Studies with Enamines and Azaenamines: Synthesis and Reactivity of 3-Dimethylamino-2-[(3-indolyl) carbonyl]propenonitrile

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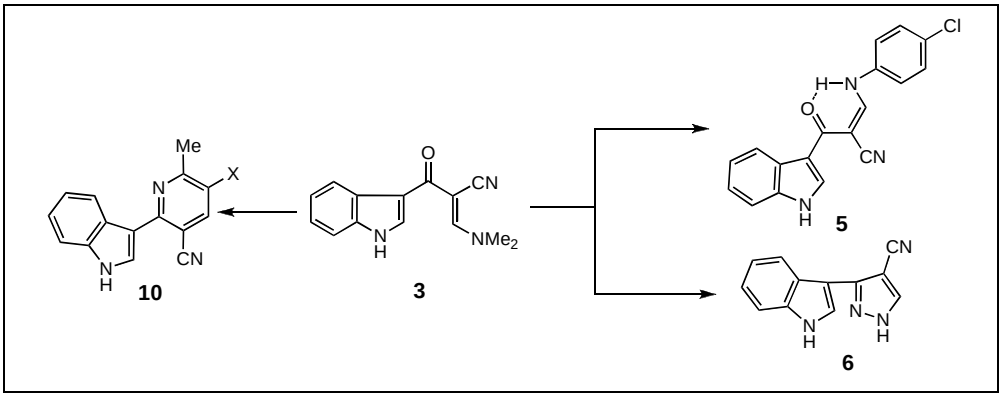

2-Oxo-3-(indol-3-yl)propanonitrile **2** condensed with dimethylformamide dimethylacetal to yield the enaminonitrile **3**. The latter reacted with 4-chloroaniline to yield the 4-chlorophenylaminoacrylonitrile **5**. Reaction of **3** with hydrazine hydrate led to formation of pyrazole-4-carbonitrile **6**. Compound **3** reacted with ethyl acetoacetate in refluxing acetic acid and in presence of ammonium acetate to yield the indolylpyridine **10**. Enamine **3** reacted with 5(1*H*)-aminotriazole **13** and 3(5)-aminopyrazole **17** to yield the pyrimidine derivatives **15** and **19**, respectively.

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INTRODUCTION

Enamines are versatile reagents and have been recently efficiently utilized for synthesis of otherwise not readily obtainable, heteroaromatics [1-4]. On the other hand, indole derivatives are biologically interesting molecules and their chemistry has attracted in the past and still attracts attention of biological chemists [5-8]. In conjunction to our group interest in utilizing enamines and azaenamines as precursors to polyfunctional heteroaromatics [9-11], I report here results of my investigation aimed at exploring the potential utility of **3** as precursor to 3-indolylazoles and 3-indolylazines.

RESULTS AND DISCUSSION

Reacting indole **1** with cyanoacetic acid in presence of acetic anhydride following recently reported procedures [6], afforded the 2-oxo-3-(indol-3-yl)propanenitrile **2**. Reaction of the latter with dimethyl-formamide dimethyl-acetal in refluxing dioxane afforded a new product, namely the enaminonitrile **3**. Although **3** may also be assigned structure **4**, structure **3** is considered to be most likely as it is apparently sterically most stable. However, structure **4** cannot be completely excluded.

When **3** was treated with 4-chloroaniline in refluxing acetic acid, condensation *via* dimethylamine elimination occurred producing the Z-enamine **5** (Scheme 1). Structure **5** is established based on X-ray crystal structure determination [12] (*c.f.* Figure 1). Preference of structure **5** is attributed to fixation of this form, although sterically crowded, by hydrogen bonding. Recently, rationalization for existence of enamines in such form has been discussed [13].

