Bull. Chem. Soc. Ethiop. **2014**, 28(1), 91-100.
Printed in Ethiopia
DOI: http://dx.doi.org/10.4314/bcse.v28i1.11
ISSN 1011-3924

SYNTHESIS AND *IN VITRO* ANTIMICROBIAL EVALUATION OF 5-AMINO-7-ARYL-6-CYANO-4*H*-PYRANO[3,2,*b*]PYRROLE DERIVATIVES CATALYZED BY REUSABLE $ZrOCl_2 \cdot 8H_2O$

A. Mohammed Hussain, S. Sheik Mansoor*, K. Aswin, K. Logaiya and S.P.N. Sudhan

Bioactive Organic Molecule Synthetic Unit, Research Department of Chemistry,
C. Abdul Hakeem College, Melvisharam – 632 509, Tamil Nadu, India

(Received July 2, 2013; revised October 28, 2013)

ABSTRACT. An efficient synthesis of a new series of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives from the reaction of 3-hydroxypyrrole, malononitrile, and various aromatic aldehydes using $ZrOCl_2 \cdot 8H_2O$, an environmentally friendly catalyst under a thermal solvent-free green procedure is described. This simple protocol offer advantages such as shorter reaction times, simple work-up and excellent yield. The catalyst $ZrOCl_2 \cdot 8H_2O$ can be reused. The reusability of the catalyst has been studied for the synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole. All the compounds were screened for their antibacterial and antifungal activity.

KEY WORDS: $ZrOCl_2 \cdot 8H_2O$, Pyranopyrrole, Malononitrile, 3-Hydroxypyrrole, Solvent-free

INTRODUCTION

Multi component reactions (MCRs) allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity [1-3].

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. 4*H*-pyran play an essential role as biologically active compounds and represent an interesting template for medicinal chemistry. Many of these compounds are known for their potential applications in pharmaceutical field. They exhibit a wide range of biological activities like such as antimicrobial [4], antiviral [5], mutagenicity [6], antiproliferative [7], sex pheromone [8], antitumor [9], cancer therapy [10] and central nervous system activity [11]. Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals [12]. Furthermore, they play a significant role as potential calcium channel antagonists which are structurally similar to biologically active 1,4-dihydropyridines [13]. Therefore, the synthesis of such compounds has attracted strong interest.

Recently, 4*H*-pyran derivatives were synthesized using different catalysts like magnesium oxide [14], SB-DABCO [15], silica nanoparticles [16], ionic liquid [bmim]BF_4 [17], Baker's yeast [18] and amino functionalized ionic liquid [19]. However, only few reports are available for the synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives [20-24]. In recent years, the synthesis of various 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives have been reported by using various promoting agents, such as ferric hydrogensulfate, $Fe(HSO_4)_3$ [20], 1-methyl-3-(triethoxysilylpropyl)-imidazolium hydrogen sulfate anchored on silica support [pmim]HSO_4 (1-propyl-3-methylimidazolium–HSO_4) [21], bis[N-(3,5-dicumylsalicylidene)anthracylaminato]zirconium(IV) dichloride as catalyst in the presence of ultrasonic irradiation [22] and melamine trisulfonic acid (MTSA) catalyst under solvent-free conditions [23]. Many of these methods however, suffer from drawbacks, such as low yields of products, the requirement of longer reaction time and high temperature. Moreover,

*Corresponding author. E-mail: smansoors2000@yahoo.co.in

preparation of required catalysts is cumbersome in some cases. Thus, development of a facile, atom-efficient, and eco-friendly method is highly desirable.

As part of our efforts to develop new synthetic methods in biologically active molecules, such as 3,4-dihydropyrimidin-2(*1H*)-ones/-thiones/imines [24], β-amino ketone compounds [25] and 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives [26] by one-pot synthesis, we became interested in the possibility of developing a one-pot synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives catalyzed by $ZrOCl_2{\cdot}8H_2O$. To the best of our knowledge, 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives catalysed by $ZrOCl_2{\cdot}8H_2O$ has not been reported.

