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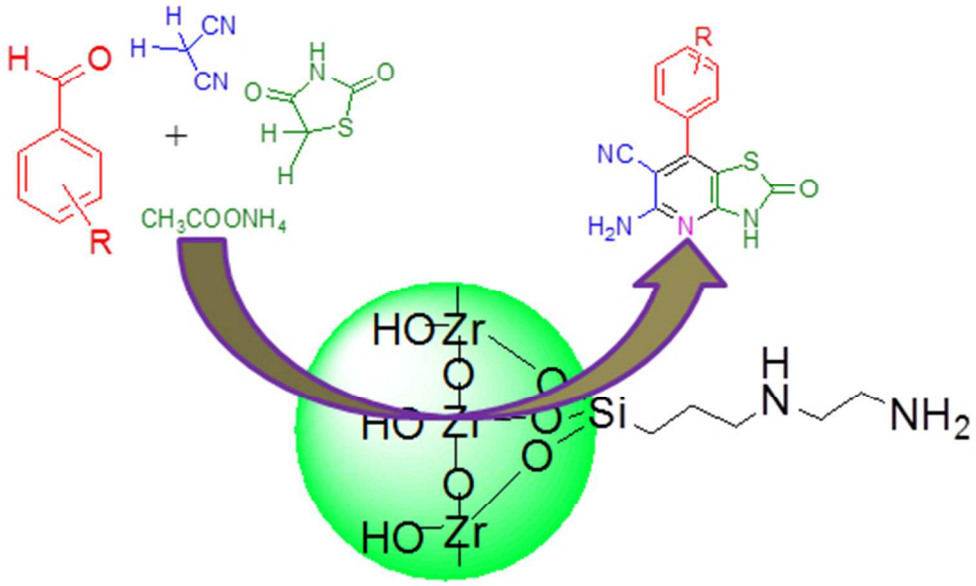

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Article

Multicomponent synthesis of Pyridines *via* diamine functionalized mesoporous ZrO_2 domino Intramolecular tandem Michael type addition

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A new and straightforward synthetic method is developed for the facile synthesis of heterocycle-fused pyridine derivatives in aqueous medium from Knoevenagel condensation between an aromatic aldehyde and an active methylene compound. This is followed by Michael type addition ketone to the activated double bond of the arylidene via intramolecular cyclization in the presence of diamine functionalized [N-(2 amino ethyl)-3-amino propyl trimethoxy silane (AAPTMS)] mesoporous ZrO_2 (AAPTMS/m-ZrO_2) to synthesize fused pyridines in high yields. This one-pot conversion which involves multiple steps, and needs no toxic/organic solvents, creating new C-C and C-heteroatom bonds, with all reactants efficiently utilized.

In contemporary drug discovery a major challenge is the design of highly capable chemical reactions suited for development of sustainable. The search for ideal and less harmful green catalysts/reagents has become a priority and necessity in synthetic organic chemistry.[1] The use of eco-friendly heterogeneous catalysts and reactions with water as a medium is rapidly increasing because these reaction eliminate the need for isolation of intermediates as well as avoidance of formation of side products.[2] Water as a solvent provides a proactive path for the sustainable progress of future science and technologies.[3] On the other hand, multi-component reactions using heterogeneous catalysts are accepted as powerful tools for the synthesis of organic compounds, since the products are formed in a single pot. Furthermore, the diversity of the products is obtained by simply varying the starting materials.[4]

