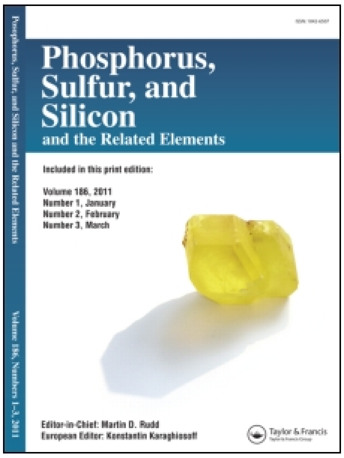

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Synthesis and Antimicrobial Screening of Some Novel AZA-Imidoxy Compounds as Potential Chemotherapeutic Agents

Shilpi Jain[a]; Devendra Prakash Nagda[a]; G. L. Talesara[a]
[a] Department of Chemistry, M. L. Sukhadia University, Udaipur, India

To cite this Article Jain, Shilpi , Nagda, Devendra Prakash and Talesara, G. L.(2006) 'The Synthesis and Antimicrobial Screening of Some Novel AZA-Imidoxy Compounds as Potential Chemotherapeutic Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 7, 1665 — 1673

To link to this Article: DOI: 10.1080/10426500500366970

URL: http://dx.doi.org/10.1080/10426500500366970

Phosphorus, Sulfur, and Silicon, 181:1665–1673, 2006
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500366970

The Synthesis and Antimicrobial Screening of Some Novel Aza-Imidoxy Compounds as Potential Chemotherapeutic Agents

Shilpi Jain
Devendra Prakash Nagda
G. L. Talesara
Department of Chemistry, M. L. Sukhadia University, Udaipur, India

*Some novel azaimidoxy compounds viz. 2-{[(4-chlorophenyl)diazenyl]oxy}-1*H*-isoindole-1,3-(2*H*)-dione (**Va**), and 1-{[1-naphthyldiazenyl]oxy}pyrrolidine-2,5-dione (**IVc**), etc. have been synthesized by a simple diazotization reaction followed by a coupling with 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (**III**) / 1-hydroxypyrrolidine-2,5-dione (**II**) of corresponding aromatic primary amine derivatives at a suitable pH. A similar reaction with* a *[1,3]thiazolo[4,5-*b*]pyridin-2-amine (**VIII**) lead us to some interesting results variable with a pH. The structure of all synthesized compounds has been established by IR, ^{1}H NMR, and mass studies. These compounds have been screened for antimicrobial activities in order to evaluate the possibility of the derivatives to be used as potential chemotherapeutic agents.*

Keywords Antimicrobial activities; azaimidoxy; coupling; diazotization; pH; spectral studies

INTRODUCTION

Azoxy derivatives form a very interesting class of compounds because of their significant biological (antibacterial, anticancer, antituberculous, and nematocidal) activities,[1] and their chemistry is consequently now receiving considerable attention. Azoxybacilin,[2] an unusual amino acid with an azoxy moiety, is active against a broad spectrum of fungi, especially against mycelial fungi, such as *Aspergillus*. Similarly,

Received July 14, 2005; accepted August 29, 2005.

The authors are thankful to Head, Department of Chemistry, M. L. Sukahdia University, Udaipur, India, for providing the necessary laboratory facilities and the Microbial Laboratory, Department of Botany, M. L. Sukahdia University, Udaipur, India, for the antimicrobial evaluation; and Director, CDRI, Lucknow, for spectral measurements and elemental analysis. Dr. Nagda is thankful to CSIR, New Delhi, for necessary financial assistance.

Address correspondence to G. L. Talesara, M. L. Sukhadia University, Department of Chemistry, Udaipur, (Raj.) 313001, India. E-mail: gtalesara@yahoo.com

valanimycin, which is a naturally occurring azoxy compound, shows good antibiotic and antibacterial activity. In addition to this, valanimycin also exhibits potent antitumor activity against in vitro cell cultures of mouse leukemia L1210, P388/S, and P388/ADR.[3–9] As part of our studies aimed at the simple and efficient synthesis of heterocyclic compounds possessing phthalimidoxy, imidoxy, or aminooxy moieties, and in continuation of our work,[10–13] it seemed interesting to synthesize some novel azoxy compounds associated with a imidoxy moiety. In this article, we report the synthesis of novel azaimidoxy compounds of aromatic amines, and sulfur-containing five-membered fused heterocyclic system, and the confirmation of structures of resulting products by spectroscopic data. The newly synthesized azamidoxy compounds appear to be a promising substrate for biological activity evaluation.