In view of the inherent properties like environmental compatibility, reusability, greater selectivity, operational simplicity, non corrosiveness and ease of isolation, we wish to describe our results on $ZrOCl_2{\cdot}8H_2O$ catalyzed one pot synthesis of reactions of 3-hydroxy pyrrole, aromatic aldehydes and malononitrile.

RESULTS AND DISCUSSIONS

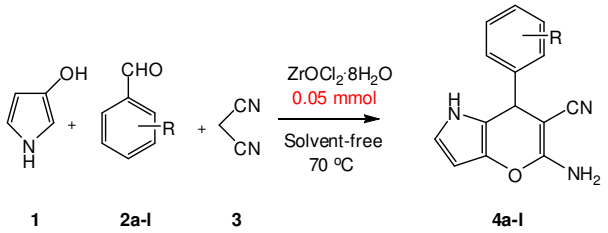
Effect of solvent, temperature and catalysis

A mixture of 3-hydroxypyrrole, benzaldehyde and malononitrile with stoichiometic ratio of 1.0:1.0:1.1 and 0.05 mmol of $ZrOCl_2{\cdot}8H_2O$ was chosen as the model reaction to check the feasibility of this synthesis. The solvents played an important role in the synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives. In order to optimize the reaction conditions, various reaction media were screened (acetonitrile, cyclohexane, ethanol, benzene, toluene and methanol) using the model reaction (Table 1, entries 1-6). It was found that the best results were obtained with 0.05 mmol $ZrOCl_2{\cdot}8H_2O$ under solvent-free conditions (Table 1, entry 7). The reaction was completed within 1.0 h and the expected product was obtained in a 94% yield. Decreasing the quantity of the catalyst to 0.02 mmol and 0.03 mmol gave the corresponding product in 55% and 73% yields in 1 h (Table 1, entries 8 and 9). The use of 0.08 mmol of $ZrOCl_2{\cdot}8H_2O$, there was no change in the yield (Table 1, entry 10). It was found that the best results were obtained with 0.05 mmol $ZrOCl_2{\cdot}8H_2O$ under solvent-free conditions at 70 ºC (Scheme 1).

Table 1. Synthesis of 5-amino-6-cyano7-phenyl-4*H*-pyrano[3,2-*b*]pyrrole derivatives from 3-hydroxy-pyrrole, benzaldehyde and malononitrile catalysed by $ZrOCl_2{\cdot}8H_2O$ under various conditions[a].

Entry	Solvent	Amount of catalyst (mmol)	Time (h)	Yield (%)
1	Acetonitrile	0.05	1.0	70
2	Cyclohexane	0.05	1.0	66
3	Ethanol	0.05	1.0	48
4	Benzene	0.05	1.0	48
5	Toluene	0.05	1.0	64
6	Methanol	0.05	1.0	55
7	None	0.05	1.0	94
8	None	0.02	1.0	55
9	None	0.03	1.0	73
10	None	0.08	1.0	94

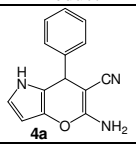
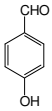
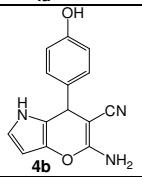
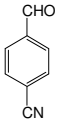
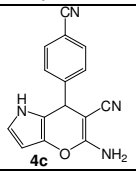
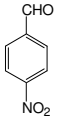
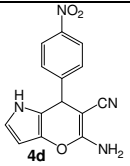
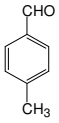
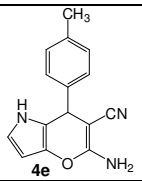
[a]Reaction conditions: 3-hydroxypyrrole (1 mmol), benzaldehyde (1 mmol) and malononitrile (1.1 mmol), the amount of solvent used for entries 1-6 was 5 mL.

