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Research Article

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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF 3-[4-(2,5-DIMETHYL AMINO-1H PYRROL-1-YL-PHENYL) [1,3,4]-OXADIAZINO [6,5-B] SUBSTITUTED INDOLE

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ABSTRACT

Fifteen new 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] substituted indole have been synthesized. The chemical structures of the products were confirmed by ^{1}HNMR, IR and mass spectral data. The compounds were screened for antioxidant activity by standard DPPH assay method. IC_{50} values of these compounds were determined. Compounds **XIIf, XIIm** and **XIIn** potent antioxidant and remaining compounds showed significant antioxidant activity. Ascorbic acid was taken as standard drug.

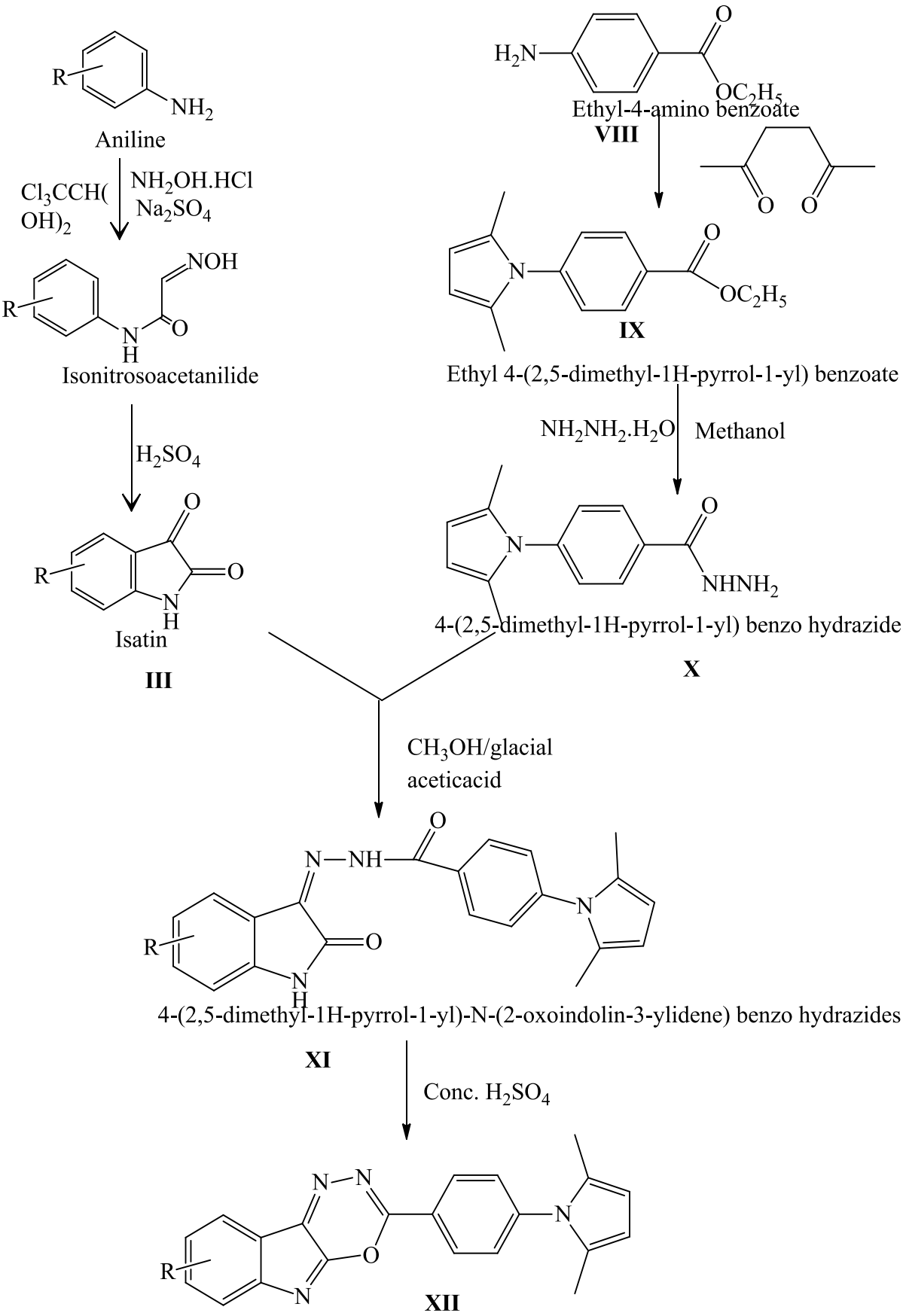
Keywords: Isatin, Antioxidant activity and oxadiazene.