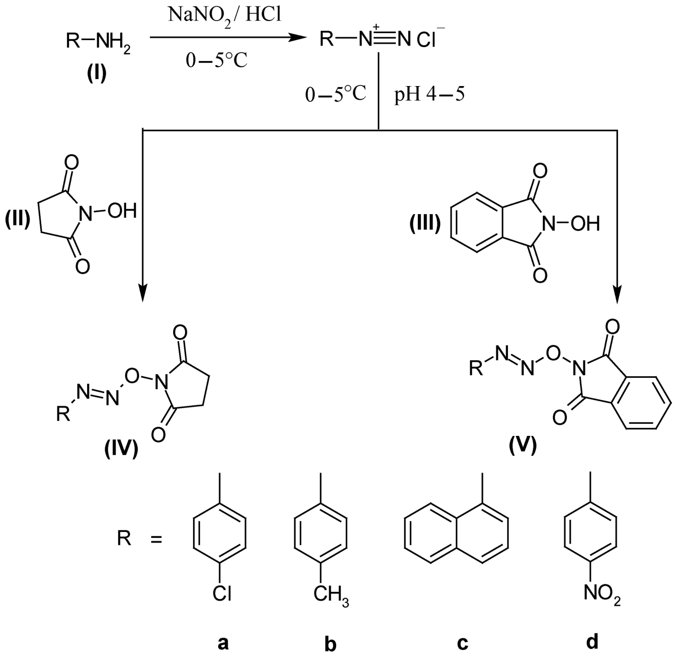
RESULTS AND DISCUSSION

All the synthesized compounds are well supported by their spectral data.

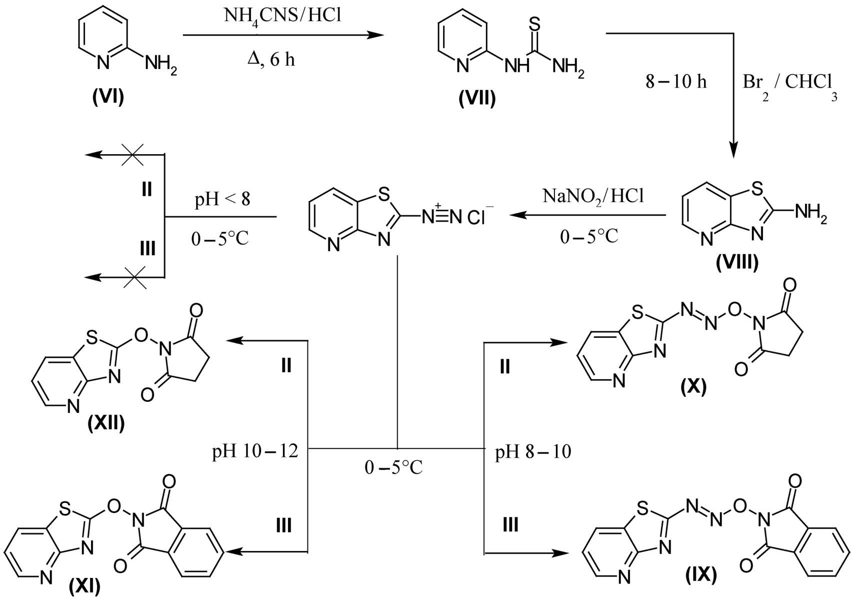
In the present investigation, the diazotization of primary aromatic amines (**I**) was carried out with $NaNO_2$ and HCl at 0–5°C, then a diazotized product was coupled with imidoxy [2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (**III**)/1-hydroxypyrrolidine-2,5-dione (**II**)] compounds between 4–5 pH. The coupled compound was characterized by the absence of a NH_2 peak at 3450–3560 cm^{-1} and a OH peak at 2700–3300 cm^{-1} in IR spectra, which was present in a precursor primary aromatic amine and imidoxy compound, respectively. The product was also confirmed by the absence of a NH_2 peak at δ 4–5 in ^{1}H NMR spectra (Scheme 1).

