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Synthesis of novel 2-amino-4-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-6-aryl-4*H*-pyran-3-carbonitrile derivatives as antimicrobial and antioxidant agents

Anand R. Saundane [a,*], Katkar Vijaykumar [a], A. Verma Vaijinath [b]

[a] Department of Post-Graduate Studies and Research in Chemistry, Gulbarga University, Gulbarga 585 106, Karnataka, India
[b] Shri Prabhu Arts, Science and J. M. Bohra Commerce College, Shorapur 585 224, Karnataka, India

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ABSTRACT

As a part of systematic investigation of synthesis and biological activities of indole analogues linked to various heterocyclic systems, we have synthesized new compounds viz., 2-amino-4-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-6-aryl-4*H*-pyran-3-carbonitriles (**2a–i**), 4,5-diamino-6-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-8-aryl-2-oxo-2,6-dihydrodipyrano [2,3-*b*:3,2-*e*]pyridine-3-carbonitriles (**3a–i**), 4-amino-5-(5′-substituted 2′-phenyl-1*H*-indol-3-yl)-7-aryl-1*H*-pyrano[2,3-*d*]pyrimidin-2(5*H*)-ones (**4a–i**), 4-amino-5-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-7-aryl-1*H*-pyrano[2,3-d]pyrimidin-2(5*H*)-thiones (**5a-i**), 4-(5′-subtituted 2′-phenyl-1*H*-indol-3′-yl)-6-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-3-amines (**6a–i**) and 5-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-7-aryl-3*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones (**7a–i**). Antibacterial activity results revealed that, compound **6a** showed promising activity versus *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. Compound **6d** exhibited good activity against *S. aureus, K. pneumoniae* and *P. aeruginosa*. Antifungal activity results indicated that, compound **4d** exhibited maximum zone of inhibition against *Aspergillus oryzae* and *Aspergillus flavus*. In case of antioxidant activity, compound **4a** showed promising radical scavenging activity, ferric ions (Fe^{+3}) reducing antioxidant power (FRAP) and metal chelating activity.

The emergence and spread of antimicrobial resistance has become one of the most serious public health concern across the world. Antimicrobial resistance refers to micro-organism that has developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents.[1] Electron-rich nitrogen heterocycles play an important role in diverse medicinal chemistry.[2] Indole derivatives substituted at C-3 position by 2-amionopyrimidine ring were successfully evaluated for their ability to inhibit various protein kinases[3] also displayed antitumor activity.[4] Numerous methods for the synthesis of indole derivatives and also their various reactions offer enormous scope in the field of medicinal chemistry such as antitumor,[5–8] anti-inflammatory,[9–11] antioxidant,[12] etc. agents. In addition, 4*H*-pyran derivatives constitute a useful class of heterocyclic compounds which are widely distributed in nature.[13,14] These compounds display wide range of biological activities, acting as fungicides, herbicides and a variety of pharmacological properties, which could be useful in the treatment of asthma and allergies.[15]

In our previous communication,[16] we have reported the synthesis, antioxidant and antimicrobial activities of indole analogues in which 3-cyano-2-aminopyridine (**1**), pyranonapthyridines (**2**),

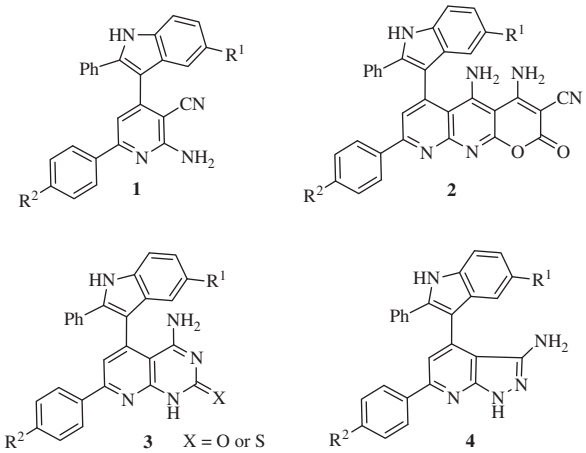

Figure 1. Motivation for synthesis of antibacterial and antioxidant active compounds.

* Corresponding author. Tel.: +91 9480272325.
E-mail addresses: arsaundane@rediff.com (A.R. Saundane), tkvijaykumar@rediffmail.com (K. Vijaykumar), vverma_chem@rediffmail.com (A.V. Vaijinath).