Nitrogen-containing heterocyclic compounds are abundant in nature. Pyridines are one of the most studied nitrogen heterocycles due to the importance of their derivatives in many fields including pharmaceutical and academic research. They are not only found in the structural cores of various naturally occurring bioactive compounds,[5] and natural products,[6] but also as polysubstituted chiral ligands, and as building blocks for chiral ligands[7] and new materials with important photo- or electrochemical properties.[8] Among them, fused pyridines are considered as privileged components in medical chemistry and pharmaceutical industry.[9] Because of the enormous importance of the pyridine nuclei, a variety of methods have been developed for their preparation.[10] Most of the existing synthetic routes to pyridines are based on reactions between amines and carbonyl compounds.[11] A survey of the literature reveals that most of the reported approaches involve multistep sequences- using organic solvents, acidic reaction conditions and high reaction temperatures; and their usefulness is also limited by the dearth of generality. One-pot synthesis involving multicomponent reactions to produce the pyridine ring are attractive due to the possibility for formation of several bonds, in a single operation. Despite advances, the development of multicomponent routes to functionalized pyridines and their heterocycle-fused derivatives still remains a challenge. Our group has interest in exploring the scope of novel heterogeneous catalysts in multicomponent reactions [3a & 4a, b] for the synthesis of various biologically vital heterocyclic compounds with water as a reaction medium. As part of our continued efforts to develop improved methods for synthesis of biologically active heterocyclic compounds, we herein report a cascade synthesis of heterocycle-fused pyridines from thiazolidine-2,4-dione *via* Knoevenagel condensation followed by Michael addition using a recyclable heterogeneous catalyst in water. This new approach provides diverse molecules in a one-pot reaction and proceeds in a highly efficient and atom-economical manner to generate new C-C and C-heteroatom bonds, which conserves time and energy by avoiding multistep separations and purifications. Using water as a solvent is ideally the best choice due to the inherent environmental and economic advantages of such process.

The literature survey shows that few methods have been reported for the synthesis of pyridine derivatives through Knoevenagel condensation followed by Michael addition using different types of recyclable heterogeneous catalysts.[12] Recently, we reported a new route for the multicomponent synthesis of pyridine derivatives with Au/MgO as a heterogeneous catalyst in ethanol media.[4a] However, most of the reported methods are associated with drawbacks like use of carcinogenic organic solvents, use of expensive and sometimes non-easily prepared catalysts. All these limitations of the reported methods encouraged us to develop an economical and eco-friendly route for the synthesis of pyridine derivatives. Review of the literature indicates the use of amine functionalized mesoporous materials as catalysts in Michael addition reactions between active methylene compounds such as malononitrile.[13] These reports prompted us to use diamine functionalized mesoporous ZrO_2 for the first time as catalyst, in the present study

involving multicomponent system.

In order to optimize the reaction conditions and to identify the ideally suited acid-base and heterogeneous catalysts, the reaction was studied in presence and absence of chosen catalysts and solvents. In our preliminary studies, we examined the multicomponent reaction of 4-bromobenzaldehyde **3a**, malononitrile **1**, thiazolidine-2,4-dione **2** and ammonium acetate **4** using a Lewis/Brønsted acids such as [Bmim]BF_4, p-toluenesulfonic acid (PTSA), CF_3COOH and Lewis base triethylamine (TEA) as catalysts, However, the reactions gave no expected products (Table 1, entries 3 and 5-7). When water was used as a solvent in catalyst-free conditions, reaction provided a 20% yield of the desired product (Table 1, entry 4) and 35% yield of the title compound was obtained by using mesoporous ZrO_2 in aqueous medium (Table 1, entry 8). We then employed (AAPTMS/m-ZrO_2), an acidic/basic nature catalyst (30 mg) with water as medium. Based on the solubility of the reactants, water mediated reactions are termed as in-water and on-water reactions. Depending on solubility, the exposed organic surface area decreases due to the formation of aggregates resulting formation of holes in the cluster structure of water with bulk water molecules either surrounding or hydrating the aggregates. [1a] Due to the above described Breslow hydrophobic effect the reaction proceeds without any further difficulty irrespective of solubility limitations. The reaction proceeded well, affording the desired product with an good 90% yield within 2 h (Table 1, entry 9). Increase in amount of catalyst to 40 mg could improve the yield only marginally. We tried the reaction with varying the amounts of water (4 ml, 5 ml, 7 ml and 10 ml) and changes in the reaction progress or yield were marginal. Lower than 4 ml water made the stirring difficult.