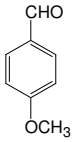
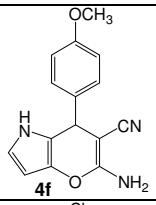
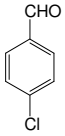
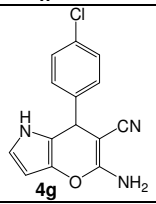
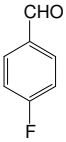
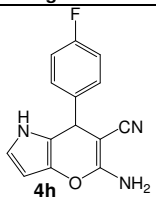
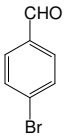
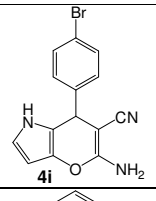
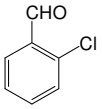
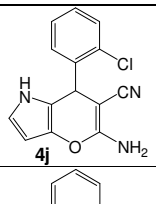
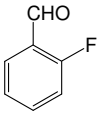
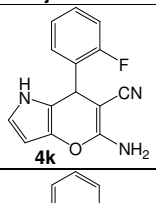
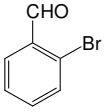
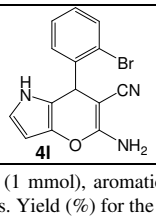


Scheme 1. Synthesis of various 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-b]pyrroles.

The reusability of the catalyst is one of the most important benefits and makes it useful for commercial applications. Thus the recovery and reusability of $ZrOCl_2·8H_2O$ was investigated. In these experiments, the reaction mixture was isolated with ethanol. The catalyst was easily reused by filtration after washing with methanol and drying at 60 ºC. The catalyst could be reused four times without any loss of its activity (Table 2 and Figure 1).

Table 2. The solvent-free synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives from 3-hydroxypyrrole, benzaldehydes and malononitrile catalysed by $ZrOCl_2·8H_2O$ (0.05 mmol)[a].

Entry	Aldehyde	Product	M.P. (ºC)	Time (h)	Yield (%)
1		 **4a**	206–208	1.0	94[b]
2		 **4b**	224–226	1.0	83
3		 **4c**	217–219	1.5	76
4		 **4d**	198–200	1.5	83
5		 **4e**	216–218	1.0	89

6		 **4f**	212–214	1.5	89
7		 **4g**	196–198	1.0	88
8		 **4h**	208–210	1.0	89
9		 **4i**	222–224	1.0	88
10		 **4j**	202–204	1.5	84
11		 **4k**	210–212	1.0	87
12		 **4l**	226–228	2.0	83

[a]Reaction conditions: 3-hydroxypyrrole (1 mmol), aromatic aldehyde (1 mmol) and malononitrile (1.1 mmol) at 70 ºC. [b]Catalyst can be reused four times. Yield (%) for the reaction was 94, 93, 92, 90.

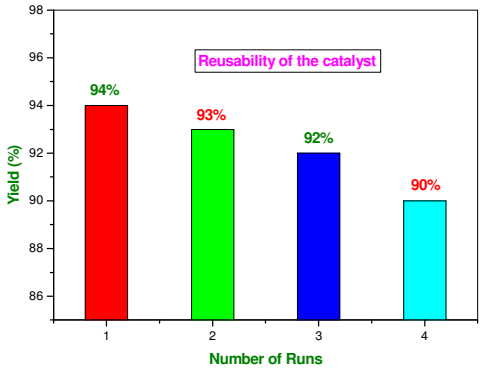


Figure 1. The reusability of the catalyst $ZrOCl_2 \cdot 8H_2O$ for the synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-b]pyrrole.

Synthesis of various 5-amino-7-aryl-6-cyano-4H-pyrano[3,2-b]pyrrole derivatives

To investigate the versatility of the catalyst, the reaction of 3-hydroxypyrrole and various aromatic aldehydes and malononitrile was carried out under solvent-free conditions in 70 ºC using 0.05 mmol of $ZrOCl_2 \cdot 8H_2O$ (Scheme 1). 5-Amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivatives containing both electron-withdrawing or electron-donating groups were formed in a short experimental time (1.0–2.0 h) with high yields (76–94%) (Table 2).