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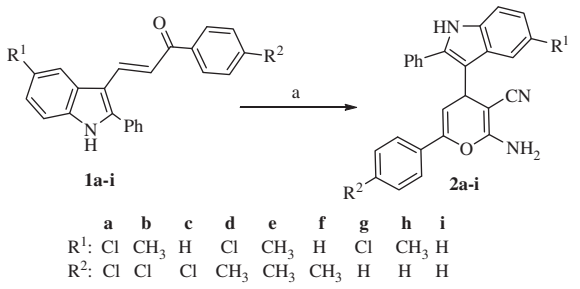
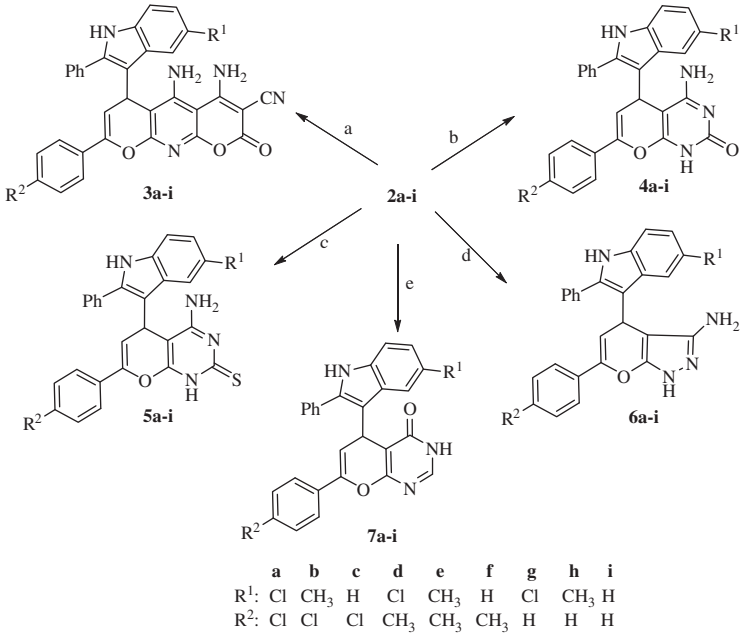


Scheme 1. Reagents and conditions: (a) $CH_2(CN)_2$/COONa, acetic acid, reflux 3 h.

pyridopyrimidine (**3**) and pyrazolopyridine (**4**) (Fig. 1) linked to 3-position of indole. Some of these compounds exhibited good antimicrobial and antioxidant activities. Prompted by these results and in continuation of our research work in the synthesis of biologically important heterocyclic compounds,[17] we herein report the synthesis of title compounds in which pyridine system is replaced by the dihydropyran nucleus in the above heterocycles (**1–4**) to evaluate the impact of these compounds on their antimicrobial and antioxidant activities.

3-(5′-Substituted 2′-phenyl-1*H*-indol-3′-yl)-1-arylprop-2-en-1-ones **1a–i** were synthesized by a base catalyzed Claisen–Schmidt condensation of 4-substituted acetophenones with 5-substituted



Scheme 2. Reagents and conditions: (a) $CNCH_2COOEt$, Et_3N, ethanol, reflux, 2 h; (b) NH_2CONH_2, ethanol, reflux, 5 h; (c) NH_2CSNH_2, ethanol, reflux, 5 h; (d) $N_2H_4\,H_2O$, ethanol, reflux, 3 h; (e) HCOOH, reflux, 6 h.

Table 1
In vitro antibacterial activities of compounds **2–7**

Compd no.	Concd (μg/ml) (zone of inhibition in mm)											
	E. coli			*S. aureus*			*K. pneumoniae*			*P. aeruginosa*		
	1000	750	500	1000	750	500	1000	750	500	1000	750	500
2a	14	13	13	13	13	13	10	10	10	10	10	10
2b	10	10	10	02	05	06	08	09	09	02	05	06
2c	03	05	05	10	10	10	02	02	02	08	08	10
2d	10	10	10	06	05	08	10	10	10	03	06	06
2e	03	04	08	14	14	14	09	09	09	08	10	10
2f	10	10	10	00	00	00	05	06	08	06	08	09
2g	10	10	10	09	09	10	10	10	10	13	12	12
2h	05	06	06	05	05	05	04	04	04	05	05	06
2i	08	08	10	10	10	10	13	13	13	09	09	09
3a	14	12	11	10	12	12	13	13	13	03	08	09
3b	13	13	13	14	13	13	09	11	11	10	10	10
3c	12	03	03	12	11	12	13	13	13	09	09	10
3d	09	10	12	03	03	05	08	08	08	02	02	02
3e	10	10	10	00	03	03	10	10	11	04	06	09
3f	08	08	09	03	05	08	10	11	12	09	05	05
3g	08	10	10	14	13	13	05	05	05	05	08	09
3h	05	09	10	04	08	09	04	04	04	00	03	03
3i	10	08	08	09	10	10	10	11	11	03	07	05
4a	10	10	09	14	13	13	09	09	09	09	09	09
4b	03	08	10	07	05	05	03	03	04	00	00	00

(*continued on next page*)

Table 1 (*continued*)

