One-Pot Multicomponent Synthesis of Novel Substituted Imidazo[1,2-*a*] Pyridine Incorporated Thiazolyl Coumarins and their Antimicrobial Activity

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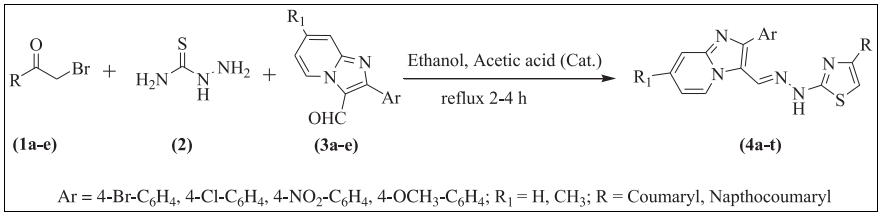

A series of novel substituted imidazo[1,2-*a*]pyridine incorporated thiazolyl coumarin derivatives (**4a–t**) were synthesized in good yields via one-pot multicomponent condensation of substituted imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3a–e**), thiosemicarbazide (**2**), and substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**1a–d**)/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**1e**) in refluxing ethanol with catalytic amount of acetic acid. All the synthesized compounds (**4a–t**) have been characterized by IR, NMR, and mass spectral studies as well as elemental analyses and evaluated for their *in vitro* antimicrobial activity against different bacterial and fungal strains. All the compounds displayed moderate antibacterial activity with minimum inhibitory concentration 150 μg/mL, but none of the compounds have shown any antifungal activity.

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INTRODUCTION

Multicomponent reactions have emerged as an efficient and powerful tool in modern synthetic organic chemistry in which three or more different starting materials react to give a final product in a one-pot procedure [1]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single step; these reactions are the best tools because of their productivity, simple procedures, and facile execution [2].

A large number of nitrogen bridgehead-fused heterocycles containing an imidazole ring have been reported in the literature as important pharmacophores [3–5]. The most widely used heterocyclic system from this group is imidazo[1,2-*a*] pyridine. Compounds derived from imidazo[1,2-*a*]pyridine were found to possess anticancer [6], anticonvulsant [7], anti-inflammatory [8], antimicrobial [9], antiviral [10], and anticoccodial [11] properties. These also act as inhibitors of hepatitis C virus replication [12], inhibitors of insulin-like growth factor-1 receptor [13], as well as melatonin receptor ligands [14] and DNA-directed alkylating agents [15]. These have high affinity towards human β-amyloid plaques [16]. They are also reported as prominent drugs such as Zolpidem, Olprinone, and Zolimidine used for the treatment of insomnia, heart failure, and peptic ulcer, respectively [17,3,4].

On the other hand, thiazole [5], coumarin [18], and thiazolylcoumarin [19–23] derivatives displayed significant biological properties such as antitumor, cytotoxic, anti-inflammatory, anticoagulant, antioxidant, antifungal, antitubercular, anticonvulsant, antimicrobial, antiviral, neuroprotective and diuretic activities. In continuation of our studies on several new heterocycles [24], we attempted to design a moiety embodied imidazo[1,2-*a*]pyridine-3-carbaldehyde, thiazole, and coumarins in a single frame work and evaluated for their *in vitro* antimicrobial activity.