In order to synthesize sulfur-containing five-membered fused aromatic heterocyclic azaimidoxy compounds, the diazotization and coupling reaction of [1,3]thiazolo[4,5-*b*]pyridine-2-amine (**VIII**) has been carried out (Scheme 2). It was prepared by a cyclization reaction of 1-pyridin-2-ylthiourea (**VII**) in the presence of a Br_2 and $CHCl_3$ and was confirmed by the presence of a C=N peak at 1646 cm^{-1} in its IR spectrum. [1,3]thiazolo[4,5-*b*]pyridin-2-amine (**VIII**) was also diazotized by its reaction with $NaNO_2$ and HCl at 0–5°C, but unlike primary aromatic amines, its coupling reaction did not occur in an acidic pH. During its diazotization and coupling reaction with imidoxy compounds, many interesting and important product variations have been obtained (Table 1) when the pH of a reaction was modified. Various results at different pH are discussed:

1. A coupled product was never obtained in an acidic pH.
2. A coupled azaimidoxy product was obtained when the pH was maintained between 8–10.

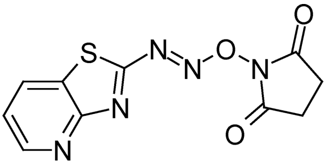
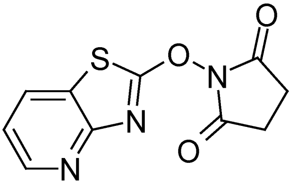


SCHEME 1



SCHEME 2

TABLE I Spectral Characterization

Coupled product obtained at pH 8–10	Product obtained at pH 10–12
	
1. Due to the chromophoric effect of N=N group, UV obtain at higher wavelength, i.e., 435 nm. 2. An IR peak of N=N group was obtain at 1566 cm^{-1}. 3. A diazonium fragment peak at 163 was obtained in mass spectra.	1. A UV band was obtained at lower wavelength, i.e., 340 nm. 2. An IR peak of N=N was not obtained. 3. A diazonium fragment peak was absent.

3. Above pH 8–10, a normal coupled aza compound was obtained with the evolution of N_2.
4. In a highly basic medium, the thiazole ring breaks with the evolution of N_2, and colloidal sulfur precipitates out.

Lastly, the presence of a C=O peak at 1700–1711 cm^{-1} and the absence of an OH peak at 2700–3300 cm^{-1} also confirmed the formation of the final compounds. 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione has been prepared by the reported method,[14] while 1-hydroxypyrrolidine-2,5-dione has been purchased by commercial resources.

ANTIMICROBIAL SCREENING

All synthesized azaimidoxy compounds were screened for their antibacterial and antifungal activities using amicacin and flucanazole, respectively, as reference compounds. The test organisms used for antibacterial studies were *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus. Aspergillus fumigatus* and *Candida albicans* were used for antifungal studies. The cup or well method developed by Collee and colleagues[15] has been followed. The results have been tabulated in the form of inhibition zones and activity index (Table II). Although all the compounds show less

TABLE II The Results of Antimicrobial Studies of Azaimidoxy Compounds. Zone of Growth Inhbition (mm) (Activity Index)#

Compound no.	Antibacterial activity (300 μg/mL)					Antifungal activity			
						Org. I		Org. II	
	Org. I	Org.II	Org.III	Org. IV	Org. V	50 ppm	100 ppm	50 ppm	100 ppm
IVa	13(0.61)	20(1.00)	19(0.82)	13(0.61)	8(0.34)	18(1.28)	26(1.18)	16(1.33)	20(1.25)
IVb	12(0.57)	12(0.60)	14(0.60)	15(0.71)	13(0.56)	14(1.00)	19(0.86)	12(1.00)	17(1.06)
IVc	15(0.71)	5(0.25)	15(0.65)	4(0.19)	4(0.17)	13(0.92)	23(1.04)	12(1.00)	16(1.00)
IVd	10(0.47)	15(0.75)	8(0.34)	16(0.76)	15(0.65)	16(1.14)	21(0.95)	10(0.83)	12(0.75)
Va	12(0.57)	15(0.75)	9(0.39)	18(0.85)	7(0.30)	16(1.14)	23(1.04)	12(1.00)	14(0.87)
Vb	13(0.61)	18(0.90)	17(0.73)	17(0.80)	6(0.26)	18(1.28)	20(0.90)	11(0.91)	15(0.93)
Vc	12(0.57)	9(0.45)	15(0.65)	6(0.28)	14(0.60)	17(1.21)	23(1.04)	10(0.83)	14(0.87)
Vd	14(0.66)	13(0.65)	14(0.60)	9(0.42)	15(0.65)	15(1.07)	19(0.86)	12(1.00)	17(1.06)
IX	9(0.42)	6(0.30)	8(0.34)	8(0.38)	18(0.78)	18(1.28)	23(1.04)	14(1.16)	16(1.00)
X	13(0.61)	12(0.60)	7(0.30)	8(0.38)	16(0.69)	17(1.21)	22(1.00)	16(1.33)	20(1.25)
Standard	21	20	23	21	23	14	22	12	16

#(Activity index)-Inhibition zone of the sample/Inhibition zone of the standard.