Compd no.	Concd (μg/ml) (zone of inhibition in mm)											
	E. coli			*S. aureus*			*K. pneumoniae*			*P. aeruginosa*		
	1000	750	500	1000	750	500	1000	750	500	1000	750	500
4c	14	13	13	14	14	14	08	10	11	13	12	12
4d	10	08	08	00	00	00	08	08	08	08	09	10
4e	14	13	13	02	05	08	10	10	10	10	10	10
4f	08	07	07	05	03	05	03	04	06	03	03	05
4g	10	10	10	03	03	03	10	10	11	05	08	09
4h	08	08	08	11	11	11	05	05	06	10	10	10
4i	05	08	10	05	10	10	10	10	10	13	12	12
5a	11	10	10	13	13	13	08	05	05	11	10	10
5b	03	03	04	11	09	09	05	03	05	09	09	09
5c	10	10	10	11	10	10	05	08	08	10	10	10
5d	09	09	10	02	03	06	09	10	10	10	10	10
5e	04	04	05	00	00	00	05	05	06	05	05	06
5f	03	08	09	04	04	06	03	09	09	03	05	05
5g	08	08	10	09	09	09	10	10	10	05	05	06
5h	08	08	08	09	09	10	04	04	05	08	08	09
5i	11	10	10	00	02	02	08	08	09	02	02	02
6a	14	13	13	14	14	14	13	13	13	09	09	10
6b	08	08	09	00	00	02	12	12	12	05	06	06
6c	14	13	13	03	04	05	05	05	05	10	10	10
6d	02	02	04	14	14	14	12	12	12	13	12	12
6e	10	09	08	05	05	07	10	10	11	04	04	08
6f	08	08	08	03	03	05	02	03	04	06	06	08
6g	09	07	07	08	08	10	05	05	06	13	12	12
6h	03	03	03	05	05	06	03	03	03	08	08	09
6i	09	09	10	02	02	02	08	09	10	12	12	12
7a	08	09	09	12	09	09	12	12	12	08	08	08
7b	08	08	08	10	10	10	05	05	05	04	04	04
7c	09	09	09	05	05	05	10	09	09	10	10	10
7d	03	03	03	03	03	05	09	09	09	08	08	08
7e	02	02	02	02	02	02	08	08	08	08	08	08
7f	03	03	03	02	02	02	06	06	06	03	03	04
7g	11	10	10	12	12	12	09	09	09	03	03	03
7h	06	06	08	10	10	11	05	05	05	05	05	05
7i	06	06	08	10	10	10	10	10	11	04	04	05
Std.	15	14	14	15	15	15	14	14	14	14	13	13

Std = Streptomycin (Standard).

Table 2
In vitro antifungal activity of compounds **2–7**

Compd no.	Concd (μg/ml) (zone of inhibition in mm)											
	A. nizer			*A. oryzae*			*A. terrus*			*A. flavus*		
	1000	750	500	1000	750	500	1000	750	500	1000	750	500
2a	10	10	10	09	10	10	–	–	–	13	12	12
2b	10	10	10	10	10	10	13	13	12	08	10	10
2c	05	06	08	03	09	09	13	13	12	02	–	–
2d	03	03	04	02	08	08	03	03	05	05	05	05
2e	00	00	00	13	13	12	09	09	00	00	00	00
2f	08	08	08	08	09	05	05	06	08	10	09	08
2g	10	09	08	03	03	08	08	08	09	03	03	03
2h	10	10	09	03	04	08	05	05	06	04	02	02
2i	10	05	06	05	09	09	03	05	09	10	10	10
3a	10	08	08	03	03	09	13	13	12	08	09	10
3b	10	10	10	03	03	04	08	09	10	05	05	05
3c	05	05	07	13	13	12	11	10	10	08	00	00
3d	03	00	00	10	10	10	03	03	03	03	05	06
3e	00	00	00	10	11	10	04	04	09	13	12	12
3f	08	02	02	06	06	06	03	05	10	00	00	00
3g	10	09	09	13	12	12	03	03	03	–	03	05
3h	10	10	10	08	08	11	04	04	09	–	00	05
3i	10	03	05	11	11	11	05	05	05	–	03	05
4a	13	12	12	09	09	09	09	09	09	04	06	06
4b	06	04	05	08	08	08	05	06	07	04	05	08
4c	05	05	05	03	05	06	04	04	06	12	12	12
4d	10	10	10	13	13	12	08	08	08	13	12	12
4e	10	10	10	00	00	00	09	09	09	02	02	02
4f	02	03	05	10	10	10	03	03	03	03	03	03
4g	08	10	10	12	12	12	03	03	03	09	10	10

Table 2 (*continued*)