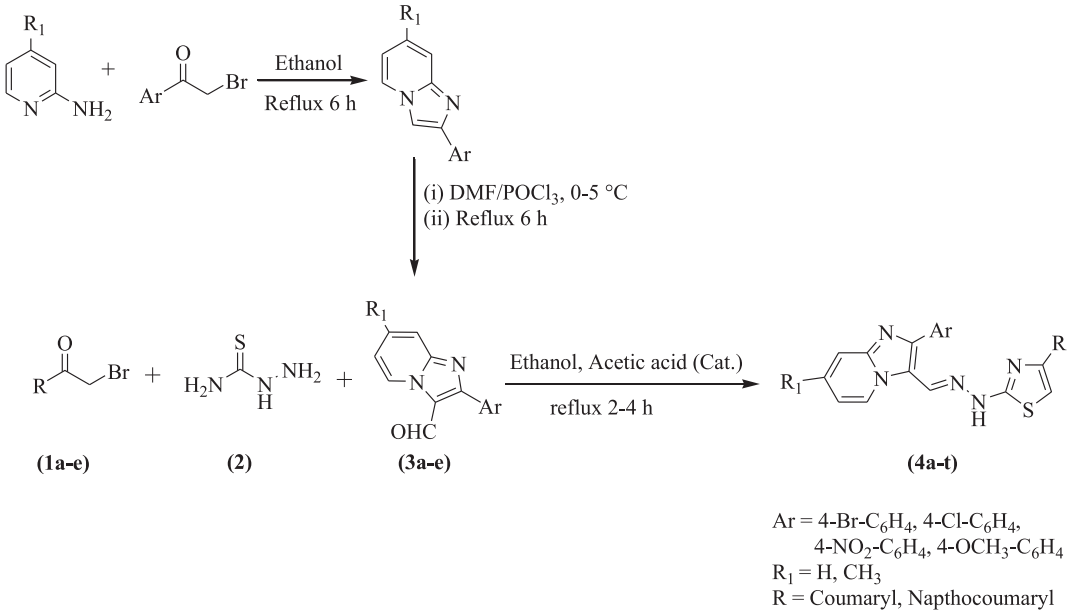
RESULTS AND DISCUSSION

Fused imidazo[1,2-*a*]pyridines-3-carbaldehydes (**3a–e**) and substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**1a–e**) were synthesized according to the literature methods [7,25]. The targeted compounds (**4a–t**) were prepared via multicomponent condensation of substituted imidazo[1,2-*a*] pyridine-3-carbaldehydes (**3a–e**), thiosemicarbazide (**2**), and 3-(2-bromoacetyl)-2*H*-chromen-2-ones/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**1a–e**) in absolute ethanol with catalytic amount of acetic acid under reflux condition with good yields. The synthetic pathway was outlined in Scheme 1.

To find out the optimal conditions, initially, a model reaction was carried out with 3-(2-bromoacetyl)-2*H*-chromen-2-one (**1a**), thiosemicarbazide (**2**), and 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3a**) in absolute ethanol and ethanol with catalytic amount of acetic acid at solvent refluxing temperature. In absolute ethanol, we obtained only 75% yield after 12 h, but we obtained 90% yield in ethanol with catalytic amount of acetic acid within 2 h.

In the IR spectrum of the compound, the appearance of a broad band at 3400 cm^{-1} for NH, 1719 cm^{-1} for C=O of lactone, and a medium band at 1605 cm^{-1} for C=N group; and in ^{1}H NMR, the presence of a singlet at 8.58 ppm

Scheme 1. Synthesis of substituted 3-(2-{*N*′-[2-aryl-imidazo[1,2-*a*]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one derivatives.



(coumarin 4th proton) and 12.5 ppm (NH) indicated the formation of product **4a**. Molecular ion peak from the mass spectrum further confirmed the formation of product.

After optimizing the reaction conditions, we examined the scope and generality of this method by extending to other substrates with different imidazo[1,2-*a*]pyridine-3-carbaldehydes (**3a–e**) and 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**1a–d**)/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**1e**). All the products were obtained in good yields (80–90%) within 2–4 h, and the results are postulated in Table 1. All the synthesized compounds were characterized by their analytical and spectral studies.

CONCLUSION

In conclusion, we have synthesized some new derivatives of imidazo[1,2-*a*]pyridine ring incorporated thiazolylcoumarins via multicomponet condensation of substituted imidazo[1,2-*a*] pyridine-3-carbaldehyde (**3a–e**), thiosemicarbazide (**2**) and 3-(2-bromoacetyl)-2*H*-chromen-2-one (**1a–d**)/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**1e**) in ethanol with catalytic amount of acetic acid under reflux condition for 2–4 h. All the compounds were evaluated for their *in vitro* antimicrobial activity. Antimicrobial results revealed that all the compounds displayed moderate antibacterial activity at MIC 150 µg/mL against all the tested bacterial strains. None of the compounds displayed antifungal activity against all the tested fungal strains.

EXPERIMENTAL

Melting points were determined in open capillaries using Stuart SMP30 apparatus (Bibby Scientific Ltd., United Kingdom) and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with F254 silica-gel precoated sheets (Merck, Darmstadt, Germany) using hexane/ethyl acetate 7/3 as eluent. Products were characterized by spectral data (IR, NMR, and mass). IR spectra were recorded on PerkinElmer 100S spectrophotometer (Perkin-Elmer Ltd., United Kingdom) using KBr pellet. NMR spectra were recorded on Bruker 400 MHz spectrometer (Bruker Corporation Ltd., Germany) using DMSO-d_6 as solvent and TMS as internal standard. Elemental analysis was performed on a Carlo Erba modal EA1108 (Triad Scientific Ltd., NJ), and mass spectra were recorded on a Jeol JMSD-300 spectrometer (Jeol Ltd., Tokyo, Japan).

