Journal of Molecular Structure 1017 (2012) 60–64

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Ionic liquid catalyzed one-pot multi-component synthesis, characterization and antibacterial activity of novel chromeno[2,3-*d*]pyrimidin-8-amine derivatives

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ARTICLE INFO

Article history:
Received 13 January 2012
Received in revised form 17 February 2012
Accepted 17 February 2012
Available online 1 March 2012

Keywords:
One-pot synthesis
Multi-component reaction
[bmim]BF_4
Chromeno[2,3-*d*]pyrimidin-8-amine
Antibacterial activity
Single-crystal X-ray diffraction

ABSTRACT

An efficient, simple and convenient method for the one-pot multi-component synthesis of novel chromeno[2,3-*d*]pyrimidin-8-amine derivatives has been accomplished by starting from α-naphthol, aryl aldehydes, malononitrile and NH_4Cl. The reaction has been catalyzed by 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 ionic liquid. The newly synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR, mass spectra, and elemental analysis. The structure of compound **4a** was confirmed by single-crystal X-ray diffraction. All the synthesized compounds were evaluated for their *in vitro* antibacterial activity.

1. Introduction

Chromenes are important heterocyclic compounds with a wide spectrum of biological and pharmacological activities viz. antimicrobial [1], antiviral [2], mutagenicity [3], antiproliferative [4], and anticancer [5]. They also act as CNS agents [6] and antioxidants [7]. They are also useful in preparing pheromones [8] and antitumor agents [9]. Some of these compounds are employed in making cosmetics, pigments [10] and potential biodegradable agrochemicals [11].

On the other hand, pyrimidine ring which is an integral part of various natural products of therapeutic importance plays a pivotal role in catalyzing both biological and chemical reactions. Pyrimidine derivatives are important biologically active heterocyclic compounds which possess antimalarial [12], antibacterial [13], fungicidal [14], antitoxoplasma [15], anticancer [16], anti-inflammatory and antitumor activities [17]. Hence, the synthesis of molecules containing both chromene and pyrimidine ring was taken up in the present investigation.

A multi-component reaction (MCR) can create highly complex molecules from readily available starting materials without the complicated purification operations. Thus, MCRs are identified as time-effective and economically favorable processes in diversity generation [18–20]. Recently, there have been tremendous developments in three and four component reactions and great efforts continue to be made to develop new MCRs [21–23]. Besides, the ionic liquids have invoked enormous interest as catalyst and solvent in organic synthesis because of their specific properties of non-volatility, non-flammability, solvating ability, thermal stability and easy recyclability [24]. Many organic reactions, including MCRs, were carried out efficiently in ionic liquids [25–28]. In continuation of our work on the synthesis of heterocyclic compounds in ionic liquids [29], we report herein four component synthesis of novel chromeno[2,3-*d*]pyrimidin-8-amines using [bmim]BF_4 ionic liquid as catalyst. A study of antibacterial activity of the products was also conducted.

2. Results and discussion

A mixture of α-naphthol (1 eq) **1**, malononitrile (1 eq) **2**, aryl aldehydes (2 eq) **3a–f** and NH_4Cl (2 eq) underwent one-pot cyclocondensation in the presence of [bmim]BF_4 and trace amount of triethylamine (TEA) in DMF producing compounds **4a–f**. To the best of our knowledge, this type of method was not found in the literature. The advantage of this method is that the compounds **4a–f** were obtained in quantitative yields directly, without the isolation of corresponding iminochromenes (Scheme 1). The reaction may proceed via an imine **5** formed from 2-amino-4*H*-chromeno-3-carbonitrile and arylaldehyde. Imine **5** reacts with NH_4Cl to give amidine **6**, followed by cyclization and aromatization to afford the compounds **4a–f** (Scheme 2).