Compd no.	Concd (μg/ml) (zone of inhibition in mm)											
	A. nizer			*A. oryzae*			*A. terrus*			*A. flavus*		
	1000	750	500	1000	750	500	1000	750	500	1000	750	500
4h	10	09	10	05	08	09	09	08	08	07	08	08
4i	03	05	05	10	10	10	03	04	06	09	09	10
5a	14	11	11	00	10	09	03	03	02	11	04	05
5b	03	05	05	09	08	09	10	03	03	04	03	03
5c	05	03	03	08	08	09	05	05	08	05	12	12
5d	10	10	10	02	02	03	08	08	09	03	03	03
5e	00	00	00	05	05	05	05	05	05	09	08	09
5f	02	05	06	09	09	10	04	04	06	03	03	03
5g	10	05	05	00	10	10	08	08	09	08	08	08
5h	08	03	04	03	03	03	08	08	09	05	06	09
5i	14	12	12	08	08	09	05	05	05	09	09	09
6a	11	10	10	10	10	10	08	09	09	05	09	09
6b	02	03	05	07	07	08	10	10	10	02	05	05
6c	03	05	07	13	12	12	11	06	08	09	09	09
6d	00	08	09	05	05	08	04	04	05	03	03	03
6e	—	09	09	09	09	10	00	00	00	03	04	04
6f	05	09	09	07	07	07	04	04	04	08	02	03
6g	05	05	06	12	12	12	03	03	02	09	12	12
6h	03	05	05	08	08	09	09	09	09	01	02	05
6i	06	05	05	10	05	06	05	05	05	03	10	10
7a	05	05	06	03	03	03	05	05	05	04	04	04
7b	11	10	10	08	08	08	06	06	06	05	05	05
7c	08	08	08	10	10	10	05	06	06	08	09	10
7d	08	08	08	13	13	12	08	08	08	06	06	06
7e	03	03	03	03	03	03	09	09	09	09	09	10
7f	11	08	08	03	03	03	08	08	08	05	03	03
7g	07	07	07	13	13	12	09	10	10	13	12	12
7h	04	04	05	09	09	09	03	03	04	08	08	08
7i	05	06	06	05	05	05	08	08	09	09	09	09
Std.	14	13	13	14	14	13	14	14	13	14	13	13

Std = Fluconazole (Standard).

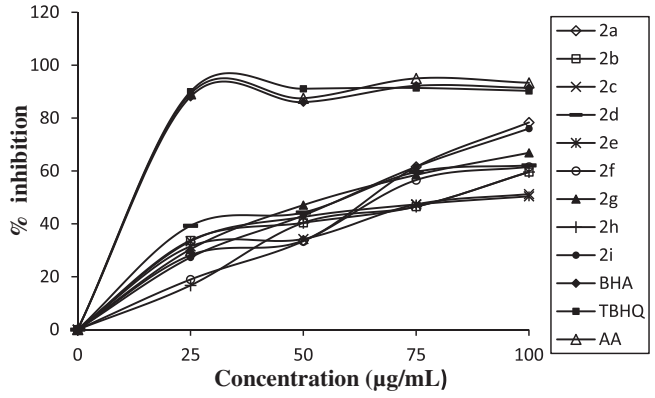


Figure 2. RSA of compounds **2a–i** at different concentrations (25, 50, 75 and 100 μg/ml).

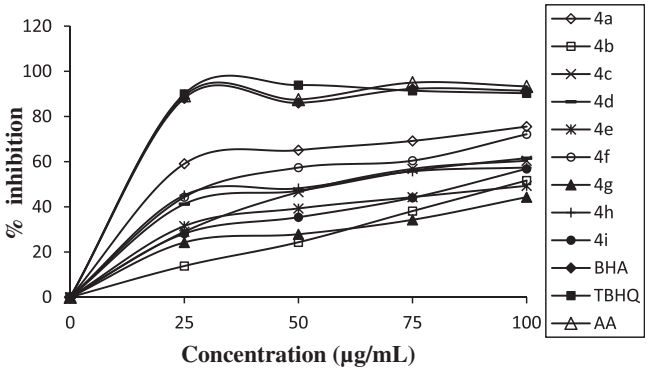


Figure 4. RSA of compounds **4a–i** at different concentrations (25, 50, 75 and 100 μg/ml).

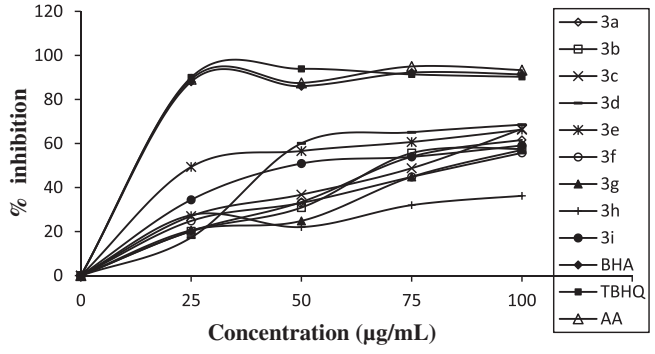


Figure 3. RSA of compounds **3a–i** at different concentrations (25, 50, 75 and 100 μg/ml).