INTRODUCTION

Isatin has been known for about 150 years and exhibit biological activity in mammals[1]. It is evident from literature, that isatin derivatives are known to be associated with broad spectrum of biological activity like antibacterial[2], analgesic and antiinflammatory[3], anti-viral[4], antianxiety[5], antihistaminic[6] and antidepressant[7]. In view of these properties it has been considered worthwhile to synthesize some new biologically potent isatins with an aim to screen for antioxidant activity. The synthesized compounds has been purified and characterized with the help of their analytical and spectral (IR, ^{1}HNMR & Mass) data.

Chemistry

The new 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] substituted indole have been synthesized by following **Scheme-I** and Characterized by IR, NMR and Mass data. Physical data of new compounds are presented in **Table-1.**


R
NH2
Aniline
Cl3CCH(OH)2
NH2OH.HCl
Na2SO4
NOH
N
H
O
Isonitrosoacetanilide
H2SO4
R
O
N
H
O
Isatin
III
H2N
O
OC2H5
Ethyl-4-amino benzoate
VIII
O
O
N
O
OC2H5
IX
Ethyl 4-(2,5-dimethyl-1H-pyrrol-1-yl) benzoate
NH2NH2.H2O
Methanol
N
O
NHNH2
4-(2,5-dimethyl-1H-pyrrol-1-yl) benzo hydrazide
X
CH3OH/glacial aceticacid
N—NH
O
R
O
N
H
N
4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(2-oxoindolin-3-ylidene) benzo hydrazides
XI
Conc. H2SO4
N
N
O
R
N
N
XII
4-(2,5-dimethyl-1H-pyrrol-1-yl-phenyl)-[1,3,4-Oxadiazino [6,5-b] substituted indole

Scheme-I

General Procedure for the synthesis of 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] substituted indole

A. Synthesis of ethyl 4-(2,5-dimethyl-1H-pyrrol-1-yl) benzoate (IX)

A mixture of ethyl-4-aminobenzoate **(VIII, 0.01 mol)** and hexane-2,5-dione **(II, 0.01 mol)** were taken into a RB flask and dissolved in minimum amount of ethyl acetate (10-15 ml). The reaction mixture was refluxed at 120^0C for 5-6hrs, progress of the reaction was monitored by TLC. The reaction mixture was cooled and extracted with ether (3 times with 20ml) and washed with 10% citric acid (3 × 20ml) and then with water (20ml). The organic layer was concentrated under reduced pressure to get brown liquid which solidifies at room temperature. The compound obtained was recrystallized with ethyl acetate.

B. Synthesis of 4-(2,5-dimethyl-1H-pyrrol-1-yl) benzo hydrazide (X)

A mixture of 1:5 ratio of ethyl 4-(2,5-dimethyl-1H-pyrrol-1-yl) benzoate (IX) and hydrazine hydrate, were transferred in to a RB flask and dissolved in minimum quantity of methanol and was refluxed for about 2 hours. The solvent was removed by distillation. The residue is triturated with crushed ice. The product, thus obtained was filtered, washed with distilled water and recrystallized from appropriate solvent.

C. Synthesis of 4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(2-oxoindolin-3-ylidene) benzo hydrazides (XI)

4-(2,5-dimethyl-1H-pyrrol-1-yl) benzo hydrazide **(V, 0.01 mol)** was condensed with isatin **(VI, 0.01mol)** in methanol and traces of glacial acetic acid for about 5-6 hours to get their respective 4-(2,5-dimethyl -1H-pyrrol-1-yl) -N'- (2- oxoindolin-3-ylidene) benzohydrazides. The resulting products was filtered and purified by recrystallization method.