A full characterization details were provided in experimental section. The molecular structure of a representative compound

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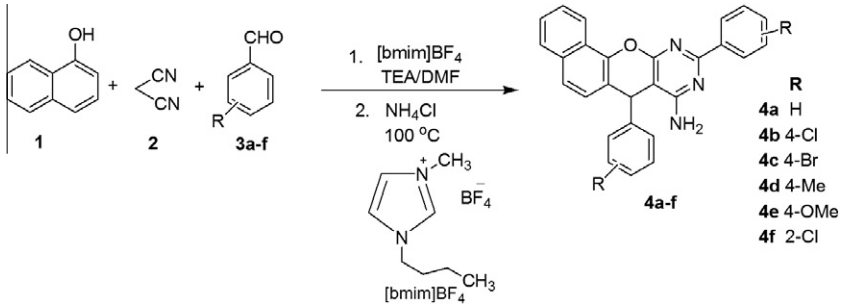
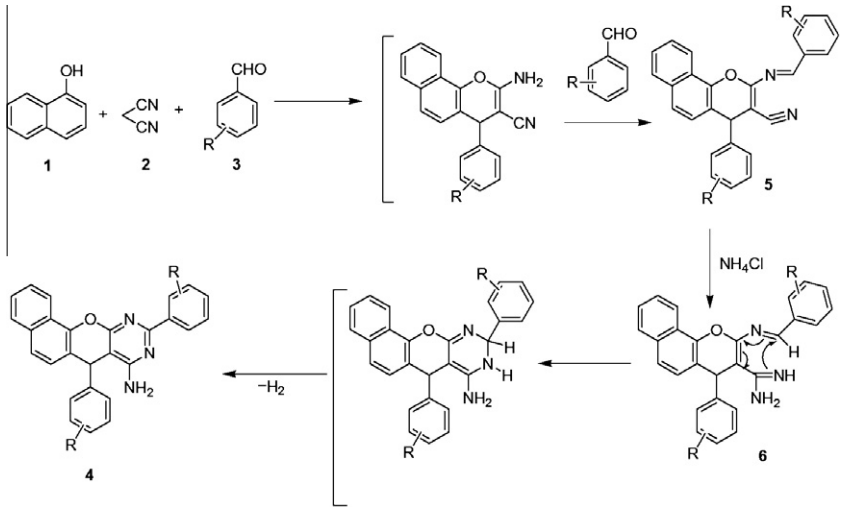
doi:10.1016/j.molstruc.2012.02.044



Scheme 1. General synthetic route of chromeno[2,3-*d*]pyrimidine-8-amine derivatives **4a–f**.



Scheme 2. Plausible mechanism for the synthesis of compounds **4a–f**.

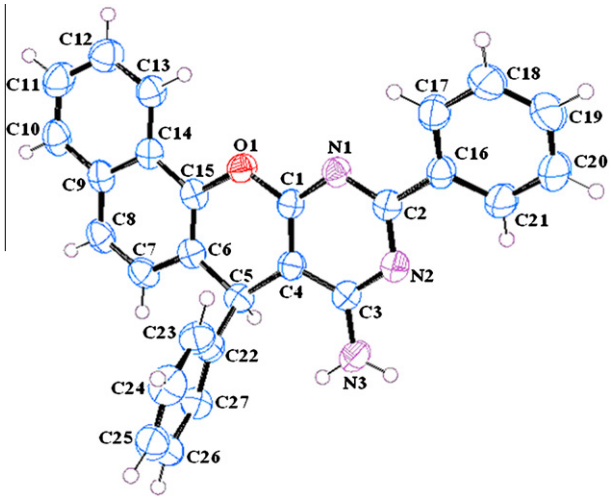


Fig. 1. ORTEP representation of compound **4a**. Thermal ellipsoids are drawn at 50% probability level.

4a was confirmed by single-crystal X-ray diffraction (Fig. 1). The scope and the generality of the present method was further demonstrated by the reaction of various aromatic aldehydes with malononitrile, α-naphthol and NH_4Cl. In all cases, quantitative yields in reasonable reaction times were obtained and ionic liquid could be reused for four times without evident loss of activity (Table 1).