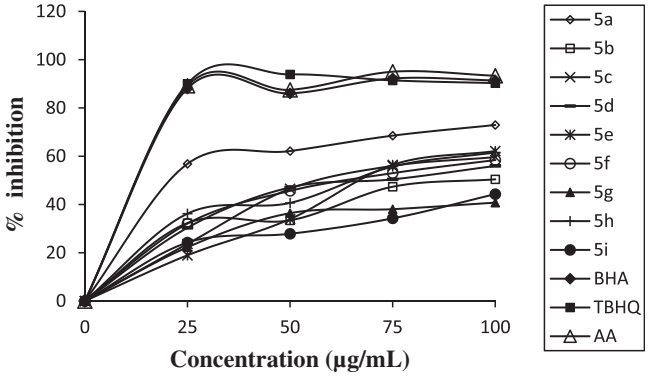


Figure 5. RSA of compounds **5a–i** at different concentrations (25, 50, 75 and 100 μg/ml).

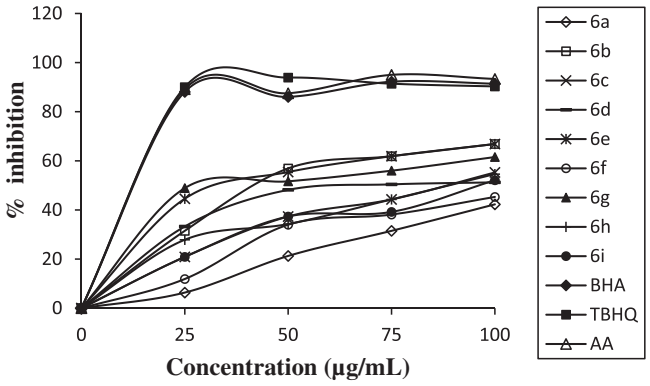


Figure 6. RSA of compounds **6a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

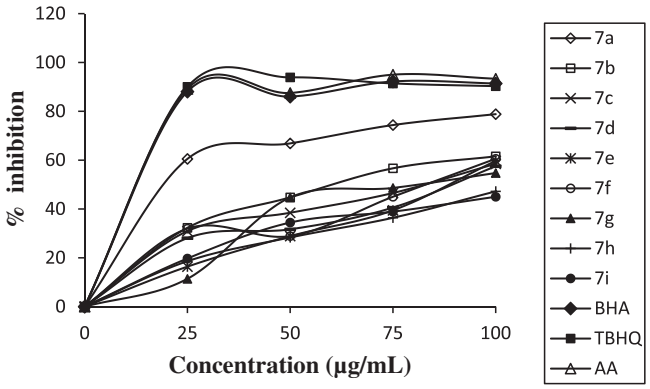


Figure 7. RSA of compounds **7a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

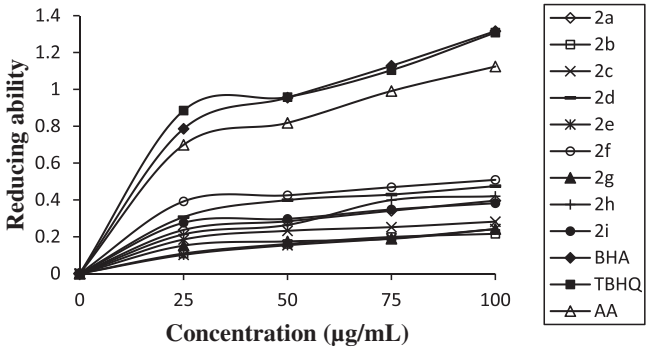


Figure 8. FRAP of compounds **2a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

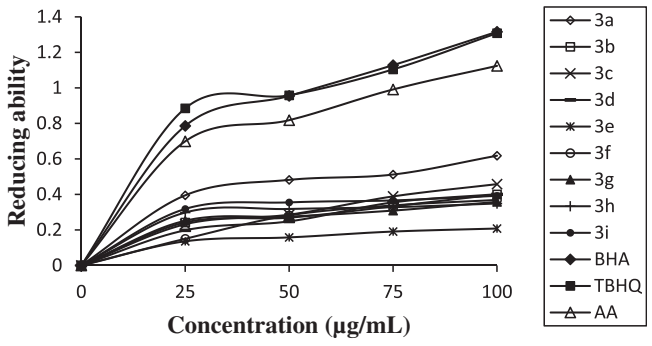


Figure 9. FRAP of compounds **3a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