Having established the optimal conditions, we assessed the efficiency of the protocol to other aldehydes and the results obtained are summarized in Table 2. A perusal of the reaction times and yields in Table 2 shows that all the reactions thrived with good to excellent yields. The AAPTMS/m-ZrO_2 catalysed reaction probably proceeds through a cyclic transition state with catalyst. The reaction is possibly facilitated by the highly effective acid-base bi-functional surface character of catalyst which is capable of mediating both the Knoevenagel condensation and Michael addition of carbonyl compounds. In the first step the formation of Knoevenagel product of arylidene-malononitrile as an intermediate is assumed. This fragment in subsequent Michael reaction with thiazolidine-2,4-dione gives the final product. The activated double bond of the arylidene presumably occurs due to the presence of acidic and basic sites in AAPTMS/m-ZrO_2 catalyst **Scheme 1**. A mechanistic rationale portraying the probable sequence of events for the formation of heterocycle-fused pyridines is given in **Scheme 2**. The recovery of AAPTMS/m-ZrO_2 catalyst was accomplished simply by filtration, and the activity of the catalyst was retained up to 6th cycle. Studies with recycled catalyst showed that it can be reused at least five times with no significant loss (<4%) of activity. The loss of activity with the regenerated catalyst could be due to partial loss of acid and base sites, surface area or by surface contamination during reaction or regeneration. Elemental and spectral (IR, ^{1}H, ^{13}C NMR and mass) analysis has been done for the catalyst and reaction products, where appropriate. Furthermore, the presence of the -NH_2 group in product structure was confirmed by ^{15}N NMR (GHSQC) (Supplementary data).

Table 1. Screening of reaction conditions for the multicomponent reaction

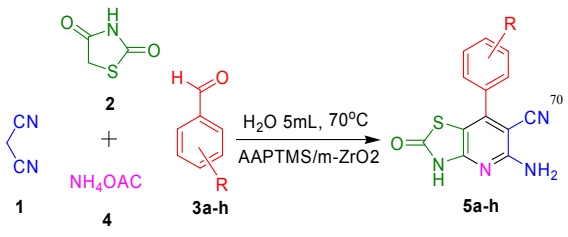
Entry	Product	Catalyst	Amount	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	**5a**	-	-	EtOH	rt	9	--[b]
2	**5a**	-	-	EtOH	70	7	--[b]
3	**5a**	[Bmim]BF_4	6 drops	-	70	9	--[b]
4	**5a**	-	-	H_2O	70	8	20
5	**5a**	PTSA	20 mg	EtOH	70	8	--[c]
6	**5a**	CF_3COOH	0.5 ml	EtOH	70	8	--[c]
7	**5a**	TEA	0.5 ml	H_2O	70	6	--[b]
8	**5a**	m-ZrO_2	30 mg	H_2O	70	7	35
9	**5a**	AAPTMS/m-ZrO_2	30 mg	H_2O	70	2	90
10	**5a**	AAPTMS/m-ZrO_2	40 mg	H_2O	70	2	93

[a] Isolated yields. [b] Product not found. [c] Trace.

Table 2. Multicomponent reaction for the synthesis of heterocycle-fused pyridines **5a-h**

Entry	Product	R	Time (h)	Yield (%)[a]
1	**5a**	4-Br	2.0	90
2	**5b**	4-Cl	2.5	95
3	**5c**	4-Methoxy	1.5	94
4	**5d**	2-Cl	2.0	92
5	**5e**	2-Methoxy	2.0	93
6	**5f**	2-Nitro	3.0	88
7	**5g**	3,4-Di methoxy	3.5	84
8	**5h**	H	3.0	86