The IR spectrum of compound **4a** exhibited absorption at 3500, 3454 cm^{-1} for (—NH_2), 3058 cm^{-1} for (aromatic C—H stretching), 1643 cm^{-1} for (—C=N), and 1261 cm^{-1} for (C—O—C). The ^1H NMR spectra of compound **4a** showed singlet at δ 5.42 ppm for pyran proton, δ 6.96 ppm for —NH_2 proton, multiplet at δ 7.18–7.96 ppm assigned for aromatic protons and δ 8.38 ppm for ArH-1. The ^{13}C NMR spectrum is in good agreement with the structure assigned. Mass spectra of compound **4a** gave molecular ion peak at *m*/*z* 402 $(M+1)^+$ corresponding to molecular formula $C_{27}H_{19}N_3O$. The elemental analysis values are in good agreement with theoretical data. All the compounds **4a–f** was screened for their antibacterial activity (Table 4).

Table 1
Synthesis of chromeno[2,3-*d*]pyrimidin-8-amines **4a–f** catalyzed by $[bmim]BF_4$.

S.No	Product 4	R	Time (min)	Yield (%)[a]
1	**4a**	H	90	92, 91, 90, 90[b]
2	**4b**	4-Cl	105	88
3	**4c**	4-Br	100	86
4	**4d**	4-Me	95	90
5	**4e**	4-OMe	110	88
6	**4f**	2-Cl	130	87

[a] Yield of isolated product.
[b] $[bmim]BF_4$ was reused for four runs.

3. Single crystal X-ray diffraction

The good quality crystals were selected for the single crystal X-ray diffraction. The data was collected on a Bruker APEX-II CCD diffractometer at 293(2) K using graphite-monochromated Mo Kα

Table 2
Salient crystallographic data and structure refinement parameters of compound **4a**.

	4a
Empirical formula	$C_{27}H_{19}N_3O$
Formula weight	401.45
Crystal system	Monoclinic
Space group	$P2_1/c$
T (K)	293(2)
a (Å)	15.061(5)
b (Å)	10.397(4)
c (Å)	12.850(4)
α (°)	90.00
β (°)	98.131(6)
γ (°)	90.00
Z	4
V (Å)^3	1992.0(12)
D_{calc} (g/cm^3)	1.339
F (000)	840.0
μ (mm^{-1})	0.083
θ (°)	1.37 to 26.05
Index ranges	$-18 \leqslant h \leqslant 18$ $-12 \leqslant k \leqslant 12$ $-15 \leqslant l \leqslant 15$
N-total	20041
N-independent	3933
N-observed	3199
Parameters	288
R_{int}	0.0406
R_1 ($I > 2\sigma(I)$)	0.0829
wR_2 (all data)	0.1657
GOF	1.183
CCDC	840878

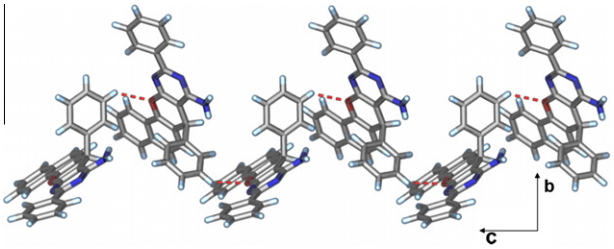


Fig. 2. A one dimensional corrugated tape with C—H···O hydrogen bonds.