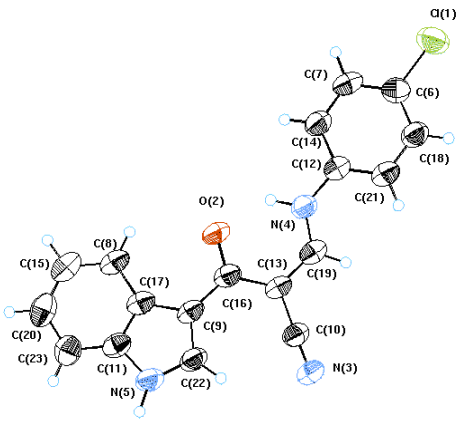
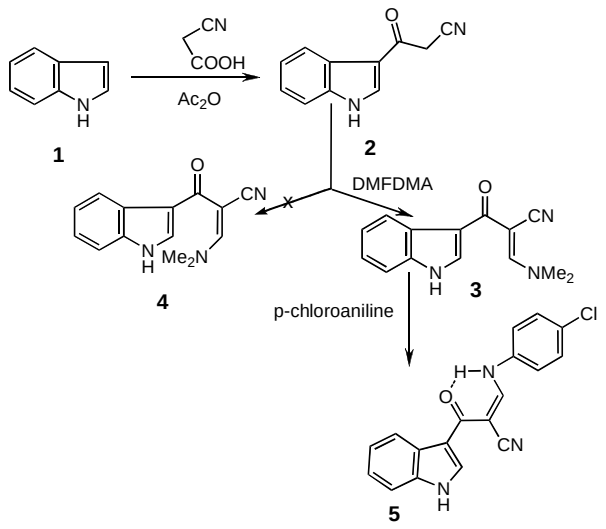


Figure 1. X-Ray crystal structure of compound **5**.

Reaction of compound **3** with hydrazine hydrate in refluxing ethanol afforded only one product, namely 4-cyano-3-(3-indolyl)pyrazole **6**. No traces of compound **7**

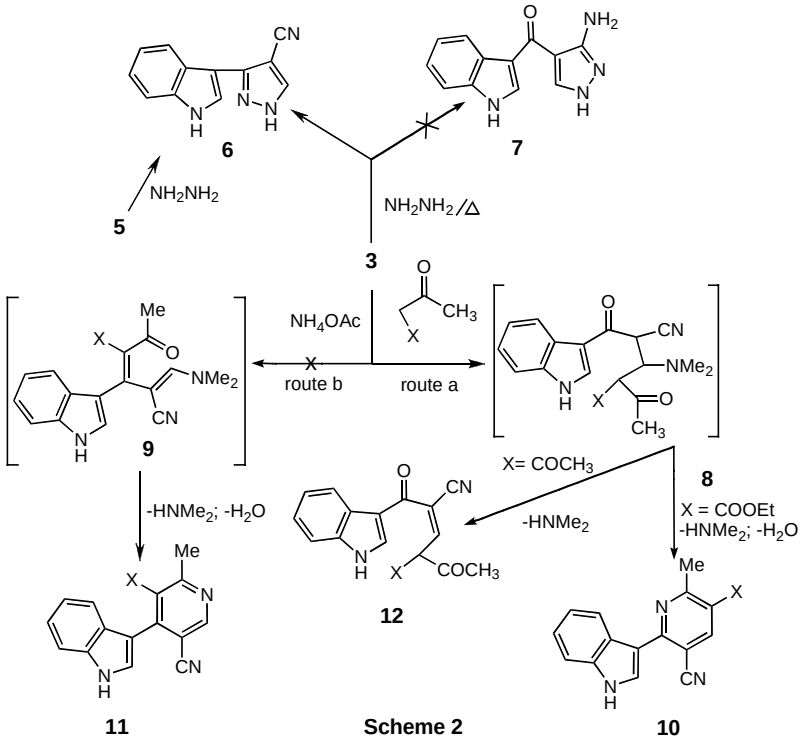


Scheme 1

could be isolated, which is a contradiction to a recent report [14]. The IR spectrum of **6** showed two NH stretching bands at 3290, 3226 cm^{-1}, in addition to a strong band at 2229 cm^{-1} attributed to the CN group. The ^{1}HNMR spectrum of compound **6** revealed the presence of a singlet signal at δ 7.98 corresponding to pyrazole H-5. Compound **6** can also been obtained *via* reaction of **5** with hydrazine hydrate in refluxing ethanol.