Various aromatic aldehydes bearing different substitutes, such as *para*-OH, CN, NO_2, CH_3, OCH_3, Cl, F, Br were favorable to the reactions (**4a–4i**). The presence of more electron releasing groups such as *para*-CH_3, OCH_3, Cl, F and Br to give the corresponding products in high yield (Table 2, entries 5-9); however, the presence of more electron withdrawing groups such as NO_2 and CN adversely affected the results (Table 2, entries 3 and 4). We carried out a study of sterically hindered *ortho*-substituted aromatic aldehydes bearing substitutes, such as Cl, F and Br (Table 2, entries 10-12) (**4j–4l**). *ortho*-substituted aromatic aldehydes generally gave very low yield. That is to say, steric factors played a key role in affecting the rate of reaction and the reaction requires a longer time. In case of *ortho*-F substituted benzaldehyde, the reaction time was less compared to other *ortho*-substituted benzaldehydes (Table 2, entry 11). The reaction was compared with *ortho*-Cl and *ortho*-Br substituted benzaldehydes (Table 2, entries 10 and 12). It should be mentioned that as minor atomic radius of fluorine atom, *ortho*-F substituted benzaldehyde displayed no above-mentioned steric hindered effect and reacted faster than any other *ortho*-substituted benzaldehydes. The catalyst was easily regenerated by filtering the reaction mixture after completion of reaction.

To explore the advantages of this $ZrOCl_2 \cdot 8H_2O$ catalyzed synthesized of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-b]pyrrole, we compared the results we obtained under the optimized conditions with results reported in the literature by other catalysts (Table 3). Among the catalysts ferric hydrogensulfate, $Fe(HSO_4)_3$ [20], 1-methyl-3-(triethoxysilylpropyl)-imidazolium hydrogen sulfate anchored on silica support [pmim]HSO_4 (1-propyl-3-methyl- imidazolium–HSO_4) [21], bis[N-(3,5-dicumylsalicylidene)anthracylaminato] zirconium(IV) [22] and melamine trisulfonic acid (MTSA) [23], $ZrOCl_2 \cdot 8H_2O$ was found to be superior in terms of yield and time of reaction.

Table 3. Comparison of catalytic activity of $ZrOCl_2{\cdot}8H_2O$ with other catalysts reported in the literature for the synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole.

Entry	Catalyst	Conditions	Time (h)	Yield (%)	Ref.
1	$Fe(HSO_4)_3$	EtOH/Reflux	6.0	86	[20]
2	$[pmim]HSO_4–SiO_2$	CH_3CN/50 °C	3.0	89	[21]
3	Zr-Catalyst	CH_3CN/Ultrasonic 50 °C	0.5	86	[22]
4	Melamine trisulfonic acid	EtOH/Reflux	1.5	92	[23]
5	$ZrOCl_2{\cdot}8H_2O$	Solvent-free/70 °C	1.0	94	This work

Biological activity

The antibacterial activity of compounds **4a-l** were tested against two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), and two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and antifungal activity against *Aspergillus flavus*, *Rhizopus schipperae*, *Aspergillus niger* and *Candida albicans.*

Antibacterial activity

Ciprofloxacin was used as the reference drug. The micro dilution susceptibility test in Muller-Hinton broth was used for the determination of antibacterial activity. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. The observed MICs are given in Table 4. In general all the synthesized compounds exert a wide range of modest antibacterial activity *in vitro* against the tested organisms.

Table 4. *In vitro* antibacterial activity of compounds **4a–l**.

Compound	Minimum inhibitory concentration (MIC) in µg/mL			
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
4a	150	100	150	150
4b	100	75	100	75
4c	50	50	75	75
4d	50	75	75	50
4e	100	75	100	75
4f	100	75	100	100
4g	100	50	75	75
4h	50	50	75	50
4i	100	50	75	75
4j	100	75	75	75
4k	50	50	75	50
4l	75	50	75	75
Ciprofloxacin	50	25	50	50

Antifungal activity

All the compounds were screened for their antifungal activity against each fungal strain in DMSO by serial plate dilution method. Amphotericin B was used as the reference drug. Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a

suspension of sore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates. The observed MICs are given in Table 5.

Table 5. *In vitro* antifungal activity of compounds **4a–l**.

