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Original Article

Facile synthesis of active antitubercular, cytotoxic and antibacterial agents: a Michael addition approach

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Abstract

Spiro derivatives of oxindole and isoxazole-5-one were synthesized by using Michael addition reaction, highlighting the regioselective approach towards the synthesis of Michael diadduct followed by condensation of Michael diadduct. The spiro compound **4** showed antitubercular activity against *Mycobacterium tuberculosis* H37Rv whereas spiro compound **9** possesses pronounced anticancer and antibacterial profile.

Keywords: Antitubercular; Cytotoxic; Antibacterial; Oxindole; Isoxazolone; Michael addition; Dieckmann condensation; Thorpe–Ziegler cyclization

1. Introduction

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis*, still remains the leading cause of worldwide death among infectious diseases [1]. Indole derivatives show interesting biological properties [2,3] and some of them are known for their antitubercular activity [4–6]. Hence, for the purpose of obtaining new and more potent antitubercular compounds that can improve the current chemotherapeutic antituberculosis treatment, we have synthesized and evaluated some spiro oxindole derivatives. Similarly, 3-phenylisoxazole-5-one derivatives are also known for their biological activity [7,8]. The recognition of the pharmacological activity of some isoxazole derivatives such as Gantricin, a sulfa drug from amino isoxazole [9], cycloserine and oxamycin, simple derivatives of 3-isoxazolidone as antibiotic [10–12] has aroused a new interest in this field.

We have contributed for the synthesis of potential antiparasitic [13], antimicrobial [14,15], antiinsecticidal [16] and anticancer [17] agents. Recently, we explored the scope of Michael addition on various heterocyclic ring systems containing active methylene/methine groups for the synthesis of spirocompounds [18,19]. Spiro nuclei have drawn considerable attention of the chemist because of their antiseptic [20,21], analgesic [22] and broad-spectrum antimicrobial activities [23]. Hence, introduction of spiro nucleus to such vital molecules will enhance their biological activity. Although it is widely recognized as one of the most important C–C bond forming reaction in organic chemistry and an important method of alkylation of active methylene compounds, there are very few reports on the Michael addition of 1-methyl/ethyl-1,3-dihydro-indol-2-one **1** [24] and 3-phenyl-4*H*-isoxazol-5-one **7** [25,26]. We now report the synthesis of spiro derivatives containing 1-methyl/ethyl-1,3-dihydro-indol-2-one **1** and 3-phenyl-4*H*-isoxazol-5-one **7** nuclei.

2. Chemistry

The aim underlying the synthesis of a spiro compound starting from **1** was to further enhance its pharmacological activity. Surprisingly, bases like pyridine, piperidine, triethylamine, metal hydroxides/alkoxides and also fluoride ions in combination with phase transfer catalyst (PTC) failed to catalyze the addition of **1** with methyl acrylate and the starting synthon was recovered in quantitative yields.

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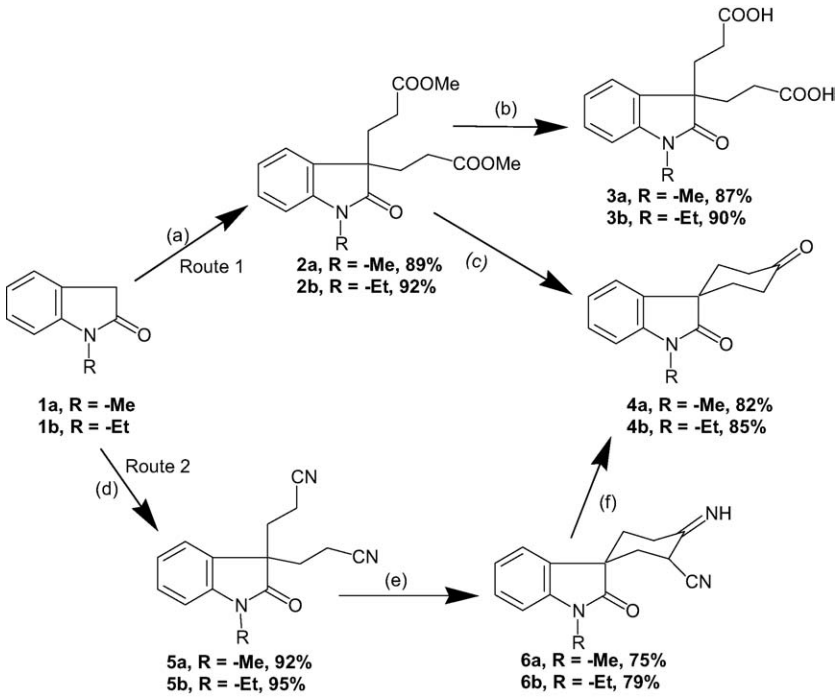