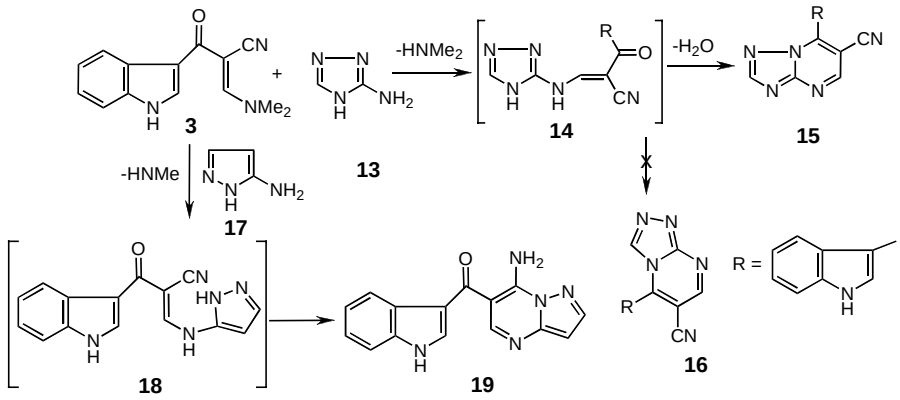
Next, we studied the reaction of compound **3** with active methylene compounds to explore the possible utility of **3** as precursor to pyridines. Thus, reaction of compound **3** with ethyl acetoacetate in refluxing acetic acid in presence of ammonium acetate yielded products that may be formulated as structure **10** or its isomeric structure **11**. Two pathways can be envisioned for formation of the final product. Thus, initial addition of active methylene moiety to activated double bond may afford adduct **8** that in presence of ammonium ion condensed with acetylcarbonyl group yielding an enamine that cyclized into final product **10** (route a). Alternatively, initial condensation with indolylcarbonyl group may yield **9** that cyclized into isomeric pyridine **11** *via* a sequence similar to that discussed [14] (route b). This alternate sequence seems however to be least likely based on established mechanism for reaction of active methylene compounds with enamines [15]. Moreover, HMBC NMR enabled for the discrimination between both structures and led us to conclude that the reaction in fact has afforded compound **10** as proton at C-4 of pyridine moiety showed a cross peak at δ 120 ppm for C-4. If I had structure **11** for the reaction product, the corresponding proton should have a cross peak with the carbon resonating at ~ 160 ppm. In contrast, **3** reacted with acetyl acetone to yield **12** that could not be cyclized into pyridine derivative (Scheme 2).

Compound **3** also reacted with 3(1*H*)-aminotriazole **13** to yield a product that may be formulated as **15** or **16** through formation of isomeric acyclic intermediate **14**. All attempts to isolate the intermediate **14** failed. The IR spectrum for the isolated product revealed absence of NH absorption bands corresponding to acyclic structure.



Scheme 2

Furthermore structure **15** is preferred over possible **16** based on ^{13}C NMR data that revealed triazole C-2 at δ 149.06 ppm whereas the corresponding carbon in structure **16** (C-3) is relatively shielded and would appear at higher field. In contrast to the behavior of amino-triazole **13**, aminopyrazole **17** reacted with **3** to yield a bicyclic product, namely (7-aminopyrazolo[1,5-*a*]pyrim-idin-6-yl)-(1*H*-indol-3-yl)-methanone **19**(Scheme 3).