D. Synthesis of 4-(2,5-dimethyl-1H-pyrrol-1-yl-phenyl)-[1,3,4-Oxadiazino [6,5-b] substituted indole (XII)

A pure compound of 4-(2,5-dimethyl -1H-pyrrol-1-yl) -N'- (2- oxoindolin-3-ylidene) benzo hydrazides. **(XI, 0.01 mol)** was treated with concentrated sulphuric acid and kept aside for 24 hrs. The resulting products was triturated with crushes ice and filtered and washed with distilled water. The new compound was purified by recrystallization from aqueous ethanol.

Spectral characterization data of the compound (XIIa)

IR (KBr, Cm^{-1}) ν

3084 (C-H, aromatic) 2946 (C-H of aliphatic), and 1594 (C=C, aromatic), 1409.80 (C-N stretch).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ

2.20 (s,6H, CH_3), 5.68(s, 2H, pyrrolyl), 7.18-7.40 (m,4H, Aromatic), 7.50-7.82 (m, 4H, Aromatic).

Mass spectrum

Recorded its heaviest ion at m/z 340, which is in agreement with the mass (mol.wt.) of its assigned structure.

Thus based on the spectral data the compound has been characterized as 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] indole (XIIa; R= H).

Antioxidant Activity

DPPH Radical Scavenging Method

Blois[8] showed that α,α-diphenyl-β-picryl hydrazyl radical (DPPH) can be used for determining antioxidant activity. DPPH in ethanol shows a strong absorption band at 517 nm and the solution appears to be deep violet in color. As the DPPH radical is scavenged by the donated hydrogen from the antioxidant, the absorbance is diminished according to the stoichiometry. Briefly, 0.5 mL of DPPH solution (0.2 mM) was mixed with 0.1 mL of various concentrations of test compounds and 1.5 mL ethanol was added. The mixture was kept at room temperature for 30 min, and then the absorbance (OD) was read at 517 nm against blank. The % reduction of free radical concentration (OD) with different concentration of test compounds was calculated and compared with standard, ascorbic acid. The results were expressed as IC_{50} values (the concentration of test required to scavenge 50% free radicals).

RESULTS AND DISCUSSION

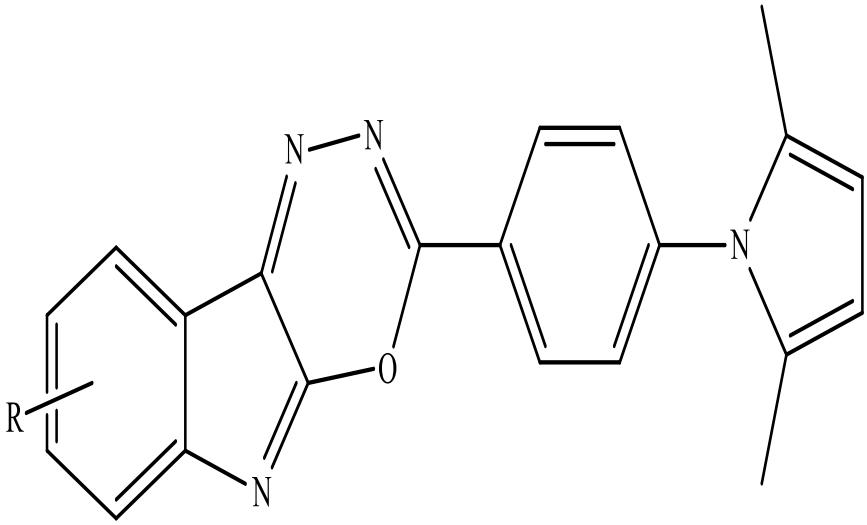
The antioxidant activity of all the synthesized compounds performed using DPPH method and the results given in **Table 2.** The values are expressed in IC_{50} that is, ability of the test compound required to decrease the concentration of test free radical by 50%. Among all the test compounds, compounds XIIf, XIIm and XIIb, exhibited more potent antioxidant activity against DPPH. Remaining compounds showed mild to modetare antioxidant activity. It is proposed that DPPH may be scavenged by an antioxidant through donation of hydrogen ($H^{\cdot}$) to form a stable DPPH-H molecule which does not absorb at 517 nm. Thus the results show

that synthesized compounds possess antioxidant activity. It was observed that the test compounds with electron withdrawing groups (halogens) on the aromatic ring favors anti-oxidant activity.