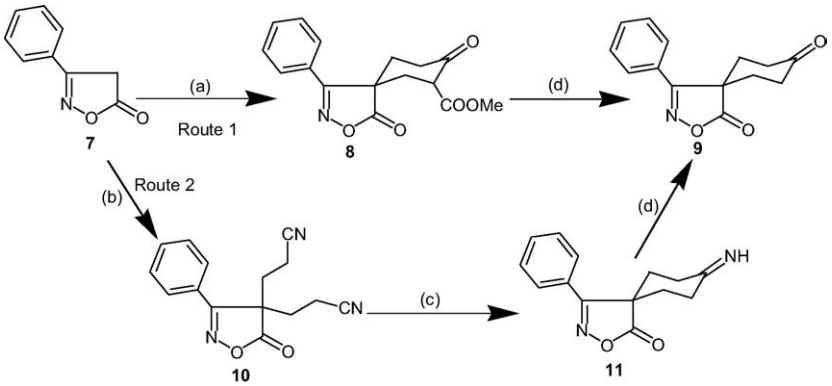
Scheme 1. Synthesis of spirocyclohexanone derivative of oxindole.
Reagents and conditions: (a) $NaNH_2$, methyl acrylate, DMF, 10–15 °C, 30 min (b) Conc. HCl, reflux, 3 h (c) Na, dry benzene, reflux, 4 h (d) $NaNH_2$, acrylonitrile, DMF, 10–15 °C, 2 h (e) NaOEt, ethanol, reflux, 4 h (f) aq. HCl, reflux, 4 h.

When **1** was reacted with methyl acrylate in presence of sodium amide in dry dimethyl formamide (DMF) at 10–15 °C, Michael diadduct **2** was obtained in quantitative yield. This compound was oily in nature and found to be unstable at room temperature. Hence, it was converted into a stable dicarboxylic acid **3** by acid hydrolysis. Here, Michael addition can take place in two ways, C-Michael addition and O-Michael addition. Presence of multiplet at δ 2.06–2.28 in ^{1}H NMR for $-CH_2$ protons, and presence of quaternary C at δ 94.8 and carbonyl group at δ 163.1 of oxindole moiety in ^{13}C NMR of **3b** confirmed the formation of C-Michael adduct, that to diadduct and not O-Michael adduct. Hence, regioselectivity of the reaction is proved on the basis of spectral analysis of the product **3**. Dieckmann condensation of **3** in presence of pulverized sodium in dry benzene gave excellent yields of spirocyclohexanone derivatives of oxindole **4** in 80–85% yield (Scheme 1, route 1).

Scope of the work was also extended to acrylonitrile as a Michael acceptor with **1**. Michael diadduct **5** was synthesized by reacting acrylonitrile with **1** in presence of sodamide in dry DMF at 10–15 °C, which was stable at room temperature. Thorpe–Ziegler cyclization of **5** in presence of sodium ethoxide in ethanol afforded desired spirocycloinamine derivative of oxindole **6**. It was then easily hydrolyzed to **4** by refluxing it in aqueous HCl in 75–80% yield (Scheme 1, route 2). Formation of **4** was confirmed by CO-IR and mixed melting point with the compound synthesized by route 1. This is an alternate route for the synthesis of **4**.