Compound	Minimum inhibitory concentration (MIC) in μg/mL and zone of inhibition in mm			
	A. flavus	*R. schipperae*	*A. niger*	*C. albicans*
4a	150	100	100	100
4b	150	100	150	100
4c	75	75	100	100
4d	75	50	100	75
4e	150	100	150	100
4f	150	100	150	100
4g	100	75	75	75
4h	75	75	100	75
4i	150	75	100	100
4j	100	75	100	75
4k	75	75	100	75
4l	100	75	100	100
Amphoterecin-B	50	25	50	25

CONCLUSIONS

In conclusion, we have developed a very simple and efficient method for the high-yielding synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrrole derivates by one-pot three-component coupling of 3-hydroxypyrrole and various aromatic aldehydes and malononitrile using $ZrOCl_2 \cdot 8H_2O$ as a catalyst. This method offers some advantages in terms of simplicity of performance, low reaction times, solvent-free condition, low cost, and it follows along the line of green chemistry. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. All the compounds were screened for their antibacterial and antifungal activities.

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX- 500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a Varion-Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

*General procedure for synthesis of pyranopyrrole derivatives (**4a–4l**)*

A mixture of 3-hydroxypyrrole (1 mmol), aldehyde (1 mmol), malononitrile (1.1 mmol) and $ZrOCl_2 \cdot 8H_2O$ catalyst (0.05 mmol) was stirred at 70 ºC in a 50 mL flask for the appropriate time, as shown in Table 2. The reaction was monitored by TLC and after completion of the

reaction; the catalyst was simply recovered by filtration and washed by ethanol. The residue was concentrated *in vacuo* and the crude product was purified by column chromatography on silica gel.

Spectral data for the synthesized compounds

*5-Amino-7-aryl-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (**4a**).* IR (KBr, cm^{-1}): 3400, 3417, 3260, 2140, 1262. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.42 (s, 1H, pyran H_4), 6.30 (d, 1H, pyrrole H_3), 6.72 (d, 1H, pyrrole H_2), 6.73(s, 2H, NH_2), 7.02-7.09 (m, 5H, Ar-H), 7.40 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.2, 55.1, 101.0, 105.0, 117.4, 121.8, 123.5, 127.4, 128.9, 129.9, 130.2, 174.7 ppm; MS (ESI): *m/z* 238 $(M+H)^+$. Anal. calcd. for $C_{14}H_{11}N_3O$: C, 70.89; H, 4.64; N, 17.72%. Found: C, 70.62; H, 4.60; N, 17.60%.

*5-Amino-7-(4-hydroxyphenyl)-1,7-dihydropyrano [3,2-b]pyrrole-6-carbonitrile (**4b**).* IR (KBr, cm^{-1}): 3462, 3412, 3415, 3236, 2206, 2195, 1245. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.16 (s, 1H, OH), 5.50 (s, 1H, pyran H_4), 6.38 (d, 1H, pyrrole H_3), 6.72 (d, 1H, pyrrole H_2), 6.74 (s, 2H, NH_2), 7.10–7.20 (m, 4H, Ar-H), 7.45 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.3, 59.0, 110.3, 111.5, 115.6, 118.6, 120.6, 128.4, 130.2, 132.4, 134.8, 135.4, 142.0, 177.0 ppm; MS (ESI): *m/z* 254 $(M+H)^+$. Anal. calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.35; N, 16.60%. Found: C, 66.38; H, 4.28; N, 16.54%.

*5-Amino-7-(4-cyanophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (**4c**).* IR (KBr, cm^{-1}): 3409, 3412, 3240, 2210, 2188, 1260. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.50 (s, 1H, pyran H4), 6.10 (d, 1H, pyrrole H_3), 6.40 (s, 2H, NH_2), 6.63 (d, 1H, pyrrole H_2), 7.21 (s, 1H, pyrrole NH), 7.25-7.33 (m, 4H, Ar-H), ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.9, 62.3, 111.0, 113.4, 114.6, 122.3, 124.7, 126.8, 129.2, 133.7, 138.9, 139.6, 177.5 ppm; MS (ESI): *m/z* 263 $(M+H)^+$. Anal. calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36%. Found: C, 67.74; H, 3.70; N, 21.12%.