CONCLUSIONS

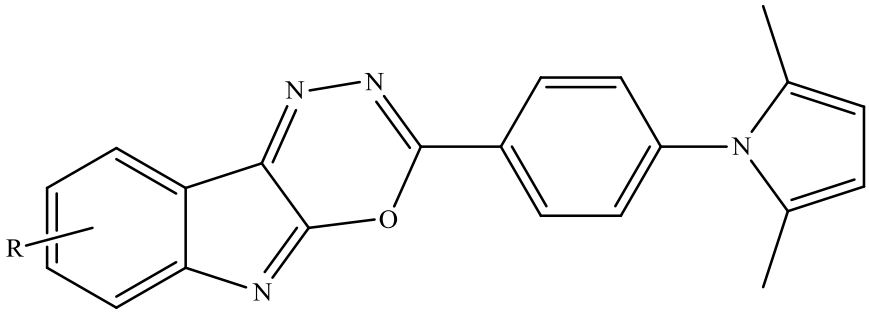
A series of as 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] substituted indole has been synthesized as shown in Scheme 1. The synthesized compounds were subjected to antioxidant activity, amongst the compounds tested substituent with an electron withdrawing group on the aromatic ring showing significant activity than the other substituted compounds.

Table 1: Physical data of 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] indole (Series-II)



S.No	Compound	Substituent (R)	Mol.Formula	Mol. Wt.	m.p (°C)	% Yield
1	XIIa	H	$C_{21}H_{16}N_4O$	340	216-218	45
2	XIIb	5-Cl	$C_{21}H_{15}N_4OCl$	374	244-246	86
3	XIIc	7-Cl	$C_{21}H_{15}N_4OCl$	374	244-246	84
4	XIId	5-CH_3	$C_{22}H_{18}N_4O$	354	232-234	81
5	XIIe	7-CH_3	$C_{22}H_{18}N_4O$	354	232-234	79
6	XIIf	5-F	$C_{21}H_{15}N_4OF$	358	248-250	78
7	XIIg	7-F	$C_{21}H_{15}N_4OF$	358	248-250	75
8	XIIh	5-Br	$C_{21}H_{15}N_4OBr$	418	284-286	92
9	XIIi	5-NO_2	$C_{21}H_{15}N_5O_3$	385	265-267	68
10	XIIj	7-NO_2	$C_{21}H_{15}N_5O_3$	385	265-267	72
11	XIIk	5-OH	$C_{21}H_{16}N_4O_2$	356	221-223	74
12	XIIl	7-OH	$C_{21}H_{16}N_4O_2$	356	221-233	74
13	XIIm	5-COOH	$C_{22}H_{16}N_4O_3$	384	248-250	69
14	XIIn	5-$COOC_2H_5$	$C_{22}H_{20}N_4O_3$	412	243-245	58

Table 2: Antioxidant activity of 3-[4-(2,5-dimethyl amino-1H pyrrol-1-yl-phenyl) [1,3,4]-oxadiazino [6,5-b] indole (Series-II)



S.No	Compound	R	IC_{50} (µg/ml)
1	XIIa	H	88
2	XIIb	5-Cl	42
3	XIIc	7-Cl	48
4	XIId	5-CH_3	72
5	XIIe	7-CH_3	79
6	XIIf	5-F	36
7	XIIg	7-F	48
8	XIIh	5-Br	53
9	XIIi	5-NO_2	62
10	XIIj	7-NO_2	68
11	XIIk	5-OH	61
12	XIII	7-OH	64
13	XIIm	5-COOH	46
14	XIIn	5-$COOC_2H_5$	59
15	**Standard**	**Ascorbic Acid**	**6.52**

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