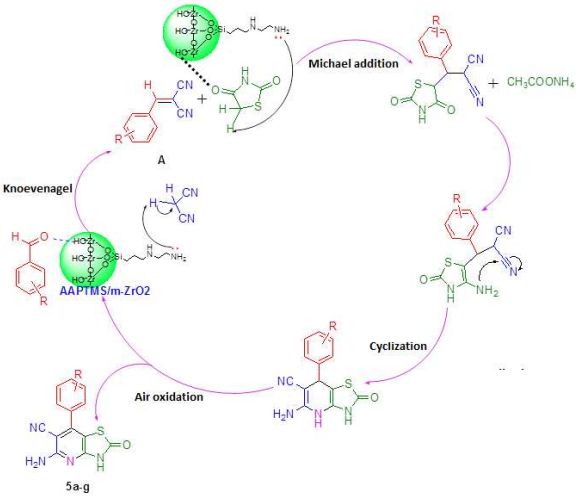
[a] Isolated yields.



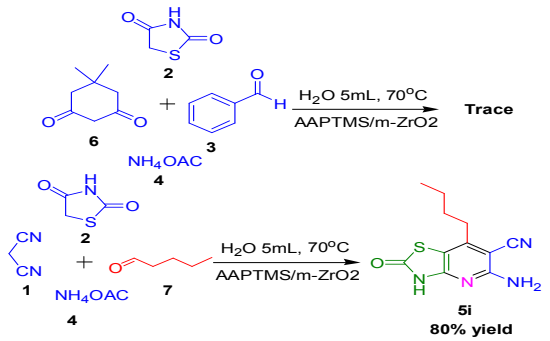
Scheme 1. Four-component synthesis of heterocycle-fused

pyridines **5a-h**.

When other compounds with active methylene like dimedone used, the corresponding heterocycle-fused pyridines were not obtained. However, when reactions using aliphatic aldehyde, such as n-butyraldehyde explored, notably n-pentanaldehyde gave the desired polysubstituted pyridine product **5i** in good yield (80%) (**Scheme 3**).



Scheme 2. Plausible reaction mechanism for the construction of compounds **5a-h**.



Scheme 3. Substrate Limitations of the multicomponent reaction

Characterization of the Catalyst material

The FTIR spectra of AAPTMS functionalized zirconia is shown in **Figure 1**. The wide band in the region of 3410 cm^{-1}, was due to the asymmetric stretching of -OH group. There were also bending vibrations of -(O-H-O)- and-(H-O-H)- bonds at around 1386and 1621 cm^{-1}. In addition, the peak at 690 cm^{-1} was due to an N-H bending vibration, while the peak at 1532 cm^{-1} was of a $-NH_2$ symmetric bending vibration of AAPTMS functionalized ZrO_2 nanoparticles. The peak at 730 cm^{-1} was attributed to the presence of a Zr-O bond. All this data supported the successful grafting of an organic amine onto the surface of mesoporous zirconia.

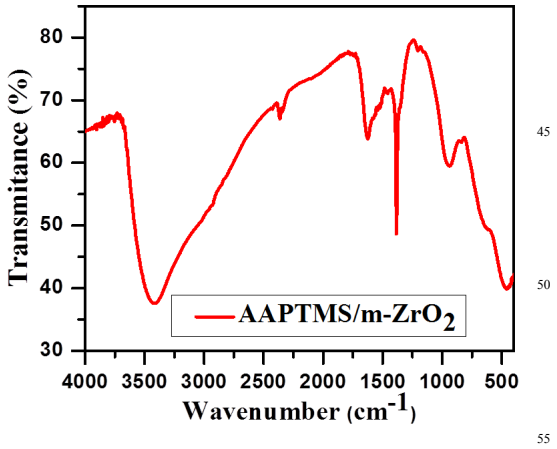


Figure 1. FT-IR spectra of AAPTMS/m-ZrO_2 sample

The ^{13}C NMR spectrum of AAPTMS/m-ZrO_2 sample is shown in **Figure 2**. The sharp peak at 8.7 ppm is attributed to the C-atom bonded to silicon. The signals at 20, 38.5, 50.5 and 65.7 ppm correspond to the methylene carbons attached to the amine groups starting from silicon atom. Hence it was proved that, the organic group was modified by surface silanol group of m-ZrO_2.