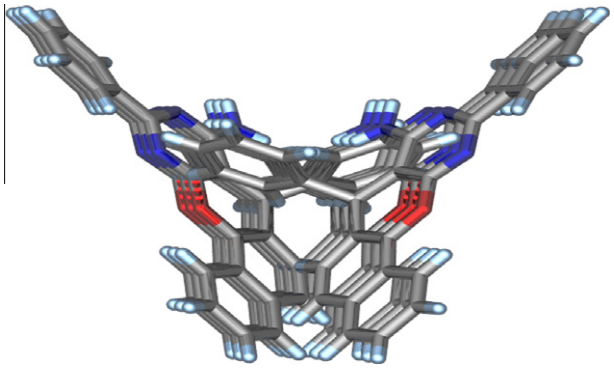


Fig. 3. A one dimensional tape viewed down *c*-axis.

radiation (λ = 0.71073 Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL [30]. The crystal structure was solved by direct method using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97 [31]. The N—H hydrogens were located from difference Fourier maps. Aromatic and aliphatic C—H hydrogens were generated by the riding model in idealized geometries. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3 and X-Seed [32]. Table 2 gives the pertinent crystallographic data, and Table 3 gives hydrogen bond parameters.

4. Crystal structure analysis

Compound **4a** crystallizes in the monoclinic $P2_1/c$ space group with one molecule in the symmetric unit (Z' = 1). The phenyl group which is attached to the pyrimidine ring is not essentially coplanar with the pyrimidine moiety (torsion angle of N2—C2—C16—C17 is 161.17°). The C—H group of the same phenyl ring which is attached the pyrimidine ring forms an intramolecular C—H···N hydrogen bond with pyrimidine nitrogen atom (C21···N2; D = 2.766(5) Å, C21—H21···N2; θ = 100°). The crystal structure analysis reveals that the molecules in the crystal form supramolecular one dimensional (1D) corrugated tapes. The C—H group of the phenyl ring which is attached to asymmetric center forms a weak C—H···O hydrogen bond with the pyran ring oxygen atom of the 2_1 screw related molecule (C26···O1; D = 3.303(4) Å, C26—H26···O1; θ = 135°) (Fig. 2) [33]. These interactions are propagated along the *c*-axis and form the one dimensional corrugated tape (Fig. 3). It is surprising that the amino (—NH_2) group has not involved in any hydrogen bonding.

5. Antibacterial activity

The antibacterial activity was determined by agar plate disk diffusion method [34] at the concentration of 50 μg per disk. All the synthesized compounds were tested *in vitro* for their antibacterial activity against microorganisms such as *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2439) (Gram positive), *Escherichia coli* (NCIM 2831), and *Pseudomonas aerugenosa* (NCIM 2863) (Gram negative) strains, using ciprofloxacin as standard antibacterial. Each test compounds were dissolved in DMSO to get a concentration of 10 mg/mL. The disk (6 mm in diameter) was impregnated with 5 μL of each test solution to get 50 μg/disk, air dried and placed on the agar medium, previously seeded with 0.2 mL of broth culture of each organism for 18 h. The plates were incubated at 37 °C for 24 h and the inhibition zones were measured in mm. Disks impregnated with DMSO were used as a control and ciprofloxacin disks as antibacterial reference standard.

The results of antibacterial activity presented in the Table 4 suggested that amongst all the synthesized compounds **4a–f**, compounds **4a** and **4e** were found to be highly active against *E. coli*. Compounds **4b** and **4d** exhibited excellent activity against

Table 3
Geometrical parameters of hydrogen bonds in compound **4a**.

Compound	D—H···A[a]	D···A (Å)	H···A (Å)	D—H···A (°)	Symmetry code
4a	Intra C21—H21···N2	2.766(5)	2.45	100	–
	C26—H26···O1	3.303(4)	2.58	135	$x, -1/2-y, -1/2+z$

[a] All of the C—H distances are neutron normalized to 1.083 Å.

Table 4
Antibacterial activity of compounds **4a–f**.

Compounds	Zone of inhibition (in mm)			
	S. aureus (NCIM 2079)	*B. subtilis* (NCIM 2439)	*E. coli* (NCIM 2831)	*P. aerug* (NCIM 2863)
4a	++	–	+++	+++
4b	+++	++	++	++
4c	–	+++	++	++
4d	+++	–	++	+++
4e	–	++	+++	++
4f	++	+++	++	++
Ciprofloxacin	+++	+++	+++	+++

'–' inactive (inhibition zone <6 mm); '+' slightly active (inhibition zone 7–9 mm); '++' moderately active (inhibition zone 10–13 mm); '+++' highly active (inhibition zone >14 mm).