We followed this strategy for the synthesis of novel spirocyclohexanone derivative of isoxazolone **9**. When **7** was reacted with methyl acrylate in the presence of bases like pyridine, piperidine, triethylamine, metal hydroxides/alkoxides and also fluoride ions in combination with PTC failed to catalyze the addition, and starting synthon was recovered in quantitative yields. When the reaction was carried out by using base like sodamide in DMF at 10–15 °C, a light pink colored solid was obtained in moderate yield. It showed the presence of an ester linkage. An important feature was that the reaction exhibited striking regioselectivity yielding **8** as the only product. Presence of triplet of methine proton at δ 3.68, multiplets at δ 2.20–2.45 of three methylene protons, singlet of methoxy group of carbmethoxy at δ 3.65 in ^{1}H NMR and peak of cyclohexanone carbon at δ 205.2 in ^{13}C NMR clearly indicated the formation of spiro α-carbmethoxy cyclohexanone derivative of isoxazolone **8** and not Michael diadduct or Michael monoadduct. This was further confirmed on the basis of Mass spectrum displaying M^+ peak at 301. It showed that the reaction went further in situ to give the Dieckmann cyclized product. Compound **8** was then converted to spirocyclohexanone derivative of isoxazolone **9** by its acid hydrolysis in 75% yield (Scheme 2, route 1).

Compound **9** was alternately prepared by reacting acrylonitrile as a Michael acceptor with **7**. Acrylonitrile was reacted with **7** in presence of Tri ethyl amine (TEA) in ethanol, Michael diadduct **10** was successfully isolated in quantitative yield. Thorpe–Ziegler cyclization of **10** in presence of sodium metal in benzene afforded desired spirocycloinamine derivative of isoxazolone **11**. It was then easily hydrolyzed in acidic condition to afford **9** in 72% yield (Scheme 2, route 2), which was confirmed by CO-IR and mixed melting point with the product prepared by route 1.



Scheme 2. Synthesis of spirocyclohexanone derivative of 3-phenyl-isoxazole-5-one. Reagents and conditions: (a) methyl acrylate, $NaNH_2$, DMF, 10–15 °C, 7 h, 77%; (b) acrylonitrile, TEA, EtOH, reflux, 10 h, 88%; (c) Na, benzene, reflux, 8 h, 72%; (d) HBr, AcOH, reflux, 4 h, 70–75%.

We have explored the scope and generality of this synthetic strategy successfully to other heterocyclic systems, which will be communicated in due course.

3. Biological activity

3.1. Antitubercular activity

Compounds **3**, **4** and **6** were screened for their activity against *M. tuberculosis* H37Rv. The medium used was prepared in 10 ml slopes in glass universal bottles. The incubation time was 28 days at 37 °C. The MIC was taken when there were fewer than 20 colonies. The control slope yielded confluent growth. The compound **4** exhibited the best activity and the MIC was observed for the concentration of 0.05 μg ml^{-1}. The compounds **3** and **6** showed the MIC at 0.1 μg ml^{-1}. This is comparable with current TB drugs like Isoniazid (MIC = 0.025–0.2 μg ml^{-1}) and Refampin (MIC = 0.06–0.5 μg ml^{-1}) (Table 1).