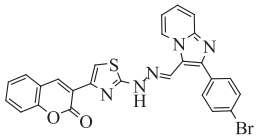
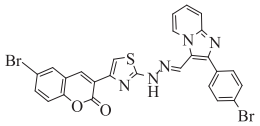
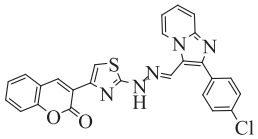
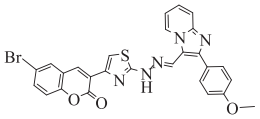
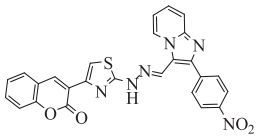
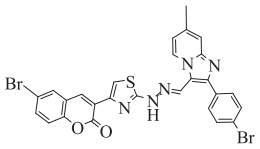
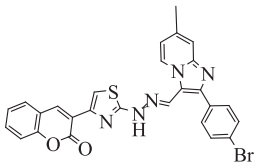
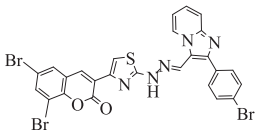
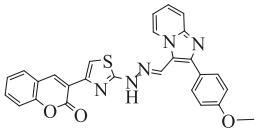
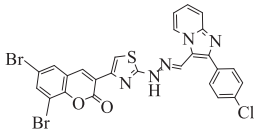
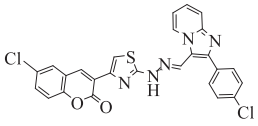
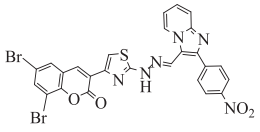
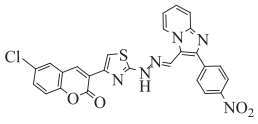
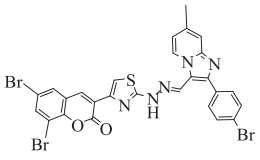
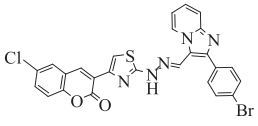
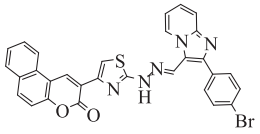
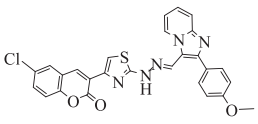
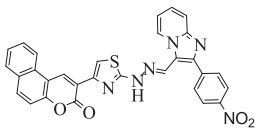
General procedure for the synthesis of (4a–q). A mixture of substituted imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3a–e**, 1 mmol), thiosemicarbazide (1 mmol) and 3-(2-bromo-acetyl)-2*H*-chromen-2-ones (**1a–d**, 1 mmol) were taken in 10 mL of ethanol, to this a catalytic amount of acetic acid was added and refluxed for 2–4 h. The progress of the reaction was monitored by TLC. The solid separated out was filtered, washed with ethanol, and recrystallized from acetic acid to afford the pure product in good yields.

3-(2-{N′-[2-(4-Bromo-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4a). Light green solid; mp: 233–235°C; IR (KBr, cm^{-1}) υ_{max}: 3400, 1719, 1605, 1578, 1425, 1008, 757, 649, 510; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (d, J = 8.0 Hz,1H), 7.46 (d, J = 8.0 Hz, 1H), 7.63–7.68 (m, 3H), 7.8 (d, J = 8.4 Hz, 2H), 7.89–7.99 (m, 4H), 8.04 (d, J = 9.2 Hz, 1H), 8.53 (s, 1H), 8.58 (s, 1H), 9.54 (d, J = 6.8 Hz, 1H), 12.5 (s, 1H); MS (ESI): *m/z* 543 (M + H); Anal. Calcd for $C_{26}H_{16}BrN_5O_2S$: C, 57.57; H, 2.97; N, 12.91; Found: C, 57.51; H, 3.04; N, 12.81.

3-(2-{N′-[2-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4b). Light green solid; mp: 260–262 °C; IR (KBr, cm^{-1}) υ_{max}: 3400, 3137, 1720, 1604, 1578, 1426, 1094, 757, 581; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39–7.48 (m, 3H), 7.62–7.68 (m, 5H), 7.83 (d, J = 8.8 Hz, 3H), 7.89 (d, J = 8.4 Hz, 2H), 8.58 (s, 1H), 9.45 (d,

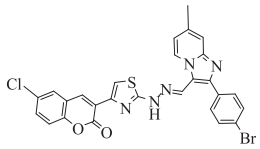
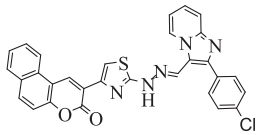
Table 1

Synthesis of substituted 3-(2-{*N*′-[2-aryl-imidazo[1,2-*a*]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one derivatives.