*5-Amino-1,7-dihydro-7-(4-nitrophenyl)pyrano[3,2-b]pyrrole-6-carbonitrile (**4d**).* IR (KBr, cm^{-1}): 3408, 3420, 3228, 2168, 1372, 1558, 1247. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.51 (s, 1H, pyran H_4), 6.13 (d, 1H, pyrrole H_3), 6.48 (s, 2H, NH_2), 6.58 (d, 1H, pyrrole H_2), 7.30 (s, 1H, pyrrole NH), 7.30-7.44 (m, 4H, Ar-H), ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.1, 59.3, 107.6, 108.2, 120.3, 121.6, 124.0, 129.4, 136.6, 141.8, 145.7, 176.9 ppm; MS (ESI): *m/z* 283$(M+H)^+$. Anal. calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85%. Found: C, 59.42; H, 3.44; N, 19.76%.

*5-Amino-1,7-dihydro-7-(4-methylphenyl)pyrano[3,2-b]pyrrole-6-carbonitrile (**4e**).* IR (KBr, cm^{-1}): 3408, 3412, 3274, 2164, 1252. ^{1}H NMR (500 MHz, DMSO-d_6): δ =2.26 (s, 3H, CH_3), 5.42 (s, 1H, pyran H_4), 6.12 (d, 1H, pyrrole H_3), 6.72 (s, 2H, NH_2), 6.90 (d, 1H, pyrrole H_2), 6.92–7.00 (m, 4H, Ar-H), 7.39 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.3, 29.4, 54.02 100.4, 106.4, 116.3, 123.4, 128.4, 129.3, 131.7, 133.7, 137.9, 173.1 ppm; MS (ESI): *m/z* 252 $(M+H)^+$. Anal. calcd. for $C_{15}H_{13}N_3O$: C, 71.71; H, 5.18; N, 16.73%. Found: C, 71.56; H, 5.14; N, 16.58%.

*5-Amino-1,7-dihydro-7-(4-methoxyphenyl)pyrano[3,2-b]pyrrole-6-carbonitrile (**4f**).* IR (KBr, cm^{-1}): 3410, 3399, 3278, 2163, 1252. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.44 (s, 3H, OCH_3), 5.41 (s, 1H, pyran H_4), 6.14 (d, 1H, pyrrole H_3), 6.80- 6.94 (m, 4H, Ar-H), 6.77 (d, 1H, pyrrole H_2), 6.80 (s, 2H, NH_2), 7.49 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.9, 54.9, 60.2, 101.5, 104.4, 119.0, 119.5, 121.5, 126.1, 127.4, 131.0, 153.9, 171.8 ppm; MS

(ESI): *m/z* 268 $(M+H)^+$. Anal. calcd. For $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73%. Found: C, 67.28; H, 4.82; N, 15.66%.

5-Amino-7-(4-chlorophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4g***). IR (KBr, cm^{-1}): 3408, 3422, 3256, 2154, 1266. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.38 (s, 1H, pyran H_4), 6.09 (d, 1H, pyrrole H_3), 6.42 (s, 2H, NH_2), 6.59 (d, 1H, pyrrole H_2), 7.03-7.10 (m, 4H, Ar-H), 7.21 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.4, 60.4, 105.4, 108.3, 119.4, 124.6, 129.4, 129.9, 130.7, 132.2, 135.8, 177.7 ppm; MS (ESI): *m/z* 272.45 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.68; N, 15.47%. Found: C, 61.80; H, 3.55; N, 15.44%.

5-Amino-7-(4-fluorophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4h***). IR (KBr, cm^{-1}): 3406, 3430, 3278, 2211, 1239. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.43 (s, 1H, pyran H_4), 6.13 (d, 1H, pyrrole H_3*)*, 6.44 (s, 2H, NH_2), 6.97-7.15 (m, 4H, Ar-H), 6.76 (d, 1H, pyrrole H_2), 7.46 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.5, 65.3, 100.0, 109.0, 116.8, 123.0, 127.0, 127.5, 129.3, 130.4, 131.5, 131.9, 138.7, 142.8, 176.5 ppm; MS (ESI): *m/z* 256 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}FN_3O$: C, 65.88; H, 3.92; N, 16.47%. Found: C, 65.75; H, 3.85; N, 16.44%.