Table 1
Antitubercular activity studies of compounds **3**, **4** and **6** against *M. tuberculosis* $H_{37}Rv$

Compounds	MIC (μg ml^{-1})
3a	0.1
3b	0.1
4a	0.05
4b	0.05
6a	0.1
6b	0.1
Isoniazid	0.025–0.2
Refampin	0.06–0.5

3.2. Cytotoxicity and antibacterial activity

Most of the isoxazolone derivatives synthesized were studied for their cytotoxic activity on cancer cells and antibacterial activity using short-term toxicity assay (in vitro) (Trypan blue exclusion method). The cells [Dalton's lymphoma ascites (DLA) and Ehrlisch's ascites carcinoma (EAC)] were maintained in the intraperitoneal cavity of Swiss albino mice. The cells were removed by aspiration and washed three times in phosphate buffered saline (PBS). Cells (1×10^6) were then incubated in 1 ml of PBS with varying concentration of drug dissolved in DMSO at 37 °C for 3 h. The cell viability was determined by Trypan blue exclusion method [27]. Viable cells exclude the dye while nonviable cells take up the dye and appear as blue color. The stained and unstained cells were counted using a hemocytometer and the percentage of cell death was calculated. All the experiments were done in duplicate and mean cytotoxicity was recorded (Table 2). Compound **8** was found to be the most active anticancer agent. Compound **10** also gave considerable anticancer activity.

The antibacterial activity of the compounds **8**–**10** was studied using drug diffusion method. Compound **8** was found to be the most active antibacterial agent. Compound **10** gave

Table 2
Anticancer activity studies of compounds **8** and **10**; short-term toxicity assay (in vitro): trypan blue exclusion method

Compounds	EAC		DLA	
	Concentration (μg ml^{-1})	% Cell death	Concentration (μg ml^{-1})	% Cell death
8	5	10	5	13
8	10	14	10	18
8	20	21	20	27
8	50	33	50	45
8	100	56	100	67
10	5	06	5	06
10	10	10	10	09
10	20	17	20	19
10	50	23	50	37
10	100	36	100	50

Table 3
Antibacterial activity studies of compounds **8**–**10**; drug diffusion method

Compounds	Concentration ($\mu g\ ml^{-1}$)	Diameter of zone of inhibitory (mm)		
		E. coli	*S. typhosa*	*S. aureus*
8	50	9	10	11
8	100	10	11	13
8	150	13	13	14
9	50	9	9	6
9	100	10	10	7
9	150	12	13	8
10	50	12	11	7
10	100	14	12	8
10	150	17	14	10
Silver sulfadiazine		14		
Gentamicin		12		

antibacterial activity. Compound **9** was moderately active against the bacteria used in the experiment. The results are comparable with current drugs like Silver sulfadiazine and Gentamicin. (Table 3)

4. Conclusion

It can be concluded that the spirocyclohexanones containing oxindole moiety have potent antitubercular activity and spirocyclohexanone containing isoxazolone moiety have considerable cytotoxicity on cancer cells and antimicrobial activities.

5. Experimental

$^{1H\ NMR}$ and ^{13}C NMR spectra were recorded on Bruker AMX 500 spectrometer at 300 K, using TMS as an internal standard. Melting points were taken in open capillaries and are uncorrected.

*5.1. Synthesis of 3-[1-ethyl-3-(2-methoxycarbonyl-ethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-propionic acid methyl ester (**2b**)*

To a well-stirred solution of sodamide (0.8 g, 20 mmol) in DMF (25 ml) was added **1b** (1.61 g, 10 mmol) at ambient temperature. The reaction was then cooled to about 10–15 °C. The cooling was followed by the dropwise addition of methyl acrylate (1.72 g, 20 mmol). The reaction mixture was then stirred at ambient temperature till TLC showed complete consumption of 1-ethyl-1,3-dihydro-indol-2-one (30 min). The contents were then poured onto crushed ice containing a little hydrochloric acid. A semisolid separated which attained an oily nature as the temperature rose to room temperature. The oil was extracted with diethyl ether, washed with water and dried over anhydrous sodium sulfate. Excess of solvent was removed to yield oil, in its pure state. The oil was found to decompose as soon as it was isolated and hence was used immediately for further reaction or was converted to a more stable carboxylic acid derivative **3b**. Yield 3.1 g (92%).