Entry[a]	Product	Time (h)	Yield[b] (%)	Entry[a]	Product	Time (h)	Yield[b] (%)
4a		2	90	**4k**		3	89
4b		2	89	**4l**		3	90
4c		2	87	**4m**		4	87
4d		3	88	**4n**		4	86
4e		2	89	**4o**		4	88
4f		3	87	**4p**		4	84
4g		3	85	**4q**		4	87
4h		3	84	**4r**		2	85
4i		3	88	**4s**		2	83

(*Continued*)

Table I
(Continued)

Entry[a]	Product	Time (h)	Yield[b] (%)	Entry[a]	Product	Time (h)	Yield[b] (%)
4j		4	87	**4t**		2	86

[a]**Reaction conditions**: Substituted imidazo[1,2-*a*]pyridine-3-carbaldehydes (1 mmol), thiosemicarbazide (1 mmol), substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (1 mmol), ethanol, catalytic amount of acetic acid, reflux.
[b]Isolated yields.

$J = 6.8$ Hz, 1H), 12.25 (s, 1H); MS (ESI): *m/z* 498 (M + H); Anal. Calcd for $C_{26}H_{16}ClN_5O_2S$: C, 62.71; H, 3.24; N, 14.06. Found: C, 62.60; H, 3.30; N, 14.17.

3-(2-{(N′-[2-(4-Nitro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4c). Orange solid; mp: 275–277 °C; IR (KBr, cm^{-1}) υ_{max}: 3379, 3136, 1720, 1630, 1600, 1567, 1519, 1347, 752, 689; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (t, $J = 6.8$ Hz, 2H), 7.72 (t, $J = 7.2$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 2H), 7.99 (s, 1H), 8.06 (d, $J = 8.8$ Hz, 3H), 8.4 (d, $J = 8.8$ Hz, 4H), 8.72 (s, 1H), 9.66 (d, $J = 6.8$ Hz, 1H), 11.43 (s, 1H); MS (ESI): *m/z* 509 (M + H); Anal. Calcd for $C_{26}H_{16}N_6O_4S$: C, 61.41; H, 3.17; N, 16.53; Found: C, 61.62; H, 3.01; N, 16.78.

3-(2-{N′-[2-(4-Bromo-phenyl)-7-methyl-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4d). Dark green solid; mp: 269–271°C; IR (KBr, cm^{-1}) υ_{max}: 3400, 3135, 1718, 1560, 1582, 1434, 779, 603, 514; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H), 7.35 (s, 1H), 7.68–7.82 (m, 7H), 8.07–8.20 (m, 3H), 8.33 (s, 1H), 8.51 (s, 1H), 9.3 (d, $J = 6.8$ Hz, 1H), 12.5 (s, 1H); MS (ESI): *m/z* 557 (M + H); Anal. Calcd for $C_{27}H_{18}BrN_5O_2S$: C, 58.28; H, 3.26; N, 12.59; Found: C, 58.36; H, 3.15; N, 12.67.

3-(2-{N′-[2-(4-Methoxy-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4e). Dark green solid; mp: 236–238°C; IR (KBr, cm^{-1}) υ_{max}: 3379, 3143, 1720, 1698, 1606, 1564, 1177, 1093, 614; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.88 (s, 3H), 7.18 (d, $J = 8.0$ Hz, 2H), 7.38–7.47 (m, 3H), 7.61–7.65 (m, 1H), 7.74 (d, $J = 8.8$ Hz, 3H), 7.84–7.9 (m, 4H), 8.57 (s, 1H), 9.47 (d, $J = 7.2$ Hz, 1H), 12.3 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): 55.31, 110.0, 114.2, 114.7, 115.8, 116.9, 119.1, 120.47, 124.6, 125.6, 127.3, 128.8, 130.3, 131.6, 134.1, 138.3, 144.22, 145.8, 148.6, 152.3, 158.7, 159.7, 167.2, 171.9; MS (ESI): *m/z* 494 (M + H); Anal. Calcd for $C_{27}H_{19}N_5O_3S$: C, 65.71; H, 3.88; N, 14.19; Found: C, 65.52; H, 3.98; N, 14.29.

6-Chloro-3-(2-{N′-[2-(4-chloro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4f). Dark green solid; mp: 279–281°C; IR (KBr, cm^{-1}) υ_{max}: 3395, 3141, 1708, 1566, 1244, 1093, 1079, 754, 564; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (t, $J = 6.8$ Hz, 1H), 7.48–7.67 (m, 5H), 7.81–8.05 (m, 5H), 8.52 (s, 1H), 8.6 (s, 1H), 9.41 (d, $J = 6.8$ Hz, 1H), 12.25 (s, 1H); MS (ESI): *m/z* 533 (M + H); Anal. Calcd for $C_{26}H_{15}Cl_2N_5O_2S$: C, 58.65; H, 2.84; N, 13.15. Found: 58.80; H, 2.93; N, 13.01.