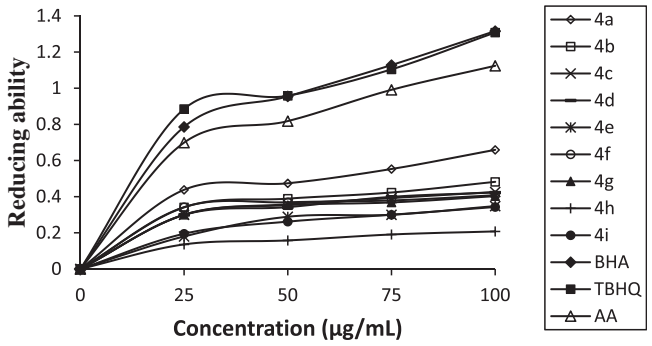


Figure 10. FRAP of compounds **4a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

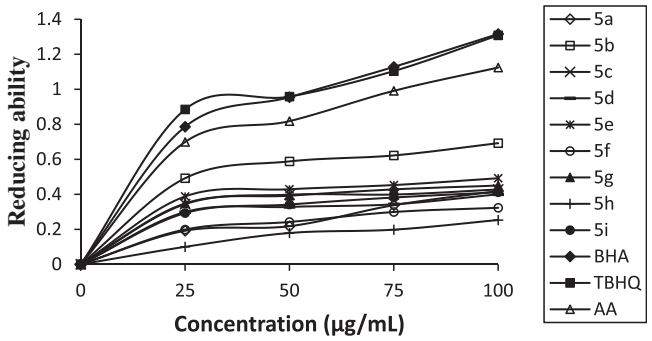


Figure 11. FRAP of compounds **5a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

2-phenyl-1*H*-indol-3-carboxaldehydes.[18] Compounds **1a–i** were subjected to cyclocondensation with malononitrile in presence of sodium acetate to afford 2-amino-4-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-6-aryl-4*H*-pyran-3-carbonitriles **2a–i** in high yield (Scheme 1).

The compounds **2a–i** when subjected to heterocyclization with economically viable and easily available reagents such as, ethyl cyanoacetate, urea, thiourea, hydrazine hydrate and formic acid afforded 4,5-diamino-6-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-8-aryl-2-oxo-2,6-dihydrodipyrano[2,3-*b*:3,2-*e*]pyridine-3-carbonitriles **3a–i**, 4-amino-5-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-7-aryl-1*H*-pyrano[2,3-d]pyrimidin-2(5*H*)-ones **4a–i**, 4-amino-5-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-7-aryl-1*H*-pyrano[2,3-*d*]pyrimidin-2(5*H*)-thiones **5a–i**, 4-(5′-subtituted 2′-phenyl-1*H*-indol-3′-yl)-6-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-3-amines **6a–i** and 5-(5′-substituted 2′-phenyl-1*H*-indol-3′-yl)-7-aryl-3*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **7a–i**, respectively in good yield (Scheme 2). The synthesized compounds were characterized by elemental and spectral analyses (please see Supplementary data).

All the synthesized compounds (**2–7**) were evaluated for their antibacterial activity against *Escherichia coli* (MTCC-723), *Staphylococcus aureus* (ATCC-29513), *Klebsiella pneumoniae* (NCTC-13368) and *Pseudomonas aeruginosa* (MTCC-1688) and antifungal activity against *Aspergillus niger* (MTCC-281), *Aspergillus oryzae* (MTCC-3567^{T}), *Aspergillus terrus* (MTCC-1782) and *Aspergillus flavus* (MTCC-1973) by cup-plate method[19] (Tables 1 and 2). The zone of inhibition (in mm) was compared with standards streptomycin and fluconazole for antibacterial and antifungal activities, respec-

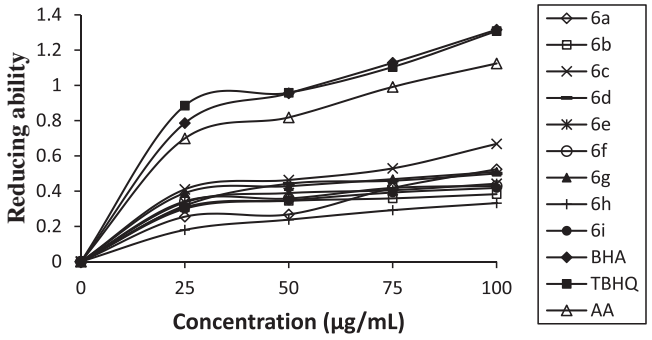


Figure 12. FRAP of compounds **6a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

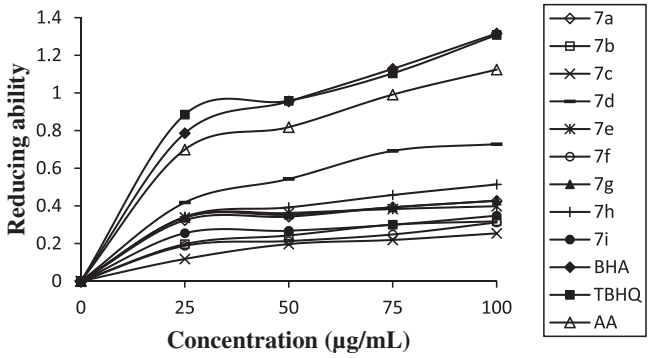


Figure 13. FRAP of compounds **7a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