*5.2. Synthesis of 3-[3-(2-methoxycarbonyl-ethyl)-1-ethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-propionic acid (**3b**)*

Compound **2b** (3.33 g, 10 mmol) was refluxed in concentrated hydrochloric acid (30 ml) for 3 h The reaction mixture was cooled when solid began to separate as crystalline compound. It was filtered, washed with water, dried and crystallized from aqueous ethanol. It went into aq. sodium bicarbonate and was regenerated by acidifying with hydrochloric acid under cold conditions in pure form. Yield 2.75 g (90%), m.p. 136 °C. IR (KBr) 1705, 1644 cm^{-1}; ^1H NMR (DMSO-d_6): ppm 1.03 (t, 3H, $J = 7$ Hz, $–CH_3$), 2.06-2.28 (m, 8H, 4X $–CH_2$), 3.6 (q, 2H, = 7 Hz, N–CH_2), 7.23–7.49 (m, 4H, aromat.) and 12.32 (s, 2H, 2 X–COOH; D_2O exchangeable), ^{13}C NMR (DMSO-d_6): δ 12.0 ($–CH_3$), 28.2, 28.3 (4 X–CH_2), 47.4 (N–CH_2), 94.8 (quaternary C), 129.0–138.6 (4X aromat. C), 163.1, 172.7 (2X C = O). Anal. ($C_{16}H_{19}NO_5$) C, H, N.

*5.3. Synthesis of 2-aza-3, 4-benz-1, 8-dioxo-2-ethyl-spiro [5.4] decane (**4b**) from (**2b**)*

Compound **2b** (3.33 g, 10 mmol) was added slowly to a mixture of finely pulverized sodium (0.03 g, 11 mmol) in 25 ml dry benzene. The reaction mixture was cooled externally till the exotherm ceased. The contents were refluxed on water bath for 4 h Benzene was removed by distillation, and then the residue treated with methanol to destroy any unreacted sodium. The reaction mixture was then poured onto crushed ice containing hydrochloric acid. A white colored compound separated out which was filtered, washed with water, dried and crystallized from chloroform, Yield 2.1 g (85%), m.p. 167 °C. IR (KBr) 1703, 1644 cm^{-1}. ^1H NMR (DMSO-d_6): ppm 1.03 (t, 3H, $J = 7$ Hz, $–CH_3$), 2.1–2.24 (m, 8H, 4X $–CH_2$), 3.6 (q, 2H, $J = 7$ Hz, N–CH_2), 7.27–7.43 (m, 4H, aromat.), ^{13}C NMR (DMSO-d_6): δ 12.0 ($–CH_3$), 28.5, 29.3 (4X $–CH_2$), 47.6 (N–CH_2), 92.7 (quaternary carbon) 128.5–129.6 (4X aromat. C), 163.7, 172.7 (2X C = O). Anal. ($C_{15}H_{17}NO_2$) C, H, N.

*5.4. Synthesis of 3-[3-(2-cyano-ethyl)-1-ethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-propionitrile (**5b**)*

To a well-stirred solution of sodium amide (0.8 g, 20 mmol) and **1b** (1.61 g, 10 mmol) in DMF (25 ml) was added acrylonitrile (1.06 g, 20 mmol) dropwise maintaining temperature between 10 and 15 °C. The reaction mixture was then stirred at room temperature for 2 h and then poured onto crushed ice containing a little HCl. A brown colored compound separated which slowly became gummy. This when chilled yielded a fine brown colored compound. It was filtered, washed with water, dried and crystallized from

DMF/water as amorphous light brown compound **5b**. Yield 2.5 g (95%). m.p. > 270 °C. IR (KBr) 2247, 1650 cm^{-1}. ^1H NMR (DMSO-d_6) ppm 1.13 (t, 3H, J = 7 Hz, –CH_3), 2.16–2.41 (m, 8H, 4X –CH_2), 3.6 (q, 2H, J = 7 Hz, N–CH_2), 7.02–7.18 (m, 4H, aromat.), ^{13}C NMR (DMSO-d_6) δ 12.8 (–CH_3), 12.5, 30.9 (4X –CH_2), 43.0 (N–CH_2), 95.5 (quaternary C), 117.8 (–CN), 120.5–140.6 (4X aromat. C), 174.0 (C=O). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