6-Chloro-3-(2-{N′-[2-(4-nitro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4g). Brown solid; mp: 293–295°C; IR (KBr, cm^{-1}) υ_{max}: 3379, 3302, 1633, 1731, 1589, 1547, 1513, 1345, 1247, 1104, 753; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (t, $J = 6.4$ Hz, 1H), 7.61 (t, $J = 7.6$ Hz, 2H), 7.83 (d, $J = 9.2$ Hz, 1H), 7.94 (s, 1H), 8.06 (d, $J = 8.4$ Hz, 3H), 8.35 (d, $J = 8.8$ Hz, 4H), 8.75 (s, 1H), 9.6 (d, $J = 6.4$ Hz, 1H), 11.38 (s, 1H); MS (ESI): *m/z* 543 (M + H); Anal. Calcd for $C_{26}H_{15}ClN_6O_4S$: C, 57.51; H, 2.78; N, 15.48; Found: C, 57.36; H, 2.85; N, 15.40.

3-(2-{N′-[2-(4-Bromo-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-6-chloro-chromen-2-one (4h). Dark green solid; mp: 281–283°C; IR (KBr, cm^{-1}) υ_{max}: 3384, 3142, 1731, 1708, 1564, 1374, 1244, 1109, 1080, 1008, 780, 647, 647, 564; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37–7.5 (m, 2H), 7.63–7.67 (m, 2H), 7.74–7.81 (m, 4H), 7.85–8.05 (m, 3H), 8.52 (s, 1H), 8.59 (s, 1H), 9.42(d, $J = 6.8$ Hz, 1H), 12.25 (s, 1H); MS (ESI): *m/z* 577 (M + H); Anal. Calcd for $C_{26}H_{15}BrClN_5O_2S$: C, 54.13; H, 2.62; N, 12.14; Found: 54.02; H, 2.73; N, 12.30.

6-Chloro-3-(2-{N′-[2-(4-methoxy-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4i). Dark green solid; mp: 297–299°C; IR (KBr, cm^{-1}) υ_{max}: 3380, 3259, 1730, 1710, 1570, 1234, 1104, 1074, 753; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.61 (s, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.86–8.01 (m, 4H), 8.47 (s, 1H), 8.52 (s, 1H), 9.47 (d, $J = 6.8$ Hz, 1H), 12.39 (s, 1H); MS (ESI): *m/z* 528 (M + H); Anal. Calcd for $C_{27}H_{18}ClN_5O_3S$: C, 61.42; H, 3.44; N, 13.26; Found: C, 61.59; H, 3.48; N, 13.17.

3-(2-{N′-[2-(4-Bromo-phenyl)-7-methyl-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-6-chloro-chromen-2-one (4j). Light green solid; mp: 272–274°C; IR (KBr, cm^{-1}) υ_{max}: 3384, 3132, 1736, 1583, 1378, 1247, 1078, 715, 596; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 7.24 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.63 (s, 2H), 7.72–7.79 (m, 4H), 7.85 (s, 1H), 8.02 (s, 1H), 8.50 (s, 1H), 8.54 (s, 1H), 9.28 (d, $J = 6.8$ Hz, 1H), 12.19 (s, 1H); MS (ESI): *m/z* 591 (M + H); Anal. Calcd for $C_{27}H_{17}BrClN_5O_2S$: C, 54.88; H, 2.90; N, 11.85; Found: C, 54.63; H, 3.02; N, 11.90.

6-Bromo-3-(2-{N′-[2-(4-bromo-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4k). Dark green solid; mp: 300–302°C; IR (KBr, cm^{-1}) υ_{max}: 3384, 2919, 1726, 1563, 1244, 1008, 824, 1008, 824, 756, 649, 584, 509; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (d, $J = 7.2$ Hz, 3H), 7.54–7.86 (m, 7H), 8.14 (d, $J = 9.6$ Hz, 1H), 8.5 (s, 1H), 8.57 (s, 1H), 9.41 (d, $J = 6.8$ Hz, 1H), 12.28 (s, 1H); MS (ESI): *m/z* 622

(M + H); Anal. Calcd for $C_{26}H_{15}Br_2N_5O_2S$: C, 50.26; H, 2.43; N, 11.27; Found: C, 50.16; H, 2.55; N, 11.31.

6-Bromo-3-(2-{N′-[2-(4-methoxy-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4l). Dark green solid; mp. 256–258°C; IR (KBr, cm^{-1}) υ_{max}: 3380, 3024, 1730, 1580, 1025, 780, 649, 589, 504; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 7.16–7.23 (m, 2H), 7.39 (d, J = 10.4 Hz, 2H), 7.49–7.75 (m, 3H), 7.86 (s, 2H), 7.90 (t, J = 9.6 Hz, 1H), 8.13 (s, 1H), 8.26 (s, 1H), 8.47–9.5 (m, 2H), 12.4 (s, 1H); MS (ESI): *m/z* 573 (M + H); Anal. Calcd for $C_{27}H_{18}BrN_5O_3S$: C, 56.65; H, 3.17; N, 12.23; Found: C, 56.42; H, 3.28; N, 12.33.