S. aureus. Compounds **4a** and **4d** were found to be highly active against *P. aerug*. Compounds **4c** and **4f** were found to be more potent against *B. subtilis*. Compounds **4c** and **4e** showed no activity against *S. aureus*. Compounds **4a** and **4d** possessed no activity against *B. subtilis*. The rest of tested compounds were found to have moderate activity.

6. Conclusion

In summary, we have developed an efficient protocol for the synthesis of novel chromeno[2,3-*d*]pyrimidin-8-amine derivatives in [bmim]BF_4 ionic liquid and compound **4a** was confirmed by single-crystal X-ray diffraction and all the synthesized compounds were assayed for their *in vitro* antibacterial activity.

7. Experimental section

7.1. General

Melting points were recorded in open capillary and were uncorrected. Column chromatography was performed using silica-gel (60–120 mesh size) purchased from Thomas Baker and TLC was carried out using aluminum sheets pre-coated with silica gel 60F254 purchased from Merck. IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AC-300 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV. CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The compound **4a** was crystallized from N,N-dimethylformamide and the crystal data was collected on a Bruker APEX-II CCD diffractometer. All the solvents and chemicals used were pure, purchased from commercial sources and were used without further purification unless otherwise stated.

8. General procedure for the synthesis of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine 4a–f

To a mixture of α-naphthol **1** (1 mmol), malononitrile **2** (1 mmol) and arylaldehydes **3a–f** (2 mmol) in 10 mL of DMF, [bmim]BF_4 (2 mmol) and trace amount of TEA (0.2 mL) was added and the reaction mixture was stirred at 100 °C for 60–90 min. The progress of the reaction was monitored by TLC and after completion of the reaction (single spot on TLC), NH_4Cl (2 mmol) was added and the reaction was continued for an additional 30–40 min. After completion of the reaction, the reaction mixture was cooled to room temperature and 20 mL of water was added. The solid separated was filtered, washed with ether, dried and purified by column chromatography using silicagel ($CHCl_3$:MeOH 9:1) to furnish **4a–f** in good yields. The residue aqueous phase was evaporated under reduced pressure, and the remaining [bmim]BF_4 was rinsed with ether (15 mL), dried under a vacuum, and reused for four runs (Table 1).

8.1. 7,10-Diphenyl-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (*4a*)

Yellow solid; mp: 176–178 °C; IR (KBr): 3500, 3454, 3058, 1643, 1261 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.42 (s, 1H, pyran —CH), 6.96 (s, 2H, —NH_2), 7.18–7.96 (m, 15H, Ar—H), 8.38 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.0, 108.2, 118.6, 120.7, 121.8, 126.2, 126.8, 127.1 127.9, 128.7, 129.2, 129.8, 130.2, 130.9, 131.4, 133.4, 135.2, 144.2, 151.6, 159.3, 167.4, 174.9; ms: *m*/*z* 402 (M+1)$^+$. Anal. Calcd. for $C_{27}H_{19}N_3O$: C, 80.78; H, 4.77; N, 10.47. Found: C, 80.71%; H, 4.61%; N, 10.52%.

8.2. 7,10-Di-(4-chlorophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (*4b*)

Yellow solid; mp: 194–196 °C; IR (KBr): 3505, 3472, 3056, 1640, 1262 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.44 (s, 1H, pyran —CH), 6.94 (s, 2H, —NH_2), 7.20–8.02 (m, 13H, Ar—H), 8.38 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.2, 108.3, 118.6, 120.9, 122.0, 126.2, 126.6, 127.2, 128.6, 129.1, 130.1, 130.8, 131.0, 131.9, 132.7, 134.1, 136.3, 143.7, 151.8, 159.5, 167.8, 175.0; ms: *m*/*z* 471 (M+1)$^+$. Anal. Calcd. for $C_{27}H_{17}Cl_2N_3O$: C, 68.95; H, 3.64; N, 8.93. Found: C, 68.86%; H, 3.67%; N, 8.99%.