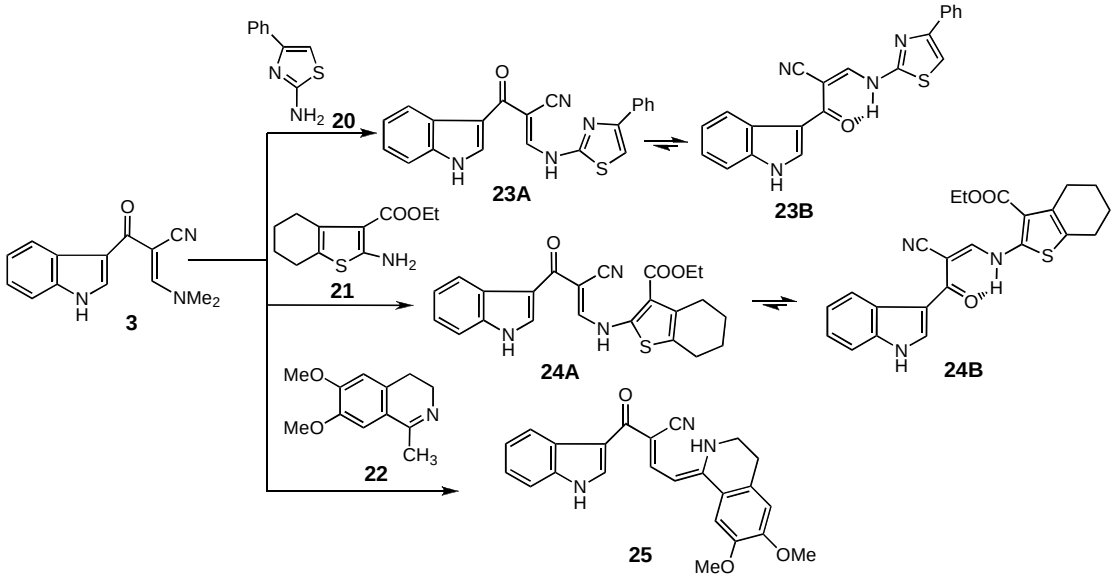


Scheme 3

On the other hand, compound **3** reacted with **20** and **21** to yield the enamines **23B** and **24B** respectively. Establishment of their structures was based on their elemental analyses and spectral data (see experimental). Although **23B**, **24B** may also exist as **23A** or **24A**, the hydrogen bonded form **23B** and **24B** seems more stable (Scheme 4). Finally 1-methyl-6,7-dimethoxyisoquinoline **22** reacted also with **3** to yield **25**. Establishing of structure **25** was based on its ^{1}H NMR data which revealed two doublets at δ 7.40 and 8.07 corresponding to olefinic protons. Although olefinic protons in **25** has J = 12 Hz pointing out to the cisoid form depicted in the text. I would like to indicate that free rotation around the single bond would allow for a *trans* form that should in theory experience less steric interaction. Also, the IR and mass spectra, are consistent with the assigned structure **25** (see experimental).

EXPERIMENTAL

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H, ^{13}C NMR and HMBC spectra were recorded in deuterated dimethylsulfoxide [D_6]-DMSO or deutrated chloroform ($CDCl_3$) at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass



Scheme 4

spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Compound **2** was previously described [6].

3-Dimethylamino-2-(1*H*-indole-3-carbonyl)-acrylonitrile (3). A mixture of compound **2** [6] (1.8 g, 10 mmoles) and dimethylformamide dimethylacetal (16 mmoles) was refluxed in dioxan for 10 min. The reaction mixture was then cooled and the solid formed was collected by filtration and crystallized from ethanol, yield: (75%), mp 186-188°C; ir: CO 1700.9, CN 2195.5, NH 3302.5 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.27 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 3.87 (s, 1H, =CH), 7.17-8.28 (m, 5H, Ar-protons), 8.41 ppm (s, 1H, NH); ms: m/z 239 (M^+), 178, 222, 144, 116, 89. *Anal.* Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.23; H, 5.62; N, 17.47.

3-(4-Chlorophenylamino)-2-(1*H*-indole-3-carbonyl)-acrylonitrile (5). A mixture of enamine **3** (1.0 g, 4 mmoles) and 4-chloroaniline (0.51 g, 4 mmoles) was refluxed in acetic acid (10 ml) for 4 hrs. The solid product formed after cooling was collected by filtration and crystallized from ethanol, yield (60%), mp 234-236 °C; ir: CO 1778, CN 2207.2, (broad NH) 3245.6 cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.1- 8.7 (m, 9H, Ar protons), 8.86 (s, 1H, Indole proton), 12.90 (s, 1H, NH), 12.95 ppm (s, 1H, NH); ms: m/z 323 (M^++2), 321(M^+), 303, 144, 116, 89. *Anal.* Calcd. for $C_{18}H_{12}N_3ClO$: C, 67.19; H, 3.76; N, 13.06; Cl, 11.02. Found: C, 67.31; H, 3.63; N, 13.18; Cl, 10.93.