5-Amino-7-(4-bromophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4i***). IR (KBr, cm^{-1}): 3404, 3414, 3300, 2186, 1260. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.51 (s, 1H, pyran H_4), 6.09 (d, 1H, pyrrole H_3*)*, 6.97–7.09 (m, 4H, Ar-H), 6.61 (d, 1H, pyrrole H_2), 7.48 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.1, 56.3, 107.5, 108.5, 121.4, 122.3, 123.4, 127.3, 128.2,131.3, 132.4, 133.4, 141.5, 177.8 ppm; MS (ESI): *m/z* 316.9 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}BrN_3O$: C, 53.18; H, 3.17; N, 13.29%. Found: C, 53.05; H, 3.10; N, 13.20%.

5-Amino-7-(2-chlorophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4j***). IR (KBr, cm^{-1}): 3412, 3433, 3250, 2150, 1258. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.44 (s, 1H, pyran H_4), 6.11 (d, 1H, pyrrole H_3), 6.44 (s, 2H, NH_2), 6.66 (d, 1H, pyrrole H_2), 7.03 -7.10 (m, 4H, Ar-H), 7.22 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.2, 60.2, 105.3, 107.9, 119.5, 124.4, 129.2, 129.9, 130.5, 132.6, 135.9, 178.0 ppm; MS (ESI): *m/z* 272.45 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.68; N, 15.47%. Found: C, 61.77; H, 3.49; N, 15.38%.

5-Amino-7-(2-fluorophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4k***). IR (KBr, cm^{-1}): 3400, 3422, 3277, 2209, 1244. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.40 (s, 1H, pyran H_4), 6.10 (d, 1H, pyrrole H_3), 6.40 (s, 2H, NH_2), 6.99-7.13 (m, 4H, Ar-H), 6.68 (d, 1H, pyrrole H_2), 7.44 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.3, 65.1, 100.4, 109.2, 116.2, 123.4, 127.3, 128.6, 129.5, 130.6, 131.5, 132.4, 138.8, 141.3, 177.0 ppm; MS (ESI): *m/z* 256 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}FN_3O$: C, 65.88; H, 3.92; N, 16.47%. Found: C, 65.70; H, 3.89; N, 16.40%.

5-Amino-7-(2-bromophenyl)-1,7-dihydropyrano[3,2-b]pyrrole-6-carbonitrile (***4l***). IR (KBr, cm^{-1}): 3408, 3418, 3307, 2177, 1272. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.44 (s, 1H, pyran H_4), 6.11 (d, 1H, pyrrole H_3), 6.97–7.09 (m, 4H, Ar-H), 6.66 (d, 1H, pyrrole H_2), 7.55 (s, 1H, pyrrole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.9, 56.0, 107.3, 108.7, 121.6, 122.7, 123.8, 127.7, 128.5,131.4, 132.8, 133.9, 141.9, 177.0 ppm; MS (ESI): *m/z* 316.9 $(M+H)^+$. Anal. calcd. for $C_{14}H_{10}BrN_3O$: C, 53.18; H, 3.17; N, 13.29%. Found: C, 53.15; H, 3.14; N, 13.11%.

ACKNOWLEDGEMENTS

We sincerely thank the management of C. Abdul Hakeem College, Melvisharam – 632 509, India, for providing the laboratory facilities. We are also thankful to Dr. A. Abdul Rahuman, Unit of Nanotechnology and Bioactive Natural Products, for useful discussion and encouragement.