The N_2 - adsorption-desorption isotherm and pore volume were carried AAPTMS/m-ZrO_2 (**Fig S1 in ESI**). The specific surface area of m-zirconia is 156 m^2/g reported in literature.[13] After modification by the amine group, the specific surface area and pore volume decreased significantly to 101 m^2/g and a pore volume 0.18 cm^3/g. According to the IUPAC classification, the modified samples exhibit type-IV isotherms with a typical hysteresis loop like parent materials.

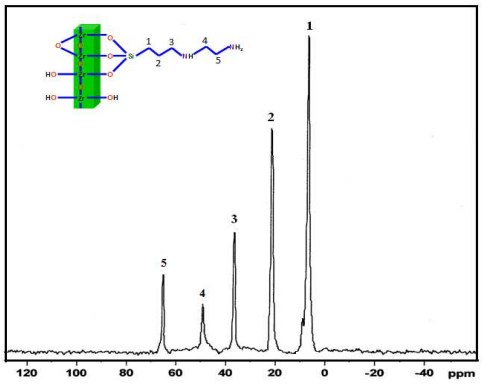


Figure 2 ^{13}C MAS NMR spectra of DF/m-ZrO_2

The small angle XRD spectrum of AAPTMS/m-ZrO_2 is shown in **Fig S2 in ESI**. According to literature,[14] m-ZrO_2 gives only one broad peak at around 1^o demonstrating the meso-structure. But after modification of AAPTMS group on the support surface, there was no change on the modified sample. Only decrease of the intensity of the modified sample still obeys the meso-structure after modification. The SEM image of AAPTMS/m-ZrO_2 is shown in **Fig S3 in ESI**. In this image, the particles have oval shaped morphology, and were well ordered and uniformly distributed over the support surface of mesoporous zirconia. The

transmittance electron micrograph (TEM) of AAPTMS/m-ZrO_2 sample is shown in **Fig S3 in ESI**. The figure illustrates that after modification the particles have oval shaped morphology.

Conclusions

In summary, an efficient and one-pot multicomponent synthetic method in aqueous media using AAPTMS/m-ZrO_2 as the heterogeneous catalyst has been developed, for the convenient synthesis of a new class of heterocycle-fused pyridines of potential synthetic and pharmacological interest. From a synthetic point of view, proposed method is simple and proceeds under mild reaction conditions. The operational simplicity, high yield, short reaction time and easy recovery and reuse of heterogeneous catalyst are the main advantages of this method. Furthermore, this protocol is safe and environmentally benign which makes a superior approach for the preparation of small heterocycle-fused pyridines.

Synthesis of diamine functionalized mesoporous zirconia

The mixture containing cetyltrimethyl ammonium bromide, 2M of NaOH (aq) and H_2O was heated at 80 ^oC for 30 min at a pH of 12. To this clear solution, zirconium butoxide and AAPTMS (1.925 ml) were added sequentially and rapidly. Following the addition, a white precipitation was observed after 3 min of stirring. The reaction temperature was maintained at 80 ^oC for 2 h. The products were isolated by a hot filtration, washed with a sufficient amount of water followed by methanol and dried under vacuum. For acid extraction, the as-obtained materials (1 g) was treated with a mixture of ethanol (100 ml) and concentrated HCl (1 ml, 38% in weight) at 80 ^oC for 6 h. The resulting (surfactant removed) solid products were filtered and washed with ethanol, and then dried at 60 ^oC. Then it was formed as AAPTMS/m-ZrO_2. The schematic representation for the catalysts synthesis is shown in **Fig S5 in ESI**.