3-(1*H*-Indol-3-yl)-1*H*-pyrazole-4-carbonitrile (6). A mixture of **3** (1.0 g, 4 mmoles) and hydrazine hydrate (5 ml) in ethanol was refluxed for 3 hrs, then poured on cold water. The solid product was collected by filtration and crystallized from ethanol, yield (72%); mp 218-219 °C; ir: CN 2228.5, 2NH 3225.8, 3290.4 cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.2-8.1 (m, 5H, Ar-protons), 7.98(s, 1H, pyrazole H-5), 8.5 ppm (s, 2H, 2NH); ms: m/z 208 (M^+), 178, 153, 126, 62. *Anal.* Calcd. for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.31; H, 3.84; N, 26.14.

General procedure for the reaction of ethyl acetoacetate or acetyl acetone with enamine (3). A mixture of enamine 3 (1.0 g, 4 mmoles) in acetic acid (10 ml) and the appropriate active methylene compound (4 mmoles) in the presence of ammonium acetate (6 mmoles) was refluxed for 6 hrs. The mixture was cooled then the solid product was collected by filtration and crystallized from acetic acid to give **10** and **12**.

5-Cyano-6-(1*H*-indol-3-yl)-2-methyl-nicotinic acid ethyl ester (10). Yield (67%), mp 238-40°C; ir: CO 1793.6, CN 2254.2, NH 3222.8 cm^{-1}; ^1H nmr($CDCl_3$): δ 1.47 (t, 3H, CH_3, J= 7.2 *Hz*), 2.08 (s, 3H, CH_3), 4.41(q, 2H, CH_2, J= 7.2 *Hz*), 7.2-8.5(m, 6H, Ar-protons), 8.76 ppm (s,1H, NH); ms:m/z 305 (M^+), 184, 144, 89. *Anal.* Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.89; H, 4.72; N, 13.52.

4-Acetyl-2-(1*H*-indole-3-carbonyl)-5-oxohex-2-enenitrile (12). Yield (62%), mp 243-245°C; ir: CO 1633.4, 1692.1, 1787.6., CN 2193.2, NH 3220.6 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.40 (s, 1H, CH), 3.27 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 3.88 (s, 1H, =CH), 7.25-8.46 (m, 4H, Ar-protons), 8.54 (s, 1H, Indole proton), 8.87 ppm (s, 1H, NH); ms: m/z 294 (M^+), 238, 221, 144, 115, 88, 62 . *Anal.* Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.50; H, 4.68; N, 9.37.

General procedure for the reaction of 13, 17, 20, 21 with enamine (3). To a solution of enamine **3** in acetic acid (10 ml) was added the appropriate heterocyclic aromatic amines **13**, **17, 20**, **21** then the mixture was refluxed for 4 hrs. After cooling, the solid product was collected by filtration and crystallized from acetic acid.

5-(1*H*-Indol-3-yl)[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (15). Yield (70%), mp 229-231°C; ir CN 2253, NH 3223 cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.25 – 7.99 (m, 7H, Ar-protons), 8.39 ppm (s, 1H, NH) ^{13}C-NMR: 102.30, 111.52, 112.36, 116.52, 121.02. 121.73, 122.43, 125.61, 131.03, 135.34, 149.06, 155.47, 157.96, 172.05; ms: m/z 259 (M^+), 237, 183, 143, 115, 89, 58. *Anal.* Calcd. for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29. Found: C, 64.67; H, 3.21; N, 32.14.