6-Bromo-3-(2-{N′-[2-(4-bromo-phenyl)-7-methyl-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4m). Dark green solid; mp: 330–332°C; IR (KBr, cm^{-1}) υ_{max}: 3379, 3049, 1730, 1583, 1245, 1068, 779, 649, 559, 509; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 7.2–7.44 (m, 2H), 7.63 (s, 1H), 7.73–7.8 (m, 5H), 7.86 (s, 1H), 8.18 (s, 1H), 8.51 (s, 1H), 8.56 (s, 1H), 9.28 (d, J = 7.2 Hz, 1H), 12.2 (s, 1H); MS (ESI): *m/z* 636 (M + H); Anal. Calcd for $C_{27}H_{17}Br_2N_5O_2S$: C, 51.04; H, 2.70; N, 11.02. Found: C, 51.22; H, 2.89; N, 11.14.

6,8-Dibromo-3-(2-{N′-[2-(4-bromo-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4n). Brown solid; mp: 286–288°C; IR (KBr, cm^{-1}) υ_{max}: 3389, 3068, 1744, 1580, 1445, 1245, 1079, 997, 758, 718, 647, 582, 560, 512; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 8.0 Hz, 3H), 7.91 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.14 (s, 1H), 8.21 (s, 1H), 8.50 (s, 1H), 8.57 (s, 1H), 9.48 (d, J = 6.4 Hz, 1H), 12.37 (s, 1H); MS (ESI): *m/z* 701 (M + H); Anal. Calcd for $C_{26}H_{14}Br_3N_5O_2S$: C, 44.60; H, 2.02; N, 10.00; Found: C, 44.45; H, 2.26; N, 10.17.

6,8-Dibromo-3-(2-{N′-*[2-(4-chloro-phenyl)-imidazo[1,2-*a*]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4o). Yellowish brown solid; mp. 290–292°C; IR (KBr, cm^{-1}) υ_{max}: 3393, 3126, 1744, 1579, 1245, 1094, 1079, 758, 647, 560, 511; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 3H), 7.82–7.89 (m, 4H), 8.14 (s, 1H), 8.29 (s, 1H), 8.5 (s, 1H), 8.6 (s, 1H), 9.44 (d, J = 6.0 Hz, 1H), 12.30 (s, 1H); MS (ESI): *m/z* 656 (M + H); Anal. Calcd for $C_{26}H_{14}Br_2ClN_5O_2S$: C, 47.62; H, 2.15; N, 10.68; Found: C, 47.53; H, 2.28; N, 10.74.

6,8-Dibromo-3-(2-{N′-[2-(4-nitro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4p). Dark brown solid; mp: 295–297°C; IR (KBr, cm^{-1}) υ_{max}: 3370, 3033, 1742, 1597, 1575, 1548, 1511, 1345, 1106, 849, 755, 510; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16–7.61 (m, 3H), 7.82 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H), 8.07 (d, J = 8.8 Hz, 2H), 8.36 (t, J = 8.8 Hz, 4H), 8.75 (s, 1H), 9.59 (d, J = 6.0 Hz, 1H), 11.37 (s, 1H); MS (ESI): *m/z* 667 (M + H); Anal. calcd for $C_{26}H_{14}Br_2N_6O_4S$: C, 46.87; H, 2.12; N, 12.61; Found: C, 46.66; H, 2.30; N, 12.49.

6,8-Dibromo-3-(2-{N′-[2-(4-bromo-phenyl)-7-methyl-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-chromen-2-one (4q). Brown solid; mp: 277–279°C; IR (KBr, cm^{-1}) υ_{max}: 3380, 3120, 1744, 1581, 1245, 758, 649, 540, 528; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.62 (s, 3H), 7.43 (s, 1H), 7.74 (d, J = 7.2 Hz, 3H), 7.84–8.20 (m, 5H), 8.48 (s, 1H), 8.51 (s, 1H), 9.36 (s, 1H), 12.35 (s, 1H); MS (ESI): *m/z* 715 (M + H); Anal. Calcd for $C_{27}H_{16}Br_3N_5O_2S$: C, 45.40; H, 2.26; N, 9.81; Found: C, 45.31; H, 2.29; N, 9.92.

General procedure for the synthesis of (4r–t). A mixture of substituted imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3a–e**, 1 mmol), thiosemicarbazide, (1 mmol) and 2-(2-bromoacetyl)-3*H*-benzo[f]chromen-3-one (**1e**, 1 mmol) were taken in 10 mL of ethanol, to this catalytic amount of acetic acid was added and refluxed for 2 h. The progress of the reaction was monitored by TLC, the solid separated out was filtered, washed with ethanol and recrystallized from acetic acid to afford the pure product in good yields.