*5.5. Synthesis of 2 aza-3, 4-benz-7-cyano-2-ethyl-8-imino-1-oxo-spiro [5.4] decane (**6b**)*

Compound **5b** (2.67 g, 10 mmol) was added to a solution of freshly prepared sodium ethoxide (0.25 g of sodium, 10 mmol) in ethanol (50 ml) at ambient temperature. The reaction mixture was then refluxed for 4 h cooled to room temperature. It was poured onto crushed ice. The solution made to neutral pH to yield dark colored compound **6b**. Yield 2.1 g (79%). m.p. 250–252 °C. IR (KBr) 2245, 1647 cm^{-1}. ^1H NMR (DMSO-d_6): ppm 1.03 (t, 3H, J = 7 Hz, –CH_3), 1.80–2.40 (m, 4H, 2XCH_2), 2.65 (d, 2H, –CH_2), 2.90 (t, 1H, –CH), 3.6 (q, 2H, J = 7 Hz, N–CH_2), 7.30–7.60 (m, 4H, aromat.), 7.96 (s, 1H, =NH), ^{13}C NMR (DMSO-d_6): δ 12.7 (–CH_3), 25.3 (–CH), 29.4, 31.8, 32.2 (3X CH_2), 42.7 (N–CH_2), 93.8 (quaternary C), 117.7 (–CN), 121.0–141.2 (4X aromat. C), 174.3 (C=O). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

*5.6. Synthesis of 2-aza-3, 4-benz-1, 8-dioxo-2-ethyl-spiro [5.4] decane (**4b**) from (**6b**)*

Compound **6b** (2.67 g, 10 mmol) and aq. hydrochloric acid (25 ml, 50%) were refluxed for 4–6 h. The solvent was removed by distillation and the contents poured onto crushed ice to yield the cream colored crystalline compound **4b**. It was filtered, washed with water, dried and crystallized from chloroform, Yield 1.8 g (75%), m.p. 167 °C, Anal. ($C_{16}H_{17}NO_2$) C, H, N.

*5.7. Synthesis of 3-aza-1,8-dioxo-7-methoxycarbonyl-2-oxa-4-phenyl-spiro [4.5] dec-3-ene (**8**)*

Compound **7** (1.61 g, 10 mmol) was dissolved in 15 ml DMF and was cooled to 10 °C. To the cold solution, a catalytic amount of sodium amide was added and stirred for 10 min. Methyl acrylate (1.8 ml, 20 mmol) was added dropwise and stirring was continued for 7 h. The contents were poured on to ice and acidified. The sticky mass thus obtained was triturated with 50 ml petroleum ether to get light pink colored solid. The product was crystallized from aqueous methanol. Yield 2.3 g (77%), m.p. = 135 °C. IR (KBr) 1760, 1720, 1598 cm^{-1}. ^1H NMR ($CDCl_3$): ppm 2.20–2.47 (m, 6H, 3X –CH_2), 3.65 (s, 3H, –CH_3), 3.68 (t, 1H, –CH), 7.56–7.83 (m, 5H, aromat.), ^{13}C NMR ($CDCl_3$): δ 29.1, 31.1, 40.4 (3X –CH_2), 51.9 (CH), 53.9 (OCH_3), 98.2 (quaternary C), 126.4–132.3 (6X aromat. C), 166.1 (–C=N), 171.6, 179.7, 212.0 (3X –C=O). MS: m/z = 301 [M^+]. Anal. $C_{16}H_{15}NO_5$ (C, H, N).