(7-Amino-pyrazolo[1,5-*a*]pyrimidin-6-yl)-(1*H*-indol-3-yl)-methanone (19). Yield (72%). mp 212-214°C; ir CO 1625, NH 3121, NH_2 3304, 3454 cm^{-1}; ^1H nmr (DMSO): δ 6.57 (d, 1H, pyrazole proton, J=12*Hz*), 7.19-7.27 (m, 2H, Ar- protons), 7.52 (d, 1H, pyrazole proton, J=12*Hz*), 8.10-8.17 (m, 2H, Ar-protons), 8.26 (s, 1H, pyrimidine proton), 8.75 (s, 1H, Indole protons), 8.78 (s, 2H, NH_2), 12.08 ppm (s,1H, NH); ms: m/z 277 (M^+), 260, 144, 117, 89. *Anal.* Calcd. for $C_{15}H_{11}N_5O$: C, 64.98; H, 3.97; N, 25.27. Found: C, 64.92; H, 4.10; N, 25.45.

2-(1*H*-Indole-3-carbonyl)-3-(4-phenylthiazol-2-yl-amino)-acrylonitrile (23). Yield (63%), mp 220-222°C; ir CO 1639.8,CN 2210.1, broad NH 3221.3 cm^{-1}; ^1H nmr ($CDCl_3$): δ 4.48 (s, 1H, CH) 7.09- 8.48 (m, 11H, Ar-protons), 8.37(s, 1H, NH), 12.16 ppm (s,1H, NH); ms: m/z 370 (M^+), 252, 195, 162, 117. *Anal.* Calcd. for $C_{21}H_{14}N_4OS$: C, 68.09; H, 3.81; N, 15.12; S, 8.66. Found: C, 68.34; H, 3.65; N, 14.98; S, 8.49.

2-[2-Cyano-3(1*H*-indol-3-yl)-3-oxo-propenylamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid ethyl ester (24). Yield (64%), mp 268-270°C; ir CO 1697, 1794, CN 2196, broad NH 3383 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.50 (t, 3H, CH_3, J= 7.2 Hz), 1.52 (m, 4H, $2CH_2$), 2.67 (m , 2H, CH_2), 2.82 (m , 2H, CH_2) 4.55(q, 2H, J= 7.2 Hz,), 7.26-8.54 (m, 5H, Ar -protons), 8.62 (s, 1H, Indole proton), 13.98 (s, 1H, NH), 14.02 ppm (s, 1H, NH); ^{13} C nmr (DMSO) 14.23, 21.90, 22.35, 24.19, 26.01, 60.63, 84.05, 112.28, 113.82, 114.88, 120.88, 121.98, 123.17, 126.12, 126.48, 132.04, 133.96, 135.98, 148.70, 151.55, 162.72, 183.11; ms: m/z 419 (M^+), 229, 144, 116, 89. *Anal.* Calcd. for $C_{23}H_{21}N_3O_3S$: C, 65.69; H, 5.27; N, 9.99; S, 11.41. Found: C, 65.82; H, 5.41; N, 9.94; S, 11.53.

4-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)-2-(1*H*-indole-3-carbonyl)-but-2-enenitrile (25). To a mixture of enamine **3** (1.0 g, 3.0 mmoles) in acetic acid (10 ml) was added (0.9 g, 3.0 mmoles) of 1-methyl-6,7-dimethoxyisoquinoline **22**. The mixture was refluxed for 7 hrs then cooled. The solid product was collected by filtration and crystallized from dimethyl-formamide, yield (76%), mp 290-292°C; ir CO 1634.6, CN 2215.0, 2NH 3423.0, 3161.5 cm^{-1}; ^1H nmr (DMSO-d_6):δ 3.14 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.93(s, 3H, OCH_3), 4.90 (m, 2H, CH_2), 7.16-8.10 (m, 7H, Ar-protons), 7.40 (d, 1H, CH proton, J=12*Hz*), 8.07 (d, 1H, CH proton, J=12*Hz*), 8.92 (s, 1H, 1NH), 11.89 ppm (s, 1H, 1NH) ; ms: m/z 399 (M^+), 382, 199. *Anal.* Calcd. for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.51; N, 10.65.

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