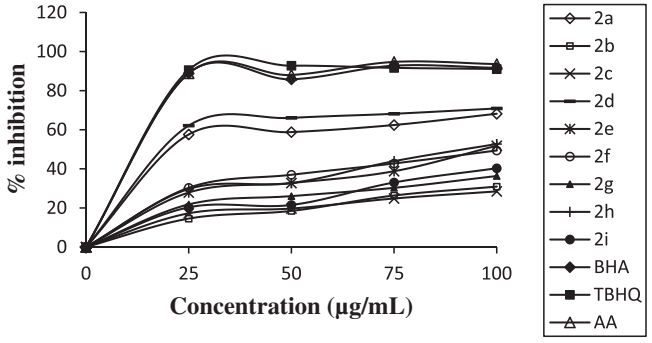


Figure 14. Metal chelating activity of compounds **2a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

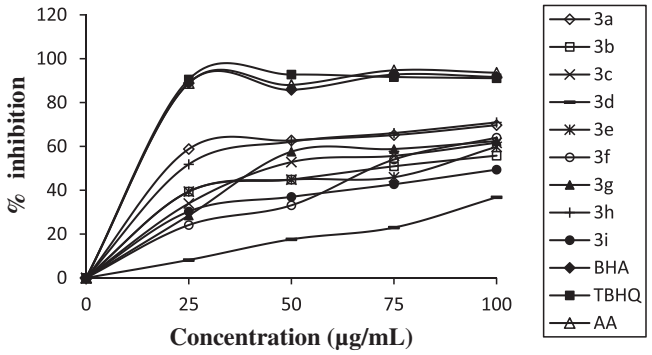


Figure 15. Metal chelating activity of compounds **3a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

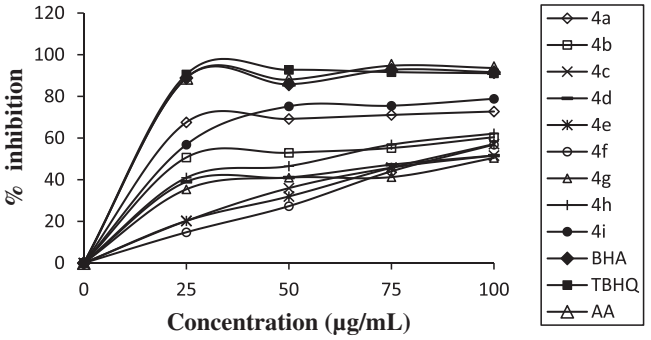


Figure 16. Metal chelating activity of compounds **4a–i** at different concentrations (25, 50, 75 and 100 µg/ml.)

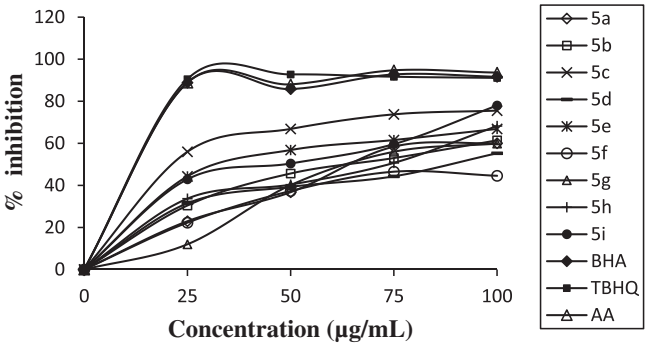


Figure 17. Metal chelating activity of compounds **5a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

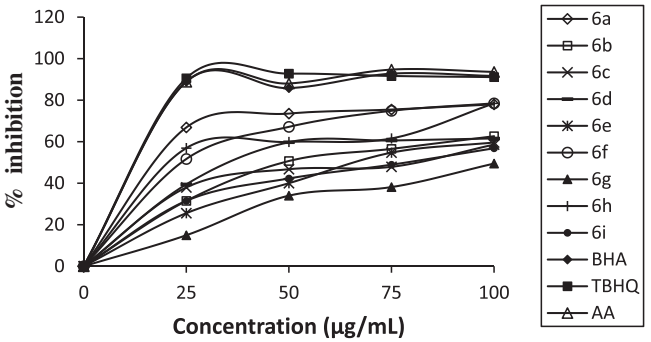


Figure 18. Metal chelating activity of compounds **6a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