*5.8. Synthesis of 3-aza-2-oxa-4-phenyl-spiro [4.5] dec-3-ene-1, 8-dione (**9**) from (**8**)*

Compound **8** (3.01 g, 10 mmol) was taken in 25 ml glacial acetic acid and 10 ml of hydrobromic acid in acetic acid was added. The reaction mixture was refluxed for 4 h. On workup a blackish brown colored solid was obtained which was crystallized from aqueous methanol. Yield 1.8 g (75%), m.p. = 172 °C. IR (KBr) 1720, 1598 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.09–2.86 (m, 8H, 4X –CH_2), 7.43–8.0 (m, 5H, aromat.), ^{13}C NMR ($CDCl_3$): δ 31.0, 31.5, 32.7, 33.7 (4X –CH_2), 96.2 (quaternary C), 128.5–134.6 (6X aromat. C), 168.8 (–C=N), 182.5, 205.2 (–C=O). MS: m/z = 243 [M^+]. Anal. $C_{14}H_{13}NO_3$ (C, H, N).

*5.9. Synthesis of 3-[4-(2-cyno-ethyl)-5-oxo-3-phenyl-4,5-dihydro-isoxazol-4yl]-propionitrile (**10**)*

Compound **1** (1.61 g, 10 mmol) was dissolved in 40 ml ethanol and triethylamine (3.45 ml, 25 mmol) was added and heated for 10 min. Acrylonitrile (1.02 ml, 20 mmol) was then added and the contents refluxed for 10 h. On working up the reaction, a sticky mass was isolated. On trituration with methanol, a white solid was obtained in pure form. Yield 2.3 g (88%), m.p. = 115 °C. IR (KBr): 2245, 1797 cm^{-1}. ^1H NMR ($CDCl_3$): ppm 2.27 (t, 4H, J = 7.5 Hz, 2X –CH_2), 2.48 (t, 4H, J = 7.5 Hz, 2X –CH_2), 7.57–7.78 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$): δ 13.8, 15.6, 19.0, 25.2 (4X –CH2), 98.9 (quaternary C), 119.0 (–CN), 126.5–131.8 (6X aromat. C), 163.6 (–C=N), 172.6 (–C=O). MS: m/z = 267 [M^+]. Anal. $C_{15}H_{16}N_3O_2$ (C, H, N).

*5.10. Synthesis of 3-aza-8-imino-2-oxa-1-oxo-4-phenyl-spiro [4.5] dec-3-ene (**11**)*

Compound **10** (2.67 g, 10 mmol) was dissolved in 25 ml benzene. Pulverized sodium (0.23 g, 10 mmol) was then added. The reaction mixture was refluxed for 8 h. The solid obtained was filtered, dissolved in water and regenerated with dilute hydrochloric acid. Methanol was added to the filtrate to react with the unreacted sodium metal. Product was recrystallized from aqueous methanol. Yield 1.9 g (72%), m.p. = 90 °C. IR (KBr): 1787, 1555 cm^{-1}.

^1H NMR ($CDCl_3$): ppm 2.15 (s, 8H, –NH), 2.25–2.40 (m, 8H, 4X –CH_2), 7.50–7.80 (m, 5H, aromat.), ^{13}CMR ($CDCl_3$): δ 29.0, 31.1, 52.0, 53.9 (4X –CH_2), 83.9 (quaternary C), 126.4–132.3 (6X aromat. C), 166.1 (–C=N), 171.6 (–C=NH), 179.7 (–C=O). MS: m/z = 242 [M^+]. Anal. $C_{14}H_{14}N_2O_2$ (C, H, N).

*5.11. Synthesis of 4-phenyl-2-oxa-3-aza-spiro [4.5] dec-3-ene-1, 8-dione (**9**) from (**11**)*

Compound **11** (10 mmol, 2.67 g) was taken in 25 ml glacial acetic acid and 10 ml of hydrobromic acid in acetic acid was added. The reaction mixture was refluxed for 4 h. On

workup a blackish brown colored solid was obtained which was crystallized from aqueous methanol. Yield 1.75 g (72%).

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