Physico-chemical characterization

The BET surface area and pore size distribution were determined by multipoint N_2 adsorption-desorption method at liquid N_2 temperature (-196 ^oC) by a Micromeritics ASAP 2020. The low angle X-ray diffractograms were recorded on a Philips PW 1710 powder diffractometer using Ni filtered Cu Kα in the 2θ range of 0-10^o. The FTIR spectra were recorded using Varian FTIR-800 in KBr matrix in the range of 4000-400 cm^{-1}. The scanning electron microscopic figures of functionalized zirconia samples were recorded using Hitachi S3400N. ^{13}C MAS NMR spectra were recorded on an AV300 NMR spectrometer.

General procedure for the synthesis of heterocycle-fused pyridines

A mixture of 4-bromobenzaldehyde (2.0 mmol) in water (5 ml) at room temperature, malononitrile (2.0 mmol), thiazolidine-2,4-dione (2.0 mmol), ammonium acetate (3.0 mmol) and AAPTMS/m-ZrO_2 (30 mg) were added to a round-bottomed flask equipped with a magnetic stir bar and condenser. The mixture was heated at 70 °C for the time specified in Table 2. The reaction progress was monitored by TLC (EtOAc/hexane = 3:7). After completion of the reaction, the mixture was cooled to room temperature and extracted with EtOAc. After filtering the solid catalyst, the solvent layer was washed with H_2O, dried over anhydrous Na_2SO_4 and the solvent removed to obtain a solid which was recrystallized from EtOH to give the pure target compound **5a** (90% yield) as an off-white solid. The recovered AAPTMS/m-ZrO_2 solid was washed with CH_2Cl_2, dried under reduced pressure and reused in the next cycles.

Compound 5a

Off-white solid: mp 170-171 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.23 (2H, s, NH_2), 7.25 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.3 Hz), 10.07 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.87, 118.05, 120.56, 124.58, 129.37, 131.60, 140.88, 153.02, 158.52, 161.99, 171.33; IR (KBr, cm^{-1}): 2163 (CN), 3207 (NH_2); MS (ESI), *m*/*z* = 370 (M+Na, 100%); Anal. Calcd ($C_{13}H_7BrN_4OS$): C 44.97, H 2.03, N 16.14%. Found: C 44.94, H 2.02, N 16.16%.

Compound 5b

Off-white solid: mp 230-231 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.24 (2H, s, NH_2), 7.31 (2H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 9.01 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.35, 117.28, 124.12, 127.95, 128.47, 132.22, 133.08, 168.51, 172.0, 175.51, 179.70; IR (KBr, cm^{-1}): 2165 (CN), 3149 (NH_2); MS (ESI), *m*/*z* = 303 (M+1, 100%); Anal. Calcd ($C_{13}H_7ClN_4OS$): C 51.58, H 2.33, N 18.51%. Found: C 51.56, H 2.30, N 18.49%.

Compound 5c

Off-white solid: mp 211-212 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.86 (3H, s), 7.15 (2H, d, *J* = 8.3 Hz), 7.29 (2H, s, NH_2), 7.94 (2H, d, *J* = 8.9 Hz), 8.35 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.35, 68.58, 114.65, 120.22, 124.12, 126.46, 128.33, 131.48, 168.21, 172.16, 175.52, 179.71; IR (KBr, cm^{-1}): 2211 (CN), 3204 (NH_2); MS (ESI), *m*/*z* = 299 (M+1, 100%); Anal. Calcd ($C_{14}H_{10}N_4O_2S$): C 56.37, H 3.38, N 18.78%. Found: C 56.34, H 3.36, N 18.75%.

