activities are concerned. Viz. anticonvulsant, alopecia agent and antineoplastic. In conclusion, we have used a facile method for the preparation of 7-amino-3-(substituted phenyl)-5-(substituted phenyl)-[1,2,4] triazolo [4,3a]pyrimidne-6-carbonitrile in ethanol under microwave-assisted condition. This method involves one-pot synthesis of triazolopyrimidine derivatives which is a simple, efficient, economical, time saving and ecofriendly process.

Analytical & Spectroscopic Data of Synthesized Products

7-Amino-5-(2-chloro-phenyl)-3-(3,4-dimethoxy-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile (5aj)

M. P.(284°C) IR (KBr):1040 (-OCH3), 854 (C-Cl), 2215(-CN), 3342(NH_2), 1493 (C=C), 3060 cm^{-1}(C-H,Ar). **^{1}H NMR:** 3.91(6H, s, -OCH_3), 7.06 (1H, d, =CH), 7.71 (1H, d, =CH), 8.05 (1H, d, =CH), 6.79-7.55 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2) **[13]C NMR:** 55.72 (-OCH3), 149.60 (>C=), 55.93 (-OCH3), 113 (=CH), 129.22 (>C=), 148.54 (>C=), 164.77 (C-NH2), 117.20 (-CN), 83.94 (>C=), 150.63 (>C=), 128.95 (>C=), 129.11 (=CH), 133.70 (C-Cl), 109.73 (=CH), 129.22 (=CH), 129.81 (=CH), 129.86 (=CH), 127.22 (=CH),

7-Amino-3-(3-chloro-phenyl)-5-(2-chloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5ba)

M. P.(249°C) IR (KBr): (cm^{-1}) 2219 (-CN), 3342 (NH_2), 851 (C-Cl), 1496 (C=C), 3050(C-H,Ar). **^{1}H NMR:** 7.16-7.55 (4H, m, -C_6H_4), 7.61-7.73 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2) **[13]C NMR:** 135.14 (C-Cl), 128.14 (2 × =CH), 128.67 (2 × =CH), 131.81 (>C=), 150.63 (>C=), 152.80 ((>C=), 164.77(C-NH_2), 117.20 (-CN), 83.94(>C=), 158.84 (>C=), 128.95 (>C=), 133.70 (C-Cl), 129.11 (=CH), 129.81 (=CH), 127.72 (=CH)

7-Amino-5-(3-bromo-phenyl)-3-(2-chloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5ca)

M. P.(278°C) IR (KBr): (cm^{-1})2220 (-CN), 3342 (NH_2), 851 (C-Cl), 851 (C-Br), 1496 (C=C), 3084 (C-H,Ar). **^{1}H NMR:** 7.11-8.02 (4H, m, -C_6H_4), 7.17 – 8.01 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2), **[13]C NMR:** 130.36 (=CH), 130.98 (=CH), 131.96 (C-Cl), 133.49 (>C=), 128.97 (=CH), 127.76 (=CH), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 84.94 (>C=), 117.20 (-CN), 158.84 (>C=), 134.90 (>C=), 126.90 (=CH), 122.25 (C-Br), 131.10 (=CH), 130.80 (=CH), 128.03 (=CH).

7-Amino-3-(4-hydroxy-phenyl)-5-(3-nitro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5df)

M. P.(283°C) IR (KBr): 1431 (-NO_2), 2214(-CN), 3336 (NH_2), 3328 (-OH), 1496 (C=C), 3060 cm^{-1} (C-H,Ar). **^{1}H NMR:** 6.79 – 8.06 (4H, m, -C_6H_4), 7.55 – 8.18 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2), 9.01 (1H, s, -OH) **[13]C NMR:** 116.80 (2X =CH), 129.12 (2X=CH), 131.81 (>C=), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 117.20 (-CN), 83.94 (>C=), 158.84 (>C=), 134.71 (>C=), 125.80 (=CH), 147.40 (C-NO2), 122.80 (=CH), 130.67 (=CH), 128.12 (=CH), 157.70 (C-OH)

7-Amino-5-(4-chloro-phenyl)-3-(2,4-dichloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5eh)

M. P.(267°C) IR (KBr): 2214 (-CN), 3342 (NH_2), 851 (C-Cl), 1496 (C=C), 3080 cm^{-1} (C-H,Ar). **^{1}H NMR:** 7.45-8.00 (4H, m, -C_6H_4), 7.51-7.53(1H, d, =CH), 7.86 (1H, s, =CH), 8.22-8.24 (1H, d, =CH), 7.83 (2H, s, -NH_2) **[13]C NMR:** 134.13 (C-Cl), 129.25 (=CH), 133.51 (C-Cl), 133.49 (>C=), 128.95(=CH), 128.66 (=CH), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 117.20 (-CN), 83.94 (=CH), 158.84 (>C=), 134.89 (>C=), 129.36 (=CH), 128.59 (=CH), 134.17 (C-Cl), 128.59 (=CH), 129.36 (=CH)

7-Amino-3-(3-bromo-phenyl)-5-(4-hydroxy-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5fc)