For antibacterial activity, Org. I = *Escherichia coli*, Org. II = *Staphylococcus aureus*, Org. III = *Proteus vulgaris*, Org. IV = *Klebsiella pneumonia*, and Org. V = *Pseudomonas aeruginosa*. Standard used = Amicacin.

For antifungal activity, Org. I = *Aspergillus fumigatus* and Org. II = *Candida albicans*. Standard used = Fluconazole.

to moderate activity against bacteria but possess very strong activity against fungi, which reveals that azaimidoxy compounds are better antifungal agents as compared to antibacterial.

EXPERIMENTAL

Melting points of all synthesized compounds were determined in an open capillary tube and are uncorrected. IR spectra (KBr) and ^{1}H NMR spectra ($CDCl_3$) were recorded on a Perkin-Elmer 1800 spectrophotometer and DRX-300 (300 MHz) spectrophotometer using TMS as an internal standard, respectively, and mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer. The purity of compounds was checked by elemental analysis and also by TLC using silica gel "G" as an adsorbent, and visualization was accomplished by iodine.

The Synthesis of 2-{[(4-Chlorophenyl)diazenyl]oxy}-1*H*-isoindole-1,3-(2*H*)-dione (Va)

4-chloroaniline (0.01 mole) was dissolved in 5N HCl and cooled. An ice-cold solution of $NaNO_2$ (0.01 mole) in water was added gradually, maintaining a temperature between 0–5°C. A cooled solution of 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione in diluted NaOH was added to a diazotized reaction mixture between 0–5°C and a pH between 4–5. The reaction mixture was stirred on a water bath for some time, and a resulting solid was filtered, washed with ethanol, and recrystallised from benzene. Yield (80%), m.p. 214°C (found: N, 13.80 $C_{14}H_8N_3O_3Cl$ requires:13.93; ν_{max} : 3104 (Ar—H), 1736 (CO—N—CO), 1133 (N—O), 1539 (N=N), 710 (C—Cl) cm^{-1}; δ(ppm): 7.2–7.4 (8H, m, ArH); m/z (%): 301 (27.3) [$M^{+\cdot}$], 162 (12.2), 155 (100), 146 (25.5), 139 (45.1), 111 (59.0).

Other compounds (**Vb–Vd**) were also synthesized in a similar way with a slight variation in the concentration of HCl required to dissolve the substituted aniline.

2-{[(4-Methylphenyl)diazenyl]oxy}-1*H*-isoindole-1,3-(2*H*)-dione (Vb)

Yield (75%), m.p. 162°C (found: N, 14.80 $C_{15}H_{11}N_3O_3$ requires: 14.94%);ν_{max} : 3090 (Ar—H), 2973 (CH_3), 1730 (CO—N—CO), 1120 (N—O), 1520 (N=N) cm^{-1}; δ: 7.0–7.3 (8H, m, ArH), 2.4 (3H, s, CH_3); m/z (%): 281 (22.7) [$M^{+\cdot}$], 162 (11.9), 146 (20.8), 135 (100), 119 (32.5), 91 (39.9).

2-{[1-Naphthyldiazenyl]oxy}-1*H*-isoindole-1,3-(2*H*)-dione (Vc)

Yield (62%), m.p. 181°C (found: N, 13.15 $C_{18}H_{11}N_3O_3$ requires:13.24%); ν_{max}: 3088 (Ar—H), 1725 (CO—N—CO), 1123 (N—O), 1524 (N=N) cm^{-1}; δ: 7.0–7.2 (8H, m, ArH); m/z (%): 317 (30.2) [$M^{+\cdot}$], 171 (100), 162 (13.4), 155 (32.2), 146 (22.7), 127 (52.3).