***2-(2-{N′-[2-(4-Bromo-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-benzo[f]*chromen-2-one (4r).** Yellowish brown solid; mp: 264–266°C; IR (KBr, cm^{-1}) υ_{max}: 3307, 3054, 1720, 1578, 1405, 1245, 1085, 742, 602, 506; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33–7.67 (m, 4H), 7.77–7.89 (m, 7H), 8.10 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 9.6 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 8.62 (s, 1H), 9.32 (s, 1H), 9.43 (d, J = 8.0 Hz, 1H), 12.37 (s, 1H); MS (ESI): *m/z* 517 (M + H); Anal. Calcd for $C_{30}H_{18}BrN_5O_2S$: C, 60.82; H, 3.06; N, 11.82; Found: C, 60.92; H, 2.96; N, 11.73.

2-(2-{N′-[2-(4-Nitro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-benzo[f]chromen-2-one (4s). Dark brown solid; mp: 335–337°C; IR (KBr, cm^{-1}) υ_{max}: 3325, 3241, 1720, 1597, 1575, 1548, 1247, 742, 602; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18–7.3 (m, 1H), 7.59–7.93 (m, 4H), 8.10–8.30 (m, 4H), 8.36–8.67 (m, 6H), 8.75 (s, 1H), 9.60 (s, 1H), 11.37 (s, 1H); MS (ESI): *m/z* 559 (M + H); Anal. Calcd for $C_{30}H_{18}N_6O_4S$: C, 64.51; H, 3.25; N, 15.05; Found: C, 64.45; H, 3.29; N, 15.36.

2-(2-{N′-[2-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-hydrazino}-thiazol-4-yl)-benzo[f]chromen-2-one (4t). Yellowish brown solid; mp. 266–268°C; IR (KBr, cm^{-1}) υ_{max}: 3379, 3060, 1720, 1586, 1407, 1097, 1008, 1247, 742, 602; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37–7.67 (m, 6H), 7.83 (d, J = 8.0 Hz, 4H), 7.89 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.61 (s, 1H), 9.3 (s, 1H), 9.43 (d, J = 6.8 Hz, 1H), 12.39 (s, 1H); MS (ESI): *m/z* 549 (M + H); Anal. Calcd for $C_{30}H_{18}ClN_5O_2S$: C, 65.75; H, 3.31; N, 12.78. Found: C, 65.70; H, 3.21; N, 12.79.

ANTIMICROBIAL ACTIVITY

All the newly synthesized compounds (**4a–t**) were evaluated for their *in vitro* antibacterial activity against three representative Gram-positive organisms viz. *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and three representative Gram-negative organisms viz. *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* with respect to the standard drugs penicillin and streptomycin. Minimum inhibitory concentration (MIC) of the compounds as well as standards was measured in μg/mL by micro dilution method recommended by Clinical and Laboratory Standards Institute standard protocol [26]. All the compounds displayed moderate antibacterial activity with MIC 150 μg/mL compared with the standard drugs against all the tested bacterial strains.

All the synthesized compounds were also screened for i*n vitro* antifungal activity against the five human pathogenic fungal cultures viz. *Candida albicans*, *Candida rugosa, Saccharomyces cervisiae, Aspergillus flavus*, and *Aspergillus niger* by taking amphotericin B as a standard drug.

Zone of inhibition was measured in millimeter by agar well diffusion method using potato dextrose agar [27]. But none of the compound has shown antifungal activity against all fungal strains.

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REFERENCES AND NOTES

[1] Ganem, B. Acc Chem Res 2009, 42, 463.

[2] Zhu, J.; Bienayme, H. Multi Component Reactions; Wiley-VCH: Weinheim, 2005.

[3] Takashi, U.; Katsufumi, M.; Kazushi, Y.; Tsutomu, T.; Masakazu, K.; Cerebrovasc Dis 2003, 16, 396.

[4] Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. J Med Chem 1965, 8, 305.

[5] Shiv Jee, K.; Vipin Kumar, G.; Pramod Kumar, S.; Nitin, K.; Rupesh, D.; Jitendra, K. G. Med Chem Res 2012, 21, 2123.

[6] (a) Dahan-Farkas, N.; Candice, L.; Amanda, R. L.; Dharmendra, Y. B.; Hajierah, D.; Charles, B.; Koning, D. Eur J Med Chem 2011, 46, 4573; (b) Kyung, H. J.; Hong-Mei, Z.; Yujeong, J.; Myung-Joo, C.; Hyunseung, L.; Sang-Won, H.; Hee-Seung, L.; Mi Kwon, S.; Soyoung, L.; Sungwoo, H.; Soon-Sun, H. Cancer Lett 2013, 328, 176; (c) Ahmed, K.; Surendranadha, R. J.; Janaki, R. M.; Dastagiri, D.; Vijaya, B. E.; Victor, P. S. M.; Pushpavalli, S. N. C. V. L.; Paramita, R.; Manika, P. B. Med Chem Commun 2010, 1, 355.