Compound 5d

Off-white solid: mp 219-220 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.23 (2H, s, NH_2), 7.26-7.44 (4H, m), 10.22 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.93, 117.90, 127.60, 128.67, 129.0, 129.16, 131.27, 132.74, 134.10, 153.51, 161,96, 169.83, 171.35; IR (KBr, cm^{-1}): 2140 (CN), 3215 (NH_2); MS (ESI), *m*/*z* = 325 (M+Na, 100%); Anal. Calcd ($C_{13}H_7ClN_4OS$): C 51.58, H 2.33, N 18.51%. Found: C 51.54, H 2.32, N 18.47%.

Compound 5e

Off-white solid: mp 239-240 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.77 (3H, s), 6.96-7.32 (6H, m, Ar-H and NH_2), 10.18 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.55, 67.70, 111.10, 118.23, 120.35, 121.90, 126.69, 128.36, 131.90, 156.24, 157.87, 162.35, 169.39, 172.09; IR (KBr, cm^{-1}): 2165 (CN), 3289 (NH_2); MS (ESI), *m*/*z* = 321 (M+Na, 100%); Anal. Calcd ($C_{14}H_{10}N_4O_2S$): C 56.37, H 3.38, N 18.78%. Found: C 56.36, H 3.37, N 18.74%.

Compound 5f

Off-white solid: mp 234-235 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.40 (2H, s, NH_2), 7.48-8.09 (4H, m, Ar-H), 10.28 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.15, 117.75, 123.16, 125.29, 129.01, 129.15, 134.24, 135.60, 147.93, 153.61, 163.53, 169.39, 171.68; IR (KBr, cm^{-1}): 2169 (CN), 3188 (NH_2); MS (ESI), *m*/*z* = 336 (M+Na, 100%); Anal. Calcd ($C_{13}H_7N_5O_3S$): C 49.84, H 2.25, N 22.35%. Found: C 49.81, H 2.23, N 22.32%.

Compound 5g

Off-white solid: mp 231-232 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.87 (6H, s), 6.74-6.76 (2H, m, Ar-H), 7.28 (2H, s, NH_2), 8.03 (1H, s, Ar-H), 10.15 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.08, 56.26, 75.70, 98.25, 107.57, 113.08, 114.15, 115.22, 130.43, 153.73, 161.30, 166.78, 169.89, 172.09; IR (KBr, cm^{-1}): 2221 (CN), 3090 (NH_2); MS (ESI), *m*/*z* = 329 (M+1, 100%); Anal. Calcd ($C_{15}H_{12}N_4O_3S$): C 54.87, H 3.68, N 17.06%. Found: C 54.85, H 3.66, N 17.02%.

Compound 5h

Off-white solid: mp 185-186 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.44 (2H, s, NH_2), 7.45-7.58 (5H, m, Ar-H), 12.59 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.46, 117.81, 123.52, 129.27, 129.95, 130.38, 131.73, 167.32, 167.89, 169.87, 171.99; IR (KBr, cm^{-1}): 2182 (CN), 3120 (NH_2); MS (ESI), *m/z* = 269 (M+1, 100%); Anal. Calcd ($C_{13}H_8N_4OS$): C 58.20, H 3.01, N 20.88%. Found: C 58.17, H 2.98, N 20.83%.

Compound 5i

Off-white solid: mp 201-202 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 0.94 (3H, t, *J* = 7.2 Hz), 1.45-1.52 (2H, m), 1.74-1.91 (2H, m), 2.64 (2H, t, *J* = 3.2 Hz), 6.24 (2H, s, NH_2), 8.10 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 17.4, 24.8, 36.9, 70.9, 118.2, 126.6, 147.9, 161.1, 168.2, 171.3; IR (KBr, cm^{-1}): 2167 (CN), 3189 (NH_2); MS (ESI), *m/z* = 249 (M+1, 100%); Anal. Calcd ($C_{11}H_{12}N_4OS$): C 53.21, H 4.87, N 22.56%. Found: C 53.32, H 4.91, N 22.59%.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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