REFERENCES

1. Domling, A. *Chem. Rev.* **2006**, 106, 17.
2. Mosaddegh, E.; Hassankhani, A. *Bull. Chem. Soc. Ethiop*. **2012**, 26, 461.
3. Karimi-Jaberi, Z.; Fakhraei, H. *Bull. Chem. Soc. Ethiop*. **2012**, 26, 473.
4. Khafagy, M.M.; El-Wahas, A.H.F.A.; Eid, F.A.; El-Agrody, A.M. *Farmaco* **2002**, 57, 715.
5. Martinez, A.G.; Marco, L.J. *Bioorg. Med. Chem. Lett.* **1997**, 7, 3165.
6. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, 395, 47.
7. Dell, C.P.; Smith, C.W. *Eur. Pat. Appl.* 537, 949, **1993**; *Chem. Abstr.* **1993**, 119, 139102d.
8. Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, 51, 2001.
9. Mohr, S.J.; Chirigos, M.A.; Fuhrman, F.S.; Pryor, J.W. *Cancer Res.* **1975**, 35, 3750.
10. Anderson, D.R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W.F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. *Bioorg. Med.Chem. Lett.* **2005**, 15, 1587.
11. Eiden, F.; Denk, F. *Arch. Pharm. Weinhein Ger (Arch. Pharm.)* **1991**, 324, 353.
12. Hafez, E.A.A.; Elnagdi, M.H.; Elagamey, A.G.A.; Ei-Taweel, F.M.A.A. *Heterocycles* **1987**, 26, 903.
13. Suarez, M.; Salfran, E.; Verdecia, Y.; Ochoa, E.; Alba, L.; Martin, N.; Martinez, R.; Quinteiro, M.; Seoane, C.; Novoa, H.; Blaton, N.; Peeters, O.M.; Ranter, C.D. *Tetrahedron* **2000**, 58, 953.
14. Ye, Z.; Xu, R.; Shao, X.; Xu, X.; Li, Z. *Tetrahedron Lett.* **2010**, 51, 4991.
15. Hasaninejad, A.; Shekouhy, M.; Golzar, N.; Zare, A.; Doroodmand, M.M. *Appl. Catal. A: Gen.* **2011**, 402, 11.
16. Banerjee, S.; Horn, A.; Khatri, H.; Sereda, G. *Tetrahedron Lett*. **2011**, 52, 1878.
17. Li, Y.; Zhao, B.; Du, B.; Jiang, Q.; Wang, X.; Cao, C. *Tetrahedron Lett.* **2013**, 54, 227.
18. Pratap, U.R.; Jawale, D.V.; Netankar, P.D.; Mane, R.A. *Tetrahedron Lett.* **2011**, 52, 5817.
19. Salvi, P.P.; Mandhare, A.M.; Sartape, A.S.; Pawar, D.K.; Han, S.H.; Koleka, S.S. *Comp. Rend. Chim.* **2011**, 14, 878.
20. Sandaroos, R.; Damavandi, S. *J. Chem. Sci*. **2012**, 124, 893.
21. Sandaroos, R.; Damavandi, S.; Salimi, M. *Monatsh. Chem.* **2012**, 143, 1655; DOI: 10.1007/s00706-012-0744-2.
22. Damavandi, S.; Sandaroos, R.; Zohuri, G. H.; Amado, S. *Res. Chem. Intermed*. **2012**, DOI: 10.1007/s11164-012-0965-3.
23. Mansoor, S.S.; Aswin, K.; Logaiya, K.; Sudhan, S.P.N. *J. Saudi Chem. Soc.* **2012**, DOI: http://dx.doi.org/10.1016/j.jscs.2012.12.010.
24. Mansoor, S.S.; Shafi, S.S.; Ahmed, S.Z. *Arab. J. Chem*. **2011**, DOI: 10.1016/j.arabjc.2011.09.018.
25. Mansoor, S.S.; Aswin, K.; Logaiya, K.; Sudhan, S.P.N. *J. Saudi Chem. Soc.* **2012**, DOI: http://dx.doi.org/10.1016/j.jscs.2012.04.008.
26. Mansoor, S.S.; Aswin, K.; Logaiya, K.; Sudhan, S.P.N. *J. Saudi Chem. Soc.* **2012**, DOI: http://dx.doi.org/10.1016/j.jscs.2012.07.011.