[7] Shrikanth, U.; Ramakrishna, S.; Aamir, S.; Vasudeva, A. A. Bioorg Med Chem Lett 2013, 23, 1502.

[8] Gaozhi, C.; Zhiguo, L.; Yali, Z.; Xiaoou, S.; Lili, J.; Yunjie, Z.; Wenfei, H.; Zhiguo, F.; Shulin, Y.; and Liang, G. Med Chem Lett 2012, 4, 69.

[9] Desai, N. C.; Pandya, M. R.; Rajpara, K. M.; Joshi, V. V.; Vaghani, H. V.; Satodiya, H. M. Med Chem Res 2012, 21, 4437.

[10] Kristjan, G. S.; Brian Johns, A. Bioorg Med Chem Lett 2007, 17, 2735.

[11] Dennis, F.; Michael, F.; Gui-Bai, L.; Xiaoxia, Q.; Chris, B.; Anne, G.; Penny, S. L.; Paul, A. L.; John, M.; Andrew, M.; Samantha, S.; Tamas, T.; Dennis, M. S.; Matthew, W.; Tesfaye, B. Bioorg Med Chem Lett 2006, 16, 5978.

[12] Inge, V.; Jan, P.; Tine, D. B.; Laura, S. L.; Matthew, P.; Hung, I. S.; Eric, M.; Nina, B.; Erik, D. C.; Hans, R.; David, O.; William, A. L.; Zhong, W.; Steven, B.; Gerhard, P.; Johan, N. J Hepatol 2009, 50, 999.

[13] Richard, D.; Iain, S.; Frederic, J. H.; Willem, N. J.; Peter, W.; Martina, F.; Graeme, E. W.; Lara, T. W.; Kevin, H. Bioorg Med Chem Lett 2011, 21, 4698.

[14] Kazzouli, S.; Griffon du Bellay, A.; Berteina-Raboin, S.; Delagrange, P.; Daniel-Henry, C.; Guillaumet, G. Eur J Med Chem 2011, 46, 4252.

[15] Ahmed, K.; Ramakrishna, G.; Janaki, R. M.; Viswanath, A.; Subba Rao, A. V.; Chandrakant, B.; Mukhopadyay, D.; Pushpavalli, S. N. C. V. L.; Manika, P. B. Med Chem Commun 2013, 4, 697.

[16] Lisheng, C.; Jessica, C.; Sebastian, T.; Mary, M. H.; Claudio, D.; David, A. W.; Robert B. I.; Victor, P. W. J Med Chem 2007, 50, 4746.

[17] Harrison, T. S.; Keating, G. M. CNS Drugs 2005, 19, 65.

[18] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[19] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; D'Ascenzio, M.; Maddalena, S. M.; Sistob, F. J Heterocyclic Chem 2010, 47, 1269.

[20] Vijesh, A. M.; Arun, I. M.; Prabhu, V.; Shaoib, A.; Shridhar, M. Eur J Med Chem 2010, 45, 5460.

[21] Raghu, M.; Nagaraj, A.; Sanjeeva Reddy, C. J Heterocyclic Chem 2009, 46, 261.

[22] Chimenti, F.; Carradori, S.; Daniela, S.; Adriana, B.; Chimenti, P.; Arianna, G.; Bizzarri, B. J Heterocyclic Chem 2009, 46, 575.

[23] Arshad, A.; Osman, H.; Mark Bagley, C.; Kit Lam, C.; Suriyati, M.; AnisSafira, M. Z. Eur J Med Chem 2011, 46, 3788.

[24] (a) Suresh Kuarm, B.; Thirupathi Reddy, Y.; Venu Madhav, J.; Peter Crooks, A.; Rajitha, B. Bioorg Med Chem Lett 2011, 21, 524; (b) Vijaya Laxmi, S.; Thirupathi Reddy, Y.; Suresh Kuarm, B.; Narsimha Reddy, P.; Peter Crooks, A.; Rajitha, B. Bioorg Med Chem Lett 2011, 21, 4329; (c) Janardhan, B.; Rajitha, B. Chin Chem Lett 2012, 23, 1015.

[25] Sushanta, S. K.; Arnaresh, M.; Rajani, B. K. Indian J Heterocycl Chem 1996, 6, 91.

[26] Wayne, P. A. Clinical and Laboratory Standards Institute (CLSI) Performance standards for antimicrobial susceptibility testing, 18th informational supplement, M100-S18, 2008.

[27] Linday, M. E. Practical Introduction to Microbiology; E and F. N. Spon Ltd.: United Kingdom, 1962; 177.