8.3. 7,10-Di-(4-bromophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (*4c*)

Yellow solid; mp: 234–236 °C; IR (KBr): 3490, 3392, 3052, 1648, 1263 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.48 (s, 1H, pyran —CH), 6.96 (s, 2H, —NH_2), 7.20–8.06 (m, 13H, Ar—H), 8.34 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.4, 108.8, 118.9, 120.9, 122.0, 122.8, 125.4, 126.4, 126.9, 127.4, 128.7, 129.3, 130.8, 131.7, 132.2, 134.3, 135.1, 144.5, 151.9, 159.6, 168.0, 175.2; ms: *m*/*z* 560 (M+1)$^+$. Anal. Calcd. for $C_{27}H_{17}Br_2N_3O$: C, 57.99; H, 3.06; N, 7.51. Found: C, 57.82%; H, 3.11%; N, 7.43%.

8.4. 7,10-Di-(4-methylphenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (*4d*)

Yellow solid; mp: 212–214 °C; IR (KBr): 3494, 3390, 3055, 1642, 1260 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 6H, —CH_3), δ 5.38 (s, 1H, pyran —CH), 6.88 (s, 2H, —NH_2), 7.10–7.86 (m, 13H, Ar—H), 8.30 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.2, 43.4, 108.3, 118.4, 120.6, 121.7, 126.1, 126.9, 127.1, 128.4, 129.0, 129.8, 130.2, 131.2, 132.3, 133.6, 137.2, 140.7, 142.4, 151.3, 159.1, 167.3, 174.8; ms: 430 (M+1)$^+$. Anal. Calcd. for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, 81.14%; H, 5.32%; N, 9.85%.

8.5. 7,10-Di-(4-methoxyphenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (*4e*)

Yellow solid; mp: 164–166 °C; IR (KBr): 3504, 3482, 3054, 1642, 1262 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.58 (s, 6H, —OCH_3), δ 5.40 (s, 1H, pyran —CH), 6.90 (s, 2H, —NH_2), 7.12–7.94 (m, 13H, Ar—H), 8.32 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.2, 58.3, 108.4, 116.7, 118.5, 120.7, 121.8, 125.3, 126.2, 126.9, 127.3, 128.7, 129.3, 130.3, 131.4, 134.0, 137.9, 152.3, 159.2, 160.1, 162.3, 168.2, 175.2; ms: *m*/*z* 462 (M+1)$^+$. Anal. Calcd. for $C_{29}H_{23}N_3O_3$: C, 75.47; H, 5.02; N, 9.10. Found: C, 75.53%; H, 5.10%; N, 9.03%.

*8.6. 7,10-Di-(2-chlorophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine (**4f**)*

Yellow solid; mp: 188–190 °C; IR (KBr): 3502, 3486, 3056, 1645, 1260 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.42 (s, 1H, pyran —CH), 6.95 (s, 2H, —NH_2), 7.15–7.94 (m, 13H, Ar—H), 8.36 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.4, 108.9, 118.7, 120.7, 122.3, 126.2, 126.9, 127.4, 128.5, 129.1, 129.4, 129.8, 130.4, 131.2, 131.8, 132.6, 133.5, 134.4, 135.3, 140.4, 145.2, 151.7, 159.2, 167.8, 174.9; ms: 471 $(M+1)^+$. Anal. Calcd. for $C_{27}H_{17}Cl_2N_3O$: C, 68.95; H, 3.64; N, 8.93. Found: C, 68.88%; H, 3.68%; N, 8.98%.

Acknowledgements

We are thankful to the Director, National institute of Technology, Warangal for providing facilities and financial support. We are also thankful to University of Hyderabad for providing single crystal X-ray data collection.

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