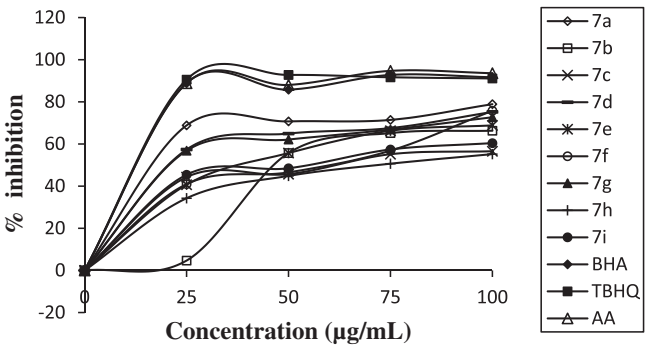


Figure 19. Metal chelating activity of compounds **7a–i** at different concentrations (25, 50, 75 and 100 µg/ml).

tively. The in vitro antioxidant activity was evaluated by three different methods viz., radical scavenging activity[20] (RSA), ferric ions (Fe^{+3}) reducing antioxidant power[21] (FRAP) and metal chelating activity[22] of ferrous ions. Most of the compounds exhibited significant to moderate activities.

Antibacterial screening revealed that, compound **6a** having chloro substitution at C-5 position of indole and C-4 position aryl ring along with pyranopyrazole system enhanced the activity against *E. coli*, *S. aureus* and *K. pneumoniae* at all concentrations. Compounds **2a**, **3a–c**, **4c**, **4e** and **6e** exhibited maximum zone of inhibition against *E. coli* at all concentrations. The compounds **2a**, **2e**, **3b**, **3g**, **4a**, **4c**, **5a** and **6d** showed good zone of inhibition against *S. aureus* at all concentrations whereas, the compounds **2i**, **3a**, **3c**, **6b**, **6d** and **7a** showed maximum zone of inhibition against *K. pneumoniae* at all concentrations. Compounds **2g**, **4c**, **4i**, **6d**, **6g** and **6i** showed good zone of inhibition against *P. aeruginosa* at all concentrations.

Antifungal activity assay revealed that, the compound **4d** exhibited maximum zone of inhibition against *A. oryzae* and *A. flavus.* This enhanced activity of **4d** may be due to presence of chloro substitution at C-5 position of indole and methyl substitution at C-4 position of aryl ring. Replacement of chloro substitution (compound **4d**) at C-4 position of aryl ring by methyl group (compound **7d**) and shifting of oxo group from 2- to 4-position, that is, in place of amino group showed increase in antifungal activity against *A. oryzae* and *A. flavus*. Compounds **4a**, **5a** and **5i** showed potent activity against *Aspergillus niger,* whereas compounds **2e**, **3c**, **3g**, **4g**, **6c**, **6g** and **7g** exhibited high activity against *A. oryzae.* Compounds **2b**, **2c** and **3a** showed potent activity against *Aspergillus terrus*, whereas, compounds **2a**, **3e** and **4c** showed good activity against *A. flavus* at all concentrations.

The RSA results (Figs. 2–7, please see Supplementary data) revealed that, introduction of chloro substitution at C-5 position of indole and C-4 position of aryl ring (compound **4a**) was found to enhance the RSA (75.54% at 100 μg/ml). Compound **7a** exhibited good RSA at 50 μg/ml concentration. Compounds **3d**, **5a** and **7a** showed promising activity at 75 μg/ml concentration. Compounds **2a**, **2i**, **4f**, **6b** and **6e** exhibited good RSA at 100 μg/ml concentration.

The FRAP results (Figs. 8–13, please see Supplementary data) revealed that, compound **7d** showed higher activity by introduction of chloro substitution at C-5 position of indole and methyl group at C-4 position of aryl ring was found to enhance the FRAP, compounds **5b** and **7d** exhibited promising activity at 25 and 75 μg/ml concentrations and compounds **3a**, **4a** and **6c** showed good activity at 75 μg/ml concentration, whereas the compounds **2f**, **6a**, **6d** and **7h** exhibited good activity at 100 μg/ml concentrations.

Ferrous ions (Fe^{2+}) metal chelating activity capacity (Figs. 14–19, please see Supplementary data) of the title compounds indicated that, introduction of chloro substitution at C-5 position of indole and C-4 position of aryl ring (compound **3a**) exhibited higher metal chelating activity (79.71% at 100 μg/ml). Compounds **2d**, **3h**, **4a**, **4i**, **5c**, **5i**, **6a**, **6f**, **6h**, **7a**, **7d**, **7f** and **7g** exhibited good metal chelating activity at all concentrations, whereas other compounds exhibited either moderate or poor chelating activity.

In general it was observed that, compounds reported in the present communication were found to be less active compare to the compounds earlier reported (**1–4**).[16] This decrease in activity may be due to the non-aromatic character of pyran ring. Thus, the preliminary results showed that the pyridine ring plays an important role to enhance antimicrobial and antioxidant activities.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.02.036.

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