2-{[(4-Nitrophenyl)diazenyl]oxy}-1*H*-isoindole-1,3-(2*H*)-dione (Vd)

Yield (64%), m.p. 155°C (found: N, 17.88 $C_{14}H_8N_4O_5$ requires: 17.92%);ν_{max} : 3106 (Ar—H), 1740 (CO—N—CO), 1540 and 1350 (NO_2), 1140 (N—O), 1542 (N=N) cm^{-1}; δ (8.1 (2H, d, Ar—H near NO_2), 7.2 (6H, m, ArH); m/z (%): 312 (35.9) [$M^{+\cdot}$], 166 (100), 162 (16.6), 150 (41.6), 146 (20.9), 122 (60.1).

Compounds (**IVa–IVd**) were synthesized similarly like (**Va**), but 1-hydroxypyrrolidine-2,5-dione(**II**) was used instead of 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione(**III**).

1-{[(4-Chlorophenyl)diazenyl]oxy}pyrrolidine-2,5-dione (IVa)

Yield (74%), m.p. 194°C (found: N, 14.82 $C_{10}H_8N_3O_3Cl$ requires: 14.92%);ν_{max} : 3020 (Ar—H), 2890 (CH_2), 1705 (CO—N—CO), 1072

(N—O), 1560 (N=N), 720 (C—Cl) cm^{-1}; δ: 7.2–7.4 (4H, m, ArH), 2.2 (4H, s, CH_2); m/z (%): 253 (32.9) [$M^{+\cdot}$], 155 (100), 139 (41.9), 114 (15.7), 111 (64.2), 98 (20.2).

1-{[(4-Methylphenyl)diazenyl]oxy}pyrrolidine-2,5-dione (IVb)

Yield (70%), m.p. 178°C (found: N, 17.85 $C_{11}H_{11}N_3O_3$ requires:18.02%); ν_{max} : 3010 (Ar—H), 2970 (CH_3), 2880 (CH_2), 1689 (CO—N—CO), 1020 (N—O), 1540 (N=N) cm^{-1}; δ: 7.1 (4H, m, ArH), 2.6 (3H, s, CH_3), 2.2 (4H, s, CH_2); m/z (%): 233 (27.6) [$M^{+\cdot}$], 135 (100), 119 (41.4), 114 (20.2), 98 (26.2), 91 (44.9).

1-{[1-Naphthyldiazenyl]oxy}pyrrolidine-2,5-dione (IVc)

Yield (62%), m.p. 220°C (found: N, 14.02 $C_{14}H_{11}N_3O_3$ requires. 14.12%) ν_{max}: 3015 (Ar—H), 2885 (CH_2), 1700 (CO—N—CO), 1040 (N—O), 1550 (N=N) cm^{-1}; δ: 7.1–7.2 (7H, m, ArH), 2.1 (4H, s, CH_2); m/z (%): 269 (34.3) [$M^{+\cdot}$], 171 (100), 155 (21.5), 127 (39.7), 114 (12.8), 98 (20.9).

1-{[(4-Nitrophenyl)diazenyl]oxy}pyrrolidine-2,5-dione (IVd)

Yield (60%), m.p. 174°C (found: N, 20.04 $C_{10}H_8N_4O_5$ requires: 21.21%); ν_{max} : 3040 (Ar—H), 2890 (CH_2), 1720 (CO—N—CO), 1520 and 1310 (NO_2), 1060 (N—O), 1560 (N=N) cm^{-1}; δ (ppm): 8.0 (4H, m, ArH), 2.3 (4H, s, CH_2); m/z (%): 264 (22.3) [$M^{+\cdot}$], 166 (100), 150 (35.6), 122 (57.9), 114 (11.4), 98 (21.9).

The Synthesis of 1-Pyridin-2-ylthiourea (VII)

2-Amino pyridine (0.01 mole) was dissolved in 1N HCl, and ammonium thiocaynate was added with stirring. The reaction mixture was refluxed for 6 h, and an excess of solvent was removed by reduced pressure. A yellow brown solid obtained was recrystallised from alcohol. Yield (64%), m.p. 182°C (found: N, 27.12 $C_6H_7N_3S$ requires: 27.43%); ν_{max}: 3380 (NH_2), 3312 (NH), 3010 (Ar—H), 1664 (C=N), 1580, 1500 (C=C), 1262 (C—N), 1212 (C=S) cm^{-1}; δ (ppm): 7.3 (4H, m, ArH), 7.8 (1H, s, NH), 7.2 (2H, s, NH_2); m/z (%): 153 (42.3) [$M^{+\cdot}$], 136 (100), 78 (35.9).