M. P.(278°C) IR (KBr): 2221 (-CN), 3342 (NH_2), 3337 (-OH), 851 (C-Br), 1496 (C=C), 3060 cm^{-1} (C-H,Ar). **^{1}H NMR:** 6.97-7.98 (4H, m, -C_6H_4), 7.17- 8.33 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2), 10.01 (1H, s, -OH) **[13]C NMR:** 118.51 (C-Br), 132.14 (=CH), 130.73 (=CH), 127.76 (=CH), 131.82 (>C=), 130.84 (=CH), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 158.84 (>C=), 117.20 (-CN), 83.94 (>C=), 134.89 (>C=), 129.58 (2 X =CH), 116.17 (=CH), 159.10 (C-OH), 116.17 (=CH)

7-Amino-3-(3,4-dihydroxy-phenyl)-5-(4-methoxy-phenyl)-[1,2,4]triazolo[4,3 a]pyrimidne-6-carbonitrile (5ig)

M. P.(256°C) IR (KBr): (cm^{-1}) 1041 (-OCH_3), 2214 (-CN), 3331 (NH_2), 3338 (-OH), 1496 (C=C), 3060 (C-H,Ar). **^{1}H NMR:** 3.82 (3H, s, -OCH_3), 6.91-6.92 (1H, d, =CH), 7.29 (1H, s, =CH), 8.05 - 8.08 (1H, d, =CH), 8.95 - 9.01 (2H, s, -OH), 7.0.4 – 7.97 (4H, m, -C_6H_4), 7.83 (2H, s, -NH_2) **[13]C NMR:** 147.76 (C-OH), 145.53 (C-OH), 113.80 (=CH), 131.83 (>C=), 129.15 (=CH), 116 (=CH), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 117.20 (-CN), 83.94 (>C=), 158.84 (>C=), 134.89 (>C=), 129.63 (2 X =CH), 113.95 (2 X =CH), 106.36 (>C=), 55.31 (-OCH_3)

7-Amino-3-(4-chloro-phenyl)-5-(2,4-dichloro-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile (5eh)

M. P.(264°C) IR (KBr): 2214 (-CN), 3334 (NH_2), 856 (C-Cl), 1489 (C=C), 3060 cm^{-1} (C-H, Ar). ^{1}H NMR: 7.45-7.47 (1H, d, =CH), 7.61-7.73 (4H, m, -C_6H_4), 7.63 (1H, s, =CH), 7.81-7.82 (1H, d, =CH), 7.83 (2H, s, -NH_2) [13]C NMR: 132.70 (2 X C-Cl), 129.75 (=CH), 128.95 (>C=), 131.45 (=CH),127.55(=CH),158.94 (>C=), 83.94(>C=), 117.20 (-CN), 164.77 (C-NH2), 150.80(>C=), 150.63 (>C=), 131.81 (>C=), 128.67 (2 X = CH), 128.14 (2 X = CH), 135.14 (C-Cl)

7-Amino-5-(3,4-dihydroxy-phenyl)-3-(4-methoxy-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5ig)

M. P.(265°C) IR (KBr): 1040 (-OCH3), 2224 (-CN), 3338 (NH_2), 3338 (-OH), 1496 (C=C), 3060 cm^{-1} (C-H,Ar). **^{1}H NMR:** 3.85 (3H, s, -OCH_3), 6.91-6.94 (1H, d, =CH), 7.30 -7.34 (1H, d, =CH), 7.98 - 8.00 (1H, d, =CH), 6.97 – 7.58 (4H, m, -C_6H_4), 8.95 (1H, s, -OH), 9.01 (1H, s, -OH), 7.83 (2H, s, -NH_2) **[13]C NMR:** 55.48 (-OCH3), 114.42 (2X=CH), 129.22 (2X=CH), 131.81 (>C=), 150.63 (>C=), 152.80 (>C=), 164.77 (-NH2), 117.20 (-CN), 83.94 (>C=), 158.84 (>C=), 134.70 (>C=), 108.56 (>C=), 145.53 (C-OH), 147.76 (C-OH), 115.50 (=CH), 129.03 (=CH), 161.10 (>C=)

7-Amino-5-(3-chlro-phenyl)-3-(3,4 dimethoxy-phenyl)-[1,2,4]triazolo[4,3-a]pyrimidne-6-carbonitrile (5jb)

M. P.(291°C) IR (KBr):1038 (-OCH3), 853 (C-Cl), 2215(-CN), 3335 (NH_2), 1493 (C=C), 3060 cm^{-1}(C-H,Ar).**^{1}H NMR:** 3.66 (6H, s, -OCH_3), 7.67- 8.32 (4H, m, -C_6H_4), 7.05(1H, s, =CH),7.08 (1H, s, =CH), 7.83 (2H, s, -NH_2) **[13]C NMR:** 127.73 (=CH), 130.00 (2X =CH), 131.82 (>C=), 134.70 (>C=), 150.63 (>C=), 152.80 (>C=), 164.77 (C-NH2), 117.20 (-CN), 83.94 (>C=), 158.84 (>C=), 128.40 (=CH), 108.90 (=CH), 148.24 (>C=), 55.72 (-OCH3), 149.60 (>C=), 55.98 (-OCH3), 107.40 (=CH), 134.30 (C-Cl), 129.13 (=CH)

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