The Synthesis of [1,3]thiazolo[4,5-*b*]pyridin-2-amine (VIII)

1-Pyridine-2-ylthiourea (0.01 mole) in $CHCl_3$ was cyclized in the presence of Br_2 in $CHCl_3$ via refluxing on a water bath for 8–10 h. The solvent was removed under reduced pressure, thus, a yellow solid obtained was recrystallized from a chloroform methanol mixture. Yield (57%), m.p. 228°C (found: N, 27.62 $C_5H_5N_3S$ requires: 27.79%); ν_{max}:

3410 (NH_2), 3016 (Ar—H), 1646 (C=N), 1586 (C=C), 1268 (C—N), 850 (C—S—C) cm^{-1}; δ: 7.7 (2H, s, NH_2), 7.2 (3H, m, ArH); m/z (%): 151 (31.4) [$M^{+\cdot}$], 135 (100), 103 (65.8), 77 (42.7).

The Synthesis of 2-{[[1,3]thiazolo[4,5-*b*]pyridin-2-yldiazenyl]oxy}-1*H*-isoindole-1,3(2*H*)-dione (IX)

[1,3]thiazolo[5,4-*b*]pyridine-2-amine (0.01 mole) was dissolved in dil HCl. An ice-cold solution of $NaNO_2$ (0.01 mole) in water was added gradually, maintaining temperature between 0–5°C. A cooled solution of 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione in diluted NaOH was added to a diazotized reaction mixture between 0–5°C and pH between 8–10. The reaction mixture was kept for some time, and a resulting solid was filtered. An orange solid obtained was recrystallized from $CHCl_3$. Yield (52%), m.p. > 300°C (found: N, 21.42 $C_{14}H_7N_5O_3S$ requires: 21.53%); ν_{max}: 3069 (Ar—H), 1711 (C=O), 1646 (C=N), 1566 (N=N), 1088 (N—O) cm^{-1}; δ: 7.2–7.4 (7H, m, ArH); m/z (%): 325 (15.9) [$M^{+\cdot}$], 179 (100), 163 (35.6), 146 (22.3), 135 (52.4), 77 (15.7).

1-{[[1,3]Thiazolo[4,5-*b*]pyridin-2-yldiazenyl]oxy}-Pyrrolidine-2,5-dione (X)

It is synthesized in similar manner in which compound (**IX**) was synthesized but 1-hydroxypyrrolidine-2,5-dione(**II**) was used for coupling instead of 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione(**III**). Yield (55%), m.p. > 300°C (found: N, 25.90 $C_{10}H_7N_5O_3S$ requires: 25.23%); ν_{max}: 3062 (Ar—H), 2880 (CH_2), 1700 (C=O), 1675 (C=N), 1565 (N=N), 1020 (N—O) cm^{-1}; δ: 7.3 (3H, m, ArH), 2.3 (4H, s, CH_2); m/z (%): 277 (28.1) [$M^{+\cdot}$], 179 (100), 163 (31.8), 135 (47.3), 98 (25.7), 77 (20.7).

2-([1,3]Thiazolo[4,5-*b*]pyridin-2-yloxy)-1*H*-isoindole-1,3(2*H*)-dione (XI)

Prepared similarly as compound (**IX**) with a slight change in pH, i.e., between pH 10–12. Yield (42%), m.p. 273°C (found: N, 13.80 $C_{14}H_7N_3O_3S$ requires: 14.13%); ν_{max} : 3060 (Ar—H), 1710 (C=O), 1640 (C=N), 1082 (N—O) cm^{-1}; δ: 7.2 (7H, m, ArH); m/z (%): 297 (32.9) [$M^{+\cdot}$], 151 (100), 135 (58.6), 146 (32.9), 77 (18.9).

1-([1,3]Thiazolo[4,5-*b*]pyridin-2-yloxy)pyrrolidine-2,5-dione (XII)

Prepared similarly as compound (**X**) with a slight change in pH, i.e. between pH 10–12. Yield (51%), m.p. 254°C (found: N, 16.65 $C_{10}H_7N_3O_3S$ requires: 16.86%); ν_{max} : 3052 (Ar—H), 2884 (CH_2), 1710 (C=O), 1645

(C=N), 1073 (N—O) cm^{-1}; δ: 7.2 (3H, m, ArH), 2.2 (4H, s, CH_2); m/z (%): 249 (25.8) [$M^{+\cdot}$], 151 (100), 135 (40.9), 98 (28.7), 77 (19.6).

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